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Reduction Products of 2-Pyridylmethylene-1-indanones. Indanols and Indenoindolizines (1)

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Several 2-pyridylmethylene-1-indanones (I) were prepared and reduced to 2-pyridylmethyl-1-indanones (II). The reductive cyclization of 5,6-dimethoxy- and 6-hydroxy-5-methoxy-2-pyridylmethylene-1-indanone gave the corresponding 5a,6,6a,7,8,9,10,11a-octahydroindeno[2,1-b]indolizines (X).

We reported earlier (2,3) the Knoevanagel reaction of 1-indanone with 2- and 3-pyridinecarboxaldehyde and the reduction of the resultant products to the corresponding 2-pyridylmethylene-1-indanones. In a continuation of this work, several substituted 1-indanones were prepared and condensed with 2-, 3-, and 4-pyridinecarboxaldehyde in the presence of piperidine acetate as catalyst. In general, a higher temperature and longer reaction time than those employed with 1-indanone were required. Table I summarizes the data on the 2-pyridylmethylene-1-indanones (I) that were prepared.

The reduction of the exocyclic double bond of several of the 2-pyridylmethylene-1-indanones to yield II was accomplished by hydrogenation of either (a) the base in ethanol with 5% palladium on carbon, or (b) the hydrochloride in aqueous ethanol with 5% palladium on carbon, or (c) the base in acetic acid with 10% palladium on carbon. Table II summarizes the data on the 2-pyridylmethyl-1-indanones (II) that were prepared.

While the conditions employed for the above reductions were by no means the optimum, the following generalization can be made: the reduction of Ia and Ic to IIa and IIc, respectively, occurs readily in ethanol whereas the reduction of the corresponding substituted 1-indanones and the 2-(3-pyridylmethylene)-1-indanones required a longer time or the use of aqueous hydrochloric acid or acetic acid as the solvent.

The addition of a methanol solution of 2-(4-pyridylmethyl)-1-indanone (IIc) to a methanol solution of sodium borohydride gave the corresponding 1-indanol (III). With 5,6-dimethoxy-2-(2-pyridylmethyl)-1-indanone (IIg), however, only the reverse addition of sodium borohydride effected the reduction of the carbonyl group to give IV and then only in a low yield (22% of the methiodide, V). The Raney nickel reduction (55 psi.) of IIg also provided a low yield (12%) of IV.

The reduction of the methiodide (VI) of Ig with platinum oxide provided VII; the sodium borohydride reduction of VII yielded the 1-indanol, VIII, which was identified as its methiodide, IX.

The hydrogenation of Ig and Ij in glacial acetic acid with platinum oxide as catalyst at 50 psi. brought about reductive cyclization to indenoindolizines (X).

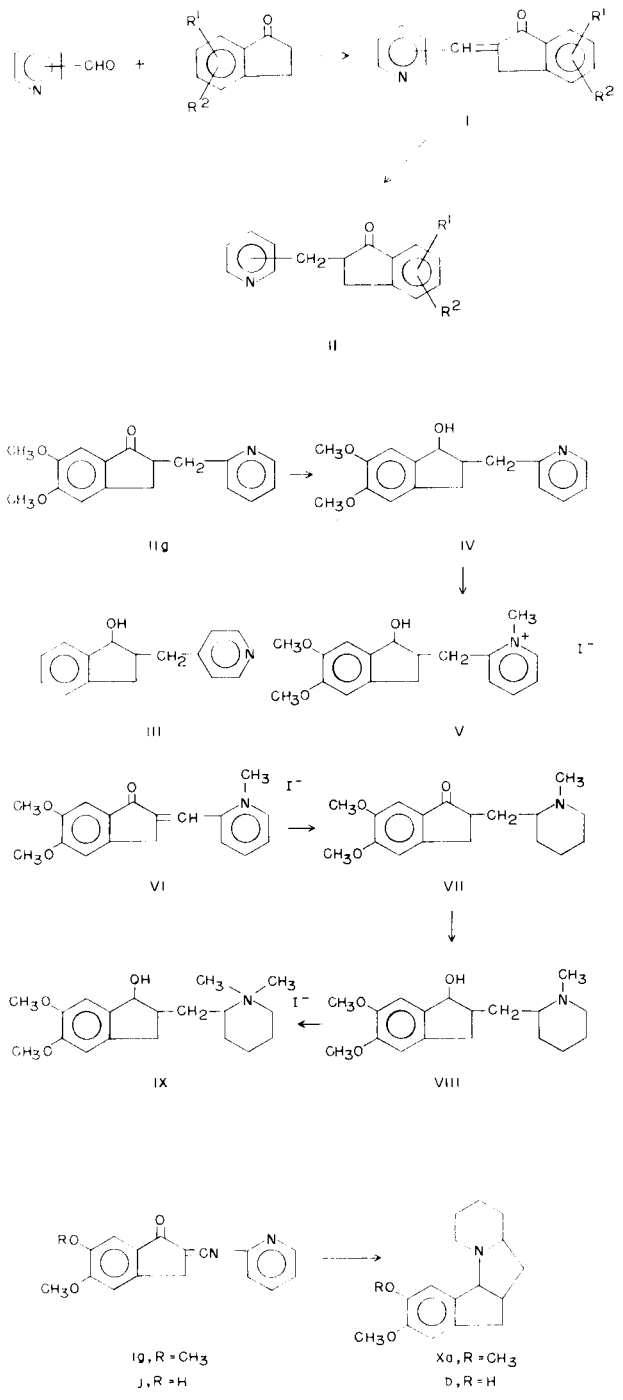
Pharmacological Results (4).

