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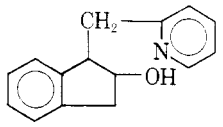
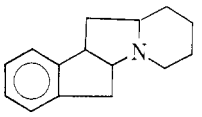
The syntheses of the title compounds are described. Preliminary pharmacological data are provided.

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.

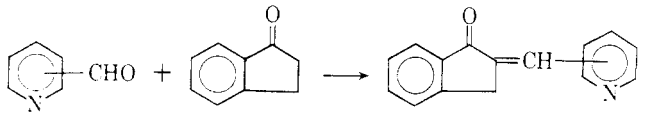


I



II

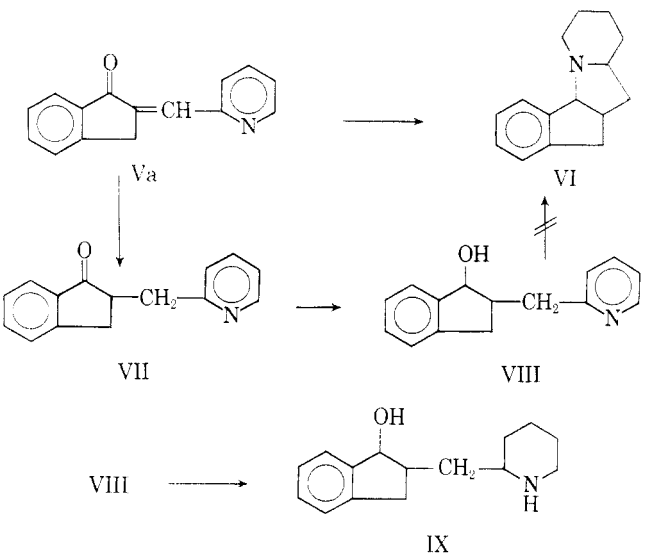
Pyridinealdehydes (III) react readily with 1-indanone (IV) to yield 2-(picolylidene)-1-indanones (V).



III IV Va, 2—pyridyl b, 3—pyridyl

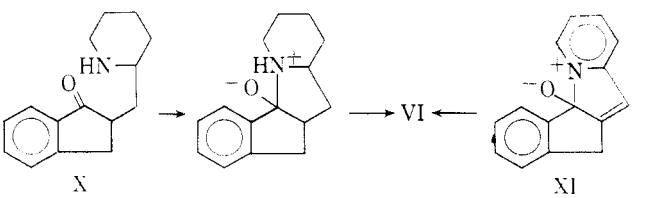
The products from the hydrogenation of V are dependent on the conditions utilized in the reduction. For example, the low-pressure reduction (3.5–4.2 kg./cm.^{2}) (50–60 p.s.i.) of 2-(2-picolylidene)-1-indanone (Va) in glacial acetic acid in the presence of catalytic quantities of platinum oxide yields 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



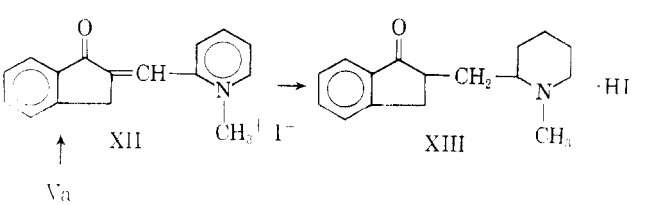
Va VI VII VIII VIII IX

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-



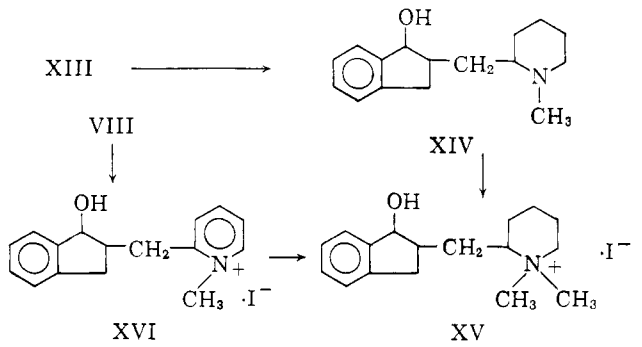
Va XII XIII

(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.

