TENTH PROGRESS REPORT

to the

COMMITTEE ON DRUG ADDICTION

of the

NATIONAL RESEARCH COUNCIL

1936

United States Public Health Service Hospital

University of Michigan University of Virginia

Part I. Clinical Studies

During the past year studies designed to determine the presence of dependence satiation in some of the new morphine derivatives were continued at the U.S.P.H.S. Hospital, Lexington, Kentucky. Certain changes in the clinical evaluation of abstinence were made so that the system now employed is not only completely objective, but reasonably quantitative. This improved system has been described in a report (to be published) of a study of the effect of "Rossium" treatment during withdrawal.

There is still no reason to believe that dependence satiation can be distinguished from addiction liability, hence, we still maintain that drugs which will maintain the state of dependence are capable of producing addiction (dependence).

By comparison of the mean values of caloric intake, body temperature, respiratory rate, blood pressure, weight, B.M.R., and blood sugar while on morphine and the new drug under investigation, data on dosage relationships are put on a more sound basis.

Alpha-isomorphine, dihydro-alpha-isomorphine, and dihydro-diacetyl-morphine have been studied and found to possess addiction liability. Alpha-isomorphine is of about the same potency as morphine, while dihydro-alpha-isomorphine and dihydro-diacetyl-morphine are about twice as potent as morphine.

At the present rate of admissions to this institution it will be possible to progress in these clinical studies at the rate of about one new drug per month, hence, a report on about 12 new drugs should be available at the time of the Fall meetings in 1937. Since the beginning of the clinical studies, a total of 22 drugs have been made available for investigation. Most of these drugs have not previously been studied in man. In view of the time necessary for the completion of each drug, however, it seems imperative to choose only one drug representative of each important structural type, and the compounds planned for study during the coming year have been selected on this basis. These drugs are as follows:

Beta chloromorphide

Dihydrohydroxycodeinone

Dihydrocodeinone enol acetate

Tetrahydrothebaine

Aminomorphine

Dihydromethylmorphimethine

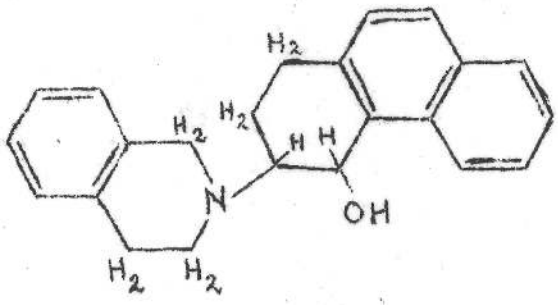
Methyldihydromorphinone

Ethylmorphine

Studies of 3-(1,2,3,4-tetrahydro-isoquinolino-)-4-hydroxy-1,2,3,4-tetrahydro-phenanthrene have been started.

The data on one of the cases who received 11-A are shown in the following table:

Dates	Mgm. Doses	Hour	Y/L	S/Rh	P/Gf	Pu/Tr	Temp.	Pulse	Resp.	Sleep	R ?	Em/Def.	A.M.	B.P.	Wt.Kgm.	Caloric.	Degree
10/4/36	3-A:50x2 25x2	0-8 8-4 4-12					36.9 36.9 37.2	52 55 64	12 17 18	6 0 1		1	98	/64	63.40	2737	0
10/5	3-A:50x2 25x2						37.0 37.2 37.5	70 75 66	10 12 17	6½ 0 1		1	94	/70	63.80	2208	0
10/6	11-A: 5 3-A:50,50 25						37.0 37.0 37.5	59 70 72	13 15 17	6 0 0			118	/60	63.30	2324	0
10/7	11-A:10 3-A:50,25 25				✓		37.0 37.5 37.7	56 75 80	11 14 17	4½ 0 1½	✓	1	106	/68	63.32	1808	0
10/8	11-A:15+20 3-A:25+50			✓	✓		37.1 37.5 37.4	58 67 80	12 12 20	4 2½ 1		1	98	/62	62.55	3888	0
10/9	11-A:25+30 3-A:25+50		✓ ✓	✓		✓ ✓	37.0 37.4 37.5	59 71 68	14 13 15	5½ 1½ 1		2	104	/62	63.10	2214	+
10/10	11-A:40,50 50+50		✓ ✓ ✓ ✓	✓ ✓	✓ ✓	✓ ✓ ✓	37.0 37.6 37.6	61 71 72	14 17 20	5½ 0 1	✓ ✓	3	106	/66	62.84	1720	++
10/11	11-A:50,75 100+100		✓ ✓ ✓ ✓ ✓ ✓	✓ ✓ ✓ ✓	✓ ✓	✓ ✓ ✓	37.7 37.8 38.1	76 100 84	17 19 20	½ 0 0	✓ ✓ ✓	4 1 5 2 4 3	116	/80	60.00	666	++++
10/12	11-A:100, 100,100 + 25		✓ ✓ ✓ ✓	✓ ✓	✓	✓ ✓	38.1 38.0 38.1	76 100 80	16 20 16	2 0 0	✓ ✓ ✓	4 1 2 2 2	104	/78	59.85	832	++++
10/13	11-A:25,50 50+50		✓ ✓ ✓ ✓	✓ ✓ ✓ ✓	✓ ✓	✓ ✓ ✓	37.9 38.1 37.9	92 88 88	18 13 12	1½ ½ 2	✓ ✓ ✓	1 1 2 2 2	104	/72	59.27	790	+++
10/14	11-A:50,50 50+50		✓ ✓ ✓ ✓ ✓	✓ ✓	✓	✓ ✓ ✓	37.5 37.7 37.6	90 86 80	13 18 16	1½ 1½ 1	✓ ✓ ✓	2 1	98	/70	58.70	921	++
10/15	11-A:50,50 +50+50 by mouth		✓ ✓ ✓ ✓			✓ ✓ ✓	37.2 37.5 37.7	87 82 88	15 14 18	4 ½ 2	✓	1 1	98	/80	58.92	1873	+
10/16	11-A:50 mgm. per os		✓ ✓	✓ ✓		✓ ✓ ✓	37.2 37.5 37.7	75 81 84	15 14 18	3 0 0	✓	1 1	106	/68	59.35	2100	+
10/17			✓ ✓ ✓	✓ ✓ ✓	✓ ✓	✓ ✓	37.4 37.5 37.6	73 79 84	10 14 18	4 0 1	✓	1	120	/76	60.32	2165	+
10/18			✓	✓ ✓	✓	✓	37.1 37.3 37.2	88 92 84	12 16 20	6 0 2		1 1	124	/60	60.67	2849	0
10/19							36.8 37.2 37.5	84 82 86	14 16 18	6 0 1½		1	122	/68	62.33	2722	0



3-Tetrahydroisoquinolino-4-hydroxy-tetrahydrophenanthrene

In view of Dr. Eddy's report that in equally effective doses this compound (11-A) is fifteen times as toxic as morphine, considerable caution must be used in making this study. Thus far it has been found that 11-A, administered in doses up to 0.4 gm. per day, has no effect on the abstinence syndrome. In other words, in the doses given, 11-A does not perceptibly support dependence. This is felt to be the most promising lead yet encountered in this cooperative study. It is hoped that it will be possible to administer this drug in more effective doses. Should 11-A continue to show no evidence of addiction liability, the prognosis for the discovery of a drug as analgetic as morphine, but possessing no addiction liability, will become definitely favorable. At present it would seem that there is definite hope in the synthetic field, hence, it is felt that every effort should be exerted to encourage and expand the researches on synthetic morphine substitutes.

3-A = Morphine Sulfate
11-A = 3-(1,2,3,4-Tetrahydroisoquinolino)-4-hydroxy-1,2,3,4-tetrahydrophenanthrene hydrochloride

Dates - as shown

Doses - in mgm. subcutaneous except as shown

Hours - Three 8-hour periods each day

Y = yawning

L = lacrimation

S = sneezing

R = rhinorrhea

G = gooseflesh

Pu = dilated pupils

Tr = tremor

Temp. = rectal in °C

Resp. = rate per minute

R = Restlessness

Sleep = hours observed

Em. = emesis, no. of observed

Def. = defecation, no. of observed

B. P. = A. M. supine

Wt = weight, Kgm., stripped

Caloric = total per day

Degree = intensity of abstinence

Two day period of stabilization on 3-A shown 10/4 and 5

Four day period of transition to 11-A shown 10/6, 7, 8, and 9

Six day period attempted dependence satiation by complete substitution of 11-A for 3-A shown 10/10, 11, 12, 13, 14, and 15

Four day period of total abstinence shown.

Data show no support of dependence by 11-A in these doses.

