

ml. of ice-water containing 1.5 ml. of sulfuric acid, and the ether layer was separated, washed with water and dried over magnesium sulfate. Evaporation of the ether followed by sublimation of the residue at 120°(0.05 mm.) gave 1.30 g. (78%) of white crystals, m.p. 139–140.5°; $\lambda_{\text{max}}^{\text{EtOH}}$ 275, 282 μ ; $\log \epsilon$ 3.38, 3.33.

Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{O}_2$: C, 78.0; H, 9.0. Found: C, 78.3; H, 9.3.

trans-1-Methyl-4-(α -hydroxy- α -methylethyl)-5-(*o*-hydroxyphenyl)-1-cyclohexene (XX) was prepared in 81% yield by the method described above, starting with the *trans*-lactone XVIII. The product was obtained as white crystals, m.p. 137.5–138°. A mixture of this material and the corresponding *cis* isomer above (m.p. 139–140.5°) melted at 112–126°; $\lambda_{\text{max}}^{\text{EtOH}}$ 276, 283 μ ; $\log \epsilon$ 3.42, 3.36.

Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{O}_2$: C, 78.0; H, 9.0. Found: C, 77.95; H, 9.0.

cis-6,6,9-Trimethyl-6a,7,10,10a-tetrahydrodibenzopyran (XXI).—A mixture of 2.33 g. of *cis*-1-methyl-4-(α -hydroxy- α -methylethyl)-5-(*o*-hydroxyphenyl)-1-cyclohexene, 20 ml. of toluene and 0.05 g. of *p*-toluenesulfonic acid was heated under reflux for 2.5 hours. During this time the color of

the reaction mixture changed from pink to dark yellow. The cooled reaction mixture was diluted with 100 ml. of ether and the solution washed twice with 100-ml. portions of 10% potassium carbonate and 3 times with water. The organic layer was dried and evaporated to give a residual oil which was rapidly distilled at a pot temperature of 175° and under 0.5 mm. pressure to give 1.29 g. (60%) of a clear liquid; $\lambda_{\text{max}}^{\text{EtOH}}$ 268, 275, 284, 306 μ ; $\log \epsilon$ 3.49, 3.48, 3.39, 3.20. The ultraviolet data indicate that this product is not homogeneous. It appears to consist largely of XXI, along with isomeric material probably arising from double bond migration, although not to a position conjugated with the aromatic ring.

Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{O}$: C, 84.2; H, 8.8. Found: C, 83.9; H, 8.7.

trans-6,6,9-Trimethyl-6a,7,10,10a-tetrahydrodibenzopyran (XXII) was prepared in 75% yield from the *trans*-diol XX by the method described above. The product was obtained in the form of white crystals, m.p. 63.3–64.3° upon recrystallization from methanol; $\lambda_{\text{max}}^{\text{EtOH}}$ 276, 284 μ ; $\log \epsilon$ 3.42, 3.40.

Anal. Calcd. for $\text{C}_{16}\text{H}_{20}\text{O}$: C, 84.2; H, 8.8. Found: C, 84.2; H, 8.9.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BRANDEIS UNIVERSITY, WALTHAM 54, MASS.]

Synthesis of Cyclized Derivatives of New Secondary Nitrogen Mustards Relationship of Structure to Toxicity^{1a,b}

BY ORRIE M. FRIEDMAN, HAROLD SOMMER AND ELIAHU BOGER

RECEIVED MARCH 2, 1960

Two new cyclic mustards 1-(2'-chloroethyl)-2-chloromethylpiperidine and 1-(2'-chloroethyl)-2-chloromethylhexamethylenimine have been synthesized. The former was also formed when the acyclic secondary nitrogen mustard, 5-chloro-1-(chloromethyl-*n*-pentyl)-2-chloroethylamine hydrochloride, was heated in phosphorus oxychloride. On similar treatment the homologous acyclic mustard did not give the latter but simply gave a rearranged product, presumably 2,7-dichloro-*n*-hexyl-2'-chloroethylamine hydrochloride. The piperidine mustard was highly toxic in mice whereas the hexamethylenimine mustard was less so [1.4 and 0.3 times, respectively, as methyl-bis-(β -chloroethyl)-amine].