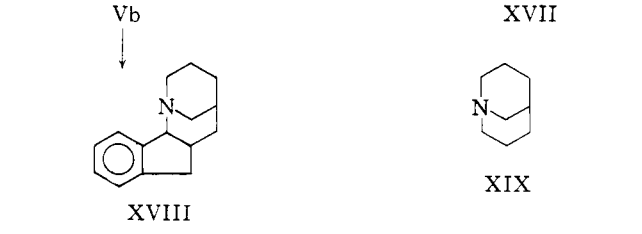
2-[(1-oxo-2-indanyl)methyl]piperidine hydriodide (X-III); none of the alcohol (XIV) was isolated. The latter was obtained by the sodium borohydride reduction of XIII and converted to the methiodide XV.



The methiodide XV also was prepared by converting VIII to the methiodide XVI followed by reduction in water with platinum oxide and treatment with methyl iodide.

The characterization of the *cis* and *trans* configurations of VIII was described in an earlier publication.[2] The products derived from VIII and described above have been assigned the *cis* configuration on the basis of our earlier work.

The reduction of the exocyclic double bond in 2-(3-picolylidene)-1-indanone (Vb) occurred less readily than with the corresponding 2-isomer; complete reduction to XVII took place only in glacial acetic acid over a 3–4-hr. period in the presence of palladium–carbon catalyst. The low-pressure platinum oxide catalyzed reduction of Vb to indenoisogranatanine (XVIII) failed to occur; however, the cyclization was accomplished in moderate yield (47%) with Raney nickel at 140 kg./cm.^{2} (2000 p.s.i.). McElvain and Adams[4] described the preparation of isogranatanine (XIX).



Pharmacological Results.[5]—Compounds Vb, VI, IX, XII, and XIII were investigated in mice and anesthetized dogs by conventional techniques. The acute intraperitoneal LD_{50} range in female albino mice was determined to be as follows: Vb (225–238mg./kg.), IX (100–150 mg./kg.), XII (1.5–2.3 mg./kg.), XIII (25–38 mg./kg.). The intravenous LD_{50} of VI in female albino mice was found to be approximately 33–50 mg./kg. All compounds produced convulsions at near lethal doses. Cyanosis was frequently observed in mice which received Vb, IX, XII, or XIII. In the anesthetized dog, Vb, IX, XII, and XIII at doses of 1–4 mg./kg. caused transient hypotension usually followed by respiratory stimulation. The rise in arterial blood pressure due to intravenous epinephrine (1 γ/kg.) was prolonged by all of the latter four compounds at doses of 4 mg./kg. and above, whereas the depressor response to intravenous acetylcholine (10 γ/kg.) was unaffected at all doses. Compound IX at 4 mg./kg. appeared to prolong the depressor response to intravenous histamine (1 γ/kg.). Compound VI at doses up to 40 mg./kg. had no significant effect on blood pressure. The compound did cause a decrease in respiratory amplitude, bradycardia, an increase in intestinal tone, and a decrease in urinary flow.

Experimental[6]

2-(3-Picolylidene)-1-indanone (Vb).—The procedure described for the synthesis of 2-(picolylidene)-1-indanone[2] (Va) was followed, using 50 g. (0.38 mole) of 1-indanone, 50 g. (0.467 mole) of 3-pyridinealdehyde, 8 g. of piperidine, and 8 g. of glacial acetic acid. The mixture was placed on a water bath (60–70°) until a homogeneous solution was formed (1 hr.). The solid which separated on standing at room temperature was recrystallized from ethanol to give 71.5 g. (85%) of product, m.p. 154–155°.

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.4; H, 5.0; N, 6.3. Found: C, 81.4; H, 5.0; N, 6.3.

