The Chemistry and Pharmacology of Some 4-Aminopiperidines and Their Derivatives[1a]

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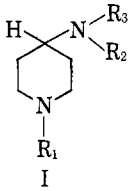
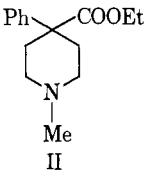
A number of 4-aminopiperidines and their derivatives (I) have been synthesized and assessed pharmacologically for central nervous system activity. These compounds were prepared from the corresponding piperidones, which were converted to their oximes and then reduced to the amino compounds.

Several workers, engaged in investigations involving the molecular modification of certain synthetic analgesics, have appreciated the possibility that typical morphine-like analgesics might be converted into nonmorphine-like compounds which could still have potential usefulness as central nervous system (CNS) drugs.[2] Since it is generally agreed that morphine-like analgesics exert their effect in the CNS, an attempt to design CNS-type drugs based on the skeletal analgesic structure seems to be a realistic approach, in that the physicochemical properties of such modified structures could be expected to be such as to allow penetration to the CNS.

As part of the program designed to prepare general CNS-depressant drugs of potential use as tranquilizing agents, we have synthesized compounds of the type I (see Table I). Such compounds are related to those reported by Janssen[2c,d] and may be regarded as modifications of the synthetic analgesic meperidine (II).



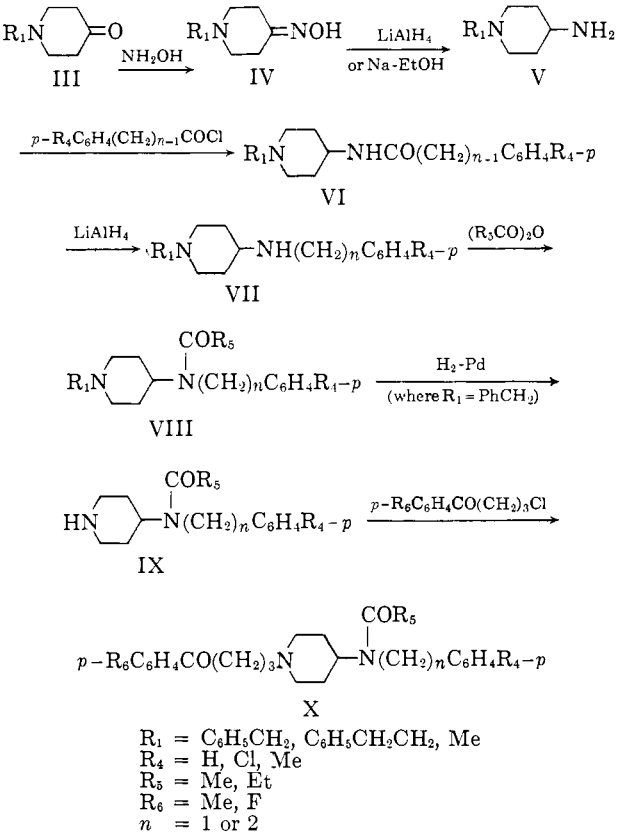
I



II

R_1 = Me, $C_6H_5CH_2$, $C_6H_5(CH_2)_2$, *p*-substituted butyrophenone
R_2 = H, $C_6H_5CH_2$, $C_6H_5(CH_2)_2$
R_3 = H, COMe, COEt, $CON(Et)_2$

Piperidones of the type III, prepared by previously reported procedures,[3] were converted readily to their respective oximes (IV) by the method of Dickerman and Lindwall.[4] Reduction of the latter with lithium aluminum hydride[5] or sodium in boiling ethanol[6] gave the corresponding 4-aminopiperidines (V) in good yield. Prolonged reflux periods were found necessary, however, when lithium aluminum hydride was employed, because the oximes (IV) had low solubility in ether. The conversion of V to VI, by reaction with the appropriate acid chloride, was carried out in the presence of sodium bicarbonate to prevent precipitation of the 4-aminopiperidines (V) as their chloroform-insoluble dihydrochloride salts. The lithium aluminum hydride reduction of VI to VII again required long reflux times since the starting material had low ether solubility. Acetylation of VII was accomplished with the appropriate acid anhydride to give VIII in good yield. To prepare compounds of the type X, 1-benzyl-4-piperidone (III, R_1 = $C_6H_5CH_2$) was employed as starting material since the 1-benzyl grouping could be removed catalytically from VIII (R_1 = $C_6H_5CH_2$) to give the corresponding nor compound (IX). This, on alkylation with the appropriate halo ketone,[2b] would then give the desired series of compounds (X). Despite the possibility that catalytic debenzylation of VIII (R_1 = $C_6H_5CH_2$, n = 1) might have resulted in the removal of both benzyl groupings,