The period of abstinence following withdrawal of 3-A is quite typical.

Considerable progress has been made in the establishment of our new laboratories for studies designed to give us information on the true nature of drug addiction. The biochemical and psychological units have been completed, and it is hoped that the physiological unit will be ready for operation in the near future. The latter unit contains a respiration chamber mounted on a platform scale, a Rein gasometaboligraph, and a gas analysis apparatus. When complete this laboratory will be air-conditioned and will contain a Sauter balance. The studies to be made first center around metabolism, and will include total, carbohydrate, and water metabolism studies with simultaneous psychiatric and psychologic investigations. The psychiatric studies will include electroencephalographic determinations of the effect of morphine at various times.

A study of the effect of morphine on the dentition of rats will be undertaken in the near future.

Future studies include: lipid metabolism, acid-base balance, Calcium-phosphorus metabolism, and the effect of morphine on organs (using the Lindberg apparatus).

After the procurement of an electroencephalograph, studies comparing the cerebral effects of morphine with new drugs will be carried out routinely.

During the past year it was shown that "Rossium" (a proprietary "drug addiction cure" developed by Ostromislensky and marketed by the Chemico-Medical Corporation) has no demonstrably beneficial effects on the abstinenee syndrome either when administered alone or in combination with the

therapeutic agents recommended by the manufacturer. The report on this study includes an account of the chemistry of "Rossium" by Dr. Small. A study of Perparin" (a synthetic papaverine derivative) revealed that it does not possess addiction liability.

The desirability of extending our clinical studies to non-addicted individuals has been emphasized repeatedly. Work of this sort was begun at the Pondville Cancer Hospital, at Wrentham, Massachusetts, early in 1935 and its inception and early results were described in our report of a year ago. In order to facilitate the continuation and extension of this work a number of conferences were held in the Spring of this year. These conferences led to the formulation of a report embodying suggestions which it is believed could furnish a systematic basis for this phase of our work. A copy of this report follows:

Memorandum No. 1

Suggestions for the systematic study of the anti-tussic action of codeine and related substances

Based upon discussion at the Middlesex County Tuberculosis Sanitorium, June 18, 1936. Those present were Drs. Alton S. Pope, Sumner H. Remick, Lowry C. Davenport, C. K. Himmelsbach, Charles I. Wright and Nathan B. Eddy.

Purpose

(1) Systematic evaluation of the minimal effective clinical anti-tussic dose of codeine.

(2) Determination of the duration of the anti-tussic effect of codeine.

(3) Determination of the possible development of tolerance to and dependence upon codeine when administer-

ed in its minimal effective dose for its anti-tussic effect over a prolonged period of time.

(4) Determination of the occurrence of incidental effects of codeine in connection with its administration in single doses or over a prolonged period.

(5) Determination of the presence or absence of objective effect on respiratory activity (rate, minute volume) of codeine administered in its minimal effective anti-tussic dose. Method to be determined later.

(6) Determination of the presence or absence of analgesic effect in the administration of codeine in its minimal anti-tussic dose, using the method of Seevers or some modification thereof.

(Nos. 5 and 6 to be in abeyance at present).

(7) Systematic evaluation of another substance in a manner exactly like that outlined for codeine, the first substance to be so evaluated being dihydroisocodeine.

Note: It was admitted that although the usual procedure was the administration of codeine in dose of 15 to 30 mgm. for the relief of cough we have no exact knowledge of its minimal effective dose or duration of its action, and that for the purpose of this study such exact knowledge is essential, in order that when similar information is obtained for a new substance an intelligible and sound comparison may be made.

Desiderata of the study

(1) All anti-tussic administration to be oral.

(2) The drug to be made available in such a way that neither the nurse, the patient, nor anyone in fact except the person supervising the study (Dr. Davenport) shall know the nature of the substance administered or its dose.

(3) Observations on the effect of the drug to be made as objective as possible.

No. 1 needs no special comment; the reasons for it are obvious.

No. 2 is essential in order to permit the simultaneous collection of the desired information in regard to codeine and another substance (specifically, dihydroisocodeine) uncolored by prejudice or expectation. It was suggested that this end might be attained in this way: Each drug is to be made available in

tablets identical in size and appearance but containing different amounts of drug as follows:

Tablet No.	
1	No drug
2	Codeine, 5 mgm.
3	Codeine, 10 mgm.
4	Codeine, 15 mgm.
5	Codeine, 20 mgm.
6	Codeine, 25 mgm.
7	Codeine, 30 mgm.
8	Dihydroisocodeine, 5 mgm.
9	Dihydroisocodeine, 10 mgm.
10	Dihydroisocodeine, 15 mgm.
11	Dihydroisocodeine, 20 mgm.
12	Dihydroisocodeine, 25 mgm.
13	Dihydroisocodeine, 30 mgm.

The tablets are to be placed in a series of numbered bottles (no other label than the number), the series of bottles being greater than the number of tablets, there being several different bottles containing the most used doses to avoid the suspicion of size of dose by the frequent repetition of the same dose number. The key to the doses in the respective bottles is to be known only to Dr. Davenport. Ordering of all anti-tussic administration for the patients included in the study is to be by container number only, neither drug nor dose is to be specified. It will probably be desirable to change the key numbers from time to time to avoid giving a clue to drug and dose by frequent repetition of the same number. If possible no one at all should be taken into Dr. Davenport's confidence as to the meaning of the numbers. Ordering of anti-tussic treatment by other members of the staff for other patients than those involved in this study would be made in the usual ways but codeine tablets identical in size and appearance with the experimental tablets should be made available for this routine use.

Patients to be used in the anti-tussic study would of course have to be carefully selected for intelligence and cooperativeness as well as for their pathological condition and need for cough treatment. They probably should have enough of the plan explained to them to insure their cooperation. Probably better results would be obtained with new patients than with others who have been in the hospital a considerable time and who have had more or less codeine experience.

The procedure for determination of minimal effective dose would be as follows: A patient free of codeine and needing cough treatment would be given a

blank tablet or the smallest dose of codeine or perhaps each alternately at regular intervals until the observer is satisfied that no cough relief is obtained. Then the next larger dose would be ordered and continued until it was determined that it did or did not have an effect on the cough. If necessary one would continue to raise the dose step by step until an effective dose was reached. During this program the occasional ordering of the blank might facilitate the determination of the effectiveness of the dose and the duration of its effect.

For the determination of the presence of effect a number of things were suggested, final determination to depend on collation and interpretation of all of them.

1. Careful counting of respiratory rate, the patient being at rest, at frequent intervals.

2. Notes by the nurse on her impressions of the patient's cough.

3. Notes by the physician in charge, gained by questioning of the patient or otherwise, on his impressions of the patient's cough.

4. Notes by the patient himself on a questionnaire basis made preferably twice a day.

5. Review of all the data by Dr. Davenport.

6. Dr. Wright suggested the possibility in suitable patients of obtaining a modified pneumograph record which would record cough objectively. He has demonstrated that such a record is easily obtainable provided that discomfort from the wearing of the pneumograph and the mechanical difficulties in the making of the record are not insurmountable obstacles.

It would be desirable to determine simultaneously the minimal effective doses of codeine and dihydroisocodeine, but a patient started on codeine should not receive dihydroisocodeine and vice versa until the minimal effective dose of the first drug for that patient has been determined.

It might be desirable after the minimal effective dose of either drug has been determined to switch to the other drug, or to determine successively the minimal effective dose of each drug in the same patient. Such a procedure would furnish a slightly different basis of comparison.

After the determination of a minimal effective dose in a patient and acquiring of information in regard to the duration of action of that dose in that patient, that dose would be administered regularly to that patient at the interval determined for the duration of its action. Such administration would be continued for a prolonged period and observations already outlined for determination of its effect would be continued. From time to time (once a month) administration of drug would be substituted for a 24-hour period by administration of blank tablets to gain an impression of the continued effectiveness of the drug and the possibility of developing dependence on the drug (addiction). The first would be indicated by exacerbation of the cough; the second by the appearance of some sort of abstinence phenomena.

The discussion of the group indicated that the procedures outlined were feasible and that over an extended period they offered the best chance of exact evaluation of the drugs under consideration and the best basis for future study which we could at present devise. The only thing required for putting the plan into operation is the preparation of a series of tablets, uniform in size and appearance, in numbers recommended by the hospital staff. It was understood that the furnishing through the Drug Addiction Committee of the Hospital's entire supply of codeine had already been offered.

