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Studies in the Synthesis and Pharmacology of Aporphines

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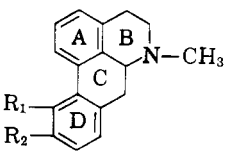
The classical synthesis of aporphine has been reinvestigated and modified. Eleven new aporphines have been prepared. Dose range studies in mice, as well as a variety of other specific pharmacological tests, have been performed on these compounds and several of their precursors. The results are described and interpreted.

The naturally occurring aporphine alkaloids have a long and interesting chemical history.[1,2] In addition, a great many of them, *e.g.*, pukateine,[3] nantenine,[4] isocorydine,[5] corydine,[6,7] bulbocapnine,[7-10] domesticine,[10] boldine,[7,11] corytuberine,[7] isothebaine,[12] laurotetanine,[1,7] and glaucine,[7] have been reported to exhibit interesting biological properties. Apomorphine (I) and apocodeine (II), aporphine derivatives arising from strong acidic treatment of morphine and codeine, respectively, are also physiologically active. The former is a remarkable emetic agent[13] which is used in pharmacological testing procedures[14] and in man, while the latter has been used in a variety of situations.[15] As an adjunct to a combined alkaloid isolation and biological testing program, which provided naturally occurring aporphines, a synthetic program was initiated in order to obtain aporphines wholly unlikely to be found in nature. Our initial efforts were directed toward molecules which like I and II, and unlike the natural materials, were unsubstituted in ring A and substituted in ring D.



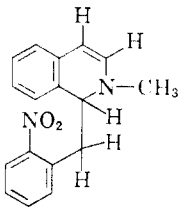
I R_1,R_2 = OH
II R_1 = OH R_2 = OCH_3
III R_1, R_2 = OCH_3

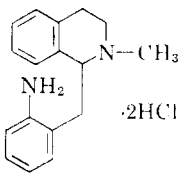
Three methods have been used successfully for preparing aporphine molecules unsubstituted in ring A. One of these, the Spaeth synthesis of apomorphine dimethyl ether,[16] employed a Bischler–Napieralski cyclization to a dihydroisoquinoline derivative, which was subsequently transformed *via* the Pschorr procedure[17] to produce III. Several groups of workers have found this sequence somewhat unsatisfactory[18] for general synthetic use. Later workers[19] effected a major change and have made it somewhat practicable.

A second method has been singularly applied to the synthesis[20] of noraporphine. This proceeds *via* 1-(2-bromobenzyl)isoquinoline to give a product transformable by standard reactions to the usual Pschorr precursor. The sequence, though circuitous, is worthy of further investigation.

The third approach is best exemplified by the classical synthesis of aporphine (VI) itself,[21] by Gadamer, *et al.* These workers condensed 2-methylisoquinolinium iodide and *o*-nitrotoluene in alcoholic base to give a product formulated as IV. This was reduced with tin and concentrated hydrochloric acid to provide a material described as V. The latter was cyclized under Pschorr conditions to VI, whose structure was validated by degradative experiments. Other

(1) R. H. F. Manske in "The Alkaloids," edited by R. H. F. Manske and H. L. Holmes, Vol. IV, Academic Press Inc., New York, N. Y., 1954, p. 119.
(2) H. G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin, 1961.
(3) B. C. Aston, *J. Chem. Soc.*, **97**, 1381 (1910).
(4) T. Takase and H. Ohashi, *J. Pharm. Soc. Jap.*, **535**, 742 (1926); **541**, 210 (1927).
(5) R. A. Waud, *J. Pharmacol.*, **50**, 100 (1934).
(6) R. A. Waud, *ibid.*, **55**, 40 (1935).
(7) T. A. Henry, "The Plant Alkaloids," P. Blakiston Co., Philadelphia, Penna., 1949, pp. 312–327.
(8) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Co., New York, N. Y., 1955, p. 213.
(9) R. S. Amadon and A. H. Craige, *J. Pharmacol.*, **54**, 334 (1935); R. S. Amadon and A. H. Craige, *J. Am. Vet. Med. Assoc.*, **88**, 737 (1936); H. Molitor, *J. Pharmacol.*, **62**, 16 (1938); E. Spiegel, *J. Pharmacol.*, **63**, 438 (1938); M. J. Oppenheimer, N. M. Glyer and R. H. Hamilton, *Proc. Soc. Exptl. Biol. Med.*, **51**, 79 (1942).
(10) T. Tobitani, *Okayama Igakkai Zasshi.*, **51**, 1447 (1939).
(11) L. Butturini, *Boll. Soc. Ital. Biol. Sper.*, **15**, 614 (1940); H. Kreitmair, *Pharmazie*, **7**, 507 (1952).
(12) B. L. Konson and P. P. Saksonov, *Farmakol i Toksikol*, **9**, 14 (1946).
(13) Reference 8, p. 1064.
(14) S. C. Wang and H. L. Borison, *Gastroenterology*, **22**, 1 (1952); T. Koppanyi and A. G. Karczmar, "Experimental Pharmacodynamics," Burgess Publishing Co., Minneapolis, Minn., 1958, p. 80.
(15) "The Merck Index," Merck and Co., Rahway, N. J., 1960, p. 94.
(16) E. Spaeth and O. Hromatka, *Ber.*, **62**, 325 (1929).
(17) D. F. DeTar, *Org. Reactions*, **9**, 409 (1957).
(18) F. W. Kay and A. Pictet, *J. Chem. Soc.*, **103**, 947 (1913); R. Kondo, *J. Pharm. Soc. Japan*, **519**, 429 (1925); D. H. Hey and L. C. Lobo, *J. Chem. Soc.*, 2246 (1954); T. R. Govindachari and K. Nagarajan, *Chem. Ind.* (London), 1358 (1954); D. H. Hey and A. L. Palluel, *ibid.*, 40 (1955); D. H. Hey and A. L. Palluel, *J. Chem. Soc.*, 4123 (1956).
(19) S. Sugasawa and R. Tachikawa, *Tetrahedron*, **4**, 205 (1958).
(20) E. Ochiai and I. Kuniyoshi, *Pharm. Bull. Jap.*, **5**, 292 (1957).
(21) J. Gadamer, M. Oberlin, and A. Schoeler, *Arch. Pharm.*, **263**, 81 (1925).


