Synthesis of *N*-Methyl-6-azabicyclo[3,2,1]octan-3-one, an Alkaloid Sub-unit

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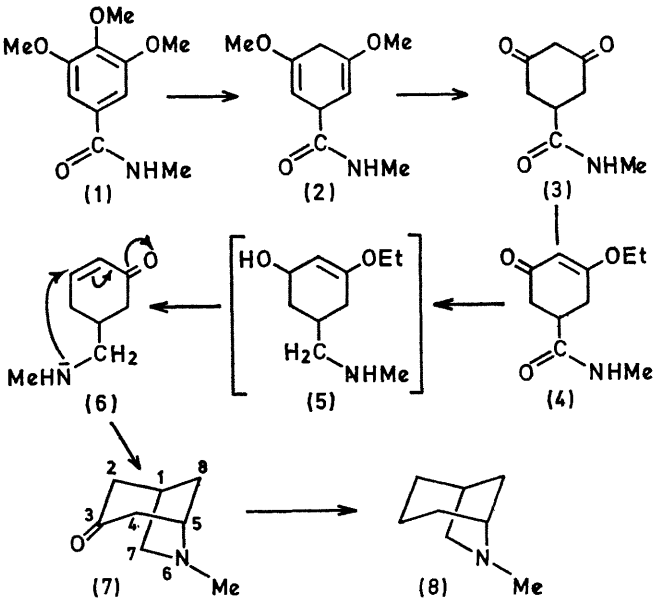
Summary The synthesis of a new azabicyclic molecule, *N*-methyl-6-azabicyclo[3,2,1]octan-3-one (**7**) is described.

THE azabicyclic molecule (**7**) which has two functional groups, is of interest from the synthetic point of view, as it is a sub-unit of natural products such as actinoboline, and more complex alkaloids like securinine.[1,2] Compound (**7**) is also an interesting substrate for studying the influence of the nitrogen on the reactivity of C-3 across the seven-membered ring, which is held in a more or less rigid conformation by the methane bridge.[3] The essential step of our synthesis is an intramolecular Michael cyclisation,[4] on a suitable intermediate (**6**) which is obtained as follows.[5]

Reduction of 3,4,5-trimethoxy-*N*-methylbenzamide by sodium in liquid ammonia and methanol,[6] yields the unconjugated dihydro-derivative(**2**) (90% yield), m.p.† 120°; i.r. ($CHCl_3$) ν 3440 (N–H), 1690 (enol-ether) 1660 cm^{-1} (amide CO); n.m.r. ($CDCl_3$) δ 2·75 (m, 5H), 3·66 (s, 6H), 3·80 (m, 1H), 4·70 (d, 2H), 5·80 p.p.m. (m, 1H). Acid hydrolysis (HCl 3%) gives the β-diketone (**3**) (100% yield) [i.r. ($CHCl_3$) ν 3440 (N–H), 1670 (amide CO), 1610 (β-diketone CO), and 1560 cm^{-1}] which on treatment with ethanol (azeotropic distillation), yields the conjugated ketone (**4**) (50% yield; m.p. 162°); i.r. ($CHCl_3$) ν 3450 (N–H), 1660 (amide CO), 1650 (ketone CO), 1600 cm^{-1} (C=C); n.m.r. ($CDCl_3$) δ 1·40(t, 3H), 2·60 (m, 5H), 2·80 (d, 3H), 3·90 (q, 2H), 5·3 (s, 1H), 6·4 p.p.m. (m, 1H).



† Melting points were taken with a standardized Kofler block.

When reduced with $LiAlH_4$ in tetrahydrofuran under reflux (8 hr.) the latter compound leads to the amino-alcohol (**5**) which is not isolated and is immediately hydrolysed in HCl (10%, 3 hr.) After treatment with $NaHCO_3$, the reaction mixture is extracted with methylene chloride, and (**7**) is separated by g.l.c. (silicone oil 20%, 130°) (yield 30%), picrate m.p. 210°;† i.r. ($CHCl_3$) ν 1705 cm^{-1} (C=O); n.m.r. ($CDCl_3$) δ 2·45 (s, 3H), 2·50 (m, 9H), 3·30 p.p.m. (m, 1H).‡ Its structure results from the physical data (*M* 139, $C_8H_{13}NO$), and also from the degradation by hydrogenolysis on PtO_2 (HCl, 1N, 3 atm. H_2)[7] to (**8**) [picrate m.p. 250°† (decomp.)] which is a known structure.[8]

We thank the DRME for financial support.

(*Received, January 26th,* 1970; *Com.* 120.)

‡ Compound (**7**) was also obtained after purification by microdistillation: in this way, 5 g of (**4**) yielded 2 g of pure (**7**). In a typical experiment starting from **38** g of (**1**) we obtained 30 g of crude (**2**) which, in turn yielded 20 g of (**4**).

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