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

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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.

\[
\begin{align*}
\text{CH}_2 & \\
(CH_2)_5 & \\
\text{N} \cdot \text{CH}_2\text{CH}_2\text{NH} \cdot \text{C} \cdot \text{NH}_2 & \\
\text{CH}_2 & \\
\text{NH} & 
\end{align*}
\]

The present paper reports a convenient method for the preparation of [2-(octahydro-1-azocinyl) ethyl] guanidine sulfate. 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.** C_{17}H_{22}N_{2}O (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%o) 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%o) of pure 2-(octahydro-1-azocinyl) ethylamine dihydrochloride was obtained, m.p. 146—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%o) of colorless crystals, m.p. 254—256°.3

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REFERENCES

IZVOD

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

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