

lein (IIa) by 1,4-addition of hydrogen. This structure, which still represents a vinylogous amide, accounts for the non-basic properties of the reduced substance. Support for the correctness of this formulation is provided by the similarity of the infrared spectrum of dihydroedulein in the carbonyl region with that of the similarly constituted 1-methyl-4-keto-7,8-methylenedioxy-1,2,3,4-tetrahydroquinoline (IV) (λ_{\max} 5.99, 6.17, and 6.34 μ), the lithium aluminum hydride reduction product of casimiroin.²

EXPERIMENTAL⁶

Demethyledeulein (γ -hydroxy-1-methyl-2-phenyl-4-quinolone) (IIb). A mixture of 90 mg. of edulein, 1 g. of potassium hydroxide, and 10 cc. of ethylene glycol was boiled under reflux for 24 hr. Water was added, the solution was filtered, the filtrate was acidified with dilute hydrochloric acid, and the precipitate was collected. Crystallization from ethanol gave 74 mg. of demethyledeulein as needles, m.p. 322–324° (dec.). The substance gave a red color with alcoholic ferric chloride.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22. Found: C, 76.25; H, 5.36.

The same substance was obtained by boiling edulein (90 mg.) with hydriodic acid (3 cc.; d 1.7) for 1 hr.

Treatment of demethyledeulein in ether suspension with ethereal diazomethane at 5° for 24 hr. regenerated edulein in almost quantitative yield.

Dihydroedulein (γ -methoxy-1-methyl-2-phenyl-4-keto-1,2,3,4-tetrahydroquinoline) (III). Edulein (150 mg.) dissolved in 25 cc. of dry tetrahydrofuran was added dropwise to a solution of 500 mg. of lithium aluminum hydride in 15 cc. of tetrahydrofuran and the mixture was boiled under reflux for 7 hr. It was then cooled, poured into ice cold dilute sulfuric acid, and extracted with ether. The ethereal extract was washed with water, dried, and evaporated. Chromatography of the residue on 3.5 g. of alumina and crystallization of the fractions eluted with pentane-benzene (1:1) from ether-pentane gave 105 mg. of dihydroedulein, m.p. 129–130°, λ_{\max} 238, 255, 283, and 375 $m\mu$ ($\log \epsilon$ 4.21, 4.37, 3.96, and 3.70, respectively), λ_{\max} 6.01, 6.20 and 6.37 μ , no hydroxyl band.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.18; H, 6.19; N, 5.25.

Identification of edulein with γ -methoxy-1-methyl-2-phenyl-4-quinoline (IIa). A sample of edulein, m.p. 200–201°, gave no melting point depression on admixture with a sample of IIa (m.p. 199–200°) obtained by Dr. J. R. Price from the bark of *Lunasia amara*. The infrared spectrum of edulein was re-determined (λ_{\max} 6.15, 6.19, 6.24, 6.33, and 6.39 μ) and was found to be completely identical with the spectrum of IIa.

Edulein picrate was prepared again and after crystallization from methanol formed yellow needles, m.p. 220–221°. There was no depression on admixture with a sample of the picrate of IIa, m.p. 220–221°, kindly supplied by Dr. Price.

Acknowledgment. We are indebted to Drs. F. A. Kincl and G. Rosenkranz (Syntex S. A., Mexico City) for the edulein used in this investigation, to Dr. Sidney Goodwin for interesting discussions and

(6) Melting points are uncorrected. The ultraviolet spectrum was measured in 95% ethanol solution on a Unicam Model S.P. 500 spectrophotometer and the infrared spectra in chloroform solution on a Baird double-beam recording spectrophotometer. The analyses were carried out in our microanalytical department under the direction of Mr. Erich Meier.

correspondence, and to Dr. J. R. Price for samples of the alkaloid IIa and its picrate.