Compounds Ij, Ik, Im, and IIh were investigated in mice for signs of toxicity and for observable pharmacologic effects. The acute intraperitoneal LD_{50}'s were 900.0 and 489.9 mg./kg. for compounds Ik and Im, respectively. Both caused ptosis and slight sedation at high doses and, additionally, signs of analgesia and convulsions in the case of Ik.

No deaths were observed at the highest dose (500 mg./kg.) of Ij, which did, however, produce clonic convulsions after a period of ataxia, depression and tremors. Depression and an inhibition of pain response were noted at 200 mg./kg. With IIh all mice died at 500 mg./kg. after ataxia, tremors, prostration and mild clonic convulsions.

General pharmacodynamic observations in unanesthetized dogs were conducted for compounds Ig, Ij, Xa, and IIg. The former three compounds were found to have no significant effects in the amounts tested for alteration of normal functions and for ability to antagonize epinephrine, acetylcholine and histamine. Compound IIg tended to increase blood pressure and to enhance the blood pressure response to epinephrine at low doses (1-4 mg./kg.). It also slowed respiration, decreased urine flow and increased intestinal tone in the dose range; 8 to 32 mg./kg. caused increasingly the occurrence of cardiac arrhythrmias. Urine flow was halted temporarily at the highest dose.

Compound Xa was tested for ability to antagonize the effect of serotonin on the isolated guinea pig ileum or to antagonize phenothiazine-induced catatonia in rats. The compound was inactive in both tests.



EXPERIMENTAL (5)

Substituted 1-indanones.

5,6-Dimethoxy-1-indanone (6), 5-hydroxy-1-indanone (7), and 6-hydroxy-5-methoxy-1-indanone (7) were prepared as described in the literature from the corresponding dihydrocinnamic acids.

5-Methoxy-1-oxo-6-indanyl isobutyrate. Method A.

A mixture of 18 g. (0.1 mole) of 6-hydroxy-5-methoxy-1-indanone and 21.2 g. (0.2 mole) of isobutyric anhydride was refluxed for 18 hours. The product (14 g., 56%) was isolated in the usual manner, with petroleum ether (30-60°) and recrystallized from aqueous ethanol; m.p. 97°.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.7; H, 6.5. Found: C, 67.9; H, 6.3.

Method B.

A solution of 50 g. (0.28 mole) of 6-hydroxy-5-methoxy-1-indanone in 250 ml. of pyridine cooled to 5°, was treated dropwise with 40 ml. of isobutyryl chloride. Thereafter the mixture was heated on a steam bath for 18 hours. The product was isolated in the usual manner and distilled at 176-178° (0.3 mm.) to give 25 g. (36%) of solid. Recrystallization from aqueous ethanol gave product, m.p. 97°. A mixture melting point with the sample obtained by Method A showed no depression.