Memorandum No. 2

Suggestions for the systematic study of the analgesic and other properties of morphine and related substances

Based upon discussion at the Pondville Cancer Hospital, June 18, 1936. Those participating were Drs. Alton S. Pope, George L. Parker, Raymond E. Militzer, C. K. Himmelsbach, Charles I. Wright and Nathan B. Eddy.

Purpose

(1) Systematic evaluation of the minimal effective clinical analgesic dose of morphine and codeine.

(2) Determination of the duration of analgesic action of the drug studied.

(3) Determination of the possible development of tolerance to and dependence upon the drug, administered in its minimal effective dose over a prolonged period of time.

SUBSTANCES TESTED (or ready for testing) IN THE CLINIC

1-A	Isocodeine Acid Tartrate
2-A	Pseudocodeine Hydrochloride
3-A	Morphine Sulfate
4-A	Codeine Hydrochloride
5-A	Dihydrodesoxymorphine-D Sulfate
6-A	Dihydroisocodeine Acid Tartrate
7-A	Dihydroheterocodeine Hydrochloride
8-A	Alpha-isomorphine Hydrochloride
9-A	Dihydro-alpha-isomorphine Hydrochloride
10-A	Diacetyldihydromorphine Hydrochloride
11-A	Tetrahydroisoquinolino-hydroxy-tetrahydrophenanthrene hydrochloride
12-A	Dihydrocodeine
13-A	Beta-chloromorphide Acid Tartrate
14-A	Diacetylmorphine Hydrochloride
16-A	Dihydrocodeinone Enol Acetate Hydrochloride (Acedicon)
15-A	Dihydrohydroxycodeinone Hydrochloride (Eukodal)
17-A	Codeine Methyl Ether
18-A	Dihydromorphine Hydrochloride
19-A	Monoacetylmorphine Hydrochloride
20-A	Monoacetyldihydromorphine Hydrochloride
21-A	Dihydrocodeinone Hydrochloride (Dicodide)
22-A	Tetrahydrothebaine hydrochloride

November 1936

COMMITTEE ON DRUG ADDICTION
Annual Meeting
November 28, 1936

AGENDA

Scientific Presentation

a. Dr Himmelsbach. Discussion by Dr. Kolb.

b. Dr. Eddy

c. Dr. Small

Executive Session

1. Minutes of last meeting.

2. Chairman's Report
   - Patents - Dihydrodesoxymorphine-D, New Patent.
   - Fourneau's Study in France.
   - Chemistry of Opium Alkaloids
   - Clinical Studies

3. Budget

4. Recommendation with regard to continuation of committee.

(4) Determination of the occurrence of incidental effects in connection with the administration of single or repeated doses.

(5) Systematic evaluation of another substance in a manner exactly like that outlined for morphine or codeine. The first substance to be so evaluated being desocodeine (dihydrodesoxycodeine-D).

Note: It was admitted that although the usual procedure was the administration of morphine subcutaneously in doses of 1/6 to 1/4 grain and of codeine orally in doses of 1/4 to 1/2 grain for the relief of pain, we have no exact knowledge of the minimal effective analgesic dose or duration of analgesic action of either morphine or codeine, and that for the purpose of this study such exact knowledge is essential, in order that when similar information is obtained for a new substance an intelligible and sound comparison may be made.

Desiderata of the study

(1) Administration may be oral or subcutaneous according to the nature of the drug.

(2) The drug should be made available in such a way that neither the nurse, the patient, nor anyone in fact except the person supervising the study (Dr. Militzer) shall know the nature of the substance administered or its dose.

(3) The evaluation of the presence of analgesic action should be made as objective as possible.

While it is advisable in connection with expected repeated administration to avoid the subcutaneous route in connection with relief of pain, promptness and intensity of action may outweigh other considerations making the subcutaneous route preferable in many cases.

No. 2 is essential in order to collect the desired data uncolored by prejudice or expectation. It was suggested that this end might be attained for morphine (or other drug to be given subcutaneously) by having the solution made up in such strength that its administration can be ordered in doses of 0.5 cc. or multiple thereof, and the solution kept in a bottle marked only with a key number. The meaning of the key is to be known only to Dr. Militzer. The same end might be attained for codeine (or other substance to be given orally) by having the drug made available in tablets

identical in size and appearance but containing different amounts of drug as follows:

Tablet No.	
1	No drug.
2	Codeine, 5 mgm.
3	Codeine, 10 mgm.
4	Codeine, 15 mgm.
5	Codeine, 20 mgm.
6	Codeine, 25 mgm.
7	Codeine, 30 mgm.

The tablets are to be placed in a series of numbered bottles and administration ordered by the number of the container only. Again Dr. Militzer could be the only one knowing the key.

Patients to be used in the analgesic study would of course have to be carefully selected for intelligence and cooperativeness as well as for their pathological condition and need for pain relief. They probably should have enough of the plan explained to them to insure their cooperation. Probably better results would be obtained with new patients who have had not more than very casual previous experience of opiate administration.

The procedure for the determination of minimal analgesic dose would be as follows: The patient, free of narcotic and needing pain relief would be given a blank injection or a dose of morphine smaller than could be reasonably expected to give any relief (an initial dose of 2 mgm. is suggested) or perhaps each alternately at regular intervals until the observer is satisfied that no pain relief is obtained. Then the next larger dose (4 mgm.) would be ordered and continued until it was determined that it did or did not have an effect on pain. If necessary one would continue to increase the dose, 2 mgm. at a time, step by step, until an effective dose was reached. During this program the occasional ordering of a blank injection might facilitate the determination of the effectiveness of the dose and the duration of its effect.

For the determination of the presence of effect a number of things are suggested, final determination to depend on collation and interpretation of all of them.

1. Notes by the nurse on her impression of the patient's pain.

2. Notes by the physician in charge gained by examining and questioning the patient on his impression of the patient's pain and on other possible ef-

fects - pupil, pulse, etc.

3. Notes by the patient himself on a questionnaire basis made preferably twice a day.

4. It would be highly desirable to make an objective determination of the presence of analgesic effect by the method of Seevers or some modification thereof. It is realized that this adds somewhat to the time required for the study and on that basis may not be feasible.

5. Review of all the data by Dr. Militzer.

For the determination of the analgesic effect of codeine the general procedure would be the same except that the start would be made with a blank tablet or a 5 mgm. codeine tablet. The continuation of the program would then be like that outlined for morphine, increasing the dose as necessary in steps of 5 mgm. until it is determined which dose in a particular patient relieves pain.

After the determination of a minimal effective dose in a particular patient and the acquiring of information in regard to the duration of analgesic action of that dose in that patient, that dose would be administered regularly to that patient at the interval determined for the duration of its action. Such administration would be continued for a prolonged period and observations already outlined for determination of its effect would be continued. From time to time (every 10 days) administration of the drug would be substituted for not less than 12 hours by administration of blank injections or blank tablets to gain an impression of the continued effectiveness of the drug and the possibility of developing dependence on the drug (addiction). The first would be indicated by exacerbation of the pain, the second by the appearance of some sort of abstinence phenomena.

The discussion of the group indicated that the procedures outlined were feasible and that over an extended period they offered the best chance of exact evaluation of the drugs under consideration and the best basis for future study which we could at present devise. Morphine supplied by the Committee is still on hand at the hospital. For the codeine study it would be necessary to supply a series of tablets like those recommended for the work at the Middlesex Hospital.

Requests for narcotic material as recommended in the above report have been forwarded by Dr. Pope and it is prob-

able that studies of the sort outlined will go forward very shortly. In concluding this portion of the report, the interest in our work and enthusiasm for cooperation by the clinicians concerned should be noted and our appreciation of this cooperation acknowledged.

Part II. Pharmacologic and Chemical Studies.

The principal features of the work on phenanthrene and dibenzofuran derivatives of Dr. Mosettig and his co-workers which have been subjected to pharmacological analysis during the past year are as follows:

1. Extension of the study of the effect of hydrogenation of the nucleus.

2. Extension of the study of alkylation of amino groups in cyclic compounds and in derivatives containing the amino group in a straight side-chain.

a. Comparison of primary, secondary and tertiary amines.

b. Comparison of the effect of introduction of different alkyl groups.

3. Effect of changing the position in relation to the nucleus of an amino group in a straight side-chain; lengthening of the side-chain.

4. The effect of acetylation of an hydroxyl in phenanthrene derivatives.

5. The effect of hydrogenation of the dibenzofuran nucleus.

Sym. octahydro- and tetrahydrophenanthrene, in comparison with phenanthrene itself, as well as derivatives of each of these compounds, have been studied and reported previously. Briefly, sym. octahydrophenanthrene, a symmetrical nucleus,

is indistinguishable from phenanthrene when administered orally to cats but tetrahydrophenanthrene is more effective than either as a depressant and even exhibits some analgesic action. 9,10-Dihydrophenanthrene, also a symmetrical nucleus, has now become available and has proven to be even more effective; the ratio of its effective dose to that of tetrahydrophenanthrene is about 3:4. It has definite analgesic action when administered orally in a dose of 300 mgm. per kilogram.