In previous publications^{2a,b} we have described the preparation of a new type of secondary amino nitrogen mustards that transformed spontaneously by intramolecular cyclization to tertiary nitrogen mustards *in vivo*. These new mustards were expected to be substantially more cytotoxic than the usual secondary nitrogen mustards and, in fact, have been found to be so.³ These mustards were developed for the synthesis of derivatives with greater selectivity in their toxicity for tumor cells than the nitrogen mustards are generally known to have. Thus nitrogen mustards detoxified by N-phosphorylation,^{1,2,4a,b} N-acylation⁵ and possibly

by other forms of N-substitution that might be reactivated by removal of the blocking group more or less selectively in tumor cells^{6a,b} are potentially even more effective chemotherapeutic agents than are the parent mustards.

It is of incidental interest that the cyclizeable nitrogen mustards IV, VII and VIII (*vide infra*) have shown significant anti-tumor activity in a variety of experimental tumors in animals.⁷ One of the factors that may contribute to their activity is the "time-fuse" mechanism imposed on their action by the time required for activation by cyclization after administration. This may allow these compounds time to reach cancer cells remote from the site of injection in active form.

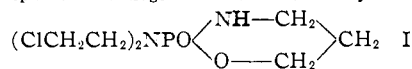
From a comparison of the acute toxicity (as measured by LD₅₀ in mice) of these cyclizeable nitrogen mustards with that of the cyclic analogs into which they are presumed to transform *in vivo* certain inferences as to their mode of action can be drawn. From previous results,⁸ for example, it appeared that the difference in toxicity between the acyclic trichloroamines II and IV was probably related to the difference in amounts of cyclized com-

(1)(a) This investigation was supported by a research grant (No. CY2130) from the National Institutes of Health, U. S. Public Health Service; (b) presented at the American Chemical Society Meeting, Cleveland, April, 1960.

(2) (a) O. M. Friedman and E. Boger, *THIS JOURNAL*, **78**, 4659 (1956); (b) O. M. Friedman and A. M. Seligman, *ibid.*, **76**, 658 (1954).

(3) A. M. Rutenburg, L. Persky, O. M. Friedman and A. M. Seligman, *J. Pharm. Exp. Therap.*, **3**, 483 (1954).

(4) (a) O. M. Friedman and A. M. Seligman, *THIS JOURNAL*, **76**, 655 (1954). (b) Recently the cyclic phosphorodiamidate I, a "transport" form of nor-HN2 which is presumably transformed to the "active" form at the site of action has shown a high therapeutic index against experimental tumors in animals and has given positive results against some forms of human cancer [R. Gross and K. Lambers, *Naturwiss.*, **45**, 66 (1958)]; for a recent review see also *Cancer Chemotherapy Reports*, June, 1959, CCNSC, U. S. Public Health Service]. We have prepared the analogous derivatives of the cyclizable nitrogen



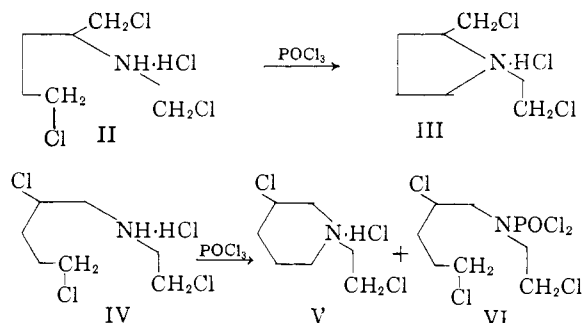
mustards IV, VII and VIII which will be reported elsewhere.

(5) O. M. Friedman and R. Chatterji, *THIS JOURNAL*, **81**, 3750 (1959).

