was dissolved in 300 cc. of absolute alcohol. The flask was placed in a water-bath at room temperature and dry urea (24.0 g., 0.4 mole) was added with stirring. After the urea was almost all dissolved, α-ethyl-α-carbethoxy-γ-phenyl-γ-butyrolactone (31.4 g., 0.12 mole) was added dropwise over a period of two hours. Stirring was continued for several more hours and the alcohol was distilled under reduced pressure (20–25 mm.) at a temperature not over 40°. Approximately 300 cc. of water was added and the solution extracted with three 50-cc. portions of chloroform. The aqueous solution was then immersed in an ice-bath and made acid to congo red with dilute hydrochloric acid (1:3). The crude barbituric acid was triturated with a small amount of ether to remove oily impurities; yield 26.5 g. The acid purified by recrystallization from dioxane–water or by solution in ether and subsequent concentration under reduced pressure melted at 214°. The procedure was the one essentially used in the preparation of the barbituric acids listed in Table III.

Method B.—5-Ethylbarbituric acid (15.6 g., 0.1 mole) was dissolved in a solution of 5.6 g. of potassium hydroxide in 80 cc. of water. The acidity of the resulting clear solution was adjusted with dilute hydrochloric acid until neutral to litmus, and styrene oxide (12.0 g., 0.1 mole) was added. The mixture was stirred at room temperature for forty-eight hours. The water solution was separated from the remaining styrene oxide and extracted with ether. Upon acidification of the solution of the sodium salt with concentrated hydrochloric acid, a sticky, viscous mass formed; the clear, supernatant solution was decanted immediately and cooled for several hours in the refrigerator. One recrystallization from water yielded 2.6 g. of a compound melting at 212–213° (cor.). No depression was observed in a mixed melting point with the barbituric acid obtained by Method A; the infrared spectra were identical.

Acknowledgment.—We are indebted to the Research Corporation for a grant supporting this work. We also wish to thank Prof. C. A. Vander Werf of the University of Kansas for his interest in this investigation and also the Pittsburgh Plate Glass Corp. for a generous gift of butadiene monoxide.

Summary

A series of α-carbethoxy-γ-phenyl- and vinyl-γ-butyrolactones has been made and used subsequently for the preparation of 5-alkyl-5-(β-phenyl- and vinyl-β-hydroxyethyl)-barbituric acids.

5-Ethyl-5(β-phenyl-β-hydroxyethyl)-barbituric acid has been alternately synthesized by a new reaction, the condensation of styrene oxide with 5-ethylbarbituric acid.

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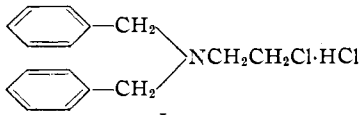
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY AND KALAMAZOO COLLEGE]

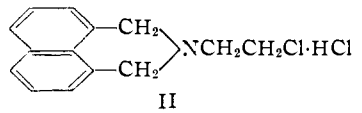
N-(β-Chloroethyl)-2,3-dihydro-1-benz[de]isoquinoline Hydrochloride

BY WILLIAM L. GARBRECHT,[1] JAMES H. HUNTER AND JOHN B. WRIGHT

In view of the strong adrenolytic activity reported by numerous investigators[2] for β-chloroethyldibenzylamine hydrochloride (I) and related compounds it appeared of interest to investigate a compound in which the two phenyl rings were



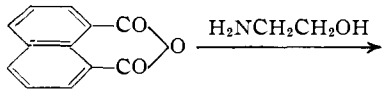
I

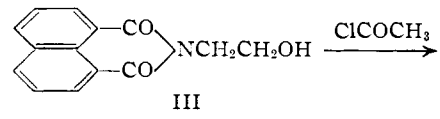


II

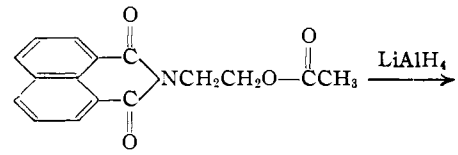
fused in a naphthalene ring. Accordingly, N-(β-chloroethyl)-2,3-dihydro-1-benz[de]isoquinoline hydrochloride[3] (II) has been synthesized and screened for adrenolytic activity.

The preparation of II was carried out according to the scheme

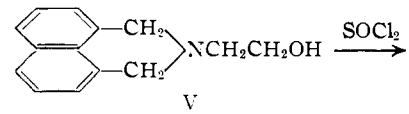




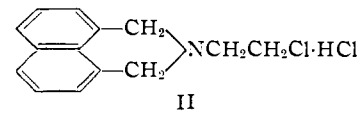
III



IV



V



II

N-(β-Hydroxyethyl)-naphthalimide (III) was prepared by the reaction between naphthalic anhydride and ethanolamine.[4] The direct reduction of III with lithium aluminum hydride in ether solution was found to be unfeasible due to the extreme insolubility of the compound in ether. After several unsuccessful attempts[5] to reduce III to

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(2) *Cf.* Nickerson, *J. Pharmacol. Exptl. Therap.*, **95** (Part II), 27 (1949).

(3) This compound has been named according to the nomenclature given for the parent ring system in "The Ring Index," Patterson and Capell, Reinhold Publishing Corp., New York, N. Y., 1940, p. 268.

(4) Fierz-David and Rossi, *Helv. Chim. Acta*, **21**, 1477 (1938).

(5) The use of tetrahydrofuran, in which the compound was somewhat soluble, as a solvent medium in the reaction gave negative results as only a tarry material was isolated from the reaction mixture.