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Spiroisindolinium Salts

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Received November 27, 1957

During an investigation of various types of quaternary ammonium salts, seven new spiroisindolinium compounds were prepared for pharmacological evaluation (Table I). These derivatives resulted from the reaction of cyclic secondary amines and various *o*-xylylene halides in the manner generally described by other investigators.^{2–5} While most of the intermediates used have been previously described, improved preparations of some of them are reported in the experimental part.

The isindolinium salts were pressor agents in dogs. No other marked pharmacological activity was noted.

EXPERIMENTAL⁶

General procedure. The isindolinium salts were prepared by heating under reflux a mixture of 0.1 mole of an *o*-xylylene halide and 0.1 mole of a cyclic secondary amine in 600 ml. of isopropyl alcohol containing 0.1 mole of sodium hydroxide and 10 ml. of water. After 6 to 18 hr. the solution was filtered, then concentrated to a volume of 50 to 150 ml. and filtered again to remove inorganic material. The product was obtained by diluting the filtrate with anhydrous ether and refrigerating the mixture.

Crude yields of 60 to 90% were obtained. The products were recrystallized and dried *in vacuo* before analysis.

Secondary amines. Hexamethyleneimine was obtained from a commercial source; 2- and 4-methyl hexamethyleneimine were prepared by the method of Blicke and Doorenbos.⁷

Intermediates. 1,2-Bis(α -bromoethyl)benzene. A mixture of 5.0 g. (0.03 mole) of 1,2-bis(α -hydroxyethyl)benzene⁸ and 100 ml. of 65% aqueous hydrobromic acid was stirred for 48 hr. at room temperature, then poured into a mixture of 250 g. of ice and 250 ml. of water. The solid was separated by filtration, washed well with water and air-dried to give 8.4 g. (96%) of pure product, m.p. 88–91°.⁹

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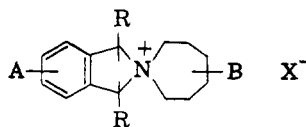
(6) All melting and boiling points as uncorrected.

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TABLE I
SPIROISOINDOLINIUM SALTS^a



No.	A	R	B	X	Formula	M.P., °C.	Analysis					
							C		H		X	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
1	...	H	2-CH ₃	Br	C ₁₅ H ₂₂ BrN	237-239 ^b	60.80	60.62	7.49	7.36	26.98	26.77
2	...	H	4-CH ₃	Br	C ₁₅ H ₂₂ BrN	216-218	60.80	60.44	7.49	7.50	26.98	26.90
3	...	CH ₃	...	Br	C ₁₆ H ₂₄ BrN	246-247 ^c	61.93	61.52	7.80	7.73	25.76	26.30
4	4-CH ₃ O-	H	...	Cl	C ₁₅ H ₂₂ ClNO	237-238 ^c	67.26	67.13	8.28	8.32	13.24	13.16
5	5,6-di-CH ₃ O-	H	...	Cl	C ₁₅ H ₂₄ ClNO ₂	218-219 ^c	64.51	64.09	8.12	8.05	11.91	11.60
6	4,5,6,7-tetra-Cl	H	...	Br	C ₁₄ H ₁₆ BrCl ₄ N	287 ^c	40.03	40.26	3.84	3.99	19.03	18.84
7	hexahydro	H	...	Br	C ₁₄ H ₂₆ BrN	289-291 ^c	58.33	58.45	9.09	9.12	27.72	27.51

^a All compounds were dried at 100° over P₂O₅ *in vacuo* for several hours before analysis. Compounds 2, 3, 4, 5, and 7 were recrystallized from isopropyl alcohol; 6 from 95% ethanol and 1 from absolute ethanol-dry ether. ^b Possible decomposition. ^c Decomposition.

Anal. Calcd. for C₁₀H₁₂Br₂: C, 41.13; H, 4.14; Br, 54.73. Found: C, 41.25; H, 4.37; Br, 54.46.