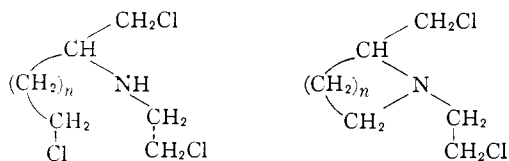
(6) (a) E. Boger and O. M. Friedman, *ibid.*, **80**, 2583 (1958); (b) A. M. Seligman, M. M. Nachlas, L. H. Mannheimer, O. M. Friedman and G. Wolf, *Ann. Surg.*, **130**, 333 (1949).

(7) Unpublished results from the Childrens Cancer Research Foundation, Boston, Mass., and the CCNSC Screening Program, N.I.H., U. S. Public Health Service.

pounds III and V, respectively, that had formed, with the implication that toxicity of these cyclizable mustards depends to some significant extent on the rate of cyclization *in vivo*.³ This idea was supported by the fact that *in vitro* the more toxic of the acyclic amines II was transformed essentially quantitatively to the cyclic form III on treatment with phosphorus oxychloride. Under the same conditions the less toxic isomer IV gave a small amount of the cyclized product V and a good yield of the dichlorophosphamide VI.^{2b}

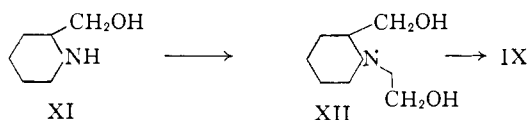


On the basis of preliminary toxicity data, however, the two higher homologs of II, 5-chloro-1-(chloromethyl)-*n*-pentyl-2-chloroethylamine (VII)^{2a} and 6-chloro-1-(chloromethyl)-*n*-hexyl-2-chloroethylamine (VIII),^{2a} appeared to behave anomalously in that VII which would be expected on chemical grounds to cyclize much more rapidly than VIII was the less toxic of the two. Although this anomaly was not confirmed by later toxicity data, discussed below, it was apparent that comparison of the toxicity of these two cyclizable amines VII and VIII with that of the cyclic derivatives IX and X into which they are presumed to transform *in vivo* would probably help clarify the relationship of structure to toxicity in this series. We report here the syntheses of these two new cyclic nitrogen mustards IX and X.



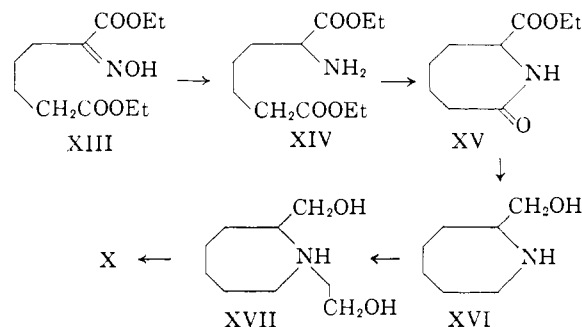
VII, $n = 3$ VIII, $n = 4$ IX, $n = 3$ X, $n = 4$

The former IX was prepared in good over-all yield from the known 2-hydroxymethylpiperidine (XI).⁸ Condensation of the piperidylcarbinol XI with ethylene oxide afforded the diolamine XII which was converted to the cyclic nitrogen mustard IX as the hydrochloride with thionyl chloride.



The latter X was prepared from ethyl 2-oximino-pimelate (XIII),⁹ catalytically reduced with platinum to the corresponding aminopimelate XIV

which gave the carbethoxylactam XV on pyrolysis. Reduction of XV with lithium aluminum hydride afforded 2-hydroxymethyl-hexamethyleneimine (XVI) which was converted successively to the diolamine XVII and then to the cyclic mustard XI by treatment with ethylene oxide and thionyl chloride.