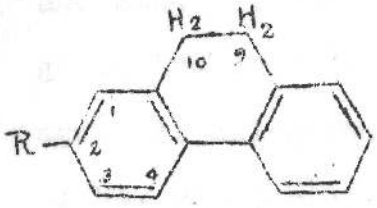
All of the derivatives of sym. octahydrophenanthrene which were studied exhibited such a degree of local irritant action as to interfere with absorption of an adequate dose after oral administration. These same substances, however, injected intramuscularly were less emetic and had some analgesic action. The tetrahydrophenanthrene derivatives were much more active and, while they were more toxic than previously studied derivatives and exhibited some emetic effect and convulsant action, in one of them the margin of safety seemed wide enough to warrant their clinical trial. The analgesic effect of this substance (No. 259, 3-(1,2,3,4-tetrahydroisoquinolino)-4-hydroxy-1,2,3,4-tetrahydrophenanthrene hydrochloride) approximates that of pseudocodeine; its effect in addicts when substituted for morphine has already been described in this report.

Five derivatives of 9,10-dihydrophenanthrene comparable to derivatives of phenanthrene itself have been studied. All of these have shown a significant degree of analgesic action,

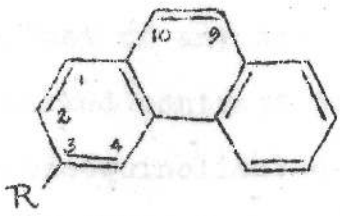
but unfortunately they have also been very emetic and some of them very convulsant. It is noteworthy that in two instances the convulsant dose for the cat is lower than the analgesic dose. The effectiveness of this group in comparison with the corresponding unhydrogenated phenanthrene derivatives is shown in the following table. All doses are in milligrams per kilogram, of the substance as administered orally to cats.

Comparison of derivatives of 9,10-dihydrophenanthrene with corresponding derivatives of unhydrogenated phenanthrene

	Minimal analgesic dose	Minimal depressant dose	Convulsant dose	Emetic dose
340. 2-[2-(Dimethylamino)-1-hydroxy-ethyl]-9,10-dihydrophenanthrene HCl.	40	40	None up to 100	25
149. 3-[2-(Dimethylamino)-1-hydroxy-ethyl]-phenanthrene HCl.	60	50	None up to 150	50
342. 2-[2-(Diethylamino)-1-hydroxy-ethyl]-9,10-dihydrophenanthrene HCl.	25	15	20	20
150. 3-[2-(Diethylamino)-1-hydroxy-ethyl]-phenanthrene HCl.	40	25	75	50
344. 2-[2-Piperidino-1-hydroxy-ethyl]-9,10-dihydrophenanthrene HCl.	20	20	25	20
151. 3-[2-Piperidino-1-hydroxy-ethyl]-phenanthrene HCl.	50	60	100	60
348. 2-[2-(Diethylamino)-1-hydroxy-n-propyl]-9,10-dihydrophenanthrene HCl.	30	25	20	20
221. 3-[2-(Diethylamino)-1-hydroxy-n-propyl]-phenanthrene HCl.	60	60	75	60
330. 2-Acetyl-9,10-dihydrophenanthrene.	300	300	None up to 300	300
7. 2-Acetylphenanthrene	None	200	None up to 300	None up to 300



Compounds 340 to 350



Compounds 149, 150, 151, 221

R = $-CHOHCH_2NR_2$

$-CHOHCH(CH_3)-NR_2$

$-CHOAcCH_2NR_2$

The following derivatives of 9,10-dihydrophenanthrene, for which no direct comparison with phenanthrene derivatives is possible at this time, have also been studied:

341. 2-[2-(Dimethylamino)-1-acetoxy-ethyl]-9,10-dihydrophenanthrene HCl.

343. 2-[2-(Diethylamino)-1-acetoxy-ethyl]-9,10-dihydrophenanthrene HCl.

345. 2-[2-Piperidino-1-acetoxy-ethyl]-9,10-dihydrophenanthrene HCl.

346. 2-[2-(1,2,3,4-Tetrahydroisoquinolino)-1-hydroxy-ethyl]-9,10-dihydrophenanthrene HCl.

347. 2-[2-(1,2,3,4-Tetrahydroisoquinolino)-1-acetoxy-ethyl]-9,10-dihydrophenanthrene HCl.

349. 2-[2-Piperidino-1-hydroxy-n-propyl]-9,10-dihydrophenanthrene HCl.

350. 2-[2-(1,2,3,4-Tetrahydroisoquinolino)-1-hydroxy-n-propyl]-9,10-dihydrophenanthrene HCl.

Of these Nos. 341, 343, 345 and 349 have effective analgesic doses of 20 to 30 mgm. per kilogram but the minimal convulsant and emetic doses of the same substances are at or below the analgesic level. On the other hand Nos. 346, 347

and 350, all tetrahydroisoquinolino compounds, are not analgesic and in fact have little effect of any sort up to 200 mgm. per kilogram. This is in marked contrast to the effect of No. 259 (3-(1,2,3,4-tetrahydroisoquinolino)-4-hydroxy-1,2,3,4-tetrahydrophenanthrene HCl), the phenanthrene derivative which has been subjected to clinical trial. Solubility is perhaps an important factor in this difference since the tetrahydroisoquinolino compounds as a group are much less soluble than the other amino alcohol-phenanthrene combinations. It should be noted, however, that the water solubility of Nos. 259 and 346 is practically identical, but there are important chemical differences between these two substances, one containing the amino alcohol arrangement within the nucleus (No. 259), the other within the side chain (No. 346). The relatively marked analgesic action of the alkylamine derivatives of 9,10-dihydrophenanthrene cannot be made use of unless some means can be found of smothering their emetic and convulsant actions. Whether or not this can be effected by modifying the alkamine side chain or by introducing new groups (OR, NR_2, R = H or alkyl) into the phenanthrene nucleus cannot be foretold. It should be noted that the substituents in the 9,10-dihydro series are located in position-2. Therefore it might be of interest to submit to pharmacological investigation analogs of Nos. 340-350 carrying the side chain in position-3, whereby it might become apparent whether the increased undesirable actions of the compounds Nos. 340-350 are due to the "9,10-hydrogenation" or to the 2-position of

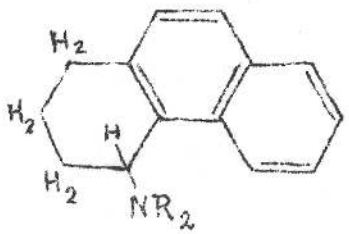
the side chain.

The importance for the development of analgesic action of the presence of nitrogen in some relation to the phenanthrene nucleus is becoming increasingly apparent. Compounds have been prepared in which the nitrogen as an amino group has been attached directly to the phenanthrene nucleus and others in which it has been placed in an alcoholic side-chain. In both groups it has been possible to compare primary, secondary and tertiary amines and also to determine the effect of alkylation when the substituent is dimethylamino-, diethylamino-, piperidino-, or tetrahydroisoquinolino-.

Of the directly linked amine compounds three pairs have been compared:

327. 4-Dimethylamino-1,2,3,4-tetrahydrophenanthrene HCl, with

295. 4-Amino-1,2,3,4-tetrahydrophenanthrene HCl;

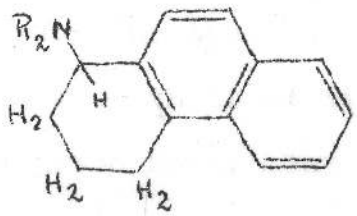


No. 327, $NR_2 = N(CH_3)_2$

No. 295, $NR_2 = NH_2$

326. 1-Dimethylamino-1,2,3,4-tetrahydrophenanthrene HCl, with

293. 1-Amino-1,2,3,4-tetrahydrophenanthrene HCl; and

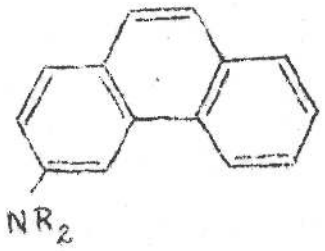


No. 326, $NR_2 = N(CH_3)_2$

No. 293, $NR_2 = NH_2$

356. 3-(Dimethylamino)-phenanthrene HCl, with

115. 3-Amino-phenanthrene.



