New Route to the Protopanes

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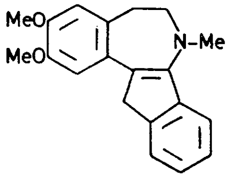
Summary A new and efficient synthetic approach to the structural features characteristic of protopine alkaloids is described.

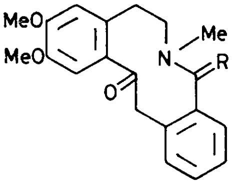
THE protopine alkaloids have been synthesized only by way of chemical[1a] or photochemical[1b] transformation of protoberberine alkaloids, which have recently been shown to be the precursor of the protopine alkaloids.[2] We now report a new method, consisting of photo-oxygenative ring enlargement of tetrahydrobenzindenoazepine by singlet oxygen and further elaboration of the resultant ten-membered amido-ketone product.

Many cases of the interaction of singlet oxygen with olefins have been studied. The oxidation of enamines has been reported to proceed by 1,2-cycloaddition followed by ready decomposition to give carbonyl and amide fragments.[3] This type of oxidative cleavage is also known for indenes, forming diketo compounds.[4] It appeared plausible that 5,6,7,12-tetrahydro-7-methylbenz[*d*]indeno[1,2-*b*]azepines might exhibit enamine- and indene-like properties and undergo an analogous oxidative cleavage with singlet oxygen.

Photo-oxygenation of the enamine (**1**)[5] was carried out in methanol–methylene chloride using Rose Bengal as sensitizer at 18 °C for 10 min, the solution being kept saturated with oxygen, with irradiation with a 650 W tungsten–iodine lamp.† The usual work-up gave the crystalline amido-ketone (**2**), m.p. 171—172 °C (EtOH), in 84% yield, ν_{max} (Nujol) 1682 and 1620 cm^{-1}, which on lithium aluminium hydride reduction in tetrahydrofuran led to the corresponding amino-alcohol, m.p. 144—146 °C (MeOH–Et$_2$O) [ν_{max} (Nujol) 3370 cm^{-1}; ^{1}H n.m.r. (CDCl$_3$) 7·35—7·05 (4H, m), 7·20 (1H, s), 6·65 (1H, s), 5·45 (1H, dd, *J* 2 and 8 Hz), and 3·96, 3·88, and 2·13 (each 3H, s)]. Subsequent oxidation of the amino-alcohol with activated manganese dioxide in chloroform at room temperature produced the amino-ketone (**3**), m.p. 170—171 °C (MeOH–Et$_2$O), in 80% yield



(1)



(2) R = O
(3) R = H$_2$

from (**2**) [ν_{max} (Nujol) 1676 cm^{-1}; ^{1}H n.m.r. (CDCl$_3$) 7·35—7·15 (4H, m, 9—12-H) 7·13 (1H, s, 1-H), 6·74 (1H, s, 4-H), 3·92 (6H, s, OMe), 3·86 (2H, br. s, 13-H$_2$), 3·65 (2H, br. s, 8-H$_2$), 3·02 and 2·60 (each 2H, m, 5- and 6-H$_2$), and 1·85 (3M, s, NMe).‡ The presence of the desired ten-membered ring system was shown by the virtually complete identity between the ^{1}H n.m.r. spectra of (**3**) and the natural products in chemical shifts and splitting patterns.§

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† The use of Methylene Blue gave a comparable yield of (**2**); this reaction did not occur in the absence of oxygen, dye, or irradiation.

‡ All compounds gave satisfactory elemental analyses.

§ *Cf.* data for crypropine and (figures in parentheses) muramine: δ 7·02 (7·07) (1H, s, 1-H), 6·71 (6·69) (1H, s, 4-H), 3·92 (3·85 and 3·80) (6H, s, OMe), 3·79 and 3·62 (4·1—3·5) (2 × 2H, br. s, 8- and 13-H$_2$), 2·97 and 2·60 (2·95 and 2·60) (each 2H, m, 5- and 6-H$_3$), and 1·90 (1·85) (3H, s, NMe) (N.S. Bhacca, L. F. Johnson, and J. N. Shoolery, 'NMR Spectra Catalog,' Vol. I, Spectrum No. 339, Varian Associates, 1962; C. J. Pouchert and J. R. Campbell, 'The Aldrich Library of NMR Spectra,' Vol 10, p. 122, Aldrich Chem. Company, Inc., 1962; A. D. Cross, L. Dolejš, V. Hanuš, M. Maturová, and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1965, 1335; F. R. Stermitz, L. Chen, and J. I. White, *Tetrahedron*, 1966, **22**, 1095; S. R. Johns, J. A. Lamberton, H. J. Tweeddale, and R. I. Willing, *Austral. J. Chem.*, 1969, **22**, 2233; *cf.* ref. 1 also).

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[5] Compound (**1**), m.p. 146—147 °C, was prepared by a modification of the known method; *cf.* K. Orito, R. H. Manske, and R. Rodrigo, *J. Amer. Chem. Soc.*, 1974, **96**, 1944; ^{1}H n.m.r. (CDCl$_3$) 7·70—7·0 (4H, m), 7·10 and 6·73 (each 1H, s), 3·96 and 3·90 (each 3H, s), 3·85 (2H, s), 3·26 and 3·20 (each 2H, m), and 3·03 (3H, s).