IV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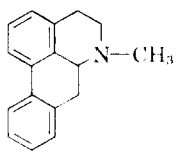
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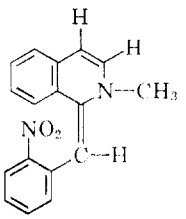
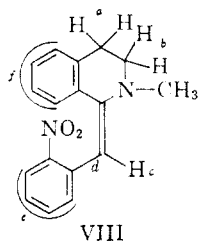

VII


VIII

workers have reported[22] reactions analogous to the initial condensation, but Gadamer's publication is the only complete and uncontested[23,24] description of this general synthesis.

Since Gadamer's procedure seemed most promising for the preparation of both aporphine and a group of related molecules, the sequence was repeated. The initial condensation according to the procedure of Gadamer yielded a compound (72%), which matched the reported product in crystalline form, color, elemental analysis and melting point. This material, which is apparently the same as the earlier product, retains its deep maroon color even upon repeated recrystallization. A review of the other literature in this area[22,24] revealed that all of the other similarly synthesized compounds are formulated in analogy to IV and are of this general color; they have been variously described as being garnet, ruby and dark red in color. Authenticity of the coloration of the maroon product was attested to by its electronic absorption spectrum, which exhibited a long tailing into the visible region having ϵ = 323 at 470 mμ. It is somewhat unlikely that a compound having structure IV will have absorption of such intensity in the visible region. For example, 2-methyl-1-phenyl-1,2-dihydroisoquinoline, representing one chromophore of IV, is reported[25] to have absorption of *ca.* ϵ = 130 at 341 mμ (alcohol), which is graphically represented as rapidly approaching zero absorption. The same authors describe 2-methyl-1,2-dihydroisoquinoline and 2-butyl-1,2-dihydroisoquinoline, even more appropriate models, which are pale yellow oils. The second chromophore of IV is best represented by *o*-nitrotoluene, which is pale yellow and has absorption of ϵ = *ca.* 110 at 380 mμ and negligible absorption at 400 mμ.

Two other formulations based on this skeletal framework (required by Gadamer's conversion to aporphine) and incorporating more extended conjugation are possible. Compound VII might arise from IV by an oxidation–reduction reaction involving excess *o*-nitrotoluene in the alkaline medium. However, this formulation is not compatible with the molecular formula required by our own as well as the earlier data. In addition, upon quantitative hydrogenation of the maroon compound, *four* moles of hydrogen are absorbed to give a product, which has as its only high intensity chromophore an *o*-alkylaniline grouping [236 mμ (log ϵ 3.84), 288 mμ (log ϵ 3.31); *cf.* *o*-toluidine,[26] 235 mμ (log ϵ 3.95), 288 mμ (log ϵ 3.33)]. The other possibility (VIII) arises from a double bond shift in the initial product IV. Structure VIII is compatible with both the microanalytical and hydrogenation data and like VII incorporates the more extended chromophore required by the ultraviolet data.

Inspection of IV, VII and VIII indicates that their nuclear magnetic resonance spectra should exhibit quite different patterns and be readily distinguishable. The spectrum of the maroon compound, described and interpreted[27] as follows, is in good accord with structure VIII and eliminates both IV and VII as possibilities.

δ[28]	Assignment
2.86	N-CH_3 group.
3.20, 4.82	Pair of triplets from the methylene groups *a* and *b*. Triplets are expected as each methylene group is coupled to the protons of the other. Presumably the group at 4.82 is *b* as it is broadened due to coupling with the nitrogen.
5.63	Unequal doublet due to one proton (compared to N-CH_3 signal of 3). It is the vinyl hydrogen, split into a doublet by inter- and non-interaction with the nitro group due to rotation of the nitrophenyl ring around bond *d*.
~6.66	Group of four peaks from aromatic protons *f*.
~7.50	A complex group from the nitroaromatic protons *e*.