No. 356, $NR_2 = N(CH_3)_2$

No. 115, $NR_2 = NH_2$

The dimethylamino- compounds are not consistently different in toxicity and convulsant action from the primary amines but they are less effective analgesics and are slightly less emetic.

Of the compounds in which the amino group in a straight side-chain has been alkylated, four pairs are available for comparison:

150. 3/2-(Diethylamino)-1-hydroxy-ethyl/-phenanthrene HCl, or,

149. 3-/2-(Dimethylamino)-1-hydroxy-ethyl/-phenanthrene HCl, with

286. 3-/2-Amino-1-hydroxy-ethyl/-phenanthrene HCl; and

221. 3-/2-(Diethylamino)-1-hydroxy-n-propyl/-phenanthrene HCl, or

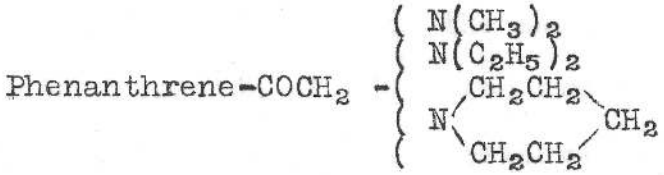
287. 3-/2-(Dimethylamino)-1-hydroxy-n-propyl/-phenanthrene HCl, with

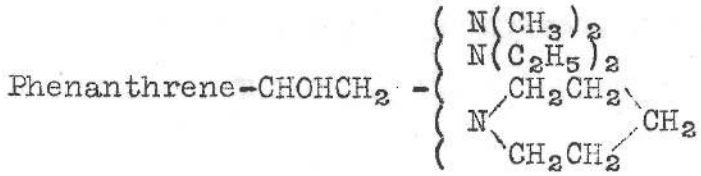
220. 3-/2-Amino-1-hydroxy-n-propyl/-phenanthrene HCl.

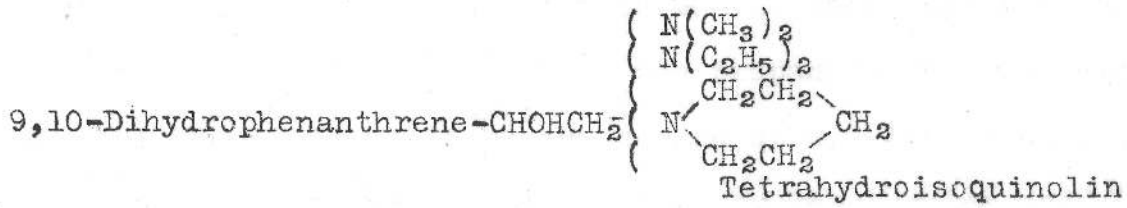
In each of these instances the primary amine shows marked emetic action apparently in large part due to local irritant action, the promptness of the vomiting obviously interferes with absorption and therefore with the full effect of a given dose. The alkylamines in this group are less

emetic and consequently relatively more effective. It would seem that in these straight chain compounds alkylation has not decreased effectiveness, rather increased it slightly. To avoid the local irritant action, one of the primary amines was given intramuscularly and by this route its minimal analgesic dose was not less than 50 mgm. per kilogram, whereas the comparable analgesic dose by mouth of its diethyl derivative was only 40 mgm. and of its dimethyl derivative was 60 mgm. per kilogram.

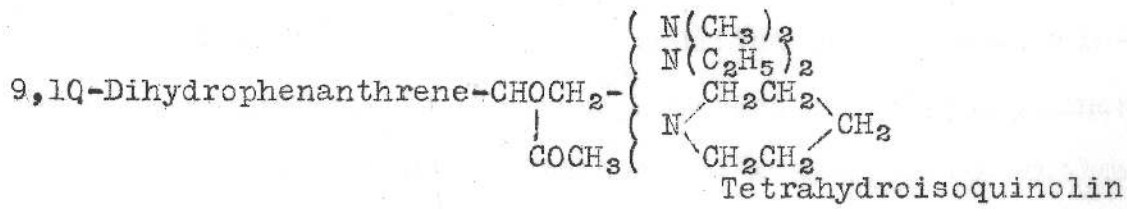
Comparing now the effectiveness of the different groups employed in alkylation of the amino group in straight side-chain compounds:



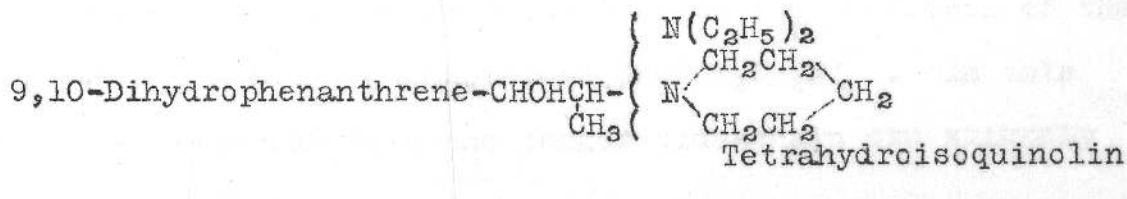




Tetrahydroisoquinolin



Tetrahydroisoquinolin



Tetrahydroisoquinolin

9,10-Dihydrophenanthrene-$CHOHCH_2CH_2$-{ $N(C_2H_5)_2$ | CH_2CH_2 | N(...CH_2...) | CH_2CH_2 | Tetrahydroisoquinolin.

In most instances the diethylamino derivatives are more effective than the dimethylamino; the piperidino compounds are approximately like the diethylamino-, therefore, more effective than the dimethylamino-; while in this series the tetrahydroisoquinolino-compounds are much less effective than any of the others. The possible role of poor solubility in the apparent ineffectiveness of the tetrahydroisoquinolino-substances has already been discussed.

Another feature of the amino alcohol type of compounds is the position of the amino group in relation to the nucleus. In a previous report a considerable series of ethanolamines and propanolamines were compared, namely the types phenanthrene-$CHOHCH_2N<$ and phenanthrene-$CHOHCH(CH_3)-N<$

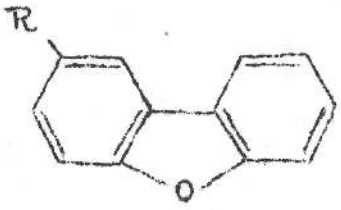
In both of these the amino group is in the same position in relation to the nucleus though in the propanolamines the side-chain has been lengthened by one carbon atom. The conclusion was drawn that nothing had been gained by lengthening the carbon chain without changing the position of nitrogen relative to the nucleus. We now have a series of propanolamines (type C) in which the N- has been moved away from the nucleus and is attached to the γ- instead of to the β-carbon of the side-chain, namely phenanthrene-$CHOHCH_2CH_2N<$. In this case the compounds with the longer side-chain are slightly

more effective but again we find that the more effective substances are more convulsant.

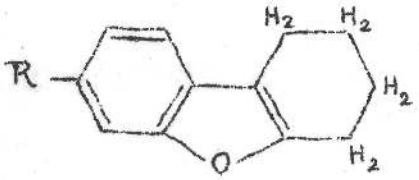
In the morphine series it has been shown again and again that muzzling the alcoholic hydroxyl increases effectiveness, increasing especially analgesic and depressant actions. Many of our phenanthrene derivatives contain a free alcoholic hydroxyl. Acetylation of the hydroxyl in four such compounds did not cause any significant change in activity. In two other instances the acetylated compound was definitely less effective than that containing the free hydroxyl but again the less effective substance is less soluble and this might have materially affected the results. There is still a possibility that a more definite change of the alcoholic hydroxyl, as alkylation or elimination, may bring about also a correspondingly greater change in physiological action.

The study of the effect of hydrogenation in the dibenzofuran series was started during the past year and tetrahydrodibenzofuran and two of its derivatives are available for comparison with analogous unhydrogenated substances. 7-Acetyl-1,2,3,4-tetrahydrodibenzofuran was definitely more effective and more persistent in its analgesic action than the acetyl derivative of dibenzofuran previously studied. However, the position of substitution of the acetyl group is not the same in both. Tetrahydrodibenzofuran itself is not significantly more effective than dibenzofuran and 7-[2-(Dimethylamino)-1-hydroxy-ethyl]-1,2,3,4-tetrahydrodibenzofuran is not more effective than its unhydrogenated analog but again the position of the substituent is different.