2-Pyridylmethylene-1-indanones (I). Table I.

The procedure described by Sam, Plampin and Alwani (2) was followed, using 2.0 g. of piperidine, 2.0 g. of glacial acetic acid, 0.15 mole of the appropriate pyridinecarboxaldehyde and 0.1 mole of the appropriate 1-indanone. The temperature, the time of the reaction, the yield and the recrystallization solvent are given in Table I. In some reactions where crystallization did not occur, the reaction mixture was diluted with water and the solid product removed by filtration and washed with ethanol. The hydrochlorides were prepared from concentrated hydrochloric acid and recrystallized from water or dilute hydrochloric acid.

2-Pyridylmethyl-1-indanones - (II) Table II. Method A.

A solution of 0.04 mole of 2-pyridylmethylene-1-indanone (I) in 80 ml. of absolute ethanol was hydrogenated at approximately 50 psi. at room temperature in the presence of 5% palladium on carbon catalyst. Hydrogenation required 2-10 hours. The catalyst was removed by filtration and the ethanol distilled. The residual material either was distilled or recrystallized from a suitable solvent or converted to a hydrochloride in the usual manner.

Method B.

A solution of 0.02 mole of 2-pyridylmethylene-1-indanone (I) in 50 ml. of water, 3 ml. of concentrated hydrochloric acid (1.18 d), and 50 ml. of methanol was hydrogenated at approximately 50 psi. at room temperature for 2-10 hours in the presence of 5% palladium on carbon catalyst. The product was isolated as described in Method A.

Method C.

The procedure described in Method A was followed except that 160 ml. of glacial acetic acid was used as the solvent and 10% palladium on carbon was used as the catalyst.

2-(4-Pyridylmethyl)-1-indanol (III).

A solution of 1.57 g. (0.007 mole) of 2-(4-pyridylmethyl)-1-indanone (IIc) in 20 ml. of methanol was added to a solution of 2 g. (0.053 mole) of sodium borohydride in 20 ml. of methanol. The mixture was refluxed on a steam bath for 2 hours and then allowed to remain at room temperature for 12 hours. The methanol was distilled and the residue diluted with water. A benzene extract of the resultant mixture was washed with water and dried over anhydrous magnesium sulfate. Distillation of the benzene left 1.2 g. (75%) of product which was recrystallized from a benzene-cyclohexane solution; m.p. 120-121°.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 80.0; H, 6.7; N, 6.2. Found: C, 80.2; H, 6.7; N, 6.3.

5,6-Dimethoxy-2-(2-pyridylmethyl)-1-indanol (IV). Method A.

Fourteen grams (0.05 mole) of 5,6-dimethoxy-2-(2-pyridylmethylene)-1-indanone in 200 ml. of ethanol was reduced in the presence of Raney nickel in the usual manner (50 psi.). After the reduction was complete, the catalyst was removed by filtration, and the solvent was distilled *in vacuo* (water aspirator). The residue was treated with acetone; 5,6-dimethoxy-2-(2-pyridylmethyl)-1-indanone (8 g., 57%) was removed by filtration, m.p. 162°. The filtrate was evaporated to dryness, and the residual oil was converted in the usual manner to a hydrochloride, m.p. 230-240°. Recrystallization from cyclohexanone gave 2.0 g. (12%) of product, m.p. 245° dec. The infrared spectrum showed no absorption at 1700 cm^{-1}.

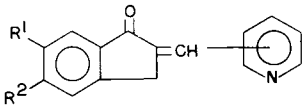
Anal. Calcd. for $C_{17}H_{20}ClNO_3$: C, 65.3; H, 7.9; N, 4.3. Found: C, 65.2; H, 7.7; N, 4.4.

Method B.