Reduction of VIII with granulated tin and hydrochloric acid, as described by Gadamer, yielded a hydrochloride apparently corresponding to V. This amorphous, powdery solid was, as reported by the earlier workers, exceedingly difficult to obtain in pure form. It was therefore directly cyclized under the Pschorr reaction conditions of Gadamer. Two crystalline compounds, A and B were isolated as hydrochlorides. Their ultraviolet spectra had maxima at 270 mμ, ϵ = *ca.* 17,000 (assuming mol. wt. 300) thus indicating the presence of a biphenyl moiety. Analyses of a pure sample of A and the corresponding free base using determinations for both ionic[29] and total chloride[30] were in good accord with its formulation as a chloro-

(22) M. Oberlin, *Arch. Pharm.*, **265**, 274 (1927); J. Müller, *Helv. Chim. Acta.*, **31**, 1111 (1948).

(23) H. Avenarius and R. Pschorr, *Ber.*, **62**, 321 (1929), have claimed a somewhat analogous synthesis of apomorphine dimethyl ether, using as an initial step the condensation of 2-methyl-3,4-dihydroisoquinolinium hydroxide with the proper *o*-nitrotoluene. This work has been challenged by J. M. Gulland and C. J. Virden, *J. Chem. Soc.*, 1791 (1929). Our own experiments indicate that the latter workers are correct in their commentary.

(24) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, 1456 (1914), and R. Robinson and J. Shinoda, *J. Chem. Soc.*, 1987 (1926), refer to a preparation of 2,3-dimethoxyaporphine using the Gadamer sequence. However, a laboratory fire which destroyed both samples and records prevented them from making a complete disclosure of their work.

(25) H. Schmid and P. Karrer, *Helv. Chim. Acta.*, **32**, 960 (1949).

(26) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, New York, N. Y., 1951, curve 84.

(27) We are grateful to Dr. G. O. Dudek, Department of Chemistry, Harvard University, for the determination and interpretation of the n.m.r. spectrum.

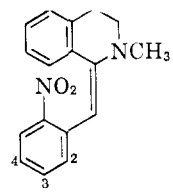
(28) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra Catalog," Varian Associates, 1962.

(29) W. W. Scott, "Standard Methods of Chemical Analysis," Vol. I, D. Van Nostrand Co., New York, N. Y., 1939, p. 271.

(30) J. B. Niederl and V. Niederl, "Micromethods of Quantitative Organic Analysis," John Wiley and Sons, New York, N. Y., 1942, p. 151; W. Schöniger, *Microchem. Acta*, 869 (1956).

TABLE I

NITROBENZALTETRAHYDROISOQUINOLINES

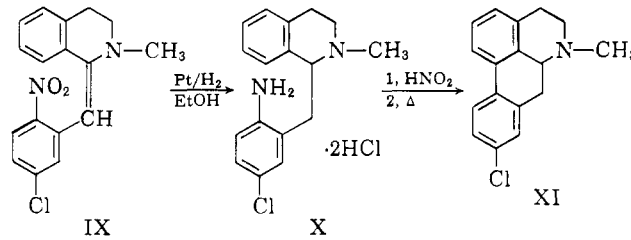


Number	Substituent	Yield %	M.p., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	2-4 = H	72	95–96	$C_{17}H_{16}N_2O_2$	72.84	5.75	9.99	72.95	5.97	9.78
2	2-Cl	89	85–86	$C_{17}H_{15}ClN_2O_2$	64.87	4.80	8.90	64.71	5.11	8.78
3	3-Cl	78	91.5–93	$C_{17}H_{15}ClN_2O_2$	64.87	4.80	8.90	64.59	5.13	8.79
4	4-Cl	93	104–106	$C_{17}H_{15}ClN_2O_2$	64.87	4.80	8.90	64.80	4.86	8.95
5	2-CH_3	59	92–94	$C_{18}H_{18}N_2O_2$	73.45	6.16	9.52	73.36	6.36	9.23
6	4-CH_3	49	63–65	$C_{18}H_{18}N_2O_2$	73.45	6.16	9.52	73.03	6.46	9.22
7	3-OCH_3	91	80.5–82	$C_{18}H_{18}N_2O_3$	69.66	5.85	9.03	69.55	5.79	9.16
8	4-OCH_3	56	90.5–92	$C_{18}H_{18}N_2O_3$	69.66	5.85	9.03	69.54	6.05	8.91
9	3-OC_2H_5	75	70–71.5	$C_{19}H_{20}N_2O_3$	70.35	6.22	8.64	70.05	6.32	8.57
10	4-F	61	89–90	$C_{17}H_{15}FN_2O_2$	68.44	5.07	9.39	68.40	5.35	9.49
11	4-CF_3	68	55–57	$C_{18}H_{15}F_3N_2O_2$	62.07	4.34	8.04	61.99	4.52	8.01

aporphine hydrochloride. Our purest samples of B appeared to be a mixture of the desired aporphine VI and the "by-product" A. Thus, a close repetition of the earlier work[21] provided a pure sample of a probably new, unknown chloroaporphine in addition to a mixture containing VI as one component. In order to make further use of this general sequence for aporphine and other analogs, it appeared necessary to ascertain the exact details of these transformations and in particular to determine the structure of compound A.

