g. of a white, oily substance distilling at 90–95° (1 mm.), yield 53%.

Anal. Calcd. for $C_7H_{15}NO_3$: C, 65.12; H, 11.63; N, 10.85. Found: C, 65.0; H, 11.7; N, 10.8.

1-(2-Hydroxyethyl)-2-hydroxymethylhexamethyleneimine (XVII).—The same procedure was used as previously described for the preparation of 1-(2-hydroxyethyl)-2-hydroxymethylpiperidine (XII). From 2.9 g. of the amino alcohol XVI in 15 cc. of ethanol, and 1.12 cc. of ethylene oxide (1:1 molar ratio) in 5 cc. of ethanol, 2.9 g. of the diolamine XVII was obtained, distilling at 140–160° (air temperature), 1.0–1.5 mm. The yield was 74%; infrared max.: 2.97–3.02, 3.46, 6.9, 7.1, 7.48–8.03, 8.77 μ.

Anal. Calcd. for $C_9H_{19}NO_2$: C, 62.43; H, 10.98; N, 8.09. Found: C, 62.5; H, 11.1; N, 8.1.

1-(2-Chloroethyl)-2-chloromethylhexamethyleneimine Hydrochloride (X).—To 1.9 g. of the diolamine XVII suspended in 20 cc. of chloroform containing 2 drops of pyridine, 4 cc. of thionyl chloride dissolved in 20 cc. of chloroform was added during a half-hour interval with stirring. The reaction mixture was then heated for 3 hours on a water-bath, with a gradual rise in temperature from 60 to 75°. The chloroform and excess thionyl chloride were evaporated under reduced pressure, benzene was added and distilled leaving a crystalline residue. This residue was dissolved in a few cc. of methanol, filtered and precipitated by addition of ether. Recrystallization from ethyl acetate gave a white crystalline product, m.p. 132–133°, 1.8 g. (67% yield).

Anal. Calcd. for $C_9H_{15}NCl_2 \cdot HCl$: C, 43.81; H, 7.30; N, 5.68. Found: C, 44.3; H, 7.6; N, 5.7.

2,7-Dichloro-*n*-hexyl-2′-chloroethylamine Hydrochloride (XIX).—6-Chloro-1-(chloromethyl)-*n*-hexyl-2′-chloroethylamine hydrochloride (VII) m.p. 85–87°, 1.0 g., in solution in 5 cc. of phosphorus oxychloride was heated under reflux for several hours. Distillation of the residue after removal of the excess phosphorus oxychloride gave a forerun, b.p. 150–160° (0.1 mm.) which solidified in the receiver. Trituration of the crude product with methanol–ether followed by recrystallization from the same solvent mixture gave a white crystalline solid, 0.15 g., 17%, m.p. 164–165°, identical in composition with the starting material VIII.

Anal. Calcd. for $C_9H_{18}N \cdot HCl$: C, 38.2; H, 6.7; N, 4.95; Cl, 50.1. Found: C, 38.4; H, 7.0; N, 5.3; Cl, 49.3.

Acknowledgment.—We are indebted to Dr. Schimon Schichor for carrying out the toxicity studies and to Mr. Charles Chapman for technical assistance.

[CONTRIBUTION FROM MCNEIL LABORATORIES, INC.]

Hypotensive Basic Ethers in the Indan Series[1]

BY JOSEPH SAM[2] AND JAMES N. PLAMPIN

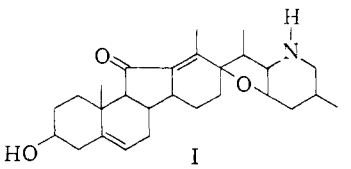
RECEIVED MARCH 3, 1960

The preparation of a number of aminoalkyl ethers of substituted indanones and derivatives is described.

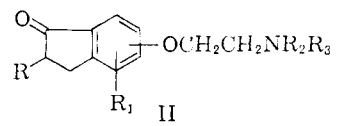
The efficacy of the veratrum ester alkaloids in producing a decrease in blood pressure is well known. Their usefulness in the treatment of hypertension, however, is limited by their manifestation of undesirable side effects.[3] The present investigation was carried out to ascertain whether less complex compounds structurally related to the characteristic veratrum nucleus would have comparable hypotensive properties with diminished side effects.

Of the many veratrum alkaloids which have been isolated, jervine (I) is unique in having a hydrogenated indanone system as part of its structure.[4] The relation of the structures of jervine and (2-aminoethoxy) indanones (II) may be seen by comparison of the formulas. Although jervine has little of the hypotensive activity characteristic of the veratrum ester alkaloids, *e.g.*, protoveratrine, it is interesting that compounds of structure II do possess hypotensive activity characteristic of the ester alkaloids.[5]

The general method of preparation of the basic ethers involved synthesis of the proper hydroxyindanone by cyclization of the appropriate hydrocinnamic acid followed by etherification with a di-