Substitution in the non-hydrogenated dibenzofuran

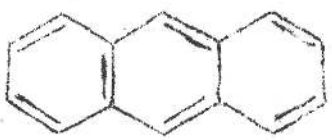


Substitution in the hydrogenated dibenzofuran

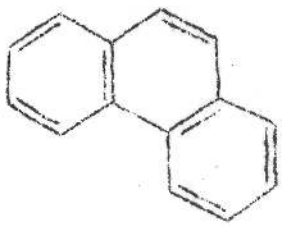


R = $COCH_3$, or $CHOHCH_2N<$

Anthracene, which is the linear isomer of phenanthrene (angular isomer), administered orally to cats up to 400 mgm. per kilogram was practically without effect. Four hundred milligrams per kilogram of 9,10-dihydroanthracene similarly administered had only a slight general depressant action, much less than 9,10-dihydrophenanthrene.



Anthracene



Phenanthrene

These figures, however, do not indicate necessarily that anthracene derivatives are useless for our purpose. Only from anthracene analogs with more complex substituents (e.g. amino alcohol - side chain) could conclusions be drawn as to whether or not the anthracene nucleus could replace the phenanthrene nucleus in physiologically active compounds.

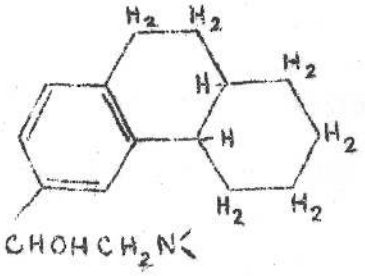
The combined chemical and pharmacological results show rather clearly the direction in which synthetic experiments

should proceed in the near future, namely:

1. Modification of the alcoholic hydroxyl by alkylation or elimination of this group in the more active amino alcohols (e.g. Nos. 150, 259) of the "straight chain" or "cyclic" type.

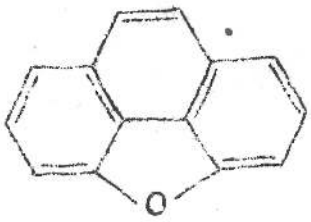
2. Introduction of a phenolic hydroxyl into amino alcohols of the above-mentioned type.

3. Synthesis of amino alcohol derived from asym.-octahydrophenanthrene of the type

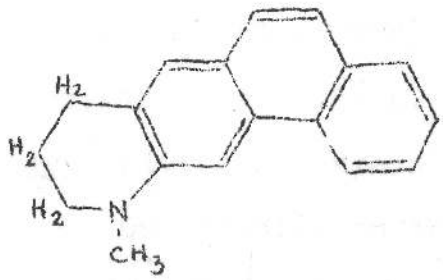


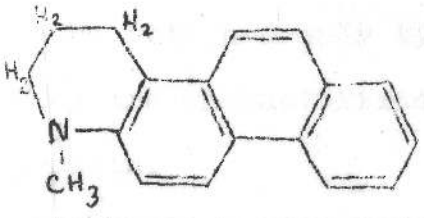
and possibly of the "cyclic" type.

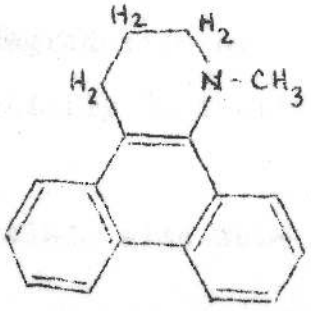
4. Synthesis of amino alcohols derived from 4,5-phenanthrylene oxide.



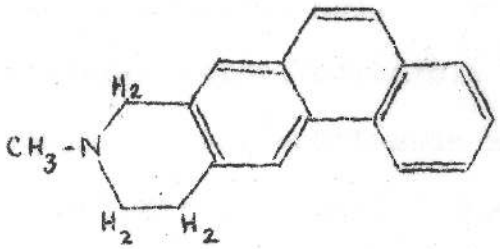
5. Synthesis of condensed ring systems consisting of a phenanthrene nucleus and a 6-membered nitrogen-containing ring.



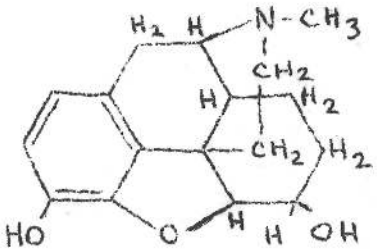


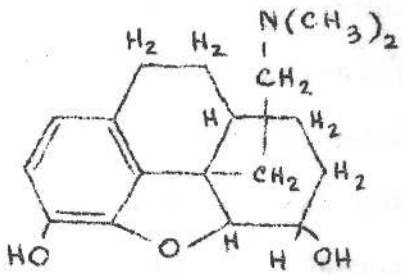


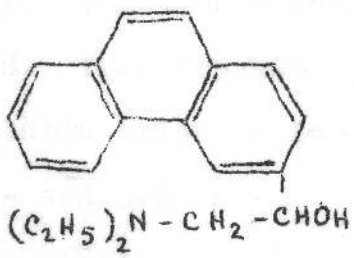
These experiments are well under way. Subsequently the synthesis of the isomers of the isoquinoline type will be attacked.



6. The preparation of two morphimethines (α-tetrahydro- and β-dihydro-) has been accomplished







Morphine (dihydro) (α)Tetrahydro-morphimethine Synthetic No. 255

The morphimethines represent the linking members between morphine or its close relatives and some of our synthetic amino alcohols. They can be obtained only by degradation of morphine derivatives. They are characterized chiefly by their <u>open</u> nitrogen-containing chain.

Our studies in the carbazole series now include nine substances:

268. 3-Aminocarbazole HCl.

307. 3-Amino-9-methyl-carbazole HCl.

317. 6-Amino-1,2,3,4-tetrahydrocarbazole

337. 1-Aminocarbazole HCl.

338. 1-Amino-9-methyl-carbazole HCl.

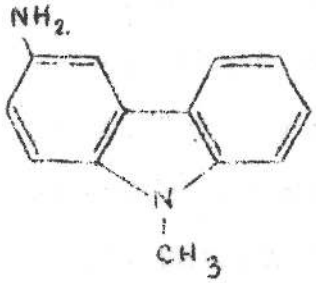
339. 3-Amino-9-ethyl-carbazole HCl.

372. 10-Hydroxy-1,2,3,10-tetrahydrocarbazole

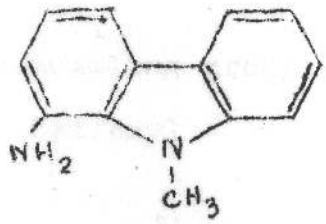
373. 1-Hydroxy-1,2,3,4-tetrahydrocarbazole

374. 3-Amino-9-acetyl-carbazole HCl.

All of these carbazoles are general depressants, cause more or less neuromuscular disturbance - muscular weakness and incoordination - and bring about a moderate fall in rectal temperature which persists for more than 5 hours. All of these carbazoles exhibit definite analgesic action, the least effective being the two hydroxy- derivatives. Vomiting sometimes occurs but emetic action is not marked. Toxicity has not been definitely determined but all available evidence indicates that it is of a low grade. 3-Amino- and 1-Aminocarbazole are practically identical in their effectiveness. The addition of an alkyl group in the 9-position (bridge nitrogen) nearly doubles the analgesic and depressant action of 3-aminocarbazole and the same effect is attained whether the added group is methyl, ethyl or acetyl. On the other hand, similar addition of a methyl group to 1-Amino- carbazole decreases its analgesic action.

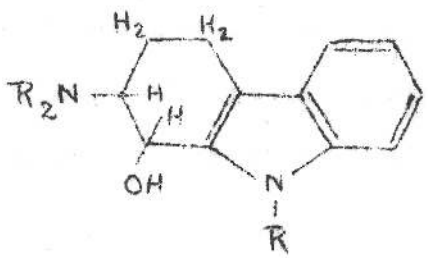


3-Amino-9-methylcarbazole



1-Amino-9-methylcarbazole

Synthesis in the carbazole group has been delayed through the departure of Dr. Meitzner, but further work is now under way which is expected to lead to N-alkyl-tetrahydrocarbazole alkylamino alcohols of the type



The principal features of the alkaloidal studies of Dr. Small and his associates, the pharmacological significance of which may be discussed at this time are:

1. Hydroxycodeinones and hydroxycodeines
2. Aminocodides
3. Benzylderivatives
4. Derivatives of the heterocodeine type
5. Muzzling hydroxyls - specific effect of the muzzling group
   a. Muzzling the phenolic hydroxyl
      1. Methylation