R_1 = $C_6H_5CH_2$, $C_6H_5CH_2CH_2$, Me
R_4 = H, Cl, Me
R_5 = Me, Et
R_6 = Me, F
n = 1 or 2

(1) (a) This work was carried out during the tenure of a scholarship awarded by Department of Scientific and Industrial Research, London, England, and comprises a portion of the thesis presented by C. F. C., in partial fulfillment of the requirements for the Ph.D. degree at the University of London. (b) National Institutes of Health, Bethesda, Md. 20014.

(2) (a) P. A. J. Janssen, C. van de Westeringh, A. H. M. Jageneau, P. J. A. Demoen, B. K. F. Hermans, G. H. P. van Daele, K. H. L. Schellekens, C. A. M. van der Eycken, and C. J. E. Niemegeers, *J. Med. Pharm. Chem.*, **1**, 281 (1959); (b) P. A. J. Janssen, *et al.*, *ibid.*, **2**, 271 (1960); (c) P. A. J. Janssen, *Brit. J. Neuropharmacol.*, **1**, 145 (1962); (d) P. A. J. Janssen, British Patent 917,078 (1961); (e) N. J. Harper and A. B. Simmonds, *J. Med. Pharm. Chem.*, **1**, 181 (1959); (f) N. J. Harper and S. E. Fullerton, *ibid.*, **4**, 297 (1961).

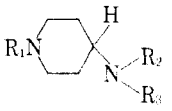
(3) N. W. Bolyard and S. M. McElvain, *J. Am. Chem. Soc.*, **51**, 922 (1929); N. W. Bolyard, *ibid.*, **52**, 1030 (1930); S. M. McElvain and K. Rorig, *ibid.*, **70**, 1820 (1948); A. H. Beckett, A. F. Casy, and G. Kirk, *J. Med. Pharm. Chem.*, **1**, 37 (1959).

(4) S. C. Dickerman and H. G. Lindwall, *J. Org. Chem.*, **14**, 530 (1949).

(5) N. G. Gaylord, "Reductions with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p. 753.

(6) P. Brookes, R. J. Terry, and J. Walker, *J. Chem. Soc.*, 3165 (1957).