Recent toxicity data based on LD₅₀ in mice which will be reported in detail elsewhere indicated that the piperidine mustard IX had a very high toxicity (1.4 times that of HN2); and that the seven-membered ring homolog X was less so but still quite toxic at about the same level as the piperidine mustard V (*i.e.*, about 30% as toxic as HN2). The acyclic precursors VII and VIII, on the other hand, were much less toxic (4.0 and 2.5%, respectively, as toxic as methyl-bis-(β -chloroethyl)-amine, HN2).

The relatively low toxicity of the acyclic mustard VII is perhaps not surprising despite its high toxicity in the cyclized form IX by analogy with the behavior of the acyclic mustard IV. Both compounds VII and IV cyclize to six-membered ring structures and presumably do so at comparable rates. This rate, moreover, is apparently small compared to that at which the ethyleneimine rings in these structures form and undergo hydrolysis. The small difference in toxicity that does exist between the acyclic compounds VII and IV would derive, under these circumstances, from the difference in toxicity of whatever small amounts of the cyclized derivatives IX and V, respectively, that are produced.

The implication that the rates of cyclization of VII and IV are comparable is again consistent with the *in vitro* results. On treatment with phosphorus oxychloride VII transformed to the cyclized form IX to about the same small extent as did IV to the corresponding cyclic product V when similarly treated.

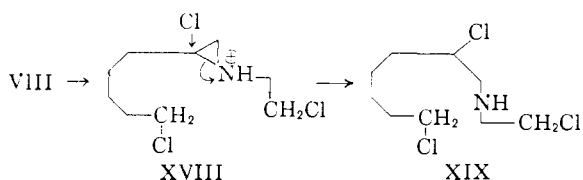
This interpretation implies, however, that the homologous acyclic amine VIII which is only slightly less toxic than VII cyclizes to the seven-membered ring mustard X at a rate that must be similar to that for the cyclization of VII to IX. This implied similarity contrasts with the known ease of formation of piperidine from 5-chloropentylamine¹⁰ as compared to the sluggish formation of hexamethyleneimine from the corresponding 6-bromohexylamine.¹¹ Moreover, on treatment with phosphorus oxychloride this higher homolog VIII has not given detectable amounts of the cyclized prod-

(8) F. F. Blicke and Chi Yung Lu, *THIS JOURNAL*, **77**, 29 (1955).
(9) W. Dieckmann, *Ber.*, **33**, 593 (1900).

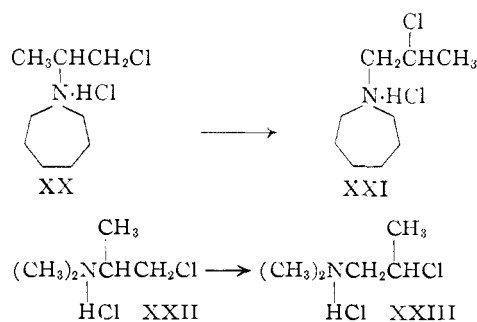
(10) S. Gabriel, *ibid.*, **25**, 421 (1892).

(11) A. Miller and P. Krauss, *Monatsh.*, **61**, 219 (1932).

uct X although a small amount of isomeric compound to which we have tentatively assigned the structure XIX was produced. It is possible, nonetheless, that sufficient of the cyclic mustard X may be produced *in vivo* to account for the toxicity of VIII.



The toxicity of XIX is about the same order as that of nor-HN2, which is consistent with the above assignment of structure since cyclization to an eight-membered ring is not apt to take place readily and the compound should behave as an alkylating agent *in vivo* essentially like a simple secondary nitrogen mustard. This isomer XIX would be formed by a rearrangement resulting from attack of chloride ion on the methine carbon atom in the ethylene immonium intermediate XVIII in the manner indicated. This isomerization is reminiscent of the reported rearrangements of 2-methyl-2-(1-hexamethyleneimino)-ethyl chloride (XX) to methyl-2-(1-hexamethyleneimino)-ethyl chloride (XXI)¹² and 2-dimethylamino-2-chloropropane (XXII) to 1-dimethylamino-2-chloropropane, (XXIII)¹³ when these two materials XX and XXII were heated above their melting points. The authors^{12,13} represent these transformations as



proceeding by way of ethylene immonium ion intermediates analogous to XVIII.