2. Ethylation

3. Acetylation

4. Benzyl derivatives

5. Methoxy methyl as a muzzling group

b. Muzzling the alcoholic hydroxyl

1. Methylation

2. Ethylation

3. Acetylation

4. Aminomorphides and aminocodides

5. Other modifications

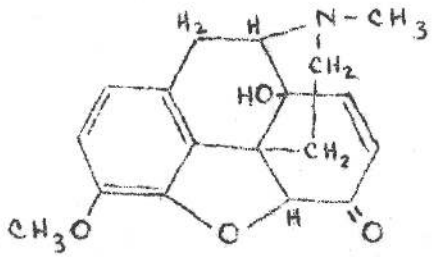
a. Substitution by chlorine

b. Substitution by hydrogen

c. Substitution by oxygen

6. A new type of methyl derivative

7. Simultaneous increase and decrease of other morphine-like actions by chemical modification.



Hydroxycodeinone

Hydroxycodeinone is an extremely toxic and convulsant poison. Its fatal dose for mice is only 23 mgm. per kilogram and its convulsant dose for the cat is only 5 mgm. per kilogram, a little below the minimal analgesic dose. Its pharmacological effect is very like that of thebaine; another very

similar substance is bromocodeinone. If, now, the new hydroxyl, graphically represented as attached to carbon-14, is acetylated, toxicity is markedly reduced, convulsant action is reduced and analgesic effectiveness is increased. The fatal dose of acetylhydroxycodeinone is 127 mgm. per kilogram, its minimal analgesic dose is 2.7 mgm., slightly more than half the effective dose of hydroxycodeinone. As with dilaudid and desomorphine, though the degree of analgesic activity is not at all comparable, the duration of effect is brief. Eukodal is dihydrohydroxycodeinone; hydroxycodeinone in which the 7-8 double bond has been removed by hydrogenation; or it is dicodid in which an additional hydroxyl has been introduced, presumably at carbon -14. Eukodal is much less toxic than hydroxycodeinone or acetylhydroxycodeinone; it is also less toxic and less convulsant than dicodid. It is more effectively analgesic than hydroxycodeinone or acetylhydroxycodeinone (twice as effective as the latter) but its analgesic power in degree and duration is practically like that of dicodid. For their effect on respiratory activity the minimal effective doses of acetylhydroxycodeinone, dihydrohydroxycodeinone and dicodid are, respectively, 0.3, 0.1 and 0.2 mgm. per kilogram.

By reduction of the ketone group in dihydrohydroxycodeinone, three isomeric dihydrohydroxycodeines are obtained. Theoretically, only two can exist, and the nature of the third isomer is uncertain. These three isomers in comparison with codeine are of relatively low toxicity and are apparently non-convulsant. Two of these isomers have a greater analgesic

effect than codeine, the minimal effective dose being about 2.5 mgm. per kilogram as compared with 8.0 for codeine. Neither is emetic. The principal difference between these two isomers is the greater exciting effect of one of them. The third isomer is peculiar in that it is apparently without effect in the cat up to 50 mgm. per kilogram.

In our work on phenanthrene derivatives it has been shown that analgesic effectiveness is greatest in those compounds containing an alkylamine group. Again it has been shown that removal or modification in various ways of the alcoholic hydroxyl of morphine or its derivatives enhances analgesic action. The possibility of utilizing both of these observations by alkylamine substitution of the alcoholic hydroxyl of morphine or codeine has been tried. The result has been disappointing. The aminomorphides and aminocodides which have been prepared and studied are not more active than the analogous compounds containing a free alcoholic hydroxyl.

On account of the marked increase in activity effected by methylation of the alcoholic hydroxyl in the production of heterocodeine, considerable attention has been given to this type of modification. There has been developed quite a complete series of methyl, ethyl and acetyl alcoholic ethers or esters of morphine and its isomers and of codeine and its isomers, as well as their hydrogenated derivatives. The complete list of these compounds now is:

CODEINE SERIES

Codeine methyl ether	Acetylcodeine
Dihydrocodeine methyl ether	Acetyldihydrocodeine
Pseudocodeine methyl ether	Acetylisocodeine
Dihydropseudocodeine methyl ether	Acetyldihydroisocodeine
	Acetylpseudocodeine
	Acetyldihydropseudocodeine
	Acetylallopseudocodeine

MORPHINE SERIES

Morphine alc. methyl ether
Dihydromorphine alc. methyl ether
Morphine alc. ethyl ether
Dihydromorphine alc. ethyl ether
α-Isomorphine alc. methyl ether
α-Dihydroisomorphine alc. methyl ether
α-Isomorphine alc. ethyl ether
α-Dihydroisomorphine alc. ethyl ether
β-Isomorphine alc. ethyl ether
γ-Isomorphine alc. methyl ether
γ-Dihydroisomorphine alc. methyl ether
γ-Isomorphine alc. ethyl ether
γ-Dihydroisomorphine alc. ethyl ether
Benzylmorphine methyl ether
Benzyldihydromorphine methyl ether
Monoacetylmorphine
Monoacetyldihydromorphine
Diacetylmorphine
Diacetyldihydromorphine
Monoacetyl-α-isomorphine
Monoacetyl-α-dihydroisomorphine
Diacetyl-α-isomorphine
Diacetyl-α-dihydroisomorphine
Monoacetyl-β-isomorphine
Diacetyl-β-isomorphine
Monoacetyl-γ-isomorphine
Monoacetyl-γ-dihydroisomorphine
Diacetyl-γ-isomorphine
Diacetyl-γ-dihydroisomorphine

From the study of this group the broad statement can be made that the alcoholic ethers have a greater effect on respiration, are more analgesic and more depressant than the corresponding compounds containing the free alcoholic hydroxyl. A more complete analysis than has been possible as yet may permit some statement in regard to the specific action or relative muzzling effect of the methyl, ethyl or acetyl group. Because of the potency and high addiction liability of some of these alcoholic ethers (approaching or equal to that of Desomorphine), control of them similar to that obtained for Desomorphine seemed indicated. With the cooperation of the Department of Justice, and especially through the valuable

assistance of Mr. J. Y. Houghton, of that Department, patent was secured on Oct. 27, 1936, covering dihydromorphine alcoholic methyl ether, morphine alcoholic ethyl ether, and dihydromorphine alcoholic ethyl ether, as well as processes for their manufacture.

In the past, two general conclusions have been drawn; first, modifying the phenolic hydroxyl in the morphine series increases convulsant action and decreases the useful actions of morphine, decreasing the latter, very broadly speaking, about tenfold; second, modifying the alcoholic hydroxyl in the morphine series may increase convulsant action but increases the useful actions of morphine, increasing the latter, very broadly speaking, about tenfold. Since the early observations were made leading to these broad conclusions, we have had the opportunity to compare, on the one hand, the effect of muzzling the phenolic hydroxyl by methyl-, ethyl-, acetyl-, benzyl- and methoxymethyl- groups, and on the other hand, the effect of muzzling the alcoholic hydroxyl by methyl-, ethyl-, or acetyl- groups, the effect of removal of the alcoholic hydroxyl, and the effect of its substitution by oxygen, chlorine, or an alkylamine. Therefore it seems advisable to review briefly at this time the data obtained from the study of these substances with a view to determining the present validity of our general conclusions or the desirability of their modification or qualification. In the accompanying tables the figures are milligrams per kilogram of alkaloidal base for average fatal dose (A.F.D.) in mice and minimal effective doses for other actions.

Effect of Modification (Muzzling) of the Phenolic Hydroxyl

	Minimal effective doses				
	A.F.D.	Con.	Anal.	Resp.	Emesis
(Morphine	539	539	0.75	0.32	0.22
(Methylmorphine (Codeine)	241	161	8.04	1.60	Na only
(Ethylmorphine (Dionin)	136	122	7.60	----	Na only
(Benzylmorphine (Peronin)	35	35	7.87	5.00	8.70
(Dihydromorphine	133	133	0.26	0.22	0.15
(Dihydromethylmorphine (Dihydro-codeine)	225	180	7.20	2.50	Na only
(Dihydrobenzylmorphine	35	35	2.40	2.00	1.20
(Dihydromethoxymethylmorphine	107	107	1.64	0.62	0.82
(Dihydrodesoxymorphine-D	104	104	0.08	0.012	None
(Methyldihydrodesoxymorphine-D (Dihydrodesoxycodeine-D)	131	66	1.96	0.077	Na only
(Benzyldihydrodesoxymorphine-D	55	55	1.59	1.0	Na only