2-(2-Picolyl)-1-indanone Hydrochloride. (VII).—A mixture of 11 g. (0.05 mole) of *cis*-2-(2-picolyl)-1-indanol (VIII), 25 g. (0.12 mole) of aluminum isopropoxide, 45.5 g. (0.25 mole) of benzophenone, and 500 ml. of dry toluene was refluxed for 24 hr.[7] The reaction mixture was cooled and washed with 10% NaOH solution and water, respectively, and then extracted with dilute HCl. The aqueous layer was neutralized with dilute NaOH solution and extracted with small batches of ether. The ether extracts were washed with water, dried ($MgSO_4$), and treated with HCl. Recrystallization of the hydrochloride from cyclohexanone gave 5.5 g. (50%) of product, m.p. 173–174.5°. A mixture melting point with the product obtained by Sam, *et al.*,[2] showed no depression.

2-(3-Picolyl)-1-indanone (XVII).—2-(3-Picolylidene)-1-indanone (Vb) (22 g., 0.1 mole) suspended in 200 ml. of glacial acetic acid was reduced in a Parr hydrogenator using 10% palladium on carbon as catalyst. After the hydrogenation was complete (3–4 hr.) the catalyst was removed by filtration and the acetic acid was distilled *in vacuo*. The residual oil was treated with a saturated solution of sodium bicarbonate and extracted with small batches of ether. The combined ether layers were washed with water and dried ($MgSO_4$). Evaporation of the ether yielded 14 g. (60%) of product which was recrystallized from acetone; m.p. 64–66°.

Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.7; H, 5.9; N, 6.3. Found: C, 80.7; H, 6.0; N, 6.3.

5a,6,6a,7,8,9,10,11a-Octahydroindeno[2,1-*b*]indolizine. (VI). A.—2-(2-Picolylidene)-1-indanone (Va) (22.1 g., 0.1 mole) was dissolved in 200 ml. of glacial acetic acid and reduced in a Parr hydrogenator using platinum oxide as catalyst. After the reduction was complete (24 hr.), the catalyst was removed by filtration. The solvent was distilled *in vacuo;* the residual oil was treated with dilute sodium bicarbonate, extracted with ether, and dried (Na_2SO_4). The dried ethereal solution was distilled, yielding 12 g. (56%) of viscous liquid, b.p. 124° (0.3 mm.), $n^{19.5}D$ 1.5598.

The infrared spectrum did not show CO or OH absorption. The usual tests for secondary amines were negative.

Anal. Calcd. for $C_{15}H_{19}N$: C, 84.5; H, 9.0; N, 6.6. Found: C, 84.6; H, 9.1; N, 6.4.

(4) S. M. McElvain and R. Adams, *J. Am. Chem. Soc.*, **45**, 2738 (1923).

(5) Pharmacological data were provided by Dr. John Ward, A. H. Robins Company, Richmond, Va.

(6) Boiling points are uncorrected. Melting points were determined on a Fisher-Johns melting point apparatus and are corrected. Microanalyses were by A. Bernhardt, Max-Planck Institut fur Kohlenforschung, Mulheim Germany, and Weiler and Strauss Laboratories, Oxford, England. Infrared spectra were determined on a Perkin-Elmer Model 137 Infracord spectrophotometer using KBr pellets.

(7) C. Djerassi, *Org. Reactions*, **6**, 207 (1951).

The picrate was prepared in the usual manner and recrystallized from acetic acid; m.p. 234–236°.

Anal. Calcd. for $C_{21}H_{22}N_4O_7$: C, 57.0; H, 5.0; N, 12.7. Found: C, 56.6; H, 5.1; N, 12.4.

The hydrochloride was prepared in the usual manner and recrystallized from acetone; m.p. 220–221°.

B.—The procedure of A was followed using 22.3 g. (0.1 mole) of 2-(2-picolyl)-1-indanone. Thirteen grams (58%) of product was obtained; b.p. 132–135° (0.3 mm.), $n^{19.5}D$ 1.5599.

The infrared spectrum, picrate, and hydrochloride were identical with those obtained with the product from A.

C.—The procedure of A was followed except that 2 g. of Raney nickel was used as catalyst and ethanol was used as the solvent. The reduction proceeded slowly; 50% of the theoretical amount was absorbed at the end of 36 hr. The catalyst was removed by filtration and the solvent was distilled *in vacuo*. The residual crude material, after treatment with ether, yielded *cis*-2-(2-picolyl)-1-indanol (VIII), m.p. 148–149°. A mixture melting point with the product obtained by Sam, *et al.*,[2] showed no depression. The ether solution was treated with picric acid to yield the picrate of VI, m.p. 234–236°. A mixture melting point with the product obtained by A showed no depression.