TABLE I



4-AMINOPIPERIDINES AND DERIVATIVES

No.	R_1	R_2	R_3	M.p., °C.	Formula	Calcd., % C	H	N	Neut. equiv.	Found, % C	H	N	Neut. equiv.
1	$C_6H_5CH_2CH_2$	H	H	340.5–341.5	$C_{13}H_{20}N_2 \cdot 2HCl$	56.3	8.0	10.1	139	56.0	7.8	10.3	110
2	$C_6H_5CH_2$	H	H	273–274[a]	$C_{12}H_{18}N_2 \cdot 2HCl \cdot H_2O$	51.3	7.9	10.0	141	51.6	7.9	9.7	111
3	CH_3	H	H	247[b]	$C_6H_{14}N_2 \cdot 2HCl$	...	...	14.9	...	...	...	15.0	...
4	$C_6H_5CH_2CH_2$	CH_3CO	H	208–210	$C_{15}H_{22}N_2O \cdot HCl \cdot H_2O$	60.0	8.3	9.4	301	59.7	8.0	9.7	299
5	$C_6H_5CH_2CH_2$	$(C_2H_5)_2NCO$	H	234–235	$C_{18}H_{29}N_3O \cdot HCl \cdot H_2O$	60.5	9.0	11.8	358	60.8	9.0	12.1	359
6	$C_6H_5CH_2CH_2$	C_6H_5CO	H	170–171	$C_{20}H_{24}N_2O$	77.9	7.9	9.0	308	77.8	8.2	8.8	308
7	$C_6H_5CH_2CH_2$	$C_6H_5CH_2CO$	H	150–151	$C_{21}H_{26}N_2O$	78.2	8.1	8.7	322	77.7	8.0	8.7	320
8	$C_6H_5CH_2$	C_6H_5CO	H	171.5–172.5	$C_{19}H_{22}N_2O$	77.5	7.5	9.5	294	77.6	7.6	9.5	295
9	$C_6H_5CH_2$	p-ClC_6H_4CO	H	196–197	$C_{19}H_{21}ClN_2O$	69.4	6.4	8.7	329	69.4	6.6	8.7	326
10	$C_6H_5CH_2$	p-$CH_3C_6H_4CO$	H	165	$C_{20}H_{24}N_2O$	77.9	7.8	9.1	308	77.2	7.5	9.5	307
11	CH_3	C_6H_5CO	H	164–165[c]	$C_{13}H_{18}N_2O$	71.5	8.3	12.8	218	71.2	8.3	12.6	218
12	$C_6H_5CH_2CH_2$	$C_6H_5CH_2$	H	313–314	$C_{20}H_{26}N_2 \cdot 2HCl$	65.4	7.7	7.6	187	65.1	7.5	7.8	184
13	$C_6H_5CH_2CH_2$	$C_6H_5CH_2CH_2$	H	329–330	$C_{21}H_{28}N_2 \cdot 2HCl$	66.1	7.9	7.3	191	66.1	8.2	7.1	191
14	$C_6H_5CH_2$	$C_6H_5CH_2$	H	334–335	$C_{19}H_{24}N_2 \cdot 2HCl$	64.6	7.4	7.9	177	64.4	7.6	7.6	180
15	$C_6H_5CH_2$	p-$ClC_6H_4CH_2$	H	329–330	$C_{19}H_{23}ClN_2 \cdot 2HCl$	58.8	6.5	7.0	194	59.1	6.6	7.0	191
16	$C_6H_5CH_2$	p-$CH_3C_6H_4CH_2$	H	323–324	$C_{20}H_{26}N_2 \cdot 2HCl$	65.4	7.7	7.6	184	65.1	7.4	7.6	190
17	CH_3	$C_6H_5CH_2$	H	296–297	$C_{13}H_{20}N_2 \cdot 2HCl$	56.3	8.0	10.1	139	56.7	8.1	9.8	141
18	$C_6H_5CH_2CH_2$	$C_6H_5CH_2$	CH_3CO	241–243	$C_{22}H_{28}N_2O \cdot HCl$	70.9	7.9	7.5	373	71.6	8.2	7.4	374
19	$C_6H_5CH_2CH_2$	$C_6H_5CH_2$	C_2H_5CO	235–236	$C_{23}H_{30}N_2O \cdot HCl$	71.4	8.1	7.2	387	71.7	8.3	7.2	386
20	$C_6H_5CH_2CH_2$	$C_6H_5CH_2CH_2$	CH_3CO	199–200	$C_{23}H_{30}N_2O \cdot HCl$	71.4	8.1	7.2	387	70.9	8.3	7.3	385
21	$C_6H_5CH_2$	$C_6H_5CH_2$	CH_3CO	215–216	$C_{21}H_{26}N_2O \cdot HCl$	70.3	7.6	7.8	359	70.1	7.6	7.6	360
22	$C_6H_5CH_2$	p-$ClC_6H_4CH_2$	CH_3CO	236–237	$C_{21}H_{25}ClN_2O \cdot HCl$	64.1	6.7	7.1	393	64.0	6.9	7.1	395
23	$C_6H_5CH_2$	p-$CH_3C_6H_4CH_2$	CH_3CO	191.5–192.5	$C_{22}H_{28}N_2O \cdot HCl$	70.9	7.8	7.5	373	70.1	8.0	7.3	375
24	$C_6H_5CH_2CH_2$	p-$CH_3C_6H_4CH_2$	CH_3CO	259–260	$C_{23}H_{30}N_2O \cdot HCl$	71.4	8.1	7.2	387	71.0	8.1	7.0	387
25	CH_3	$C_6H_5CH_2$	CH_3CO	232[d]	$C_{15}H_{22}N_2O \cdot HCl$	63.7	8.2	9.9	283	63.7	8.2	10.1	283
26	CH_3	$C_6H_5CH_2$	C_2H_5CO	173.5–174.5	$C_{16}H_{24}N_2O \cdot HCl$	64.5	8.5	9.4	298	64.3	8.3	9.2	300
27	H	$C_6H_5CH_2$	CH_3CO	193–194	$C_{14}H_{20}N_2O$	72.4	8.7	12.0	232	72.4	8.5	11.8	232
28	H	p-$ClC_6H_4CH_2$	CH_3CO	220–222	$C_{14}H_{19}ClN_2O \cdot C_6H_3N_3O_7$	...	...	14.1	496	...	...	14.2	491
29	H	p-$CH_3C_6H_4CH_2$	CH_3CO	204.5–205.5	$C_{15}H_{22}N_2O \cdot C_6H_3N_3O_7$	53.0	5.3	14.7	476	52.9	5.4	14.7	475
30	p-$FC_6H_4CO(CH_2)_3$	$C_6H_5CH_2$	CH_3CO	228.5–229.5	$C_{24}H_{29}FN_2O_2 \cdot HCl$	66.5	7.0	6.5	433	65.9	7.1	6.3	435
31	p-$FC_6H_4CO(CH_2)_3$	$C_6H_5CH_2$	H	267–269	$C_{22}H_{27}Cl_2FN_2O \cdot 2HCl$	61.8	6.8	6.6	214	61.8	6.8	6.7	220
32	p-$CH_3C_6H_4CO(CH_2)_3$	$C_6H_5CH_2$	CH_3CO	208.5–209.5	$C_{25}H_{32}N_2O_2 \cdot HCl$	70.0	7.8	6.5	429	70.1	8.0	6.6	428
33	p-$FC_6H_4CO(CH_2)_3$	p-$ClC_6H_4CH_2$	CH_3CO	246–247	$C_{24}H_{28}ClFN_2O_2 \cdot HCl$	61.7	6.3	6.0	467	61.5	6.5	6.4	470
34	p-$FC_6H_4CO(CH_2)_3$	p-$CH_3C_6H_4CH_2$	CH_3CO	244–245[e]	$C_{25}H_{31}FN_2O_2 \cdot HCl$	67.2	7.2	6.3	447	66.8	7.3	6.4	453