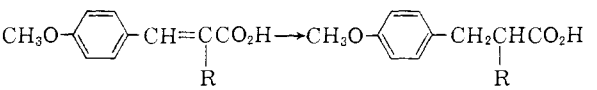


I



II

alkylaminoalkyl chloride. The hydrocinnamic acids (IV) were prepared by several methods which involved either: (1) catalytic reduction of the corresponding cinnamic acids[6] (III), (2) condensation of *p*-methoxybenzyl chloride with substituted malonates[7,8] or (3) condensation of *p*-methoxy-



IIIa, R = H
b, R = CH_3
c, R = C_2H_5
d, R = C_6H_5

IVa, R = H
b, R = CH_3
c, R = C_2H_5
d, R = C_6H_5

benzyl chloride with ethyl α-ethoxalylpropionate. It has been observed in this Laboratory as well as

(1) Presented before the Division of Medicinal Chemistry at the 125th Meeting of the American Chemical Society, Kansas City, Mo., March 27, 1954.

(2) University of Mississippi, University, Mississippi.

(3) O. Krayer and G. Acheson, *Physiol. Rev.*, **26**, 383 (1946).

(4) (a) D. H. R. Barton, O. Jeger, V. Prelog and R. B. Woodward, *Experientia*, **10**, 81 (1954); (b) W. A. Jacobs and S. W. Pelletier, *J. Org. Chem.*, **18**, 765 (1953); (c) B. M. Iselin and O. Wintersteiner, THIS JOURNAL, **77**, 5318 (1955).

(5) D. F. Marsh, *Federation Proc.*, **13**, 384 (1954).

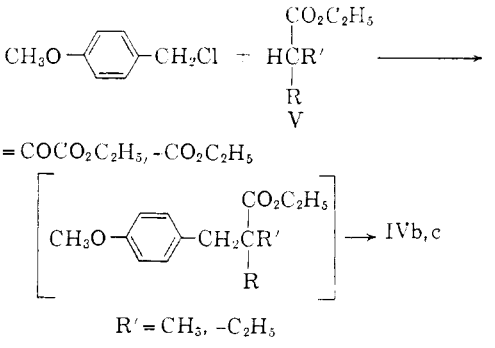
(6) (a) W. S. Johnson and W. E. Shelberg, THIS JOURNAL, **67**, 1853 (1945); (b) E. H. Woodruff and T. W. Conger, *ibid.*, **60**, 465 (1938); (c) D. Papa, H. F. Ginsberg, I. Lederman and V. deCamp, *ibid.*, **75**, 1107 (1953); (d) D. S. Morris, *J. Chem. Soc.*, 1913 (1950).

(7) P. Cagniant, *Bull. soc. chim. France*, **9**, 884 (1942).

(8) G. Levy, *Ann. chim. (Paris)*, **9**, 5 (1938).

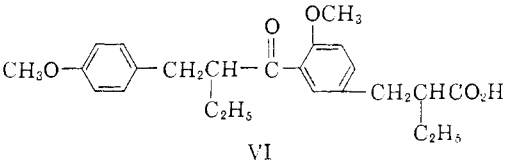
by others[9] that the reduction of *p*-methoxycinnamic acid (IIIa) with Adams catalyst proceeds rapidly with the uptake of 4 moles of hydrogen. Interruption of the hydrogenation after the absorption of 1 mole of hydrogen resulted in a product which was difficult to purify. This problem was eliminated by the application of palladium-on-carbon which catalyzed the uptake of only 1 mole of hydrogen and resulted in a product easily purified.

The reaction of *p*-methoxybenzyl chloride with diethyl methyl- or ethylmalonate and ethyl α-ethoxalylpropionate (V, R = $COCO_2C_2H_5$, R′ = CH_3) may be carried out without isolation of the intermediate products. With diethyl methyl- or ethylmalonate, hydrolysis and decarboxylation were accomplished essentially in one step, and a good yield (70–80%) of the substituted hydrocinnamic acids (IVb and c) was obtained. The use of ethyl α-ethoxalylpropionate, which involved decarbonylation, hydrolysis and decarboxylation, gave a considerably lower yield (31%).



Cyclization of the appropriately substituted acids to the corresponding indanones was accomplished using anhydrous hydrogen fluoride[6a,9] or polyphosphoric acid[10]; or the acid chlorides were converted to the indanones *via* the Friedel–Crafts reaction[6a] (Table I). Yields in the cyclization of *p*-methoxyhydrocinnamic acid to 6-methoxy-1-indanone using the Friedel–Crafts method were much lower than those described in the literature.[6a] In contrast to these results, the yields obtained in the preparation of 6-methoxy-2-methyl-1-indanone using an identical method were generally good. Satisfactory results also were obtained by the polyphosphoric acid cyclization of *p*-methoxy-α-methyl- and α-ethyl-*p*-methoxyhydrocinnamic acids to the corresponding indanones, whereas *p*-methoxyhydrocinnamic acid and *p*-methoxy-α-phenylhydrocinnamic acid gave poor or negative results.

