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# ONE-POT SYNTHESIS OF 1,2,3,6,7,11b-HEXAHYDRO-4H-BENZO[a]QUINOLIZIN-4-ONES: KEY SYNTHONS FOR BENZO[a]QUINOLIZINES

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Abstract - Michael adduct of 3,4-dihydro-1-methylisoquinolines (1) and methyl acrylate on $NaBH_4$ reduction led to the title compounds (3)

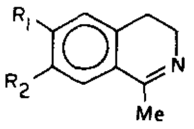
The methods so far known[1-5] for the preparations of 1,2,3,6,7,11b-hexahydro-4H-benzo[a]quinolizin-4-ones (3) involve several steps with low overall yields. In view of our current interest in the field of the benzo[a]quinolizine alkaloids[6], we attempted and achieved a one-pot synthesis of compounds 3a-d. We essentially took advantage of the reported Michael reaction of the conjugated esters[5,7-12] with compounds capable of existing in imine-enamine tautomeric forms. Thus, 3,4-dihydro-1-methylisoquinolines (1) reacted with methyl acrylate to form the intermediate adducts (2) which were reduced in situ with $NaBH_4$ to furnish the corresponding quinolizin-4-ones (3) in moderate yields. As a typical example, 9,10-dimethoxy-1,2,3,6,7,11b-hexahydro-4H-benzo[a]quinolizin-4-one (3b), a key intermediate in the synthesis of the therapeutically important[4] benzo[a]quinolizine class of compounds including the ipecac alkaloids[5] was prepared as follows.

To a solution of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline[13] (1b, 4.87 g) in benzene-methanol (1:1, 60 ml), methyl acrylate (1.3 molar equiv.) was added and kept at 30°C for 5 days (TLC monitored). The solvent and the excess reactant were removed under reduced pressure. Sodium borohydride (3 g) was added portionwise to a methanolic solution of the oily product at 0°C and stirred for 1h. The reaction mixture was then left overnight at room temperature. Usual work-up thereafter afforded an oil (6.60 g) which could be induced to solidify on repeated chromatography over silica gel, trituration with ether and standing (24 h, 0°C).

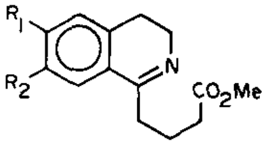
Crystallisation from ether-light petrol yielded 3b (2.82 g; 47%)[14] in granules, mp 88-89°C. Support to the structure 3b was secured as in the sequel.

The compound 3b was converted to the corresponding thiolactam[15], mp 164°C($CHCl_3$-light petrol), with $P_4S_{10}$. The thiolactam was reduced with Raney-Ni in refluxing ethanol to the corresponding benzo [a] quinolizine. Alternatively, 3b could be directly reduced with lithium aluminium hydride in ether to the same benzo [a] quinolizine[4] which was characterised as hydrochloride, mp 220-225°C(isopropanol-ether).

Three other benzo [a] quinolizin-4-ones, viz., 3a[16], 3c[17] and 3d[18], were prepared from the corresponding 1-methyldihydroisoquinolines 1a[19], 1c[20], 1d[21] following the procedure already stated.



1



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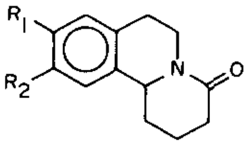

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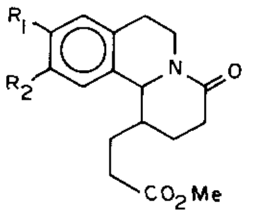

4

a : $R_1 = R_2 = H$

b : $R_1 = R_2 = OMe$

c : $R_1 = OMe$; $R_2 = OBz$

d : $R_1 = OBz$; $R_2 = OMe$

In order to confirm the intermediacy of the Michael adduct in the above reaction, the product obtained from the reaction of 3,4-dihydro-6,7-dimethoxy-1-methyl-isoquinoline (1b)with methyl acrylate was purified as the picrate, mp 170°C (ethanol). The structure of the regenerated base (2b)was in agreement with the spectral data[22]. The possibility of a second Michael addition was also investigated. Thus, the compound 1b and methyl acrylate (3 equiv.) were taken up in benzene-methanol (1:1) and kept at room temperature for three days and then another lot of methyl acrylate (3 equiv.) was identically treated. The volatile matters were removed under vacuum, the residue was taken up in methanol and treated with $NaBH_4$ at 0°C. Usual work-up afforded white needles (57%), mp 149-150°C (chloroform-light petrol). The physical data[23] of the compound were compatible with the expected structure 4b.