The introduction of a bound chlorine atom into an aporphine molecule during a *successful* Pschorr cyclization in dilute sulfuric acid seemed most unlikely; the only chloride in the reaction medium was derived from the anion of amine salt. V. Therefore our interest was focused on the earlier step, a tin–hydrochloric acid reduction of the nitro compound VIII to the cyclization starting material V. A search of the literature unearthed several early reports[31] of introduction of chlorine during tin–hydrochloric acid reduction of simple nitrotoluenes and xylenes. Later authors[32] have concluded that the halogen atom was introduced *para* to the nitrogen functionality. A possible mechanism for these transformations involves reduction of the nitro to the corresponding hydroxylamine and subsequent reaction with hydrochloric acid to form the N-chloro derivative which rearranges to the ring chlorinated product. The later stages of this sequence have been tested[33] using pure N-phenylhydroxylamine.

In order to avoid this complicating factor, the reduction of VIII was accomplished by catalytic hydrogenation in ethanol. When 10% palladium on carbon was used as catalyst, rapid uptake of three moles of hydrogen was observed, with a slow absorption of a fourth mole. The use of platinum dioxide resulted in rapid introduction of all four moles and gave clean V in 76% yield. Pschorr cyclization of this material gave an excellent yield[34] (50.1%) of the expected aporphine VI; no trace of the chloroaporphine by-product (compound A) was detected.



The successful synthesis of VI from pure V, obtained by catalytic reduction, reinforced the hypothesis that the tin–hydrochloric acid reduction of VIII had yielded a mixture of V and a chloro V, this latter molecule being the precursor of compound A and best represented by X. That this situation did in fact obtain was proved by synthesis of compound A = XI from 2-methylisoquinolinium iodide and 2-nitro-5-chlorotoluene,[35] *via* IX and X. This sequence, as illustrated, incorporates the corrected structural formulas and improved experimental procedures evolved in this work. As modified, it has been found useful and convenient for preparation of the compounds cited in Tables I–III. In all cases the laboratory preparations were closely analogous to those described in the Experimental section for successful synthesis of aporphine.

Pharmacological Methods.—The synthetic aporphines and several precursors were subjected to two basic screening procedures: the mouse dose range, and a test for local anti-inflammatory activity utilizing the rat. In the dose range, graded doses of the compound were administered orally to mice which were then observed for gross behavioral changes, pupillary alterations, reaction to thermal pain, lowering of rectal temperature, muscle tonus, and toxicity. Presumptive evidence for local anti-inflammatory activity was measured using three parameters: pain, skin temperature, and edema. Pain was measured by the pressure method of Randall and Selitto.[36] Skin temperature

(31) F. Beilstein and A. Kuhlberg, *Ann.*, **156**, 66 (1870); P. Jannasch, *Ann.*, **176**, 55 (1875).

(32) C. Weygand, "Organic Preparations," Interscience Publishers Inc., New York, N. Y., 1945, p. 218; P. Karrer, "Organic Chemistry," 4th English ed., Elsevier Publishing Co., New York, N. Y., 1950, p. 452.

(33) E. Bamberger, *Ber.*, **35**, 3697 (1902).

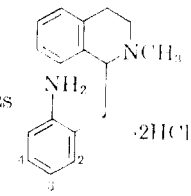
(34) Yields in Pschorr cyclizations to aporphines are usually in the 10–25% range (see reference 17). The electronic and/or steric factors responsible for the divergency observed in this report are under investigation and will be the subject of a future communication.

(35) J. B. Cohen and H. J. Hodsman, *J. Chem. Soc.*, **91**, 970 (1907).

(36) L. D. Randall and J. J. Selitto, *Arch. Int. Pharmacodyn.*, **111**, 409 (1957).

TABLE II

AMINOBENZYLTETRAHYDROISOQUINOLINES

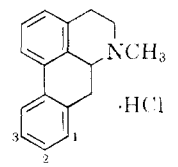


Number	Substituent	Yield, %	M.p.,[a] °C	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
12	2-4 = H	76	272–273	$C_{17}H_{22}Cl_2N_2$	62.77	6.82	8.61	62.51	6.47	8.33
13	2-Cl	85	245–247.5	$C_{17}H_{21}Cl_3N_2$	56.76	5.88	7.79	56.53	5.67	8.00
14	3-Cl	87	252–255	$C_{17}H_{21}Cl_3N_2$	56.76	5.88	7.79	56.67	6.04	7.85
15	4-Cl	94	228.5–231	$C_{17}H_{21}Cl_3N_2$	56.76	5.88	7.79	56.84	6.14	8.10
16	2-CH_3	90	268–269	$C_{18}H_{24}Cl_2N_2$	63.72	7.13	8.26	63.87	7.33	8.23
17	4-CH_3	87	256–259	$C_{18}H_{24}Cl_2N_2$	63.72	7.13	8.26	63.64	7.22	8.51
18	3-OCH_3[b]	83	185–187	$C_{19}H_{28}Cl_2N_2O_2$	58.91	7.23	7.23	58.56	6.90	7.32
19	4-OCH_3	95	228–230	$C_{18}H_{24}Cl_2N_2O$	60.85	6.81	7.88	60.71	6.99	7.90
20	3-OC_2H_5	79	210–212	$C_{19}H_{26}Cl_2N_2O$	61.79	7.10	7.59	61.61	7.30	7.63
21	4-F	93	260–262	$C_{17}H_{21}Cl_2FN_2$	59.48	6.17	8.16	59.58	6.17	8.38
22	4-CF_3	77	235–236	$C_{18}H_{21}Cl_2F_3N_2$	54.97	5.38	7.12	55.40	5.23	7.04

[a] Decomposition points. [b] As methanolate.