D.—The procedure of A was followed using ethanol as the solvent. The reduction was incomplete; trace amounts of both VIII, m.p. 148–150°, and the picrate of VI, m.p. 234–236°, were obtained. Mixture melting points with authentic samples of VI (picrate) and VIII, respectively, showed no depression.

***cis*-2-(2-Pipecolyl)-1-indanol (IX).**—*cis*-2-(2-Picolyl)-1-indanol[2] (VIII) (22 g., 0.1 mole), suspended in 200 ml. of glacial acetic acid, was reduced at 3.86 kg./cm.^{2} (55 p.s.i.) with platinum oxide catalyst. After reduction was complete (8 hr.), the catalyst was removed by filtration. The acetic acid was distilled *in vacuo*, and the residual oil was treated with a saturated sodium bicarbonate solution. The precipitate was removed by filtration and recrystallized from acetone to give 16 g. (73%) of product, m.p. 141–142°.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.9; H, 9.2; N, 6.1. Found: C, 77.9; H, 9.3; N, 6.2.

1-Methyl-2-[(1-oxo-2-indanylidene)methyl]pyridinium Iodide (XII).—In a 250-ml. round-bottomed flask fitted with a reflux condenser were placed 18 g. (0.08 mole) of 2-(2-picolylidene)-1-indanone (Va), 50 ml. of N,N-dimethylformamide, and 10 ml. of methyl iodide. The mixture was refluxed on a steam bath for 4 hr. during which time solid separated from solution. The mixture was cooled and the product was removed by filtration. The solid (18 g., 61%) was washed with acetone and recrystallized from water; m.p. 213–215°.

Anal. Calcd. for $C_{16}H_{14}INO$: C, 52.9; H, 3.9; I, 34.9; N, 3.9. Found: C, 52.9; H, 3.7; I, 35.1; N, 3.9.

1-Methyl-2-[(1-oxo-2-indanyl)methyl]piperidine Hydriodide (XIII).—1-Methyl-2-[(1-oxo-2-indanylidene)methyl]pyridinium iodide (XII) (18 g., 0.05 mole) suspended in 200 ml. of water was reduced in the usual manner at 3.86 kg./cm.^{2} (55 p.s.i.) using platinum oxide catalyst. After hydrogenation was complete (6–8 hr.), the catalyst was removed by filtration and the filtrate was evaporated to dryness. The residual oil, after treatment with cold acetone, yielded a crystalline solid. Recrystallization of the solid from toluene resulted in 14 g. (76%) of product, m.p. 158–159°. The infrared spectrum contained strong carbonyl absorption at 5.83 μ.

Anal. Calcd. for $C_{16}H_{22}INO$: C, 51.8; H, 6.0; I, 34.2; N, 3.8. Found: C, 51.5; H, 6.2; I, 33.2; N, 4.0.

***cis*-1,1-Dimethyl-2-[(1-hydroxy-2-indanyl)methyl]piperidinium Iodide. (XV). A.**—*cis*-1-Methyl-2-[(1-hydroxy-2-indanyl)methyl]-pyridinium iodide (XVI) (18 g., 0.05 mole), suspended in 200 ml. of water, was reduced in the usual manner at 3.86 kg./cm.^{2} (55 p.s.i.) using platinum oxide catalyst. After the reduction was complete (6–8 hr.), the catalyst was removed by filtration; the solution was concentrated to a small bulk and neutralized with dilute NaOH solution. The material which separated from solution was extracted with benzene and converted to a methiodide in the usual manner. Washing with boiling acetone gave product, m.p. 179–181°.

Anal. Calcd. for $C_{17}H_{26}INO$: C, 52.7; H, 6.8; I, 32.8; N, 3.6. Found: C, 52.7; H, 6.9; I, 32.6; N, 3.8.