It is curious, however, that the three cyclic homologs: the pyrrolidine mustard III, the piperidine mustard IX and the hexamethyleneimine mustard X, structurally so similar, should differ so widely in toxicity (62, 140 and 25%, respectively, as toxic as HN2). These compounds would be expected to have the same order of activity as alkylating agents, a factor which will be evaluated by comparison of their hydrolytic behavior, although this is probably not the only feature that determines toxicity *in vivo*.

Experimental¹⁴

1-(2-Hydroxyethyl)-2-hydroxymethylpiperidine (XII).—To 5 g. of 2-hydroxymethylpiperidine (XI),⁸ dissolved in 20 cc. of ethanol, 2.2 cc. of ethylene oxide in 20 cc. of ethanol

was added, after both solutions were cooled in an ice-salt mixture. The mixture was kept in the refrigerator for 3 days and after standing for 1 day at room temperature the alcohol was evaporated under reduced pressure. The residue, a white oily liquid, was distilled under reduced pressure and the fraction distilling between 130–140° (1.0–1.5 mm.) was collected; 5.5 g. (80% yield) was obtained.

Anal. Calcd. for: C₈H₁₇NO₂: C, 60.38; H, 10.70; N, 8.80. Found: C, 60.3; H, 10.9; N, 8.7.

1-(2-Chloroethyl)-2-chloromethylpiperidine Hydrochloride, (IX). (a) From XII.—Thionyl chloride, 10 cc., dissolved in 50 cc. of chloroform was gradually added during a half-hour interval at room temperature to 4.9 g. of 1-(2-hydroxyethyl)-2-hydroxymethylpiperidine, (XII) in 50 cc. of chloroform containing a few drops of pyridine. The reaction mixture was then heated on a water-bath for 4 hours, starting at 50° and gradually raising the temperature to 70°. After the solvent was evaporated under reduced pressure, benzene was added and evaporated to eliminate traces of thionyl chloride. The residue became crystalline on cooling. The crystalline product was dissolved in a small volume of methanol, filtered and precipitated by addition of ether. Crystallization from ethyl acetate gave a pure white crystalline product melting at 135–136°, yield 4.7 g. (66%).

Anal. Calcd. for C₈H₁₆NCl₂: C, 41.29; H, 6.88; N, 6.02. Found: C, 41.0; H, 7.0; N, 6.1.

(b) From VII.—The same compound IX was also obtained as a by-product when 5-chloro-1-(chloromethyl-*n*-pentyl)-2-chloroethylamine hydrochloride (VII) was phosphorylated with phosphorus oxychloride.^{2a} The trichloroamine VII, 0.9 g., and 5 cc. of phosphorus oxychloride were heated for 20 hours under reflux. The excess phosphorus oxychloride was distilled and the residue fractionated at reduced pressure. A fore-run distilling at 133–140° (0.1 mm.) solidified in the condenser and was collected. Recrystallization from ethyl acetate gave 0.15 g., m.p. 135–136° (18% yield). A mixture with the product IX above melted at the same temperature.

Diethyl α -Aminopimelate (XIV).—Ethyl-2-oximinopimelate,⁹ 60 g., was dissolved in 120 cc. of absolute alcohol and dry hydrochloric acid gas was passed through the solution. Platinum oxide, 3 g., was added and the mixture was hydrogenated under pressure of 30–35 lb. per sq. in. After the absorption of hydrogen ceased, the platinum was filtered and the ethanolic filtrate evaporated in the absence of moisture. The residue was taken up in 250 cc. of chloroform and shaken with 50 g. of sodium bicarbonate dissolved in 500 cc. of water. After separation, the aqueous layer was extracted twice more with 200-cc. portions of chloroform. The chloroform layers were combined and dried over sodium sulfate. Evaporation of the chloroform yielded 48 g. of a viscous oily product (85% yield). This material was crystallized as the dibasic oxalate by addition of an ethanol solution of 0.46 g. of oxalic acid to 0.6 g. of the amine in ethanol. The resulting precipitate was recrystallized from ethylene glycol monoethyl ether as a white crystalline solid, m.p. 136–137°. Infrared max.: 3.42, 5.79, 6.09, 6.82, 7.27, 7.7, 8.84–8.55, 9.13, 9.8, 11.15 μ .

