SYNTHESIS OF COMPOUNDS RELATED TO ERYTHRINA ALKALOIDS—PART I

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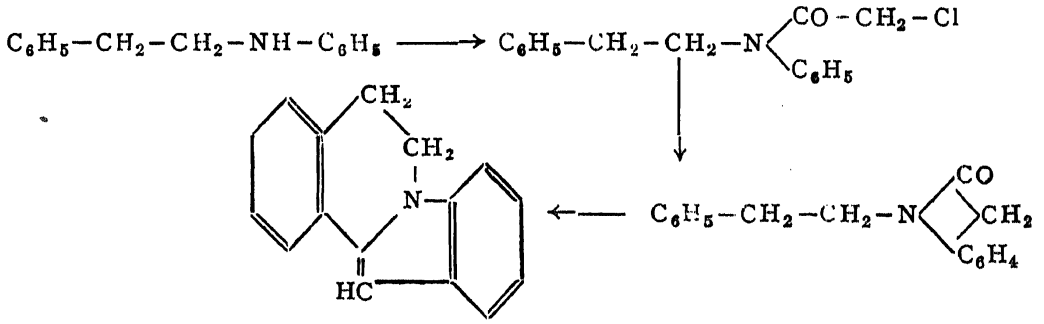
Received January 3, 1949

Altamirano[1] showed that extracts of the seeds of *Erythrina americana* Mill produce a strong curare action, *i.e.*, a selective paralysing action on motor nerve endings of striated muscle. After many years Ramirez and Rivero,[2] and Lehman[3] confirmed the curare action of the crude extracts. Folkers and his collaborators[4] carried out a very detailed examination of several species of Erythrina leading to the isolation and characterisation of a number of well-defined alkaloids. The oxidation of erythramine methohydoxide by aqueous permanganate gave hydrastic acid. The nitrogen atom was found to be tertiary and common to two nuclei. Alkaline fusion of some of the alkaloids yielded indole. On the basis of the above and examination of ultraviolet absorption spectra, a constitution incorporating a hydrindole nucleus and a hydro-isoquinoline nucleus, with the nitrogen atom common to the two heterocyclic rings was suggested.

The present work was undertaken with the object of synthesising condensed ring systems of the above type leading ultimately to the synthesis of the alkaloids. The method adopted is cyclodehydration of N-β-phenyl-ethyl indole by the application of Bischler Napieralsky reaction:



The synthesis of the substituted oxindole by the condensation of oxindole with β-phenyl ethyl chloride did not give satisfactory encouragement. The nitrogen substituted oxindole was obtained in fairly good yield by the ring closure of N-chlor acetyl-N-β-phenyl ethyl aniline, which in turn was obtained by chloracetylation of β-phenyl ethyl aniline. The oxindole ring closure proceeded with facility and the further ring closure was effected by phosphorus oxychloride in boiling benzene.

The synthesis of other members of this group is in progress.

Experimental

N-β-Phenyl ethyl aniline.—A mixture of 42·1 g. (0·3 mol.) of phenyl ethyl chloride and 83·7 g. (0·9 mol.) of aniline was boiled under reflux for two hours. The crystalline hydrochloride that separated out on cooling was dissolved in water and basified with sodium hydroxide. The liberated base was dried over anhydrous potassium carbonate and the fraction distilling at 185–190°/10 mm. was redistilled yielding a colourless viscous oil boiling at 186–187°/10 mm. (48 g., 80%).

Found: C, 85·02%; H, 7·62%. $C_{14}H_{15}N$ requires 85·27% and 7·61%.

N-Chloracetyl-N-β-phenyl ethyl aniline.—49·2 g. (0·25 mol.) of phenyl ethyl aniline were dissolved in 40 c.c. of pure acetone and 25 c.c. of dry pyridine added. This solution, kept cooled in an ice-bath, was treated drop-wise with a solution of 32 g. (excess) of chloracetyl chloride in acetone under stirring. The reaction mixture, which was almost a solid mass, was allowed to remain at room temperature (28°) for one hour and then heated for ten minutes on a boiling water-bath. The cooled product was treated with dilute acid and the product that separated out as an oil soon solidified to a mass of crystals. It crystallised from methyl alcohol in colourless crystals melting at 75–76° (60 g., 87%). The substance produces a very unpleasant sensation in contact with the skin.

Found: C, 70·20%; H, 6·09%. $C_{16}H_{16}NOCl$ requires 70·20% and 5·85%.

N-β-Phenyl ethyl oxindole.—27·4 g. (0·1 mol.) of N-chloracetyl-N-β-phenyl ethyl aniline and 26 g. (about 0·2 mol.) of freshly prepared anhydrous aluminium chloride were intimately mixed and heated, under exclusion of moisture, in an oil-bath. The vigorous reaction that ensued at 100° was allowed to subside and then the temperature was slowly raised to 140° and maintained at that point till the evolution of hydrogen chloride ceased. The cooled, brown viscous mass was poured on to ice, acidified with hydrochloric acid and allowed to stand till the oily product that separated solidified. On repeated crystallisation (animal charcoal) a colourless product was obtained melting at 95° (18 g., 75%).

Found: C, 80·93%; H, 6·45%. $C_{16}H_{15}NO$ requires 81·01% and 6·32%.

Molecular weight (cryoscopic method-benzene) 241. The substance dissolved in cold concentrated sulphuric acid forming a colourless solution which turns intensely red on treatment with powdered potassium dichromate.

Cyclisation of N-β-phenyl ethyl oxindole.—10 g. of the oxindole dissolved in 200 c.c. of dry benzene was treated with 15 g. of phosphorus oxychloride and refluxed on a boiling water-bath till the evolution of hydrogen chloride practically ceased (6 hours). The cooled solution was treated with crushed ice, the benzene layer washed free of acid, dried and the solvent removed. The residue, on standing, became semi-solid. It was stirred up with a little glacial acetic acid, collected and washed with a small volume of ethyl acetate, when a nearly white crystalline powder was obtained. The washings yielded about 2 g. of the unchanged oxindole. The product, crystallised from a mixture of benzene and absolute alcohol, separated in white plates melting at 200–201° (1·5 g.).

Found: C, 87·84%; H, 6·12%. $C_{16}H_{13}N$ requires 87·67% and 5·93%.

The substance dissolved in cold concentrated sulphuric acid forming a colourless solution, in the cold, with a strong bluish violet fluorescence. On warming, this becomes intensely green. The cold sulphuric acid solution becomes deep blue with dichromate.

Summary

The synthesis of a heterocyclic ring system containing an iso-quinoline ring fused to an indole ring, with the nitrogen atom common to the two rings, is reported.

References

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