A stirred suspension of 6.0 g. (0.021 mole) of 5,6-dimethoxy-2-

TABLE I

2-Pyridylmethylene-1-indanones

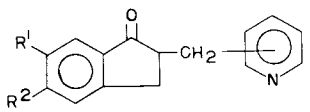


No.	Isomer (a)	R^1	R^2	React. temp., °C	React. time, hrs.	Yield %	M.p., °C	Recryst. Solvent (b)	Molecular Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ia	2	H	H	55-60	0.5	81	154-155 (c)	M	$C_{15}H_{11}NO$						
Ib	3	H	H	60-70	1.0	84	154-155 (d)	E	$C_{15}H_{11}NO$						
Ic	4	H	H	60-70	0.5	55	169-170	M	$C_{15}H_{11}NO$	81.4	5.0	6.3	81.1	5.3	6.3
	4	H	H				196-197	M	$C_{15}H_{13}NO_2$ (e)	75.3	5.5	5.9	75.0	5.4	6.0
Id	2	H	OH	65-70	1.5	41	219-221	H	$C_{15}H_{14}ClNO_3$ (e, f, g)	61.8	4.8	4.8	62.0	4.8	4.6
	2	H	OH				255 dec.		$C_{15}H_{11}NO_2$						
Ie	3	H	OH	135-140	0.5	75	300 dec.	H	$C_{15}H_{12}ClNO_2$ (f, h)	65.8	4.4	5.1	65.7	4.6	5.2
	3	H	OH				280 dec.		$C_{15}H_{11}NO_2$						
If	4	H	OH	135-140	0.5	62	290-293	W	$C_{15}H_{12}ClNO_2$ (f, i)	65.8	4.4	5.1	65.8	4.5	5.1
	4	H	OH				280 dec.		$C_{15}H_{11}NO_2$						
Ig	2	OCH_3	OCH_3	100-110	0.5	67	161-162	B	$C_{17}H_{15}NO_3$	72.6	5.4		72.4	5.5	
VI	2	OCH_3	OCH_3				230 dec.	E	$C_{18}H_{20}INO_4$ (e, j)	49.0	4.6	3.2	49.3	4.8	3.1
Ih	3	OCH_3	OCH_3	110-120	1.5	82	174-175	E	$C_{17}H_{15}NO_3$	72.6	5.4	5.0	72.2	4.9	5.7
Ii	4	OCH_3	OCH_3	110	0.5	55	210-211	E	$C_{17}H_{15}NO_3$	72.6	5.4	5.0	72.1	5.6	5.2
Ij	2	OH	OCH_3	100-110	1.0	50	205	E	$C_{16}H_{13}NO_3$	71.9	4.9		71.2	5.2	
Ik	3	OH	OCH_3	135-140	0.5	63	255 dec.	I	$C_{16}H_{13}NO_3$	71.9	4.9	5.2	71.3	5.0	5.0
Il	4	OH	OCH_3	100-110	0.5	37	245 dec.	I	$C_{16}H_{13}NO_3$	71.9	4.9	5.2	71.4	5.4	5.3
Im	2	$OCOCH(CH_3)_2$	OCH_3	50-60	0.5	59	165-166	E	$C_{20}H_{19}NO_4$	71.2	5.7	4.2	71.2	5.8	3.9

(a) Refers to the position of the substituent in the pyridine ring. (b) B = benzene, E = ethanol, H = dil. hydrochloric acid, I = isoamyl alcohol, M = methanol, W = water. (c) Ref. 2. (d) Ref. 3. (e) Monohydrate. (f) Hydrochloride. (g) Calcd.: Cl, 12.2; Found: Cl, 12.0. (h) Calcd.: Cl, 12.9; Found: Cl, 12.8. (i) Calcd.: Cl, 12.9; Found: Cl, 12.9. (j) Methiodide (prepared according to the procedure described for V).

