Synthesis and Stereochemistry of Dicrotaline, a Macrocyclic Pyrrolizidine Alkaloid

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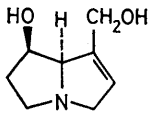
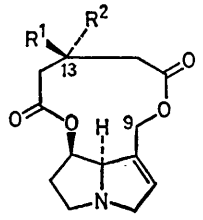
Summary Dicrotaline (**3**) and its C-13 epimer (**4**) have been synthesized and the absolute configuration at C-13 of both alkaloids has been established by specific degradation of each epimer to optically active mevalonolactone.

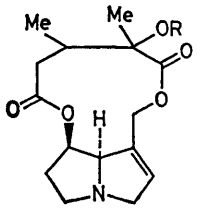
PYRROLIZIDINE alkaloids frequently occur naturally as macrocyclic diesters, in which a pyrrolizidine diol (necine) is esterified with a diacid to produce 11-, 12-, 13-, or 14-membered rings.[1] Retronecine (**1**) is the most common necine, and its macrocyclic diesters are hepatotoxic. About 25 naturally occurring 11-membered pyrrolizidine alkaloids have been isolated, but synthesis of these macrocyclic diesters has proved difficult.[2] Robins and Sakdarat constructed an unnatural 11-membered macrocyclic diester (**2**) from (+)-retronecine and 3,3-dimethylglutaric anhydride.[3] Recently, Huang and Meinwald synthesized the acetate (**5**) of crobarbatine (a natural diester) and a diastereoisomer.[4] Unfortunately, they could not determine which of their two products was a derivative of natural crobarbatine (**6**). We now report the synthesis of dicrotaline (**3**), an 11-membered diester of retronecine, its identity with natural material, and the determination of its absolute configuration at C-13 by correlation with optically active mevalonolactone.



(1)



(2) $R^1 = R^2 = Me$
(3) $R^1 = OH$, $R^2 = Me$
(4) $R^1 = Me$, $R^2 = OH$

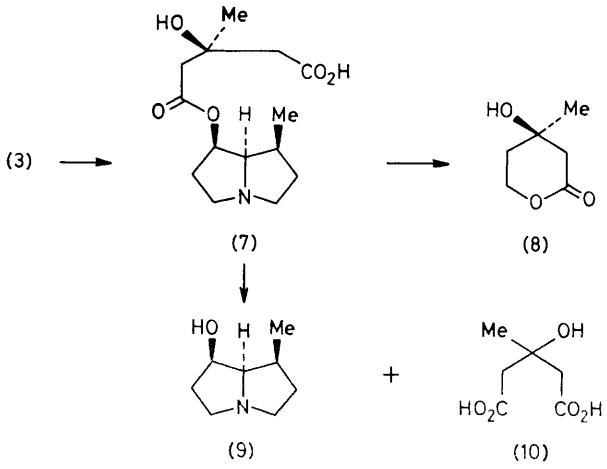


(5) R = Ac
(6) R = H

Retronecine has been synthesized by a number of groups[5,6] and resolved[5] to give the natural (+)-enantiomer (**1**). We obtained (+)-retronecine by alkaline hydrolysis of retrorsine, the major alkaloid present in *Senecio isatideus* plants. 3-Hydroxy-3-methylglutaric acid (dicrotalic acid) was synthesized,[7] converted into its anhydride,† and protected as its trimethylsilyl ether. Treatment of this material with (+)-retronecine gave a quantitative yield of the 7- and 9-monoesters of retronecine in about equal amounts judged from the ^1H n.m.r. spectrum taken in [$^2H_5$]pyridine.[3] This mixture was cyclised by the Corey–Nicolaou method[8] utilising the pyridine-2-thiol esters. The crude reaction products were purified by dissolving them in acid and washing with chloroform. Basification and extraction with chloroform gave two major products, as indicated by t.l.c. on silica gel ($CHCl_3$–MeOH–NH_3, 80 : 15 : 1).

A sample of dicrotaline, obtained by extraction of seeds of *Crotalaria dura*,[9] had the same R_f value as the faster running component of the synthetic mixture. After preparative t.l.c. the faster running component was obtained in 30% yield as an oil. A mixture of this base and dicrotaline could not be resolved by t.l.c. The base was characterised as its hydrochloride,† m.p. 210—211 °C (lit.[9] m.p. *ca.* 200 °C). The mass spectrum of the free base showed peaks at M^+ 281·1259, ($C_{14}H_{19}NO_5$ requires M 281·1263), 237, 222, 179, 136, 120, 119, 93, and 80. This fragmentation pattern is typical for a macrocyclic diester of retronecine.[1] The ^1H n.m.r. spectrum of the free base in deuteriochloroform showed a methyl singlet at δ 1·40 and multiplets for two CH_2CO groups at δ 2·4—2·6 in addition to the usual signals for retronecine. In particular, an AB quartet was observed at δ 4·16 and 5·40, J 12 Hz, due to the non-equivalent protons at C-9. This chemical shift difference of 1·24 p.p.m. is the largest observed for an 11-membered macrocyclic diester of retronecine (other values reported range from 0·0 to 0·92 p.p.m.[1]), but is the same as that observed for the related macrocycle (**2**).[3] The identity of this base with dicrotaline was evident from closely similar i.r., n.m.r., and mass spectra, and undepressed mixed m.p. of the hydrochlorides.

The epimer of dicrotaline was also isolated as an oil in 30% yield after preparative t.l.c., and characterised as its hydrochloride,† m.p. 158—161 °C (decomp.). An accurate mass measurement on this base gave M^+ 281·1254 ($C_{14}H_{19}NO_5$ requires M 281·1263). The main difference in the ^1H n.m.r. spectral characteristics of this epimer was a smaller chemical shift difference of 0·98 p.p.m. for the C-9 protons (AB q, δ 4·19 and 5·17, J 12 Hz).



SCHEME

The formulation of dicrotaline as the (13*S*)-isomer (**3**) was made by converting dicrotaline into optically active mevalonolactone (Scheme). Thus, hydrogenolysis of synthetic dicrotaline in acetic acid over PtO_2 gave a single compound (**7**).† [Basic hydrolysis of (**7**) gave (−)-retronecanol (**9**) and dicrotalic acid (**10**).] Treatment of (**7**) with sodium in liquid ammonia, a reagent known to reduce esters in the presence of acids,[10] gave (*R*)-mevalonolactone (**8**), $[\alpha]_D^{20}$ −20° (EtOH) (lit.[10] −23°). The i.r. and ^1H n.m.r. spectra of the material obtained were identical with those of an authentic sample of (±)-mevalonolactone. The material obtained from degradation of dicrotaline was converted into its benzhydrylamide, m.p. 98—99 °C (lit.,[11] 98—99 °C). The benzhydrylic proton gave two singlets (rotamers) in the ^1H n.m.r. spectrum recorded in the presence of Eu(hfc)$_3$ (a doubling of the signals for the benzhydrylic proton was observed with the racemate[11]), indicating that

† Satisfactory spectroscopic and analytical data were obtained for all new compounds.

no detectable racemisation had taken place during the degradation. Therefore dicrotaline (**3**) has the (13*S*) absolute configuration.

In an analogous manner, the epimer (**4**) of dicrotaline was degraded to (*S*)-mevalonolactone, $[\alpha]_D^{20}$ +19° (EtOH), and the benzhydrylamide, m.p. 99—100 °C, showed a single enantiomer in the ^{1}H n.m.r. spectrum in the presence of the europium shift reagent. Thus the (13*R*) absolute configuration is confirmed for the epimer (**4**) of dicrotaline.

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