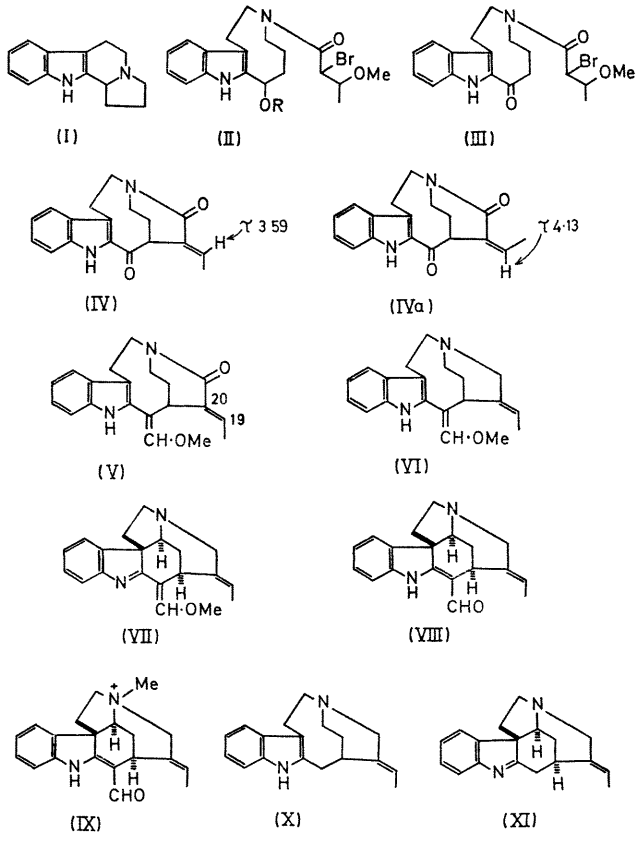
Total Synthesis of (±)-Fluorocurarine, the Racemate of a Calabash-curare Alkaloid

By G. C. CRAWLEY and JOHN HARLEY-MASON*
(*University Chemical Laboratory, Lensfield Road, Cambridge* CB2 1EW)

Summary We report a total synthesis of (±)-fluorocurarine iodide in eleven stages from tryptamine.

WE have recently reported[1–4] a number of total syntheses of *Strychnos*-type alkaloids containing *C*-ethyl groups in which the first step involved cleavage of the hexahydroindolopyrrocoline (I) with αα′-dichlorobutyric anhydride. We now report an extension of this approach leading to the first total synthesis of the racemate of a Calabash-curare alkaloid, (±)-fluorocurarine (IX), which contains a *C*-ethylidene group.

2-Bromo-3-methoxybutyric acid[5] was converted into its anhydride using dicyclohexylcarbodi-imide, and on reaction with the hexahydroindolopyrrocoline (I) in acetonitrile at room temperature gave the amide-ester [II; R = MeCH(OMe)·CHBr·CO], which on mild alkaline hydrolysis gave the alcohol (II; R = H). Oxidation with lead tetra-acetate gave the keto-amide (III) [in 48% overall yield from (I)]. Treatment of the latter with sodium 2,2-dimethylpropoxide (4 mole) in refluxing tetrahydrofuran for 1 min resulted in both ring-closure and elimination of methanol to give a mixture (1·4 : 1) of the *cis*- and *trans*-isomers (IV and IVa) of the ethylidene keto-lactam in 70% overall yield. These were separated on an alumina column and were readily distinguished by their n.m.r. spectra: in the case of the desired material (IV) the one vinyl proton is strongly deshielded by the neighbouring amide carbonyl group. Treatment of (IV) with methoxymethylenetriphenylphosphorane† (2·2 mole) in tetrahydrofuran then gave the enol ether (V). Reductive removal of the lactam carbonyl group proved difficult, since concomitant reduction of the 19,20-double bond occurred very readily. Eventually, aluminium hydride[6] was employed, though even this



† In an earlier synthesis[4] we had used dimethylsulphonium methylide as a means of adding a one-carbon functional group. Application of this reagent to the case of (IV) led to the expected ethylene oxide, but this entirely failed to rearrange to the desired aldehyde.

reagent gave some of 19,20-dihydro-compound together with the desired amine (IV). The mixture was then oxidised with platinum and oxygen[7] to the indolenine (VII) (with some 19,20-dihydro-compound) which with cold dilute acid gave a mixture of (±)-norfluorocurarine (VIII) and (±)-dihydronorfluorocurarine.[4] The mixture was separated on an alumina column, yielding crystalline (±)-norfluorocurarine,‡ m.p. 183—185°, identical in all respects (apart from optical activity) with a natural specimen kindly provided by Professor H. Schmid. Quaternisation with methyl iodide yielded (±)-fluorocurarine iodide (IX), m.p. 290—292° (decomp.). Application of a similar reaction sequence to the other isomer (IVa) of the ethylidene keto-lactam led to the formation of isonorfluorocurarine, readily distinguishable from the natural product on t.l.c.

It is of interest that the oxidative cyclisation (VI)→(VII) proceeds only in the direction indicated and we were unable to find any indication of the formation of the alternative aspidospermatidine skeleton. The same is true of our earlier syntheses of geissoschizoline[2,4] and dihydronorfluorocurarine.[4] Furthermore, the amine (X), prepared from (IV) by conversion into the dithioacetal with ethanedithiol followed by Raney nickel desulphurisation and reduction with aluminium hydride similarly cyclised only to (XI).§ This is in marked contrast to the behaviour of the 19,20-dihydrocompound which is known[1,7] to cyclise in both possible directions.

(−)-Fluorocurarine has earlier[8] been converted to the dimeric Calabash-curare alkaloid C-dihydrotoxiferine-I.

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‡ (−)-Norfluorocurarine is widely used in medical practice in the U.S.S.R. under the name vincanine as a central nervous system stimulant (M. M. Shemyakin, Plenary lecture, VIIth IUPAC Symposium on the Chemistry of Natural Products, Riga, 1970.)

§ Both (X) and (XI) are degradation products of akuammicine (G. F. Smith and J. T. Wrobel, *J. Chem. Soc.*, 1960, 792) and were identified by direct comparison.

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