TABLE II

2-Pyridylmethyl-1-indanones



No.	Isomer (a)	R^1	R^2	Yield %	Method	M.p., °C	Recryst. Solvent (b)	Molecular Formula	Analyses, % Calcd. C	H	Cl	N	Found C	H	Cl	N
IIa	2	H	H	74	A	173-174.5	Cy	$C_{15}H_{14}ClNO$ (c,d)								
IIb	3	H	H	75	C	64-66 (e)	Ac	$C_{15}H_{13}NO$ (c)								
IIc	4	H	H	63	A	63-64 (f)	Cx	$C_{15}H_{13}NO$	80.7	5.9		6.3	80.9	5.9		6.3
IIe	3	H	OH	70	B	212-214	M	$C_{15}H_{14}ClNO_2$ (d)	65.4	5.1	12.9	5.1	65.5	5.1	12.8	5.0
IIf	4	H	OH	65	B	256-258	E	$C_{15}H_{14}ClNO_2$ (d)	65.4	5.1	12.9	5.1	65.3	5.2	12.9	4.9
IIg	2	OCH_3	OCH_3	50	C	162	Ac	$C_{17}H_{17}NO_3$	72.2	6.0			71.8	6.0		
IIh	3	OCH_3	OCH_3	66	C	153-154	Bz	$C_{17}H_{17}NO_3$	72.2	6.0		4.9	72.2	6.2		4.9
IIi	4	OCH_3	OCH_3	32	C	190-191	M	$C_{17}H_{17}NO_3$	72.2	6.0		4.9	72.1	6.0		5.1
	4	OCH_3	OCH_3	88	B	232-234	M	$C_{17}H_{18}ClNO_3$ (d)								
IIj	2	OH	OCH_3	37	C	238-240	M	$C_{17}H_{18}INO_3$ (g)	49.7	4.4		3.4	49.7	4.5		3.2
IIk	3	OH	OCH_3			172-174	W	$C_{16}H_{15}NO_3$	71.4	5.6		5.2	71.0	5.9		5.2
	3	OH	OCH_3	53	B	240-242	M	$C_{16}H_{16}ClNO_3$ (d)	62.8	5.3	11.6	4.6	63.0	5.4	11.6	4.7
IIl	4	OH	OCH_3	15	B	258-260 dec.	M	$C_{16}H_{16}ClNO_3$ (d)	62.8	5.3	11.6	4.6	63.0	5.5	11.3	4.6
IIm	2	$OCOCH(CH_3)_2$	OCH_3	50	C	204-206	Cy	$C_{20}H_{22}ClNO_4$ (d)	63.9	5.9		3.7	63.6	5.9		3.8

(a) Refers to the position of the substituent in the pyridine ring. (b) Ac = acetone, Bz = benzene, Cx = cyclohexane, Cy = cyclohexanone, E = ethanol, M = methanol, W = water. (c) Ref. 3. (d) Hydrochloride. (e) B.p. 164-172° (0.25 mm.). (f) B.p. 164-169° (0.25 mm.). (g) Methiodide (prepared according to the procedure described for V).

(2-pyridylmethyl)-1-indanone (IIg) in 100 ml. of ethanol was treated with 6.0 g. of sodium borohydride in small portions over a 20-25 minute period so that the refluxing was moderate. Thereafter the mixture was refluxed for 2 hours on a steam bath and then allowed to remain at room temperature for 18 hours. The solvent was distilled under reduced pressure and the residue was treated with 200 ml. water and extracted with small portions of ether. The ether extract was dried over anhydrous sodium sulfate and then evaporated to dryness.

The residual oil was dissolved in a minimum amount of N,N-dimethylformamide and refluxed with an excess of methyl iodide for 8 hours. The precipitate was removed by filtration and washed with acetone to give 2 g. (22%) of 2-(5,6-dimethoxy-1-hydroxy-2-indanylmethyl)-1-methylpyridinium iodide (V) melting at 185-186°. The infrared spectrum showed no carbonyl absorption.

Anal. Calcd. for $C_{18}H_{22}INO_3$: C, 50.6; H, 5.2; N, 3.3; I, 29.7. Found: C, 50.8; H, 5.2; N, 3.1; I, 29.3.

2-(5,6-Dimethoxy-1-oxo-2-indanylmethyl)-1-methylpiperidine hydriodide (VII).

A suspension of 21 g. (0.05 mole) of the methiodide of Ig in 200 ml. of water was reduced in the usual manner (50 psi.) in a Parr hydrogenator with platinum oxide as catalyst. The catalyst was removed by filtration and the water was distilled under reduced pressure. The residue was washed with acetone to give a quantitative yield of product, m.p. 253-255°. Recrystallization from aqueous ethanol did not alter the melting point.

Anal. Calcd. for $C_{18}H_{26}INO_3$: C, 50.2; H, 6.1; N, 3.2. Found: C, 50.0; H, 6.2; N, 3.2.

2-(5,6-Dimethoxy-1-hydroxy-2-indanylmethyl)-1,1-dimethylpiperidinium iodide (IX).