Anal. Calcd. for C₁₁H₂₁NO₅· $\frac{1}{2}$ C₂H₄O₂: C, 52.17; H, 7.97; N, 5.07. Found: C, 52.3; H, 8.0; N, 5.0.

2-Hydroxymethylhexamethyleneimine (XVI).—The oily diethyl- α -aminopimelate (XIV) 48 g., obtained above, was heated on an oil-bath for 6 hours at 190°. The pyrolyzed product, the carbethoxylactam XVI was twice distilled in a short path distillation apparatus employing a series of glass bulbs heated in an air-bath. The fraction distilling between 150–160° (air temperature in the oven), 1–2 mm., was collected. The yield was 9.2 g. (24%). Infrared max.: 2.98, 3.45, 5.78, 6.04, 6.85, 7.18, 7.3, 7.71, 8.45–8.52, 9.15–9.22, 9.82, 11.05 μ .

To 5 g. of lithium aluminum hydride dissolved in 150 cc. of dry ether 9.2 g. of the lactam XVI in 60 cc. of ether was gradually added and the mixture refluxed for 3 hours. After decomposition of the excess lithium aluminum hydride by careful introduction of water, the precipitate was filtered, twice extracted with 100-cc. portions of ethanol and the alcoholic extracts added to the ether filtrate. The solvents were evaporated under diminished pressure leaving an oily, viscous residue. Vacuum distillation yielded 3.4

(12) F. F. Blicke and N. J. Doorebas, *THIS JOURNAL*, **76**, 2318 (1954).

(13) E. M. Schulz and J. M. Sprague, *ibid.*, **70**, 48 (1948).

(14) Microanalyses were performed by Dr. Carol K. Fitz, Needham Heights, Mass. Melting and boiling points are uncorrected.

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 $C_9H_{18}NCl_2 \cdot HCl$: 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 fore-run, 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 Series¹

BY JOSEPH SAM² AND JAMES N. PLAMPIN

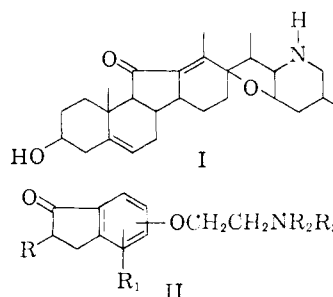
RECEIVED MARCH 3, 1960

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

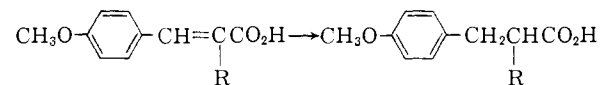
The efficacy of the veratrum ester alkaloids in producing a decrease in blood pressure is well known. Their usefulness in the treatment of hypertension, however, is limited by their manifestation of undesirable side effects.³ The present investigation was carried out to ascertain whether less complex 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-



alkylaminoalkyl chloride. The hydrocinnamic acids (IV) were prepared by several methods which involved either: (1) catalytic reduction of the corresponding cinnamic acids⁶ (III), (2) condensation of *p*-methoxybenzyl chloride with substituted malonates^{7,8} or (3) condensation of *p*-methoxy-



IIIa, R = H
b, R = CH₃
c, R = C₂H₅
d, R = C₆H₅

IVa, R = H
b, R = CH₃
c, R = C₂H₅
d, R = C₆H₅

benzyl chloride with ethyl α -ethoxypropionate. 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).