Isolation of by-products in the cyclizations, with one exception, was not attempted. The polyphosphoric acid cyclization of α-ethyl-*p*-methoxyhydrocinnamic acid yielded, in addition to 6-methoxy-2-ethyl-1-indanone, a high boiling base-soluble substance which, on the basis of analysis, infrared and neutralization equivalent, and demethylation to the diphenolic derivative, has been assigned structure VI.



VI

Demethylation of the substituted methoxyindanones was effected with anhydrous aluminum bromide since the relatively low temperature at which demethylation occurred favored the use of this agent. It was found that yields were excellent in every case (Table II). The reduction of 6-hydroxy-2-methyl-1-indanone to 2-methyl-5-indanol was accomplished using the Clemmensen, Wolff–Kishner and catalytic methods.

The syntheses of the basic ethers described in Table III are covered in the Experimental section. It is interesting to note that the base-catalyzed condensation of 2-methyl-6-hydroxy-1-indanone with dimethylaminoethyl chloride hydrochloride or aminoethyl bromide hydrobromide under aqueous conditions failed to yield the appropriate basic ether. The latter compound also failed to give a basic ether under anhydrous conditions.

TABLE I

SUBSTITUTED 1-INDANONES

Substituents	Condensing agent[a]	Temp., °C.	Reaction time, hr.	Yield,[b] %
6-OCH_3[c]	$AlCl_3$			31
	PPA	75	2	4.5
6-OCH_3-2-CH_3[d]	$AlCl_3$			60–66
	PPA	75	2	17–47
6-OCH_3-2-C_2H_5[e]	PPA	75	1	58–62
6-OCH_3-2-C_6H_5[f]	HF			0
	$AlCl_3$			42–49
	PPA	60	1	0
	PPA	90–95	5	0
6-OH-5-OCH_3[g]	HF			61
5-OH[g]	HF			68
	PPA	60	0.5	22
	PPA	90–95	0.25	13.5
4-OCH_3-7-CH_3[h]	$AlCl_3$			99[i]

[a] Where $AlCl_3$ was used, the procedure described in ref. 6a was followed; see Experimental for polyphosphoric acid (PPA) method. [b] The yield is based on purified product except where noted. [c] Ref. 6a. [d] Previously described by J. M. van der Zanden and G. de Vries, *Rec. trav. chim.*, 68, 407 (1949). [e] See Experimental. [f] Recrystallized from benzene, m.p. 145–146°. *Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.6; H, 5.9. Found: C, 80.6; H, 6.3. [g] Ref. 9. [h] Ref. 7. [i] Crude product, m.p. 77–82°.

(9) R. V. Heinzelmann, H. G. Kolloff and J. H. Hunter, THIS JOURNAL, **70**, 1386 (1948).

Experimental[11]

Substituted Hydrocinnamic Acids.—The preparations of the requisite hydrocinnamic acids were accomplished using the procedures described below.

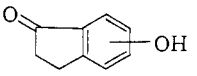
***p*-Methoxy-α-methylhydrocinnamic Acid. Method A.**—A modification of the general method of Levy[8] for the preparation of α-ethyl-*p*-methoxyhydrocinnamic acid was followed. To a solution of 157 g. (0.9 mole) of diethyl methylmalonate in ethanolic sodium ethoxide, prepared from 20.1 g. (0.88 g. atm.) of sodium and 400 ml. of absolute ethanol, was added gradually with stirring 136 g. (0.88 mole) of *p*-methoxybenzyl chloride and the resulting mixture heated on a steam-bath for 5 hours. A solution of 200 g. (3.7 moles) of potassium hydroxide in 250 ml. of water was added and the mixture refluxed for 15 hours. Most of the solvent was distilled *in vacuo*, an additional 500 cc. of water added, the

(10) H. R. Snyder and F. X. Werber, *ibid.*, **72**, 2965 (1950).

(11) All melting points and boiling points are uncorrected. Infrared spectra were determined with a Baird double beam infrared recording spectrophotometer using potassium bromide pellets.

TABLE II

HYDROXY-1-INDANONES

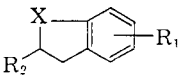


Substituents	Yield,[a] %	Recrystallization solvent	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
6-OH[b]	82	Methanol	151–153	$C_9H_8O_2$				
2-CH_3-6-OH	88	MeOH–water	107–108	$C_{10}H_{10}O_2$	74.1	74.5	6.2	6.3
2-C_2H_5-6-OH	90	MeOH–water	111.5–112.5	$C_{11}H_{12}O_2$	75.0	74.9	6.9	6.7
2-C_6H_5-6-OH	90	Benzene	171–172	$C_{15}H_{12}O_2$	80.3	80.6	5.4	5.7
7-CH_3-4-OH	52[c]	Benzene	196.5–197	$C_{10}H_{10}O_2$	74.1	74.3	6.2	6.3

[a] Yields are based on recrystallized product. [b] Previously described by C. K. Ingold and H. A. Piggott, *J. Chem. Soc.*, 1469 (1923). [c] Difficulties were encountered in isolation due to insolubility of product in aqueous sodium hydroxide.