[a] Lit.[6] m.p. 275°. [b] Sintered at 244°, lit.[6] m.p. 242–244°. [c] Sandoz Ltd., British Patent 740,307 (1955), gives m.p. 164–165°. [d] Sintered at 229°. [e] Sintered at 239°.

selective cleavage of the 1-benzyl group was achieved with palladium on charcoal in ethanol. This finding confirms a previous report[7] that activated hydrogen would not remove the benzyl group from certain N-benzylacylamides. Alkylation of IX was accomplished with the appropriate γ-chlorobutyrophenone, using a trace of potassium iodide as catalyst.[2b]

TABLE II

PHARMACOLOGICAL DATA

No.[a]	Analgesic effects on mice, s.c.[b] (meperidine = 1)	Antiamphetamine activity on mice, oral[c] (chlorpromazine = 1)	Conditioned response rate, oral[d] (chlorpromazine = 1)
18	1.5	*e*	0.08
19	2.3	*f*	*g*
20	*h*	*g*	*i*
24	1.3	*g*	*i*
25	*g*	*g*	*i*
26	*g*	*g*	*i*
30	0.5	0.05	0.25
31	1.0	*i*	*i*
32	0.4	*g*	*g*
33	0.5	*j*	*i*
34	1.1	0.06	0.33

[a] For compound numbers, see Table I. [b] For method of assay, see N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953). [c] See L. Lasagna and W. P. McCann, *Science*, **125**, 1241 (1957). [d] See L. Cook and E. Weidley, *Ann. N. Y. Acad. Sci.*, **66**, 740 (1957). [e] Slight positive at 120 mg./kg. (5/10 protected). [f] Slight positive at 60 mg./kg. (6/10 protected). [g] No activity at dose levels tested. [h] Slight positive at 30 mg./kg. (3/5 with analgesia). [i] No data available. [j] Positive at 100 mg./kg.