B.—To 8 g. of 1-methyl-2-[(1-oxo-2-indanyl)methyl]piperidine hydriodide (XIII) dissolved in water was added slowly (15–20 min.), with stirring, 8 g. of sodium borohydride. After the initial heat of reduction subsided, the mixture was heated under reflux for 2 hr. The oil which separated was extracted with small batches of benzene. The combined benzene extracts were washed with water and dried ($MgSO_4$). The methiodide (5 g., 60%) was prepared in the usual manner; m.p. 179–181°. A mixture melting point with the product obtained from A showed no depression.

***cis*-1-Methyl-2-[(1-hydroxy-2-indanyl)methyl]pyridinium Iodide (XVI).**—A solution of 14.0 g. (0.062 mole) of *cis*-2-(2-picolyl)-1-indanol[2] (VIII) and an excess of methyl iodide in 150 ml. of benzene was refluxed on a steam bath for 30 min. The precipitate which formed was removed by filtration and recrystallized from ethyl alcohol to give 11.0 g. (78%) of product, m.p. 188–189°.

Anal. Calcd. for $C_{16}H_{18}INO$: C, 52.3; H, 4.9. Found: C, 52.5; H, 4.9.

Indeno[1,2-*b*]isogranatanine (XVIII).—A solution of 11.02 g. (0.05 mole) of 2-(3-picolylidene)-1-indanone (Vb) in 190 ml. of methanol was hydrogenated with 2 g. of Raney nickel at 70 kg./cm.^{2} (1000 p.s.i.) at 100° for 24 hr. Since only 50% of the theoretical amount of hydrogen was absorbed at the end of this time, the pressure was increased to 1700 p.s.i. and the reduction was allowed to proceed for 2 hr. The pressure was then increased to 119.5 kg./cm.^{2} (2300 p.s.i.) and the reduction was allowed to proceed for an additional 18 hr.; the theoretical amount of hydrogen was absorbed at the end of this period. The catalyst was removed by filtration and the residual solution was distilled to give 5 g. (47%) of product, b.p. 160° (1.5 mm.), $n^{26.5}D$ 1.5284.

The infrared spectrum showed some carbonyl absorption at 5.9 μ; hydroxyl group absorption was absent. The usual tests for secondary amines were negative. A picrate was prepared in the usual manner and recrystallized from ethanol; m.p. 166–167°. Recrystallization from acetone gave product, m.p. 174–176°. The infrared spectrum did not show carbonyl absorption.

Anal. Calcd. for $C_{21}H_{22}N_4O_7$: C, 57.0; H, 5.0; N, 12.7. Found: C, 57.5; H, 5.6; N, 12.5.

A methiodide was prepared in the usual manner and recrystallized from ethanol; m.p. 183–185°.

Anal. Calcd. for $C_{16}H_{22}IN$: C, 54.1; H, 6.2; I, 35.7; N, 3.9. Found: C, 54.1; H, 6.4; I, 35.7; N, 4.1.

Pharmacological Results.[5]—Fasted female albino mice (22–32 g.) were used in determining the LD_{50}. The animals were observed closely for signs of toxicity and pharmacologic effect during the first 4 post-treatment hr. They were observed daily, thereafter, for 3 days. Gross autopsies were performed on all animals that succumbed and on those that survived the observation period. Compounds Vb, IX, XII, and XIII were administered intraperitoneally; VI was given intravenously into a lateral tail vein at the manually controlled rate of 0.05 ml./10 sec.

Mongrel dogs of either sex were anesthetized by the intravenous administration of phenobarbital sodium, 125 mg./kg. A carotid artery was cannulated for recording arterial blood pressure, a jugular vein was cannulated for recording venous blood pressure, the trachea was cannulated for recording respiration, both ureters were cannulated for recording urinary flow, the urinary bladder was catheterized and connected to a closed system for recording urinary bladder activity, and needle electrodes were inserted under the skin of each limb for recording the electrocardiogram. Recordings were made with appropriate transducers on an 8-channel Grass polygraph.

The drugs were given intravenously into an exposed femoral vein. The initial dose of each compound was 1 mg./kg. and each subsequent dose was doubled until death occurred or it became impractical to increase dosage further.

The responses to intravenous injections of epinephrine (1 γ/kg.), acetylcholine (10 γ/kg.), and histamine (1 γ/kg.) were obtained before and after each dose of an experimental compound.