TABLE III

SUBSTITUTED ETHERS OF INDANONES, INDANOLS AND INDANS



R_1	R_2	X	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
6-$(C_2H_5)_2NCH_2CH_2O$	H	C=O	183–184[a]	$C_{15}H_{22}ClNO_2$	63.5	63.9	7.8	8.0	4.9	4.9
6-$(CH_3)_2NCH_2CH_2O$	H	C=O	210–211[a]	$C_{13}H_{18}ClNO_2$	61.1	61.0	7.0	7.1	5.5	5.4
6-$(C_2H_5)_2NCH_2CH_2O$	CH_3	C=O	177–179[a]	$C_{16}H_{24}ClNO_2$	64.5	64.6	8.1	8.0	4.7	4.5
6-$(CH_3)_2NCH_2CH_2O$	CH_3	C=O	199–201[a]	$C_{14}H_{20}ClNO_2$	62.3	62.3	7.5	7.5	5.2	5.2
6-($C_7H_{14}NO$)[b]	CH_3	C=O	199–201[a]	$C_{17}H_{24}ClNO_2$	65.9	65.7	7.9	7.8	4.5	4.6
6-($C_7H_{14}NO$)[b]	H	C=O	198–200[a]	$C_{16}H_{22}ClNO_2$	65.0	65.0	7.4	7.5	4.7	4.5
6-$(CH_3)_3\overset{+}{N}CH_2CH_2O$, $\bar{I}$	CH_3	C=O	200–202	$C_{15}H_{22}INO_2$	48.0	48.3	5.9	6.0	3.7	3.5
6-$(CH_3)_2NCH_2CH_2O$	CH_3	CHOH	142–143[a]	$C_{14}H_{22}ClNO_2$	61.9	62.1	8.2	8.1	5.2	5.2
6-$(CH_3)_2NCH_2CH_2O$	CH_3	CHOR[c]	174–175[a]	$C_{18}H_{28}ClNO_3$	63.3	63.2	8.2	8.2	4.1	4.2
6-$(CH_3)_2NCH_2CH_2O$	CH_3	CHOR[d]	[e]	$C_{21}H_{25}NO_3$	74.3	73.8	7.4	7.3	4.1	4.3
4-CH_3-7-$(Et)_2NCH_2CH_2O$	H	C=O	224–226[a]	$C_{16}H_{24}ClNO_2$	64.5	64.7	8.1	7.9	4.7	4.8
6-$(CH_3)_2NCH_2CH_2O$	C_2H_5	C=O	169–170[a]	$C_{15}H_{22}ClNO_2$	63.5	63.6	7.8	7.8	4.9	5.0
5-OCH_3-6-$(Et)_2NCH_2CH_2O$	H	C=O	172–173[a]	$C_{16}H_{24}ClNO_3$	61.2	61.3	7.7	7.8	4.5	4.5
5-$(CH_3)_2NCH_2CH_2O$	H	C=O	210–211[a]	$C_{13}H_{18}ClNO_2$	61.1	61.1	7.1	6.9	5.5	5.4
6-$(CH_3)_2NCH_2CH_2O$	Br	C=O	182–183[f]	$C_{13}H_{17}Br_2NO_2$	41.2	41.0	4.5	4.5	3.7	3.8
5-$(CH_3)_2NCH_2CH_2O$	CH_3	CH_2	160.5[a]	$C_{14}H_{22}ClNO$	65.7	66.0	8.7	8.5	5.5	5.3
6-$(CH_3)_2NCH_2CH(CH_3)O$	CH_3	C=O	208–210[a]	$C_{15}H_{22}ClNO_2$	63.5	63.6	7.8	8.0	4.9	5.1
6-$C_2H_5NHCH_2CH_2O$	CH_3	C=O	217.5–219[a]	$C_{14}H_{20}ClNO_2$	62.3	62.3	7.5	7.6	5.2	5.4
6-$(C_2H_5)_2NCH_2CH_2O$	C_6H_5	C=O	237–239[g]	$C_{31}H_{31}N_3O_{10}S$	58.4	58.2	4.9	4.8	6.6	6.5
5-$(C_2H_5)_2NCH_2CH_2OCH_2$	H	CH_2	[h]	$C_{16}H_{25}NO$	77.7	77.4	10.2	10.2	5.7	5.6
6-$BrCH_2CH_2O$	CH_3	C=O	71–72	$C_{12}H_{13}BrO_2$	53.6	53.7	4.9	4.9	..	..
6-$H_2NCH_2CH_2O$	CH_3	C=O	163–165[i]	$C_{16}H_{19}NO_6$	59.8	59.8	6.0	6.0	4.4	4.3
6-($C_{10}H_8NO_3$)[j]	CH_3	C=O	149–150	$C_{20}H_{17}NO_4$	71.6	71.9	5.1	5.2	4.2	4.1
7-CH_3-4-$(Et)_2NCH_2CH_2O$	H	C=O	177.5–179[a]	$C_{16}H_{24}ClNO_2$	64.5	64.5	8.1	8.2	4.7	4.7