Effect of Modification of the Alcoholic Hydroxyl

	Minimal effective doses				
	A.F.D.	Con.	Anal.	Resp.	Emesis
Morphine	539	539	0.75	0.32	0.22
Desoxymorphine	101	101	0.45	0.016	Na only
α-Chloromorphide	36	18	3.57	0.042	Na only
Morphine alcoholic methyl ether (heterocodeine)	72	80	0.48	0.016	Na only
Morphine alcoholic ethyl ether (heterodionin)	109	90	0.31	0.011	Na only
Morphine alcoholic acetyl ether (monoacetylmorphine)	293	180	0.18	0.027	Na only
Dihydromorphine	133	133	0.26	0.22	0.15
Dihydrodesoxymorphine-D	104	104	0.08	0.012	None
Dihydrochloromorphide	27	18	0.13	0.012	None
Dihydromorphinone	84	67	0.18	0.027	0.08
Dihydromorphine alcoholic methyl ether (dihydro-heterocodeine)	71	71	0.18	0.019	Na only
Dihydromorphine alcoholic ethyl ether (dihydro-heterodionin)	93	69	0.23	0.011	Na only
Dihydromorphine alcoholic acetyl ether (dihydro-monoacetylmorphine)	99	90	1.35	0.18	Na only

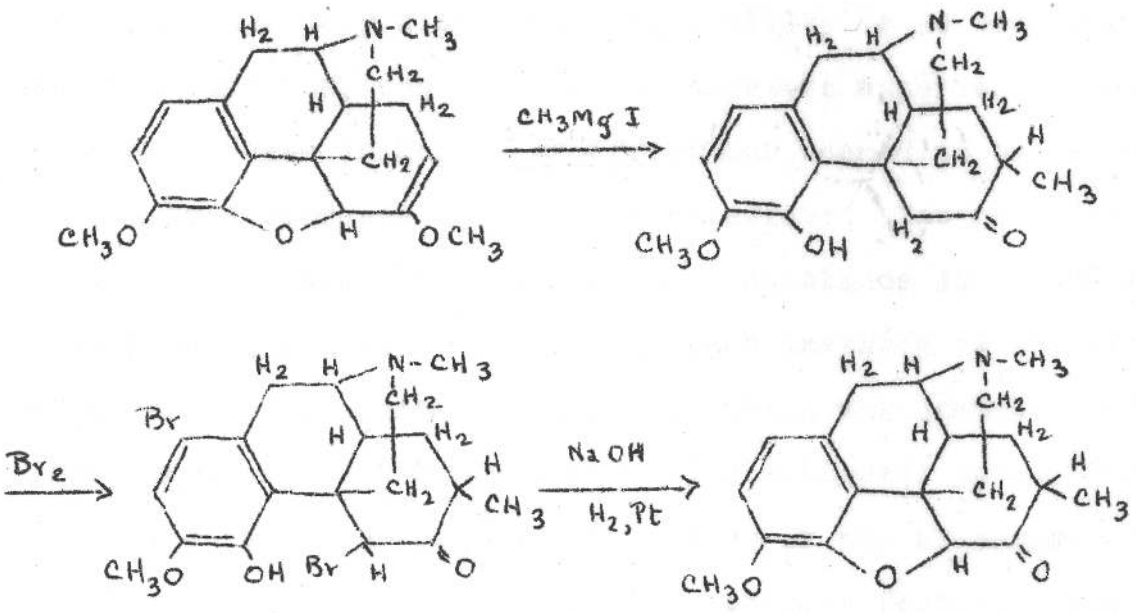
The general conclusion in regard to muzzling the phenolic hydroxyl is abundantly confirmed and requires no modification. The same change results whether the muzzling group is methyl, ethyl, benzyl or methoxymethyl. The end sought in the trial of benzyl derivatives, increase in duration of action, was attained but the benzyl derivatives are very toxic and convulsant. Besides, evidence was obtained of slow and irregular absorption and they showed somewhat greater emetic action than the methyl or ethyl derivatives. Of this group methoxymethyldihydromorphine is the most active derivative, possibly because of hydrolysis to dihydromorphine in the body, a change which occurs very readily outside the body.

In regard to modification of the alcoholic hydroxyl the general conclusion holds throughout, with only two exceptions; namely, α-chloromorphide and dihydromonoacetylmorphine, in both of which the change in activity is in the reverse direction.

Two other general observations may be made upon these data. First, emetic action is reduced if either of the hydroxyls is modified. Second, there is abundant evidence here of unequal modification of the several actions of morphine in the body as the result of chemical modification, which is the general hypothesis upon which this whole study is based.

One other group of substances in the alkaloidal field gives promise of great interest. This is an entirely new class of morphine derivative, in which a methyl group has been attached directly to Ring 3, probably in the 7-position. The

series is derived from dihydrothebaine through the Grignard reaction, followed by bromination, ring closure, debromination, and demethylation.



By demethylation at the methoxyl group, methyldihydromorphinone is obtained, by reduction at the ketone group we get methyldihydrocodeine or methyldihydromorphine. By controlled acetylation we arrive at methyldihydroheroin or methylacedicon, in fact a whole new chemistry of the dihydromorphine series is open.

The pharmacological examination of three compounds of this type is under way:

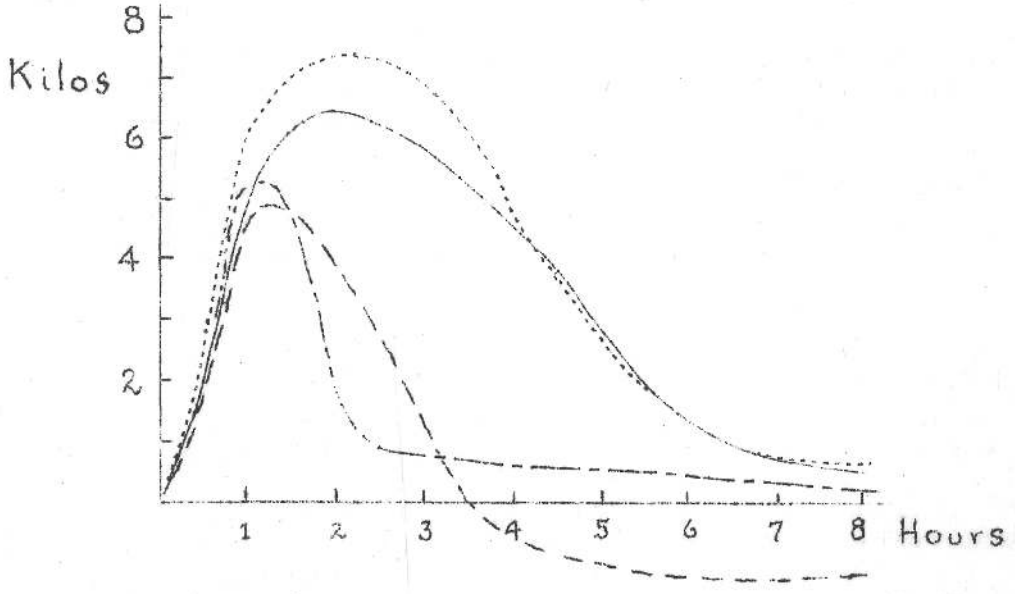
Methyldihydrocodeinone

Methyldihydrocodeine

Methyldihydromorphinone.

The methyl derivatives of dicodid and dilaudid show increased toxicity and increased analgesic activity; the methyl derivative of dihydrocodeine is much less toxic than dihydro-

codeine and relatively very poor in analgesic action. The methyl derivative of dilaudid is especially noteworthy. Its minimal effective analgesic dose is only 0.07 mgm. per kilogram and this very high degree of activity is as persistent as with morphine, contrary to our previous experience in which marked increase in degree of effect has seemed to be accompanied by a decrease in duration of effect. The relative duration of analgesic action of this substance is shown in the accompanying graph. The curve in each instance is the mean of a group of 10 animals to each of which was administered intramuscularly the minimal effective analgesic dose. The base line is the average for the group of the kilograms of pressure required to evoke a response before the drug was given and the curve shows the deviation from this response at each hourly observation. Methyldihydromorphinone has relatively little exciting effect on the cat which may indicate a relatively poor euphoric action.



DURATION OF ANALGESIC RESPONSE

—— Methyldihydromorphinone - - - - - - Dihydromorphinone
..... Morphine — — — — Dihydrodesoxymorphine-D

We have enjoyed the continued cooperation of the industrial firms interested in our project. The two Squibb fellowships, and the Merck and Mallinckrodt fellowships have been renewed. Merck and Co. has supplied without cost 10 kilograms of thebaine (value about $1800) and Merck and Mallinckrodt have converted approximately 50 pounds of morphine into codeine for us. From Du Pont and Co. we have received the gift of 60 pounds of cyclohexanone, for use in both the octahydrophenanthrene and tetrahydrocarbazole series. The Dow Chemical Co. has supplied quantities of beta-phenylethyl alcohol at greatly reduced prices.

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