TABLE III

APORPHINES



Number	Substituent	Yield, %	M.p.,[a] °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
23	1-3 = H	50	255	$C_{17}H_{18}ClN$	75.13	6.68	5.15	75.12	6.46	4.95
24	1-Cl	52	266	$C_{17}H_{17}Cl_2N$	66.67	5.60	4.57	66.23	5.22	4.61
25	2-Cl[b]	45	125.5–126.5	$C_{17}H_{16}ClN$	75.71	5.93	5.19	75.70	6.14	5.31
26	3-Cl	56	296	$C_{17}H_{17}Cl_2N$	66.67	5.60	4.57	66.81	5.89	4.77
27	1-CH_3	46	267	$C_{18}H_{20}ClN$	75.64	7.05	4.90	75.50	7.38	4.76
28	3-CH_3	50	279	$C_{18}H_{20}ClN$	75.64	7.05	4.90	75.76	7.32	4.83
29	2-OCH_3	22	265	$C_{18}H_{20}ClNO$	71.63	6.68	4.64	71.45	6.84	4.43
30	3-OCH_3	20	256	$C_{18}H_{20}ClNO$	71.63	6.68	4.64	71.53	6.57	4.73
31	2-OC_2H_5	37	255	$C_{19}H_{22}ClNO$	72.25	7.02	4.44	72.02	7.10	4.42
32	3-F	58	292	$C_{17}H_{17}ClFN$	70.46	5.91	4.83	70.47	6.13	4.50
33	3-CF_3	60	295	$C_{18}H_{17}ClF_3N$	63.63	5.04	4.12	63.38	4.99	4.22

[a] Decomposition points except for compound 25. [b] Free base.

was measured with a "Banjo" surface probe and Telethermometer, and reduction of edema, by gross observation. In order to determine whether certain structures actually lowered body temperature, a compound which lowered skin temperature was tested for its ability to lower rectal temperature in the yeast-fevered and in the non-fevered rat.[37]

Where reduction of edema in the yeast injected paw was uncomplicated by toxicity, pleural fluid volume studies,[38] an extension of anti-inflammatory testing, were carried out. In this procedure, rats pretreated with the compound to be evaluated were lightly anesthetized with ether and an aqueous solution of Evans blue injected into the pleural cavity. Six hours after dye injection the animals were sacrificed with ether, the pleural cavity was opened, and the fluid collected and measured. Such clinically useful agents as aspirin and phenylbutazone bring about a reduction in the fluid volume. To evaluate analgesic properties a modification of the D'Amour–Smith[39] test was employed. Local anesthetic action was determined by the method of Rose.[40]

Cardiovascular studies were carried out in the chloralose anesthetized cat. Mean carotid pressure was recorded by means of a mercury manometer on a smoked kymograph drum. All drugs were administered intravenously *via* the femoral vein. Blood pressure responses to the test compound were recorded as well as the integrity of the peripheral and ganglionic autonomic nervous system. The latter was measured by several specific test agents. These were epinephrine, norepinephrine, DMPP (1,1-dimethyl-4-phenylpiperizinium iodide), FTM (furfuryltrimethylammonium iodide) and peripheral vagal stimulation. Antihistaminic activity was detected by blockade of the depressor response to injected histamine, and centrally acting compounds by blocking the pressor effect due to bilateral carotid occlusion.

Antiemetic studies[41] were carried out in dogs of known sensitivity to apomorphine. The compound to be evaluated was administered orally one hour prior to a subcutaneous dose of apomorphine hydrochloride and the number of emetic episodes recorded over a 40 min. period after the apomorphine challenge.

Discussion of Results.—All of the compounds screened in the mouse dose range with the exception of no. 13 (which produced only mydriasis at the tested

(37) P. K. Smith and W. E. Hambourger, *J. Pharmacol. Exptl. Therap.*, **54**, 346 (1935).

(38) I. Merits, "Chemical Studies of Inflammatory Edema, Experimentally Induced," Ph.D. Thesis, Northwestern University, July, 1955.

(39) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1941).