It can be seen, from Table II, that the replacement of both the 4-phenyl and 4-carbethoxy groups of meperidine (II), by N-benzylacetamido (**25**) or N-benzylpropionamido (**26**), completely abolishes all analgesic activity without the appearance of other CNS effects. However, analgesic activity is restored when the 1-methyl group is replaced by 1-phenethyl (*cf.* **18** and **25**; **19** and **26**), giving compounds with higher potency than meperidine itself. In this series, analgesic activity increases on going from 4-N-benzylacetamido to 4-N-propionamido (*cf.* **18** and **19**), while a slight decrease is observed when a *p*-methyl group is introduced into the 4-N-benzyl moiety (*cf.* **18** and **24**). Since general CNS-depressant properties (as detected by the antiamphetamine and conditioned response tests) were either weak (*e.g.*, **18**) or completely absent (**19** and **24**) in this group of compounds, it was considered that they were predominantly morphine-like in action. The closely related compound 4-(N-phenylpropionamido)-1-phenethylpiperidine has recently been reported[8] to possess morphine-like activity, with a potency 200 times that of morphine itself.

Further modification of the molecule by the introduction of a 1-(3-benzoylpropyl) grouping (**30–34**)

(7) S. Sugasawa and T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 587 (1958).

(8) P. A. J. Janssen, *Brit. J. Anaesthesia*, **34**, 260 (1962); J. F. Cardocki and J. Yelnosky, *Toxicol. Appl. Pharmacol.*, **6**, 48 (1964).

markedly alters the spectrum of CNS activity. Although all such compounds are analgesically active in the hot plate test, they are less effective than their 1-phenethyl analogs (*cf.* **18**, **30**, and **32**; **24** and **34**). Analgesic potency is little affected by *p*-chloro substitution in the 4-N-benzyl group (*cf.* **30** and **33**), while a *p*-methyl group causes a twofold increase (*cf.* **30** and **34**). It is interesting to note that hydrolysis of 4-(N-benzylacetamido)-1-(3-*p*-fluorobenzoylpropyl)piperidine (**30**) to 4-benzylamino-1-(3-*p*-fluorobenzoylpropyl)-piperidine (**31**) results in a twofold increase in analgesic activity. In this series, general CNS-depressant properties are only observed when a 3-*p*-fluorobenzoylpropyl group occupies the 1-position (*cf.* **30** and **32**). Those compounds which do exhibit activity in the antiamphetamine and conditioned response tests (*e.g.*, **30** and **34**) undoubtedly owe part of their activity in the hot plate test to their general CNS-depressant properties and, therefore, cannot be considered as true morphine-like analgesics. Some of the compounds described also exhibit other interesting pharmacological properties including diuretic activity (**19**) and the ability to block the sympathetic nervous system (18 and **30**).

Experimental

Melting points were taken in a glass capillary and are uncorrected for stem exposure since this work was completed before the recent American Chemical Society directive. Equivalent weights of the bases, and their picrates, were determined by titration with 0.02 *N* perchloric acid in acetic acid, with oracet blue B as indicator. Titrations of the salts were carried out in the same solvent, in the presence of mercuric acetate.[9] Microanalyses were carried out by Mr. G. S. Crouch of the School of Pharmacy, University of London, and Drs. G. Weiler and F. B. Strauss of the Microanalytical Laboratory, Oxford, England.

The reactions involved in the synthesis of 4-(N-benzylacetamido)-1-(3-*p*-fluorobenzoylpropyl)piperidine will be found below. All other related compounds, and their intermediates, were prepared in a similar manner except where they are described separately.

1-Phenethyl-4-piperidone Oxime (IV, R_1 = $C_6H_5CH_2CH_2$) Hydrochloride.—A solution of hydroxylamine hydrochloride (3.4 g.) in water (10 ml.) was added to a solution of III (R_1 = $C_6H_5CH_2CH_2$) (10.0 g.) in ethanol (10 ml.), and the mixture refluxed for 0.5 hr. The solid which separated after storage at −5° was crystallized from ethanol–ether to give colorless needles (9.7 g.), m.p. 237.5–238.5°.

Anal. Calcd. for $C_{13}H_{19}ClN_2O$: C, 61.3; H, 7.5; N, 11.0; neut. equiv., 255. Found: C, 61.4; H, 7.3; N, 11.0; neut. equiv., 253.