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14. Lit.[4] mp 89-90°C; ms : m/z (rel.int.): 261 ($M^+$, 40), 260(25), 246(20), 233(10), 230(20), 205(10), 191(100), 190(30), 176(26); ir(KBr) : 1630 and 1620 $cm^{-1}$; $^1H$ nmr ($CDCl_3$, 100 MHz) : $\delta$ 1.44-2.16 (m, 4H), 2.16-3.08 (m, 5H), 3.84 (s, 6H), 4.48-4.80 (m, 1H), 4.80-5.04 (m, 1H), 6.60 (s, 1H) and 6.64 (s, 1H).

15. MS : 279 ($M^+$+ 2, 3.7) 277 ($M^+$, 56), 276 (98), 243 (100), 228(55), 216(48), 191(62), 190(65); $^1$H nmr ($CDCl_3$) : $\delta$ 1.80-2.00 (m, 4H), 2.60-3.40 (m, 5H), 3.83 (s, 6H), 4.60-4.80 (m, 1H), 5.50-5.72 (m, 1H), 6.64 (s, 2H).

16. **3a** : (yield 27%); mp 77-78°C; ms : 201 ($M^+$, 15), 145(100), 131(63), 130(64); ir(KBr) : 1625 and 1605 cm $^{-1}$; $^1$H nmr($CDCl_3$) : $\delta$ 1.48-3.12 (m, 9H), 4.52-5.00 (m, 2H) and 7.04-7.40 (m, 4H).

17. **3c** : (58%); mp 84-85°C; ms : 337($M^+$, 20), 267(4), 246(72), 218(7), 190(7), 176(14) and 91(100); ir(KBr) : 1635 and 1625 cm$^{-1}$; $^1$H nmr($CDCl_3$) : $\delta$ 1.32-3.08 (m, 9H), 3.93 (s, 3H), 4.24-5.04 (m, 2H), 5.16 (s, 2H), 6.68 (s, 1H), 6.72 (s, 1H), 7.24-7.64 (m, 5H).

18. **3d** : (45%); mp 90-92°C; ms : 337($M^+$, 17), 267(4), 246(14), 217(80), 218(12), 190(6), 176(19) and 91(100), ir(KBr) : 1635 cm$^{-1}$; $^1$H nmr($CDCl_3$): $\delta$ 1.48-2.96 (m, 9H), 3.84 (s, 3H), 4.44-4.96 (m, 2H), 5.08 (s, 2H), 6.64 (s, 1H), 6.68 (s, 1H) and 7.16-7.56 (m, 5H).

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22. MS : 291 ($M^+$, 2.8), 276(1), 260(25), 259(100), 258(44), 244(65), 231(17), 230(42), 216(32), 205(52), 190(8); ir(nujol) : 1725 cm$^{-1}$; $^1$H nmr($CDCl_3$) : $\delta$ 1.88-2.16 (m, 2H), 2.36-3.00 (m, 6H), 3.64 (s, 3H), 3.60-3.80(m, 2H), 3.92 (s, 3H), 3.94 (s, 3H), 6.72 (s, 1H) and 7.14 (s, 1H).

23. MS : 347($M^+$), 332, 319, 316, 291, 288, 260, 191, 190, 176; ir(KBr) : 1728, 1635 and 1625 cm$^{-1}$; $^1$H nmr ($CDCl_3$) : $\delta$ 1.10-3.10 (m, 12H), 3.60 (s, 3H), 3.88 (s, 6H), 4.68-5.24 (m, 2H), 6.62 (s, 1H) and 6.64 (s, 1H).

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