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TABLE IV

SUMMARY OF DOSE RANGE AND ANTI-INFLAMMATORY TESTING

	Dose range, mouse, oral		Anti-inflammatory, rat, oral			
Number	Dose, mg./kg.	Observation	Dose, mg./kg	Analgesia	Anti-pyresis	Edema reduction
12	500	Sl. CNS depression, ↑ pain threshold	200	+	+	−
	1000	As above, hypothermia				
	2000	Tremors, convulsions, death				
13	100	Sl. mydriasis	100	+	+	−
	200–300	Marked mydriasis				
14	200–300	Sl. CNS depression (Rat, 200 mg./kg. orally; no overt effects)	50	+	+++	−
			100	+	+++	−
			200	+++	+++	−
16	200	Sl. to mod. CNS depression, hypothermia, sl. hypotonia	50	+	+	−
	300	Marked CNS depression, hypothermia, mod. hypotonia dyspnea, tremors, convulsions.				
17	300	Sl. to mod. CNS depression, dyspnea, hypothermia, ↑ pain threshold	100	++	+	−
19	200	Sl. CNS depression, ↑ pain threshold	100	+	+	−
21	100–200	Sl. CNS depression, mod. mydriasis	100	+	+++	−
	300	As above, convulsions				
22	300	Sl. CNS depression (Rat, 200 mg./kg. orally. No overt effects)	50	++	+	−
			100	+	+	−
			200	+	+	−
23	50	Sl. CNS depression	50[a]	+	+++	+
	100–250	Mod. to marked CNS depression, hypothermia, ↑ pain threshold, ptosis	100[a]	++	+++	+
			200[a]	+++	+++	+
24	100	Mod. CNS depression (1 of 4 mice only)	75[b]	+	++	−
	250	As above (2 of 4 mice), ↑ pain threshold				
	500	Mod. to marked CNS depression, ↑ pain threshold, Straub tail				
25	100	Sl. CNS depression	100	+	+++	+
	250	As above, hypotonia	200[c]	+	+++	+
	500	Mod. CNS depression, hypotonia, ptosis, ↑ pain threshold				
	1000	Marked CNS depression, and as above				
26	50	↑ Pain threshold	75[d]	+	+++	+
	100	As above, sl. to mod. CNS depression				
	250	As above, marked effects, prostration, tremors.				
	500	Marked neurological deficit, tremors, dyspnea, hypotonia, convulsions				
	1000	Toxic				
27	25	Sl. to mod. CNS depression	25	+	+	−
	50	As above, hypothermia				
	100	As above, ↑ pain threshold				
	200	Toxic (rat, 50 mg./kg. orally, tremors, convulsions)				
28	50–250	Sl. CNS depression	200	+	+	−
	500	Toxic				
29	100	CNS depression, hypothermia, dyspnea	100	++	+++	−
	200–300	As above, marked CNS depression, marked mydriasis	100			
30	50–100	Sl. to mod. CNS depression, hypothermia, miosis	100	++	+	−
31	100	Sl. to mod. CNS depression, ↑ pain threshold	500	+	+	−
	200	Mod. to marked CNS depression, ↑ pain threshold, hypothermia, ptosis, convulsions (1 or 2 mice)				
32	25	Sl. CNS depression	50[e]	++	+++	−
	50	As above, hypothermia, ↑ pain threshold				
	100	As above, mod. to marked effects				
	200	Toxic				
33	100	Sl. mydriasis, ↑ pain threshold	Not tested			
	250	Mod. to marked depression, ataxia, Straub tail, convulsions				
	1000	As above, delayed death				

[a] Depression, tremors or convulsions. [b] Convulsions (10%). [c] Toxic. [d] Depression, hyperpnea. [e] Marked depression, hypotonia, tremors.

dose levels) produced CNS depression (Table IV). In most instances, a dose response effect was seen. Doses approximating or higher than the minimal dose required to elicit CNS depression were generally characterized by a increase in thermal pain threshold (tested by a modification of the hot plate method of Eddy[42])

(42) N. B. Eddy, C. F. Touchberry, and J. E. Lieberman, *J. Pharmacol. Exptl. Therap.*, **98**, 121(1950).

and hypothermia (a decrease in rectal temperature). A slight degree of ptosis was observed with no. 23, 25, and 31. Mydriasis was an accompanying feature of 13, 19, 21, 29, and 33. Toxicity, when present at the tested dose levels, took the form of tremors, and/or convulsions, and in some cases death. The toxic doses ranged from 200 mg./kg. to >300 mg./kg. in this series.

In the Randall and Selitto test for local anti-inflammatory activity, toxic manifestations were sometimes evident in the rat at correspondingly lower doses than in the mouse. The differences in toxicity may be due to species differences or to the fact that testing for anti-inflammatory activity was carried out in fasted animals, which apears to lower the threshold to toxicity. Most of the members of this series of compounds were either devoid of, or exhibited very weak, analgetic activity. Those that exhibited some dose response action were complicated by toxicity (no. 23). Compound 14 appeared to be the most potent antipyretic substance—a 50 mg./kg. dose afforded marked antipyresis. Numbers 23, 26, and 32 were also potent antipyretics, but this action was accompanied by untoward side effects.

Reduction of edema of the yeast-injected paw was observed after oral administration of 50 to 100 mg./kg. of no. 23, 25, and 26. Pleural fluid volume studies were carried out on no. 14 and 25 at 200 and 100 mg./kg., respectively. A significant reduction of pleural fluid volume was not observed at these dose levels.

Analgetic potency was also determined for no. 14 23, and 25 according to a modification of the method of D'Amour and Smith. Again, only weak analgetic activity (33% maximum) could be demonstrated at the tested dose levels (Table V).

TABLE V

ANALGESIA (D'AMOUR–SMITH)

No.	Dose, mg./kg. orally	% Analgesia
14	100	33
	200	0
	300	19
23	25	33
	50	17

One compound (14) was administered orally at doses of 20 and 100 mg./kg. to yeast-fevered and non-fevered rats. No reduction in rectal temperature occurred in either group. Acetanilide, in the range of 64 mg./kg., elicits a positive hypothermic response in the yeast-fevered rat, but has an insignificant effect in the non-fevered animal.

Cardiovascular studies of those structures tested yielded fairly uniform results (Table VI). Hypotension was generally transient and occurred after acute intravenous doses ranging from 0.5 to 10 mg./kg. Toxicity, when present, was evident in the range of 2.5 to 10 mg./kg. Adrenolytic activity was observed in all of the compounds tested.