To 5 g. (0.0012 mole) of 2-(5,6-dimethoxy-1-oxo-2-indanylmethyl)-1-methylpiperidine hydriodide (VII) suspended in water was added slowly with stirring 5 g. of sodium borohydride in small portions. When the initial heat of the reaction subsided, the mixture was refluxed for 2 hours and then allowed to remain at room temperature for 18 hours. A benzene extract of the resultant mixture was washed with water and dried over anhydrous magnesium sulfate. The benzene extract was treated with an excess of methyl iodide and heated under reflux for 0.5 hour. The methiodide, which formed, was removed by filtration and recrystallized from acetone and then from ethanol to give product melting at 220-221°.

Anal. Calcd. for $C_{19}H_{30}INO_3$: C, 51.0; H, 6.8; N, 3.1; I, 28.4. Found: C, 50.9; H, 6.7; N, 3.0; I, 28.1.

2,3-Dimethoxy-5a,6,6a,7,8,9,10,11a-octahydroindeno[2,1-b]indolizine (Xa).

A solution of 14 g. (0.05 mole) of 5,6-dimethoxy-2-(2-pyridylmethylene)-1-indanone (Ig) in 200 ml. of glacial acetic acid was reduced (50 psi.) in a Parr hydrogenator using platinum oxide catalyst. After the reduction was complete (72 hours), the catalyst was removed by filtration, and the solvent distilled under reduced pressure. The residual liquid was distilled at 236-240° (0.35 mm.) to give 8.0 g. (59%) of product, m.p. 78-80°.

The hydrochloride was prepared in the usual manner and recrystallized from cyclohexanone; m.p. 267-268°.

Anal. Calcd. for $C_{17}H_{24}ClNO_2$: C, 65.9; H, 7.8; N, 4.5. Found: C, 65.2; H, 7.7; N, 4.4.

The picrate was prepared in the usual manner and recrystallized from either cyclohexanone or methyl ethyl ketone; m.p. 239-240° dec.

Anal. Calcd. for $C_{23}H_{26}N_4O_9$: C, 55.0; H, 5.2; N, 11.2. Found: C, 54.7; H, 5.2; N, 11.1.

The methiodide was prepared by refluxing 1 g. of the amine with an excess of methyl iodide in N,N-dimethylformamide for 72 hours. The solid was removed by filtration and washed with boiling tetrahydrofuran; m.p. 221-222°.

Anal. Calcd. for $C_{18}H_{26}INO_2$: C, 52.1; H, 6.3; N, 3.4; I, 30.6. Found: C, 51.7; H, 6.5; N, 3.1; I, 31.2.

2-Hydroxy-2-methoxy-5a,6,6a,7,8,9,10,11a-octahydroindeno[2,1-b]indolizine (Xb).

A solution of 6-hydroxy-5-methoxy-2-(2-pyridylmethylene)-1-indanone (Ij) (27 g., 0.1 mole) in 300 ml. of glacial acetic acid was reduced as described above for the preparation of Xa. After removal of the solvent, the residual material was treated with a saturated aqueous solution of sodium bicarbonate and then filtered. The filtrate was extracted with ether and the ether extract dried over anhydrous sodium sulfate. Distillation of the ether left 9 g. (34%) of a viscous oil. A picrate, prepared in the usual manner and recrystallized from isoamyl alcohol, melted at 245° dec.

Anal. Calcd. for $C_{22}H_{24}N_4O_9$: C, 54.1; H, 5.0. Found: C, 54.1; H, 5.0.

Pharmacological Methods.

Fasted female albino mice (19-28 g.) were used. The animals were observed closely for signs of toxicity and pharmacologic effect during the first 4 post-treatment hours. 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. All compounds were administered intraperitoneally.

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 catherized 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, or intraperitoneally. 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 (1γ/kg.), acetylcholine (10γ/kg.), and histamine (1γ/kg.) were obtained before and after each dose of an experimental compound.

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

(5) Melting points were determined on a Fisher-Johns or Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined in pressed disks of potassium bromide on a Perkin-Elmer Model 137 Infracord Spectrophotometer.

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Received September 13, 1965 University, Mississippi