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Synthesis of Methyl Adirubine

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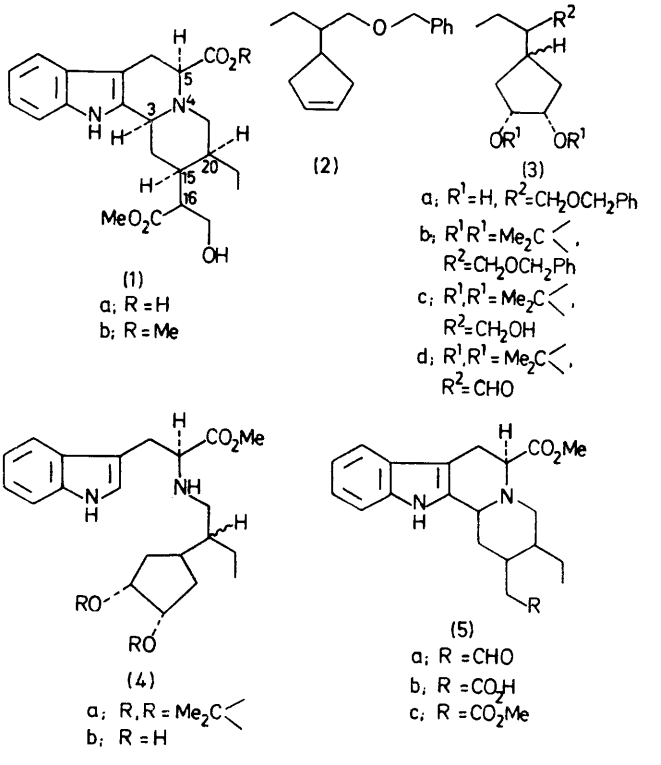
Summary Starting from the cyclopentene (**2**) and methyl tryptophanate, a total synthesis of methyl adirubine (**1b**) has been completed.

A member of the rapidly growing family of 5-carboxy indole alkaloids, adirubine, was the first corynanthé base to be isolated in which the α-amino-acid unit of precursor tryptophan remains intact.[1] We report a synthesis of methyl adirubine (**1b**) which, in addition to being the first of a corynanthé representative for this class, also permits elaboration of the stereostructure of adirubine to (**1a**).†

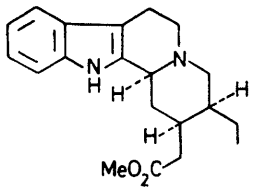
The (±)-diol ether (**3a**),[2] a mixture of diastereoisomers best prepared by hydroxylation of (**2**) with $KMnO_4$[3] rather than OsO_4,[2] was converted (98%) into the (±)-acetal (**3b**) (b.p. 140 °C at 0·5 mmHg) by means of acetone–2,2-dimethoxypropane (toluene-*p*-sulphonic acid catalyst). After catalytic hydrogenolysis (Pd) of the ether group in (**3b**) to give the alcohol (**3c**) (100%) (b.p. 130 °C at 0·5 mmHg), Collins oxidation[4] produced (85%) the relatively unstable (±)-acetal aldehyde (**3d**) [δ ($CDCl_3$; 60 MHz) 0·91 (3H, t, CH_2Me), 1·29 and 1·45 (6H, 2 × s, Me_2C), 4·65 (2H, m, $CHCMe_2$), and 9·38 and 9·45 (1H, 2 × s, *CHO* diastereoisomers)].

The amino-acid unit was attached by sodium cyanoborohydride-promoted[5] reductive alkylation of the aldehyde (**3d**) with methyl L-tryptophanate in acetonitrile at room temperature. The resulting glassy mixture of the diastereoisomers of (**4a**) (55%) was treated immediately with H_2O–MeOH–HCl to give, after 5 days at room temperature, the diol diastereoisomers (**4b**) in 73% yield (71%



† On the basis of spectral and other considerations, R. T. Brown and his co-workers (ref. 1b) previously suggested the C-3, C-5, and C-15 relationship portrayed in (**1**).

conversion) after t.l.c. (silica gel). Without further purification, the diol mixture was cleaved by periodic acid in tetrahydrofuran–aqueous $MeCO_2H$–$MeCO_2Na$ buffer, and