Picrotoxin potentiation studies were undertaken with compounds 23, 24, 25, 26, and 33; no. 25 and 26 were the most active structures tested; a 50 mg./kg. oral dose caused potentiation in 50 to 66% of the rats. These results do not seem to indicate a specific pharmacologic reaction. In these studies potentiation of picrotoxin may well be the result of unmasking of latent toxicity.

TABLE VI

No.	Minimal hypotensive dose, mg./kg.	Toxic dose, mg./kg.
12	0.5	10
21	2.5	5
23	0.5	>10[a]
26	0.5	10
28	0.5	2.5[a]
32	0.5	5
33	0.5	10

[a] Block of pressor response to bilateral carotid occlusion.

Compound 29, 30, 31, and 32 at an oral dose of 25 mg./kg. had no effect on the number of emetic episodes in the dog after a challenging dose of apomorphine hydrochloride. Local anesthetic properties were seen with compounds 23 and 30. Using procaine hydrochloride as the standard, 23 appeared to be approximately twice as potent, while 30 was slightly less, or equal, in potency. An oral dose of 200 mg./kg. of no. 12 did not elicit a diuretic response in the saline hydrated rat.

On the basis of the tests described it is concluded that the compounds reported in this study do not have clinical usefulness as therapeutic agents.

Experimental[43]

1-(2-Nitrobenzal)-2-methyl-1,2,3,4-tetrahydroisoquinoline (VIII).—Isoquinoline methiodide (140.0 g., 0.515 mole) and *o*-nitrotoluene (145.0 g., 1.05 moles) were added to a warm, stirred solution of sodium (35.0 g., 1.52 mole) in absolute ethanol (1400 ml.). The resultant solution was kept at 25° for 18 hr., cooled to 0° and filtered to yield a red crystalline solid (104.9 g., 72%). Recrystallization from methanol gave maroon needles, m.p. 95–96° (lit.[21] 90°) of analytical purity. λ_{max}^{EtOH} 234 mμ (log ε 4.07), 262 mμ (log ε 3.84), 329/mμ (log ε 3.99), with long tailing into the visible, having intensities at 400 mμ (log ε 2.70) and 470 mμ (log ε 2.51).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.95; H, 5.97; N, 9.78.

A quantitative microhydrogenation at *ca.* atmospheric pressure using platinum oxide in absolute ethanol resulted in the uptake of 4 moles of hydrogen.

1-(2-Aminobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (V).—A mixture of 1-(2-nitrobenzal)-2-methyl-1,2,3,4-tetrahydroisoquinoline (10.02 g., 0.036 mole) (VIII), platinum oxide (1.0 g.) and absolute ethanol (250 ml.) was shaken with hydrogen (initial pressure 3.52 kg./cm.²) in a Paar shaker apparatus for one 100 min. Uptake of hydrogen was essentially complete (*ca.* 4 moles) after the first 15 min. Filtration and concentration *in vacuo* yielded a viscous oil. Addition of ethanolic hydrogen chloride produced a fine, powdery white precipitate (8.26 g., 76%). Recrystallization from methanol-chloroform yielded an analytical sample, m.p. 272–273° dec.; λ_{max}^{EtOH} 236 mμ (log ε 3.84), 288 mμ (log ε 3.31).

Anal. Calcd. for $C_{17}H_{22}Cl_2N_2$: C, 62.77; H, 6.82; N, 8.61; Cl, 21.80. Found: C, 62.51; H, 6.47; N, 8.33; Cl, 21.82.

A similar reduction using 10% palladium on carbon catalyst yielded the same product. However, an extended period (*ca.* 16–24 hr.) was required for complete uptake of the fourth mole of hydrogen.

Aporphine Hydrochloride (VI).—A solution of sodium nitrite (4.25 g., 0.061 mole) in water (40 ml.) was added dropwise to a cold, stirred solution of 1-(2-aminobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline dihydrochloride (18.33 g., 0.056 mole) in acetic acid (240 ml.) and sulfuric acid (18 ml.). The mixture was kept at 5–10° for 15 min.; sulfamic acid (1.0 g., 0.01 mole) and cold sulfuric acid (3 *N*, 350 ml.) were added. The mixture was stirred and heated on the steam bath for 30 min. Zinc dust

(43) Melting points were taken in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Ultraviolet absorption spectra were obtained using a Cary Model 14 spectrometer. Microanalyses were carried out by Mrs. Doris Rolston and her associates at Smith Kline and French Laboratories and at the Huffman Microanalytical Laboratory, Wheatridge, Colorado.

(20 g.) was added and the stirring and warming continued for an additional 30 min. The hot solution was filtered, the filtrate cooled with ice and made alkaline with ammonia. The mixture was extracted with chloroform; the extract was washed with saturated sodium chloride solution, dried over sodium sulfate and taken to dryness *in vacuo*. The resultant dark viscous oil was chromatographed on a Woelm no. 1 neutral alumina column (125 g., 2.5 cm. diameter) prepared in benzene and using benzene as eluent. The product was obtained as a pale yellow oil, which was crystallized from 6 *N* aqueous hydrochloric acid as a powdery white solid (7.73 g., 50.1%). Recrystallization from methanol–ethyl acetate yielded an analytical sample, m.p. 255° dec. as white needles; λ_{max}^{EtOH} 270 mμ (log ε 4.27), 282 mμ (shoulder log ε 4.19).