1-Benzyl-4-aminopiperidine (V, R_1 = $C_6H_5CH_2$) Dihydrochloride.—A suspension of 1-benzyl-4-piperidone oxime (m.p. 227–228°, lit.[6] m.p. 223–225°) (35.8 g.) in anhydrous ether (100 ml.) was added dropwise to a stirred suspension of lithium aluminum hydride (10.0 g.) in anhydrous ether (50 ml.), refluxed for 19 hr., and decomposed with the calculated amount of water. The inorganic precipitate was filtered off and washed with ether, and the ethereal solutions were combined and dried (Na_2SO_4). After removal of the solvent at the aspirator, the residue (30.0 g.) was dissolved in ethanolic HCl (10% w./v.), and the solid which separated was crystallized from ethanol–ether to give colorless plates (28.5 g.) of the **monohydrate**, m.p. 273–274°.

1-Phenethyl-4-aminopiperidine (V, R_1 = $C_6H_5CH_2CH_2$) Dihydrochloride.—A solution of sodium ethoxide, prepared from sodium (1.3 g.) and ethanol (40 ml.), was added to a suspension of IV (R_1 = $C_6H_5CH_2CH_2$) hydrochloride (9.2 g.) in ethanol (70 ml.) and refluxed for 45 min. After the precipitated NaCl had been filtered off, sodium (12.9 g.) cut into small pieces was added to the cooled filtrate over a period of 40 min. The reaction mixture was refluxed for 35 min. and allowed to stand at room temperature for 12 hr., water (150 ml.) was added, and the ethanol was removed by distillation under reduced pressure. The aqueous solution was saturated with solid K_2CO_3 and extracted with three 70-ml. portions of ether. The combined ethereal extracts were dried (Na_2SO_4) and the solvent was removed to give a mobile yellow oil (6.5 g.) which was dissolved in ethanolic HCl (10% w./v.). The solid which separated on cooling was crystallized from ethanol–ether to give colorless prisms, m.p. 340.5–341.5° dec. (3.3 g.).

4-Benzamido-1-benzylpiperidine (VI, R_1 = $C_6H_5CH_2$; R_4 = H; n = 1).—Benzoyl chloride (16.7 g.) was added dropwise to a stirred and cooled mixture of V (R_1 = $C_6H_5CH_2$) (15.0 g.), sodium bicarbonate (19.9 g.), and chloroform (300 ml.). The reaction mixture was refluxed for 9 hr. and stirred for 48 hr., the solid was filtered off and washed with chloroform, and the combined chloroform solutions were evaporated to dryness. The residue was crystallized from acetone to give colorless needles (20.0 g.), m.p. 171.5–172.5°.

1-Benzyl-4-benzylaminopiperidine (VII, R_1 = $C_6H_5CH_2$; R_4 = H; n = 1) Dihydrochloride.—A suspension of VI (R_1 = $C_6H_5CH_2$; R_4 = H; n = 1) (41.5 g.) in anhydrous ether (200 ml.) was added dropwise to a stirred suspension of lithium aluminum hydride (5.4 g.) in anhydrous ether (100 ml.). The reaction mixture was refluxed for 20 hr. and decomposed with the calculated amount of water, the inorganic precipitate was filtered off and washed with ether, and the combined ethereal solutions were dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give a residue (28.5 g.) which was dissolved in ethanolic HCl (10% w./v.). The solid which separated on storage at −5° was crystallized from ethanol–ether to give colorless needles (27.0 g.), m.p. 334–335°.

1-Benzyl-4-(N-benzylacetamido)piperidine (VIII, R_1 = $C_6H_5CH_2$; R_4 = H; R_5 = CH_3; n = 1) Hydrochloride.—A mixture of VII (R = $C_6H_5CH_2$; R = H; n = 1) (21.0 g.), acetic anhydride (50 ml.), and acetic acid (50 ml.) was refluxed for 0.5 hr., the solvent was removed at the aspirator, and the residue was dissolved in ethanolic HCl (10% w./v.). The solid which separated was crystallized from ethanol–ether to give colorless needles (19.4 g.), m.p. 215–216°.