V directly with this reagent, the alcohol (III) was converted to its acetate (IV) with acetyl chloride and the latter reduced with lithium aluminum hydride in ether solution to 2,3-dihydro-1-benz[de]-isoquinoline-2-ethanol (V)[6] which was converted to its chloro derivative by treatment with thionyl chloride.

Preliminary pharmacological results[7] indicate that II is practically devoid of any adrenolytic activity. Of interest in this regard is the fact that the structure of II, as indicated by studies with Fisher–Hirschfelder models, is such that the nitrogen atom is held rigidly out of the plane of the naphthalene ring, whereas in β-chloroethyldibenzylamine hydrochloride (I) the nitrogen atom may become coplanar with the phenyl rings by rotation about carbon–carbon single bonds. It would seem reasonable to expect, therefore, that the conjugated intermediate,[8] which has been postulated as a possible pharmacologically active intermediate, would be less likely to form in II than in I.

Experimental[9,10]

N-(β-Hydroxyethyl)-naphthalimide (III) was prepared according to the method of Fierz-David and Rossi,[4] and was recrystallized from 3-A[11] alcohol.

N-(β-Acetoxyethyl)-naphthalimide (IV).—A mixture of 40.7 g. (0.17 mole) of N-(β-hydroxyethyl)-naphthalimide and 143 ml. of acetyl chloride was refluxed and stirred for three and one-half hours. The excess acetyl chloride was distilled from the reaction mixture and the last traces decomposed by the cautious addition of water. The reaction mixture was neutralized with aqueous sodium bicarbonate. The brown precipitate was recrystallized from alcohol after treatment with decolorizing charcoal; yield 36.5 g. (76.0%) of colorless needles, m. p. 139.5–140.5°.

Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.83; H, 4.62; N, 4.95. Found: C, 67.71; H, 4.50; N, 4.92.

2,3-Dihydro-1-benz[de]isoquinoline-2-ethanol.—Anhydrous ether (500 ml.) and 8.1 g. (0.21 mole) of lithium aluminum hydride were stirred and refluxed for two hours. The reflux condenser was then replaced by a Soxhlet extraction apparatus with 20.0 g. (0.07 mole) of N-(β-acetoxyethyl)-naphthalimide in the extraction thimble and the ethereal solution refluxed for twenty hours. The excess hydride was then decomposed by the cautious addition of water, the mixture acidified with concentrated sulfuric acid, the layers separated and the aqueous layer poured into 1 l. of 10 *N* sodium hydroxide solution. The resulting mixture was extracted repeatedly with benzene, the extracts dried over anhydrous magnesium sulfate, and the solvent removed under reduced pressure to yield a brown sirup which resisted all attempts at crystallization. This sirup was dissolved in 250 ml. of anhydrous ether, and the hydrochloride prepared by the addition of an ethereal hydrogen chloride solution; yield 11.2 g. (68.5%), m. p. 199–200°. Recrystallization from an absolute alcohol–ethyl acetate mixture gave yellow needles possessing the same melting point.

Anal. Calcd. for $C_{14}H_{15}NO\cdot HCl$: C, 67.39; H, 6.47; Cl, 14.20. Found: C, 67.53; H, 6.39; Cl, 14.33.

Five grams of the hydrochloride salt was dissolved in water and neutralized with an aqueous sodium carbonate solution. The resulting oil crystallized on scratching; yield 4.7 g. (99%), m. p. 53–56°. After recrystallization from petroleum ether (Skellysolve "B"), the yellow needles, which seemed to be a monohydrate, melted at 56°.

Anal. Calcd. for $C_{14}H_{15}NO\cdot H_2O$: C, 72.69; H, 7.41; N, 6.06. Found: C, 73.23; H, 7.31; N, 6.14.

N-(β-Chloroethyl)-2,3-dihydro-1-benz[de]isoquinoline Hydrochloride.—To a solution of 4.0 g. (0.02 mole) of 2,3-dihydro-1-benz[de]isoquinoline-2-ethanol in 30 ml. of dry benzene, cooled in an ice-bath, was added, dropwise, a solution of 3 ml. (approximately 0.04 mole) of thionyl chloride in 15 ml. of benzene. The mixture was refluxed for one and one-half hours, cooled and the precipitate recrystallized from absolute ethanol. The pale yellow microcrystals (3.0 g., 61.2%) melted above 300°.

Anal. Calcd. for $C_{14}H_{14}NCl\cdot HCl$: C, 62.70; H, 5.64; N, 5.22; Cl, 26.44. Found: C, 62.74; H, 5.67; N, 5.43; Cl, 26.30.

Summary

1. The synthesis of N-(β-chloroethyl)-2,3-dihydro-1-benz[de]isoquinoline hydrochloride, a fused-ring analog of the active adrenolytic, β-chloroethyldibenzylamine hydrochloride, is described.

2. Preliminary pharmacological results indicate that this compound possesses practically no adrenolytic activity.

KALAMAZOO, MICHIGAN RECEIVED SEPTEMBER 10, 1949

(6) The acetyl group of IV was at the same time reduced to ethyl alcohol which was removed in the working-up process.

(7) For conducting these tests, grateful acknowledgment is made to Dr. Milton J. Vander Brook of the Department of Pharmacology and Endocrinology.

(8) Nickerson, *J. Pharmacol. Exptl. Therap.*, **95** (Part II), 40 (1949).

(9) All melting points and boiling points are uncorrected.

(10) Appreciation is expressed to Mr. Harold Emerson and his staff for analyses reported.

(11) Commercially available denatured ethanol containing 5% methanol.