[a] Hydrochloride. [b] 1-Ethyl-3-piperidyloxy. [c] R = $(CH_3)_2CHCO$. [d] R = C_6H_5CO. [e] Isolated as the base, b.p. 195–199° (0.4 mm.). [f] Hydrobromide. [g] Flavianate. [h] Isolated as the base, b.p. 108° (0.2 mm.) [i] Maleate. [j] 2-Phthalimidoethoxy.

solution cooled, neutralized with concentrated hydrochloric acid and extracted with ether. Evaporation of the ether left a brown oil which was distilled under reduced pressure. The rate of heating was regulated in order to maintain a pressure less than 100 mm. during the evolution of carbon dioxide. When decomposition was complete (about 3 hours), the residue was distilled to yield 122 g. (73%) of *p*-methoxy-α-methylhydrocinnamic acid,[6b] b.p. 140–145° (0.7 mm.).

Method B.—A solution of 38.4 g. (0.2 mole) of *p*-methoxy-α-methylcinnamic acid[6b] in 200 ml. of glacial acetic acid was hydrogenated at 4 atm. in the presence of 0.5 g. of 10% Pd–C catalyst. The reduction stopped after absorption of 0.2 mole of hydrogen. Isolation of the product in the usual way gave 35 g. (90%) of distillate, b.p. 138–143° (0.4–0.5 mm.).

Method C.—To a solution of 10.8 g. (0.2 mole) of sodium methoxide and 40.4 g. (0.2 mole) of ethyl α-ethoxyalylpropionate in 150 ml. of methanol was added gradually with stirring 31.2 g. (0.2 mole) of *p*-methoxybenzyl chloride. The mixture was heated on a water-bath for 4 hours. Most of the solvent was distilled *in vacuo* and water added to the residue. The oily layer was extracted with ether, the ether evaporated and the residue distilled. The oil distilled with evolution of carbon monoxide giving 27 g. of distillate, b.p. 178–180° (2 mm.). The resulting distillate was hydrolyzed and decarboxylated as described in method A to give 12 g. (31%) of product, b.p. 143–150° (0.8 mm.).

Cyclization of Hydrocinnamic Acids with Polyphosphoric Acid (PPA).—The general method of Snyder and Werber[10] as illustrated in the example below was employed for the preparation of the indanones listed in Table I.

2-Ethyl-6-methoxy-1-indanone.—To 630 g. of PPA (Victor Chemical Corp.), pre-heated to 75°, was added gradually with stirring 100 g. (0.5 mole) of α-ethyl-*p*-methoxyhydrocinnamic acid and the resulting mixture stirred at this temperature for 1 hour. The mixture while hot was poured into 500 cc. of water. The oily layer was extracted with ether and the ether extract washed with water, aqueous potassium carbonate and water, respectively. After drying over anhydrous potassium carbonate, the ether was evaporated leaving 53 g. (58%) of product which was

recrystallized from petroleum ether (b.p. 30–60°), m.p. 43–45°.

The 2,4-dinitrophenylhydrazone was prepared in the usual way and recrystallized from ethyl acetate, m.p. 205–207°.

Anal. Calcd. for $C_{18}H_{18}N_4O_5$: C, 58.4; H, 4.9; N, 15.1. Found: C, 58.2; H, 4.7; N, 15.1.

The aqueous potassium carbonate solution obtained above was neutralized with dilute hydrochloric acid and extracted with ether. Evaporation of the ether and distillation of the residue gave 25 g. of **α-ethyl-3-(α-ethyl-4-methoxyhydrocinnamoyl-4-methoxyhydrocinnamic acid**, b.p. 250° (0.6 mm.), $n^{26.50}D$ 1.5531. The infrared spectrum showed maxima at 5.9, 5.97 and 8.02 μ, characteristic of the carbonyl, carboxyl and ether groups.

Anal. Calcd. for $C_{24}H_{30}O_5$: C, 72.3; H, 7.6; neut equiv., 389. Found: C, 72.5; H, 7.6; neut. equiv., 400.

Demethylation by refluxing with stirring for 4 hours a mixture of 10 g. of 3-(*p*-methoxy-α-ethylhydrocinnamoyl)-4-methoxy-α-ethylhydrocinnamic acid, 30 g. of aluminum bromide and 200 ml. of benzene followed by work-up in the usual way gave 8.5 g. of **3-(*p*-hydroxy-α-ethylhydrocinnamoyl)-4-hydroxy-α-ethylhydrocinnamic acid**, b.p. 250° (0.1 mm.).

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.3; H, 7.1. Found: C, 71.2; H, 7.3.

Substituted Hydroxyindanones.—The indanones listed in Table II were prepared according to the procedure illustrated by the following example:

6-Hydroxy-2-methyl-1-indanone.—A solution of 58 g. (0.33 mole) of 6-methoxy-2-methyl-1-indanone in 200 ml. of dry thiophene-free benzene was added gradually to a well stirred mixture of 225 g. (0.84 mole) of anhydrous aluminum bromide[12] and 800 ml. of dry thiophene-free benzene. The mixture was refluxed 3 hours, cooled and decomposed by pouring cautiously into a mixture of ice and concentrated hydrochloric acid. The benzene layer was separated and extracted with 10% sodium hydroxide solution. The basic solution was cooled and neutralized with concentrated hydrochloric acid. The solid (50 g., 94%) was removed by filtration and recrystallized from a mixture of methanol and water to give 39 g. (73%) of product, m.p. 107–108°.