4-(N-Benzylacetamido)piperidine (IX, R_1 = H; R_4 = H; R_5 = CH_3; n = 1).—A solution of VIII (R_1 = $C_6H_5CH_2$; R_4 = CH_3; n = 1) hydrochloride (10.6 g.) in ethanol (75 ml.) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of 10% w./w. palladium on charcoal (1.0 g.). After 8 hr. the theoretical amount of hydrogen had been adsorbed. The mixture was filtered, the filtrate was evaporated to dryness at the aspirator, and the residue was treated with aqueous NaOH (40% w./v.), saturated with potassium carbonate, and extracted with three 50-ml. portions of toluene. The combined toluene extracts were dried (Na_2SO_4) and the solvent was evaporated at the aspirator to give a residue (4.6 g.) which was crystallized from petroleum ether (b.p. 60–80°)–benzene to give colorless prisms (4.0 g.), which sintered at 191°, m.p. 193–194°.

4-(N-Benzylacetamido)-1-(3-*p*-fluorobenzoylpropyl)piperidine (X, R_4 = H; R_5 = CH_3; R_6 = F; n = 1) Hydrochloride.—A mixture of IX (R_1 = H; R_4 = H; R_5 = CH_3; n = 1) (2.0 g.), 4-chloro-4′-fluorobutyrophenone (1.9 g.), sodium bicarbonate (0.8 g.), a crystal of potassium iodide, and toluene (50 ml.) was refluxed for 4 days. The inorganic solid was filtered off and washed with three 20-ml. portions of chloroform, and the combined chloroform solutions were evaporated to dryness at the aspirator. The residue (3.4 g.) obtained was dissolved in ethanolic HCl (10% w./v.) and the solid, which separated on storage at −5°, crystallized from ethanol–ether to give colorless needles (2.9 g.), m.p. 228.5–229.5°.

4-Benzylamino-1-(3-*p*-fluorobenzoylpropyl)piperidine Dihydrochloride.—A mixture of X (R_4 = H; R_5 = CH_3; R_6 = F; n = 1) hydrochloride (1.9 g.) and aqueous HCl (20% w./v.) (10 ml.) was refluxed for 10 hr., made alkaline with aqueous NaOH (10% w./v.), and extracted with three 50-ml. portions of ether. The combined ethereal solutions were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a viscous yellow oil which was dissolved in ethanolic HCl (10% w./v.). The solid which separated was crystallized from ethanol to give colorless rosette crystals (1.2 g.), m.p. 267–269°.

(9) C. W. Pifer and E. G. Wollish, *J. Am. Pharm. Assoc., Sci. Ed.*, **40**, 609 (1951).

4-(N',N'-Diethylureido)-1-phenethylpiperidine Hydrochloride.—A mixture of V (R_1 = $C_6H_5CH_2CH_2$) (5.0 g.), sodium bicarbonate (6.1 g.), diethylcarbamoyl chloride (3.7 g.), and toluene (50 ml.) was stirred and refluxed for 24 hr. The inorganic residue was filtered off, washed with three 10-ml. portions of toluene, and the combined toluene extracts were evaporated to dryness. The residue obtained was dissolved in ethanolic HCl (10% w./v.) and the solid which separated was crystallized from ethanol–ether to give the **monohydrate** as colorless plates (4.5 g.), m.p. 234–235°.

Acknowledgment.—The biological screening of these compounds was carried out by Dr. D. K. Vallance of Smith Kline and French Laboratories, Welwyn Garden City, Herts., England.

Reductive Cyclization of 2-(Picolylidene)-1-indanones to Octahydroindeno[2,1-*b*]indolizine and Indenoisogranatanine[1]

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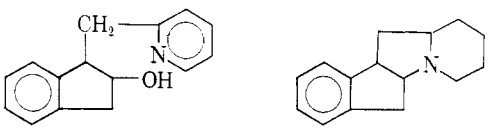
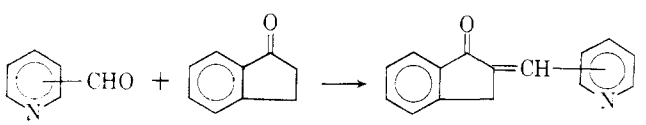
The syntheses of the title compounds are described. Preliminary pharmacological data are provided.

In an earlier publication[2] we described the reductive cyclization of 1-(2-picolyl)-2-indanol (I) to octahydroindeno[1,2-*b*]indolizine (II). Our interest in structural relatives of the veratrum alkaloids[3] prompted us to investigate compounds related to II.



