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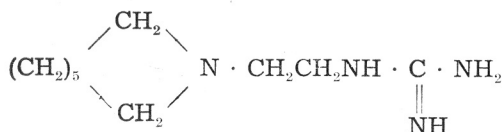
Note on the Synthesis of [2-(Octahydro-1-azocinyl) ethyl] Guanidine Sulfate*

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Received March 17, 1964

A series of *N,N*-alkylenimino-alkylguanidine compounds which have been investigated for their antihypertensive properties showed a particular characteristic long lasting effect. [2-(Octahydro-1-azocinyl) ethyl] guanidine was found to be of special interest as a valuable therapeutic agent.¹



The present paper reports a convenient method for the preparation of [2-(octahydro-1-azocinyl) ethyl] guanidine sulfate.²⁻⁴ The starting material was octahydroazocine which was condensed with β -bromo ethylphthalimide in the presence of potassium carbonate to give the corresponding 2-(octahydro-1-azocinyl) ethylphthalimide. Hydrolysis of the latter with hydrochloric acid as well as hydrazinolysis with hydrazine hydrate gave the expected 2-(octahydro-1-azocinyl) ethylamine. When this compound was treated with guanidine hydrochloride at a temperature above 120° the corresponding [2-(octahydro-1-azocinyl) ethyl] guanidine was obtained and converted with dilute sulfuric acid into [2-(octahydro-1-azocinyl) ethyl] guanidine sulfate.

EXPERIMENTAL

2-(Octahydro-1-azocinyl) ethylphthalimide and its hydrochloride (I)

To a mixture consisting of 11.3 g. (0.1 mole) of octahydro-azocine, 20 ml. of xylene and 9.6 g. (0.07 mole) of potassium carbonate, a solution of 25.4 g. (0.1 mole) of β -bromoethylphthalimide in 30 ml. of xylene was added. After heating under reflux for 14 hours, the reaction mixture was cooled, potassium bromide filtered off, and xylene evaporated *in vacuo*. The brown oily residue was dissolved in benzene, treated with 10 percent hydrochloric acid and the layers were separated. The aqueous layer was neutralized with a saturated solution of sodium carbonate, extracted with benzene and dried over anhydrous potassium carbonate. After filtration and evaporation of the solvent 18 g. (63%) of a yellowish oily residue was obtained. It crystallized from ethanol, m.p. 46.5–47.5°. For analysis a sample was distilled at 148–149°/0.09 mm Hg.

Anal. C₁₇H₂₂N₂O (286.36) calc'd.: C 71.30; H 7.74; N 9.78%
found: C 71.56; H 7.49; N 9.92%

* Yug. Pat. Applic. 157/1963

Crude 2-(octahydro-1-azocinyl) ethylphthalimide (17 g.) was dissolved in a small amount of ethanol and acidified with ethanolic hydrochloric acid. Ethanol was evaporated *in vacuo* and the crystalline residue recrystallized from 96% ethanol to give 16.8 g. (55%) of pure 2-(octahydro-1-azocinyl) ethylphthalimide hydrochloride, m.p. 218—220°.

Anal. C₁₇H₂₃ClN₂O (322.827) calc'd.: C 63.15; H 7.17; N 8.66%
found: C 62.91; H 6.71; N 8.87%

2-(Octahydro-1-azocinyl) ethylamine (II)

A mixture consisting of 22 g. (0.07 mole) of 2-(octahydro-1-azocinyl) ethylphthalimide hydrochloride, 4 ml. of water and 27 ml. of 12 N hydrochloric acid was heated under reflux for 8 hours. A precipitate of phthalic acid formed which was filtered off and the filtrate evaporated to dryness. The product was crystallized from ethanol and 12.4 g. (80%) of pure 2-(octahydro-1-azocinyl) ethylamine dihydrochloride was obtained, m.p. 148—148.5°.

2-(Octahydro-1-azocinyl) ethylamine dihydrochloride was dissolved in water, the solution made alkaline with a 40 percent aqueous solution of sodium hydroxide, extracted with a small amount of ether and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent, 2-(octahydro-1-azocinyl) ethylamine was obtained as a bright yellow oil which was distilled at 108—111°/14 mm Hg.³

[2-(Octahydro-1-azocinyl) ethyl] guanidine sulfate (III)

In a three necked flask fitted with a mechanical stirrer, an air condenser and a thermometer 10 g. (0.07 mole) of 2-(octahydro-1-azocinyl) ethylamine and 6.1 g. (0.07 mole) of guanidine hydrochloride were placed and heated at 135—145°. After a clear melt was obtained, the temperature was raised and the heating prolonged for four additional hours at 145—150°. A vigorous evolution of ammonia was observed during the heating. The resulting thick brown oil was dissolved in ethanol, carefully acidified with cold 2N sulfuric acid (pH 5—6) and crystals of 2-(octahydroazocinyl) ethyl guanidine sulfate separated. The product was filtered off with suction and recrystallized from a mixture of ethanol and ether to give 10.1 g. (53%) of colorless crystals, m.p. 254—256°.⁵

Acknowledgment. Thanks are due to Mrs. A. Markovac for kind discussion of the problem.

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IZVOD

Sinteza [2-(Oktahidro-1-azocinil)etil] gvanidin sulfata

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Kondenzacijom oktahidroazocina sa β -brom-etil-ftalimidom dobiven je 2-(oktahidro-1-azocinil) etil-ftalimid, koji je hidrolizom preveden u 2-(oktahidro-1-azocinil) etilamin. Reakcijom 2-(oktahidro-1-azocinil) etilamina sa gvanidin hidrokloridom uz naknadnu obradu produkta sa sumpornom kiselinom dobiven je [2-(oktahidro-1-azocinil) etil] gvanidin sulfat.

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Primljeno 17. ožujka 1964.