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.1; H, 6.2. Found: C, 74.5; H, 6.3.

The 2,4-dinitrophenylhydrazone was prepared in the usual way and recrystallized from ethyl acetate, m.p. 235–236°.

Anal. Calcd. for $C_{16}H_{14}N_4O_5$: N, 16.4. Found: N, 16.2.

7-Hydroxy-4-methyl-1-indanone.—The general method of Auwers[13] was followed. To 60 g. (0.45 mole) of aluminum chloride, preheated to 165° in an oil-bath, was added gradually with stirring 53 g. (0.22 mole) of *p*-tolyl β-bromopropionate. The mixture was heated at 165–175° for 4 hours. During the heating period, the mixture gradually thickened to a solid mass. After cooling, the solid was chipped from the reaction flask and treated with dilute hydrochloric acid. The gummy residue was extracted with several portions of benzene and dried over anhydrous sodium sulfate. Evaporation of the benzene left a brown solid which resisted recrystallization. Steam distillation of the residue gave 12 g. (34%) of product which was recrystallized from petroleum ether (b.p. 30–60°), m.p. 111–112°.

2-Methyl-5-indanol. Method D.—Reduction of a solution of 16.2 g. of 6-hydroxy-2-methyl-1-indanone in glacial acetic acid in the presence of 10% Pd–C catalyst gave 4.2 g. of product, b.p. 95° (0.8 mm.), and 9 g. of starting material. Crystallization of the product from petroleum ether (b.p. 30–60°) gave needles melting at 65°.

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.0; H, 8.2. Found: C, 81.2; H, 8.4.

Reduction of a suspension of 1-indanone in water in a similar way gave indan, b.p. 177–178°.

Method E.—The modified Wolff–Kishner procedure described by Huang-Minlon[14] for the reduction of ketones was employed. From 10 g. (0.06 mole) of 6-hydroxy-2-methyl-1-indanone, 8.3 g. (0.21 mole) of hydrazine hydrate, 85 ml. of triethylene glycol and 11.8 g. (0.21 mole) of potassium hydroxide was obtained 4 g. (44%) of 2-methyl-5-indanol, b.p. 80–83° (0.2 mm.). The product solidified on cooling and was recrystallized from petroleum ether (b.p. 30–60°), m.p. 65–66°. A mixed melting point with the product obtained by the catalytic method showed no depression.

Method F.—The Clemmensen procedure described by Fieser and Seligman[15] for the preparation of 4-chloro-7-methylindan was followed. From 10 g. of 6-hydroxy-2-methyl-1-indanone was obtained 3.2 g. of product, b.p. 110° (1 mm.), m.p. 65–67°. A mixed melting point with the products obtained above showed no depression.

Preparation of Basic Ethers Listed in Table III.—The methods described below for the preparation of 6-(β-dimethylaminoethoxy)-2-methyl-1-indanone (method G) and 6-(β-diethylaminoethoxy)-5-methoxy-1-indanone (method H) are illustrative of the procedures used for the preparation of the basic ethers listed in Table III.

6-(β-Dimethylaminoethoxy)-2-methyl-1-indanone. Method G.—To a solution of 11.1 g. (0.2 mole) of sodium methoxide and 32.4 g. (0.2 mole) of 6-hydroxy-2-methyl-1-indanone in 200 ml. of methanol was added gradually with stirring a solution of β-dimethylaminoethyl chloride[16] in 300 ml. of benzene and the resulting solution was refluxed with stirring for 7 hours. The solvent was distilled *in vacuo*, 200 ml. of water added to the residue and the oily layer extracted with ether. Evaporation of the ether and distillation of the residue gave 30 g. (65%) of product, b.p. 143–146° (0.6 mm.), $n^{22}D$ 1.5435.

The hydrochloride was prepared in the usual way and recrystallized from a mixture of methanol and methyl ethyl ketone, m.p. 199–201°.

Anal. Calcd. for $C_{14}H_{20}ClNO_2$: C, 62.3; H, 7.5; N, 5.2. Found: C, 62.3; H, 7.5; N, 5.2.

Reaction of 6-(β-dimethylaminoethoxy)-2-methyl-1-indanone with methyl iodide in the usual manner gave **2-(2-methyl-1-oxo-6-indanoxy)-ethyltrimethylammonium iodide** which was crystallized from isoamyl alcohol, m.p. 200–202°.

Anal. Calcd. for $C_{15}H_{22}INO_2$: C, 48.0; H, 5.9; N, 3.7. Found: C, 48.3; H, 6.0; N, 3.5.