I II

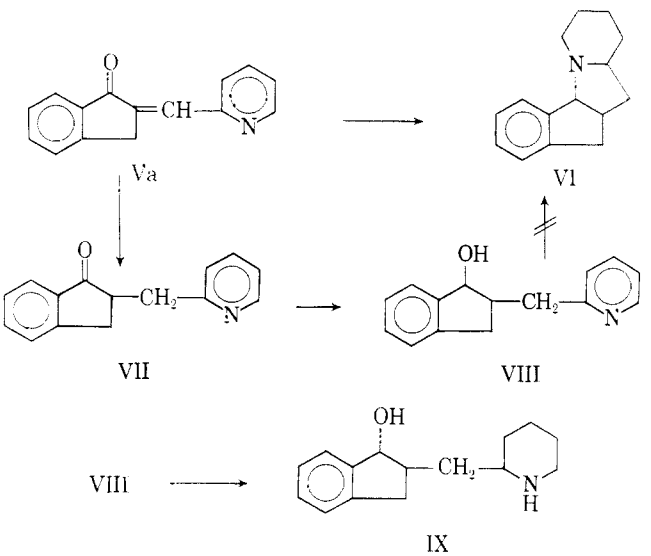
Pyridinealdehydes (III) react readily with 1-indanone (IV) to yield 2-(picolylidene)-1-indanones (V).



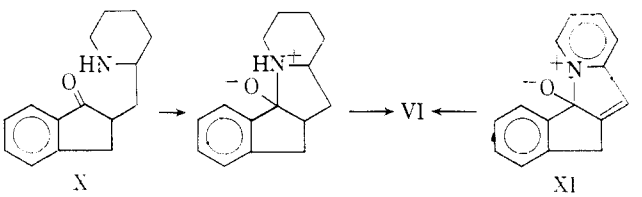
III IV Va, 2-pyridyl b, 3-pyridyl

The products from the hydrogenation of V are dependent on the conditions utilized in the reduction. For example, the low-pressure reduction (3.5–4.2 kg./cm.^{2}) (50–60 p.s.i.) of 2-(2-picolylidene)-1-indanone (Va) in glacial acetic acid in the presence of catalytic quantities of platinum oxide yields 5a,6,6a,7,8,9,10,11a-octahydroindeno[2,1-*b*]indolizine (VI); palladium–carbon hydrogenation in ethanol yields 2-(2-picolyl)-1-indanone[2] (VII); Raney nickel and ethanol yields a mixture of VI and *cis*-2-(2-picolyl)-1-indanol (VIII); and H_2, platinum oxide, and ethanol likewise yields a mixture of VI and VIII.

It was of interest to determine whether the reductive cyclization of Va to VI was a direct process or proceeded in a stepwise manner from Va through VII and VIII to VI. The platinum oxide reduction of VIII in acetic acid produced *cis*-2-(2-pipecolyl)-1-indanol (IX); the

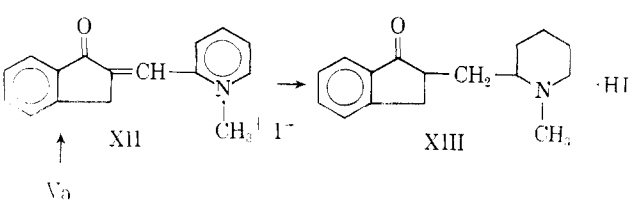


reduction of VII in glacial acetic acid with platinum oxide gave VI. It is speculated that the reduction of Va to VI is either a direct process (cyclization to XI followed by reduction to VI) or proceeds through 2-(2-pipecolyl)-1-indanone (X).



X XI

Although the latter was not isolated, evidence for the existence of X as an intermediate was obtained in the reduction of 1-methyl-2-[(1-oxo-2-indanylidene)-methyl]pyridinium iodide (XII) with platinum oxide in water. The only product obtained was 1-methyl-



XII XIII Va

(1) (a) The authors are grateful to A. H. Robins Company for financial support of the project. (b) Presented before the Division of Medicinal Chemistry, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1964.

(2) J. Sam, J. N. Plampin, and D. W. Alwani, *J. Org. Chem.*, **27**, 4543 (1962).

(3) O. Jeger and V. Prelog, "The Alkaloids," Vol. VII, R. R. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, Chapter 17.