Anal. Calcd. for $C_{17}H_{18}ClN$: C, 75.13; H, 6.68; N, 5.15; Cl, 13.05. Found: C, 75.12; H, 6.46; N, 4.95; Cl, 13.25.

Pschorr Ring Closure Using Precursor Obtained with Tin–Hydrochloric Acid.[21]—Nine runs were made, which were combined at the indicated point for product isolation. To a cold stirred mixture of dihydrochloride [10.0 g., 0.032 mole, using the assumption that it is a 1:1 mixture of 1-(2-aminobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline dihydrochloride and the corresponding (1-(5-chloro-2-aminobenzyl) compound], ice (100 g.), sulfuric acid (5 ml.), and water (145 ml.) there was added gradually a solution of sodium nitrite (2.14 g., 0.031 mole) in water (15.5 ml.). The solution was kept at 0° for 1 hr.; copper powder (10 g.) was added and the mixture kept at 0° for 1 hr. and then at 26° for 20 hr. The mixture was filtered and the collected solid and the resulting liquid filtrate were processed separately. In our hands, it was convenient to combine at this stage the products of 9 identical experiments. The solid material was suspended in ammoniacal aqueous ether and then filtered; any insoluble residue was discarded. The ether layer was separated and the aqueous solution was extracted repeatedly with fresh ether. The combined ethereal extracts were washed with saturated sodium chloride solution and dried over sodium sulfate. Removal of solvent *in vacuo* yielded a pinkish, crystalline product (16.1 g.). Recrystallization from methylene chloride–95% ethanol produced an analytical sample as white prisms, m.p. 125.5–126.5°; λ_{max}^{EtOH} 276 mμ (log ε 4.35), 304 mμ (shoulder, log ε 3.65).

Anal. Calcd. for $C_{17}H_{16}ClN$: C, 75.71; H, 5.93; N, 5.19; Cl, 13.14. Found: C, 75.70; H, 6.14; N, 5.31; Cl, 13.27.

The filtrate was treated with zinc dust (45 g.) and hydrochloric acid (125 ml.), vigorously heated on the steam bath for 20 min., filtered and made alkaline with aqueous ammonia. The mixture was extracted with ether and the organic extract washed with saturated sodium chloride solution and dried over sodium sulfate. Removal of solvent *in vacuo* yielded a viscous oil (16.7 g.). No pure compound was isolable from this material by chromatographic or crystallization procedures.

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Reserpine Analogs; Phenethylamine Derivatives[1]

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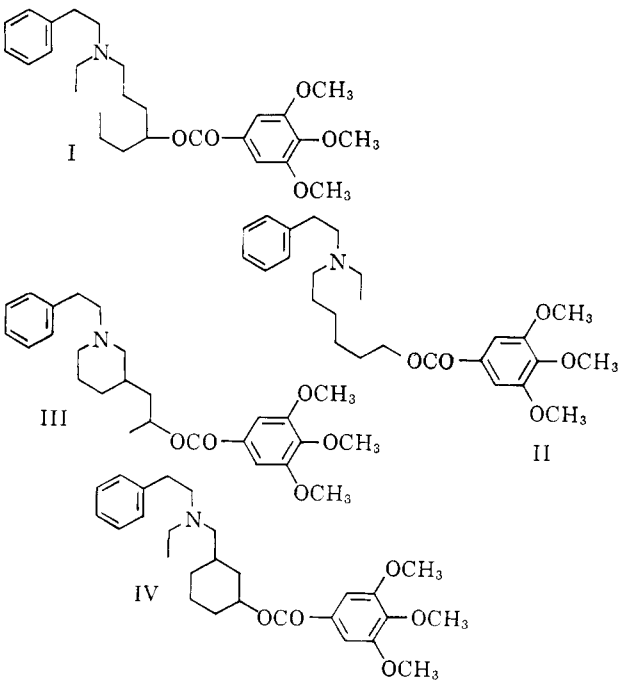
The pharmacological properties of reserpine analogs containing phenethylamine moieties are described. The most interesting pharmacological effects found are blood pressure depression, spasmolysis and adrenolysis. A discussion is given of the structure–activity relationship. A new class of spasmolytics is described with other structure–activity relationships than normally found in aminoalkyl esters.

The natural alkaloid reserpine shows various interesting pharmacological actions.[2] It was of interest to investigate which, if any, pharmacological properties of reserpine are retained in compounds that are simplified models of this alkaloid. In previous publications[1a,b] we have given a survey of the literature of the synthesis of reserpine analogs. We also have given the reasons why we have prepared phenethylamine derivatives in which some features of the reserpine structure are retained. The synthesis and the physical data of those new compounds have been described in detail.[1c] This article now describes the pharmacological investigations of these compounds and their structure–activity relationships. The compounds described may be considered as derivatives of four basic structures (I–IV). They differ in many respects from reserpine, but all contain the phenethylamine structure.

These four basic structures were varied by substituting several groups in the phenyl group, a hydroxyl group at the β-carbon atom (β-phenylethanolamines) and a methyl group at the α-carbon atom (β-phenyl-



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