6-(β-Diethylaminoethoxy)-5-methoxy-1-indanone. Method H.—A solution containing 17.8 g. (0.1 mole) of 6-hydroxy-5-methoxy-1-indanone, 19 g. (0.11 mole) of diethylaminoethyl chloride hydrochloride, 9 g. (0.22 mole) of sodium hydroxide, 150 ml. of methanol and 100 ml. of water was refluxed for 66 hours. The methanol was distilled *in vacuo* and the residue extracted with ether. Evaporation of the ether and distillation of the residue gave 12 g. (43%) of product, b.p. 181° (0.6 mm.), $n^{23.5}D$ 1.5547.

Anal. Calcd. for $C_{16}H_{23}NO_3$: N, 5.1. Found: N, 5.1.

The hydrochloride was prepared in the usual way and recrystallized from methyl ethyl ketone containing a small amount of methanol, m.p. 172–173°.

Anal. Calcd. for $C_{16}H_{24}ClNO_3$: C, 61.2; H, 7.7; N, 4.5. Found: C, 61.3; H, 7.8; N, 4.5.

5-(β-Dimethylaminoethoxy)-2-methylindan.—Reduction of a solution of 28 g. (0.12 mole) of 6-(β-dimethylaminoethoxy)-2-methyl-1-indanone in 200 ml. of 7% hydrochloric acid in the presence of 10% Pd–C catalyst at 4 atm. gave 20 g. of product, b.p. 106–110° (0.4 mm).

The hydrochloride was prepared in the usual way and recrystallized from methyl ethyl ketone, m.p. 160–162°.

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.7; H, 8.7; N, 5.5. Found: C, 66.0; H, 8.5; N, 5.3.

A mixed melting point with the product obtained by the reaction of 2-methyl-5-indanol with β-dimethylaminoethyl chloride, method G for preparation of basic ethers, showed no depression.

6-(β-Dimethylaminoethoxy)-2-methyl-1-indanol. Method I.—Reduction of a solution of 27 g. (0.1 mole) of 6-(β-dimethylaminoethoxy)-2-methyl-1-indanone

(12) A commercial grade of aluminum bromide (Michigan Chemical Corp.) gives sufficiently good results to warrant its use.

(13) K. Auwers, *Ber.*, **44**, 3695 (1911).

(14) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

(15) L. F. Fieser and A. M. Seligman, *ibid.*, **58**, 2482 (1936).

(16) The β-dimethylaminoethyl chloride was prepared by neutralizing 40 g. (0.28 mole) of the hydrochloride with concentrated sodium hydroxide, extracting with benzene and drying over anhydrous potassium carbonate.

hydrochloride in 100 ml. of water using 10% Pd–C catalyst gave 16 g. of **6-(β-dimethylaminoethoxy)-2-methyl-1-indanol hydrochloride**, m.p. 142–143°.

Anal. Calcd. for $C_{14}H_{22}ClNO_2$: C, 61.9; H, 8.2; N, 5.2. Found: C, 62.1; H, 8.1; N, 5.2.

Neutralization of the hydrochloride with 10% sodium hydroxide solution and extraction with ether gave the base which was recrystallized from petroleum ether (b.p. 30–60°), m.p. 75–76°.

Anal. Calcd. for $C_{14}H_{21}NO_2$: N, 6.0. Found: N, 6.1.

The isobutyrate hydrochloride was prepared from 6-(β-dimethylaminoethoxy)-2-methyl-1-indanol and isobutyryl chloride in the usual manner and recrystallized from methyl ethyl ketone, m.p. 174–175°.

Anal. Calcd. for $C_{18}H_{28}ClNO_3$: C, 63.3; H, 8.2; N, 4.1. Found: C, 63.2; H, 8.2; N, 4.2.

Method J.—The procedure described by Nystrom and Brown[17] for the lithium aluminum hydride reduction of ketones was employed. From 22 g. (0.09 mole) of 6-(β-dimethylaminoethoxy)-2-methyl-1-indanone and 1.8 g. (0.5 mole) of lithium aluminum hydride was obtained 21 g. of oil (by extraction with isoamyl alcohol and subsequent evaporation) which solidified on cooling, m.p. 78–80°. Recrystallization from petroleum ether (b.p. 30–60°) gave product, m.p. 79.5–80.5°. A mixed melting point with the indanol obtained by catalytic reduction showed no depression.

5-(β-Diethylaminoethoxymethyl)-indan.—To a solution of 5.4 g. (0.1 mole) of sodium methoxide in 23.4 g. (0.2 mole) of freshly distilled β-diethylaminoethanol was added gradually 16.7 g. (0.1 mole) of 5-chloromethylindan.[18] The reaction was exothermic and required cooling. The resulting mixture was heated on a water-bath for 4 hours with occasional shaking, cooled, treated with water and extracted with ether. Evaporation of the ether and distillation of the residue gave 10 g. (40%) of product, b.p. 108° (0.2 mm.), $n^{30}D$ 1.5091.

Anal. Calcd. for $C_{16}H_{25}NO$: C, 77.7; H, 10.2; N, 5.7. Found: C, 77.4; H, 10.2; N, 5.6.