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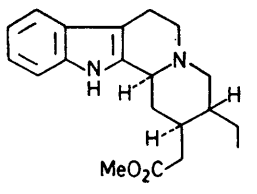

(7)

after cyclization *in situ* of the intermediate dialdehyde to the tetracyclic aldehyde (**5a**), silver oxide oxidation provided the acid (**5b**), which was converted without purification into the dimethyl ester (**5c**) by MeOH–$Me_2C(OMe)_2$–HCl. After preliminary separation of the diastereoisomeric diester mixture [40% overall from the diol (**4b**)] by preparative layer chromatography (p.l.c.) on silica gel, multiple elution p.l.c. provided five relatively pure diastereoisomers of (**5c**). One of these, (**5c′**) [m.p. 253·5—255 °C, *m/e* 384·0531 (M^+)], bore a striking spectral resemblance to an authentic sample of methyl adirubine:[1b] it displayed Bohlmann bands in the i.r. region (2890, 2870, 2810, and 2775 cm^{-1}); the c.d. spectrum (dioxan) revealed a strong positive Cotton effect, maximum 273 nm [$\Delta\epsilon$ + 4560; and n.m.r. (100 MHz) peaks were located at *inter alia* δ 0·91 (3H, t, CH_2Me), 3·74 and 3·85 (3H, 2 × s, CO_2Me), *ca.* 7·2 (5H, m, indole C*H*), and 7·82 (1H, s, indole N*H*); all characteristics consonant with structure (**5c′**) having the α,α arrangement of hydrogen atoms at C-3 and C-15. Although the n.m.r. method of Trager *et al.*[6] for stereochemical assignments at C-15 and C-20 in the indole alkaloid series was not applicable to methyl adirubine and its relatives, this spectral approach did permit *cis* assignment of these two centres in the ester (**5c′**). As in the case of various corynantheidine (*allo*) derivatives,[6] (**5c′**) features a characteristically shaped, well defined C-18 methyl triplet at δ 0·91, very different from the corresponding signals in the n.m.r. spectra of dihydrocorynantheine (normal) and related cases.[6] [We have shown that the tetracycles (**6**) and (**7**) give the n.m.r. patterns expected from ref. 6]. The configuration at C-5 follows from the stereochemical nature of the starting tryptophan.‡

Completion of the synthesis of (**1b**) involves C-16 formylation of (**5a**) followed by reduction[7] of the intermediate β-hydroxyacrylate to β-hydroxypropionate, achieved by treatment with lithium dicyclohexylamide–methyl formate in tetrahydrofuran–hexamethylphosphoric triamide followed by sodium borohydride in MeOH. After t.l.c. (silica gel) of the product mixture, the two C-16 epimers corresponding to (**1b**) were isolated, one of them [9·3% from (**5c′**)] being identical in all respects (n.m.r., i.r., m.s., R_f, and m.p.) with an authentic sample of methyl adirubine. Accordingly, the stereochemistry depicted in (**1b**) follows from the foregoing findings.§

On a purely chemical basis, the biosynthesis of sarpagine, ajmaline, and related cases is better rationalized as proceeding *via* C-5 oxidative decarboxylation of an adirubine type molecule rather than *via* dehydrogenation of a tryptamine-derived tetracycle, to a 4–5 iminium ion, either process being followed by addition of the nucleophile at C-16 to C-5.[8] The stereochemical relationship between adirubine and these other systems which is now apparent favours the former proposition, which can readily be tested through feeding of appropriate radio-labelled substances of the adirubine type.

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‡ On the basis of similar spectral information, the most abundant product of the sequence (**4b**) → (**5c**) is regarded as having the *pseudo* stereochemistry (C-3β, C-15α, and C-20β). The data for the remaining three diastereoisomers which, along with (**5c′**), were formed only in small yield, were not sufficient for stereochemical assignments.

§ In a personal communication, Dr. R. T. Brown indicated that similar conclusions regarding the stereochemistry of adirubin were reached on the basis of a correlation with 5α, 20α-methoxycarbonyldihydromancunine.

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