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Note

Pyrid[2,1-c]oxazine Derivatives

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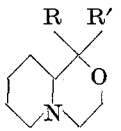
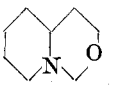
In a recent publication, Rink and Eich[1] describe octahydropyrid[2,1-c]oxazine (I: R, R′ = H) and octahydropyrid[1,2-b]-oxazine (II). Numerous derivatives of (II) have been prepared



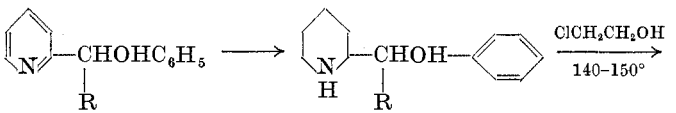
(I)



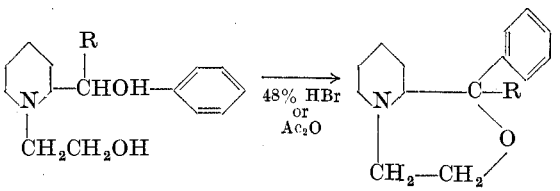
(II)

and investigated for their central stimulant activity[2-4] but similar derivatives of (I) do not seem to have received attention. In view of their current interest, we report derivatives of (I) where R = C_6H_5, R′ = H, and R and R′ = C_6H_5.

The compounds were prepared according to the scheme:



R = H or C_6H_5



Pharmacological Results

The compounds are without central stimulation, as judged by locomotor activity in rats, and cause no reduction in appetite in

the same species. Monoamine oxidase inhibition was of an extremely low order [0·008 × iproniazid (standard)]. No other pharmacological activity of interest was encountered.

Experimental

1,1-Diphenyloctahydropyrid[2,1-c]oxazine nitrate. A mixture of α,α-diphenyl-2-piperidylmethanol (15 g, 0·056 mole) and ethylene chlorohydrin (100 ml) was heated under 200 lb pressure of nitrogen for 5 h at 150°. After the reaction had cooled to room temperature, the solution was concentrated to a viscous syrup. The syrupy residue was distilled under reduced pressure; the main fraction (6·4 g) boiled between 150–158°/0·15 mm. Acetic anhydride (20 ml) was added to a solution of the distillate in chloroform (50 ml). After the reaction had refluxed for 3 h, it was concentrated to dryness. The residue was dissolved in ether and extracted with dilute hydrochloric acid. The acid portion was, in turn, saturated with potassium carbonate, extracted with ether, and the extract was dried over potassium carbonate. After the desiccant had been removed by filtration, an ether solution of nitric acid was added. The precipitate that formed was filtered and then crystallized from a solution of methanol and ethyl acetate; yield 3·3 g, m.p. 170° (uncorr.).

Anal. Calcd. for $C_{20}H_{23}NO.HNO_3$: C, 67·4; H, 6·74. Found: C, 67·41; H, 6·77.

The ultraviolet spectrum showed no phenyl group–double bond conjugation, and the infrared spectrum showed no characteristic hydroxyl group absorption. This eliminates the alternative 1-(β-hydroxyethyl)-2-benzylhydrylidenepiperidine structure.

1-Phenyloctahydropyrid[2,1-c]oxazine hydrochloride. 1-(β-Hydroxyethyl-2-(α-hydroxybenzyl)piperidine (3·3 g, 0·014 mole) was treated with 40 per cent hydrobromic acid (25 ml) under reflux for 2 h. The acid was then removed by distillation, the residue made alkaline and the product collected in ether. After drying, the base was converted to the hydrochloride with methanolic hydrogen chloride. It was obtained in crystalline form from benzene and purified by recrystallizing several times from acetone–ethyl acetate and finally from acetone, m.p. 188–189°.

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66·26; H, 7·94. Found: C, 66·37; H, 7·95.

The infrared spectrum was in agreement with the postulated structure showing absorption bands at 2330 cm^{-1} (ϵ 147); 2260 cm^{-1} (ϵ 160); (amine salt) 1441 cm^{-1} (ϵ 152), 1424 cm^{-1} (ϵ 97), (CH_2 doubled up towards lower frequencies in the presence of a neighbouring O atom); 1065–1100 cm^{-1} (C—O—C).

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References

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