6-(β-Bromoethoxy)-2-methyl-1-indanone.—A solution of 22 g. (0.14 mole) of 6-hydroxy-2-methyl-1-indanone and 10 g. (0.19 mole) of potassium hydroxide in 125 ml. of methanol was added gradually over a 0.5-hour period to 101 g. (0.54 mole) of boiling ethylene bromide. The mixture was refluxed 7 hours, cooled and diluted with water. The oil was extracted with chloroform and washed with 5% sodium hydroxide solution and water, respectively. After drying over anhydrous sodium sulfate, the chloroform was evaporated and the residue (19 g., 52%) distilled at 140–142° (0.2 mm.). Recrystallization of the product from petroleum ether (b.p. 30–60°) gave product, m.p. 71–72°.

Anal. Calcd. for $C_{12}H_{13}BrO_2$: C, 53.6; H, 4.9; Br, 29.7. Found: C, 53.7; H, 4.9; Br, 29.9.

6-(β-Ethylaminoethoxy)-2-methyl-1-indanone.—A mixture of 13.5 g. (0.05 mole) of 6-(β-bromoethoxy)-2-methyl-1-indanone, 100 ml. of methanol and 60 ml. of 70% aqueous ethylamine (0.93 mole) was heated at 100–125° for 19 hours. The solvent was distilled *in vacuo* and the residue neutralized with 10% sodium hydroxide solution. The resulting mixture was extracted with ether and the product was separated from 6-(β-bromoethoxy)-2-methyl-1-indanone by extracting the ether solution with dilute hydrochloric acid. The acid solution was neutralized with solid potassium carbonate and extracted with ether. Evaporation of the ether and distillation of the residue gave 6 g. (51%) of product, b.p. 150° (0.5 mm.).

Anal. Calcd. for $C_{14}H_{19}NO_2$: N, 6.0. Found: N, 6.2.

N-[2-(1-Oxo-2-methyl-6-indanoxy)-ethyl]-phthalimide.—A mixture of 13.5 g. (0.05 mole) of 6-(β-bromoethoxy)-2-methyl-1-indanone, 9.3 g. (0.05 mole) of potassium phthalimide and 200 ml. of *n*-butyl alcohol was refluxed 18 hours. On cooling the clear alcoholic solution, a white solid precipitated. Removal of the solid (16 g.) by filtration and recrystallization from methanol gave product, m.p. 149–150°.

Anal. Calcd. for $C_{20}H_{17}NO_4$: C, 71.6; H, 5.1; N, 4.2. Found: C, 71.9; H, 5.2; N, 4.1.

6-(β-Aminoethoxy)-2-methyl-1-indanone.—To a suspension of 11 g. (0.03 mole) of N-[2-(1-oxo-2-methyl-6-indanoxy)-ethyl]-phthalimide in 150 ml. of methanol was added 1.7 g. (0.03 mole) of hydrazine hydrate and the mixture heated in a water-bath for 0.5 hour. The resulting solution was cooled, treated with 20 ml. of concentrated hydrochloric acid and heated on a water-bath for 15 minutes. The solid phthalyl hydrazide was removed by filtration and the filtrate concentrated *in vacuo*. The residue was neutralized with 10% sodium hydroxide solution, extracted with ether and dried over anhydrous potassium carbonate. Evaporation of the ether gave 4.5 g. of an oil. A hydrochloride was prepared, m.p. 215–217°, but was difficult to crystallize. Treatment of a solution of the above oil in ether with an ethereal solution of maleic acid gave **6-(β-aminoethoxy)-2-methyl-1-indanone maleate**, which was recrystallized from methyl ethyl ketone, m.p. 163–165°.

Anal. Calcd. for $C_{16}H_{19}NO_6$: C, 59.8; H, 6.0; N, 4.4. Found: C, 59.8; H, 6.0; N, 4.3.

2-Bromo-6-(β-dimethylaminoethoxy)-1-indanone Hydrobromide.—The procedure employed by Wilds[19] for the preparation of 2-bromo-1-keto-1,2,3,4-tetrahydrophenanthrene was followed. To a solution of 4.7 g. (0.02 mole) of 6-(β-dimethylaminoethoxy)-1-indanone in 200 ml. of ether and 200 ml. of methanol was added, dropwise with stirring, 1.5 ml. (0.03 mole) of bromine. The mixture was stirred for 2 hours and then allowed to stand overnight at room temperature. Evaporation of the solvent and recrystallization of the residue from a mixture of methanol and methyl ethyl ketone gave 1.5 g. of product, m.p. 182–183°.

Anal. Calcd. for $C_{13}H_{17}Br_2NO_2$: C, 41.2; H, 4.5; N, 3.7. Found: C, 41.0; H, 4.5; N, 3.8.

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(17) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 1197 (1947).

(18) R. T. Arnold, *ibid.*, **61**, 1405 (1939 .

19) A. L. Wilds, *ibid.*, **64**, 1421 (1942).