3-Methoxyphthalic anhydride. Oxidation of 3-methoxy-o-xylene¹⁰ with potassium permanganate using the method of Grewe¹¹ gave a 49% yield of 3-methoxyphthalic anhydride, m.p. 159-160° after recrystallization from toluene. This melting point agrees well with published values for the same compound prepared in other ways.¹²

3-Methoxy-o-phthalyl alcohol. A Soxhlet apparatus containing 19.4 g. (0.11 mole) of 3-methoxyphthalic anhydride was attached to a flask containing a solution of 8.3 g. (0.22 mole) of lithium aluminum hydride in 600 ml. of anhydrous ether. After 48 hr. of refluxing, 17.4 g. (0.098 mole) of anhydride had been extracted. The stirred complex was decomposed by carefully adding 20 g. of ethyl acetate, then 40 ml. of water. After filtration, the solution was evaporated to dryness. Recrystallization of the residue from petroleum ether (75-90°) gave 4.3 g. (26%) of pure product, m.p. 95-96°.

Anal. Calcd. for C₉H₁₂O₃: C, 64.27; H, 7.19. Found: C, 64.23; H, 7.36.

3-Methoxy-o-xylene chloride. A mixture of 4.0 g. (0.024 mole) of 3-methoxy-o-phthalyl alcohol, 28 g. (0.24 mole) of thionyl chloride and 50 ml. of dry benzene was heated at reflux temperature for one hour, then evaporated under reduced pressure. The residue was diluted with 50 ml. of dry benzene and again evaporated.

The residual brown oil was not purified, but was used directly to prepare Compound 4 (Table I).

4,5-Dimethoxy-o-xylene chloride. This intermediate, used to prepare Compound 5 (Table I), was synthesized by the method of Wood and co-workers.¹³

3,4,5,6-Tetrachloro-o-phthalyl alcohol. The addition of a benzene solution of tetrachlorophthalic anhydride to an excess of lithium aluminum hydride in anhydrous ether followed by the usual isolation procedure gave 20 to 26% yields of 3,4,5,6-tetrachloro-o-phthalyl alcohol; m.p. 224-226°, after recrystallization from methanol.

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Anal. Calcd. for C₉H₆Cl₄O₂: C, 34.82; H, 2.19; Cl, 51.40. Found: C, 35.14; H, 2.41; Cl, 50.85.

The same melting point has been reported for this compound prepared by another method.¹⁴

3,4,5,6-Tetrachloro-o-xylene bromide. A mixture of 14 g. (0.051 mole) of 3,4,5,6-tetrachloro-o-phthalyl alcohol and 300 ml. of 65% aqueous hydrobromic acid was stirred for 12 hr. at room temperature, then for 3 hr. at 100°. The material was poured into a mixture of ice and water and the crude solid was separated and air-dried to give 18.3 g. (89%), m.p. 108-114°. An analytical sample recrystallized from isopropyl alcohol melted at 117-118°.

Anal. Calcd. for C₈H₄Br₂Cl₄: C, 23.91; H, 1.00; Halogen, 75.08. Found: C, 24.01; H, 1.24; Halogen, 75.10.

When prepared by bromination of 3,4,5,6-tetrachloro-o-xylene, the reported melting point was 114-117°. ^{14,15}

Hexahydro-o-xylene bromide. A mixture of 13 g. (0.09 mole) of *cis-d*-hexahydrophthalyl alcohol¹⁶ prepared by lithium aluminum hydride reduction of hexahydrophthalic anhydride, and 150 ml. of 65% aqueous hydrobromic acid was stirred overnight at room temperature then for 4 hr. at 90°. The mixture was poured into a slurry of ice and water, and the product was extracted with several portions of ether. After the combined ether extracts were washed with water, solvent was removed and the residue was distilled to give 18.5 g. (76%) of pure product; b.p. 143-146° (14 mm.); *n*_D²⁵, 1.5410.

Anal. Calcd. for C₈H₁₄Br₂: C, 35.58; H, 5.23; Br, 59.19. Found: C, 36.39; H, 5.46; Br, 59.10.

Birch and co-workers¹⁶ prepared this compound in a different manner.

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