The Synthesis of (±)-Aplysin and (±)-Debromoaplysin

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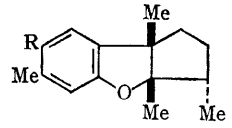
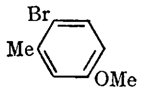
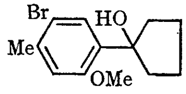
WE report the synthesis of (±)-apylsin (I; R=Br) and (±)-debromoaplysin (I; R=H).

On treatment with phenyl-lithium in ether, 4-bromo-3-methylanisole (II)[1] was converted into the lithium derivative, which was treated with cyclopentanone to give (III). During the distillation of (III) under reduced pressure (25 mm.) dehydration occurred to afford a cyclopentene derivative (IV)† (30%; m.p. 56—57°). The presence of two sharp singlets (6·65 and 7·28 p.p.m.) due to aromatic protons in the n.m.r. spectrum of the product confirmed the formulation as (IV).


(I)


(II)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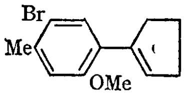
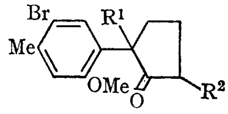
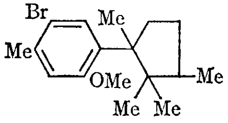
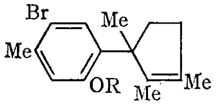

(IV)


(V) $R^1=R^2=H$
(VI) $R^1=Me$, $R^2=H$
(VII) $R^1=Me$, $R^2=CHO$
(VIII) $R^1=R^2=Me$


(IX)


(X) R=Me
(XI) R=H

Oxidation of the cyclopentenyl compound (IV) was achieved by treatment with performic acid to give the substituted cyclopentanone (V) (52%) [m.p. 131—132°; ν_{max} (KBr), 1730 cm.$^{-1}$].

Methylation at the benzylic carbon atom α to the carbonyl function was effected by treating the cyclopentanone (V) with sodium hydride in 1,2-dimethoxyethane and then with methyl iodide to afford (VI) (96%) [m.p. 121—122°; ν_{max} (KBr), 1735 cm.$^{-1}$]. Condensation of (VI) with ethyl formate (MeONa–benzene) gave the formyl derivative (VII) which was heated under reflux in acetone with methyl iodide and potassium carbonate. The resulting product was hydrolyzed, without purification, in ethanolic 10% potassium hydroxide to give the cyclopentanone (VIII) (31%) [m.p. 134—136°; ν_{max} (KBr), 1735 cm.$^{-1}$].

Treatment of the cyclopentanone (VIII) with methylmagnesium iodide in benzene yielded the cyclopentanol derivative (IX) [m.p. 136—138°; ν_{max} (KBr), 3520 cm.$^{-1}$] which was dehydrated with 50% sulphuric acid–benzene under reflux to afford the cyclopentene (X) (43%) (m.p. 124·5—125·5°). Demethylation of the methoxy-group in (X) was effected by treating the compound with methylmagnesium iodide in a sealed tube at 165—170°. The phenolic products containing (XI) were heated under reflux in acetic acid–toluene-*p*-sulphonic acid. Deeply coloured materials were removed from the reaction mixture by column chromatography on silicic acid (chloroform as solvent). Repetition of the preparative v.p.c. (Carbowax 20M and Apiezon L) gave racemic aplysin (I; R=Br) (10%) (m.p. 99—100°), which was shown to be identical with the natural aplysin[2] by i.r., u.v., n.m.r., and mass spectral and v.p.c. comparison. Debromoaplysin (I; R = H), which is also a natural product,[2] was obtained as a racemate from the reaction mixture by v.p.c. separation [(3—7%); the yield depends on the temperatures employed for demethylation of (X)]. In addition, a liquid product was obtained (15%) which was isomeric with aplysin. The structure of this compound is under investigation.

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† All new compounds have been fully characterized by elemental analyses and i.r., u.v., n.m.r., and mass spectra data. The n.m.r. data refer to carbon tetrachloride solutions.

[1] R. Quelet and M. Paty, *Proces-verbaux Seances Soc. Sci. Phys. Nat. Bordeaux*, 1944—1945, 19.
[2] S. Yamamura and Y. Hirata, *Tetrahedron*, 1963, **19**, 1485.