DEACYLATION OF 3-ACETYL-4-OXO-6,7-DIHYDRO-12H-INDOLO[2,3-a]QUINOLIZINE

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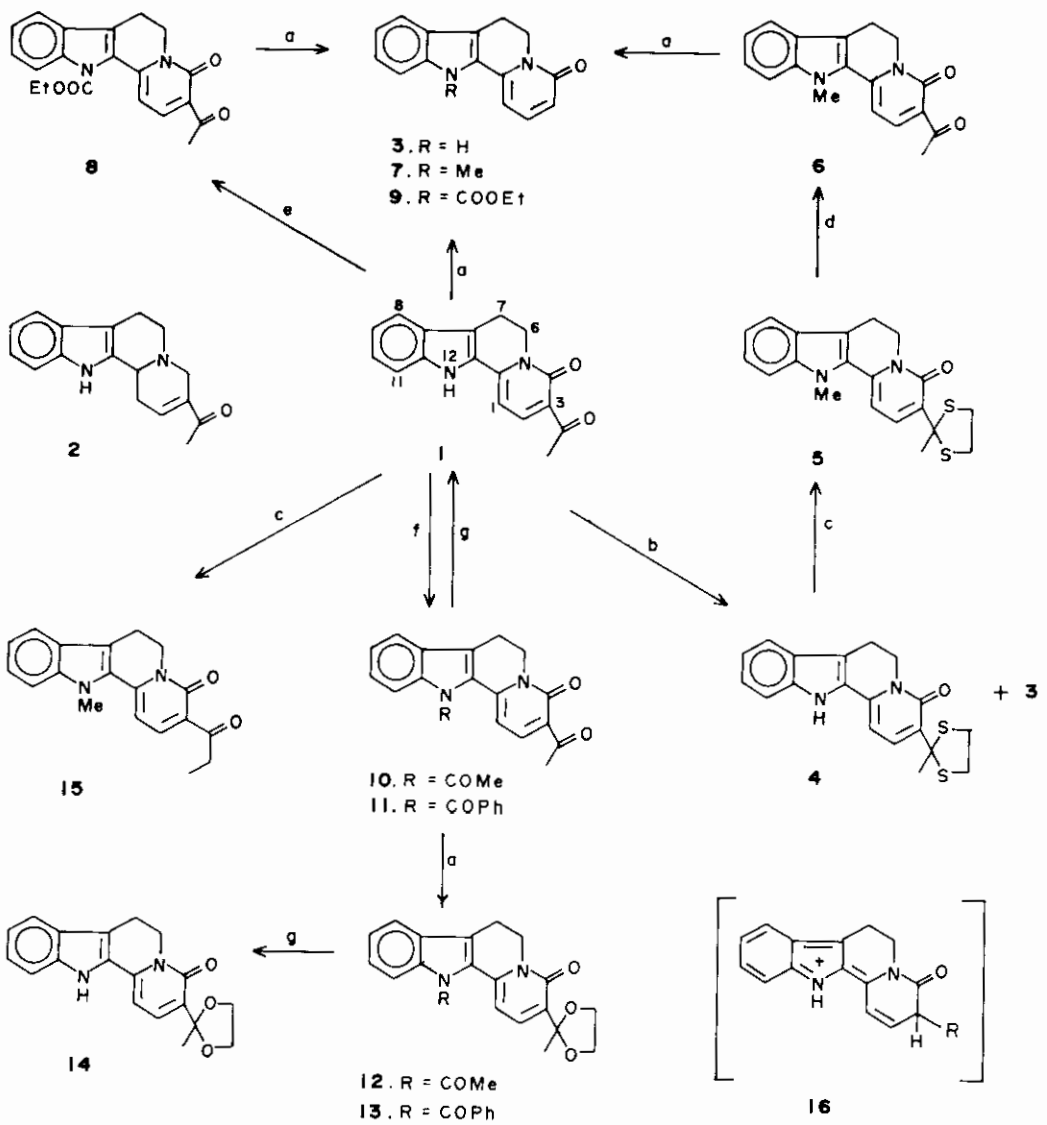
Abstract - An unexpected deacylation of 3-acetyl-4-oxo-6,7-dihydro-12H-indolo[2,3-a]quinolizine (1) on attempted ketalization with ethylene glycol or ethanedithiol and p-toluenesulphonic acid in refluxing benzene to 4-oxo-6,7-dihydro-12H-indolo[2,3-a]quinolizine (3) has been observed.

We recently reported[1] a one-pot synthesis of compound 1. To utilize it for the preparation of 3-acetyl-1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine (2), a key intermediate in the synthesis[2] of ajmalicine, we sought to ketalize the acyl function. Contrary to our expectation, however, heating 1 (0.01 mmol) with ethylene glycol (1 ml) and TsOH (0.002 mmol) in benzene (30 ml) under reflux in a Dean-Stark apparatus for 5 h furnished the deacetylated compound 3, mp 305-306°C (dec.) as the sole product (ca. 70%), characterised primarily from its spectral data (Table 1). Under the same condition, ethanedithiol also provided 3 in 18% yield though the desired thioketal 4, mp 288-289°C (dec.) was the major product (61%). The latter could, nevertheless, be obtained in 96% yield by treatment of 1 (0.01 mmol) with ethanedithiol (1.5 ml) in acetic acid (5 ml) in presence of BF_3.etherate (0.25 ml) at room temp. for 10 h.

On the other hand, replacement of ethylene glycol with different mono- or dihydric alcohols like *MeOH, EtOH, n-BuOH and propane-1,3-diol*, use of TsOH alone in refluxing benzene or in higher boiling aromatic hydrocarbons (eg. toluene, xylene) or treatment with deacylating agents, such as, HBr or HCl in acetic acid under reflux or 75% H_2SO_4, mostly led to the recovery of the starting material and, in some cases, to intractable tars.

Participation of ethylene glycol in particular and less efficiently of ethanedithiol thus appeared to be essential in the deacylation. The involvement of the lone pair of electrons of indole nitrogen also became apparent from the observed substituent effects as in the sequel.

The N-methyl derivative 6, mp 186-188°C, gave the deacetylated compound 7 (66%, mp 170-172°C), the structure of which was confirmed by N-methylation of 3. Incidentally, the most convenient method of preparation of 6 (73%) was found to be through the thioketals 4 and 5, mp 230-232°C (dec.), since direct N-methylation with



a. Ethylene glycol / TsOH; b. Ethanedithiol / TsOH; c. (i) NaH / DMF, (ii) MeI; d. $HgCl_2$/ $CdCO_3$/aq. acetone; e. (i) NaH / DMF, (ii) ClCOOEt; f. (i) NaH / THF, (ii) RCOCl; g. Basic Al_2O_3

Table 1. Spectral data of compounds 3-15

Compd.*	IR (ν cm^{-1}, Nujol)	^1H NMR (δ ppm, $CDCl_3$)	MS m/z (rel. int.)
3	3160-3120, 1640	3.16, 4.50 (2x2H t), 6.38, 6.56 (2x1H dd), 7.12-7.55 (4H, m), 7.66 (1H, d), 8.50 (1H, br)	236 (M^+, 77), 235 (100), 207 (77), 206 (82), 205 (51)
4	3230, 1635	2.22 (3H, s), 3.12, 4.52 (2x2H t), 3.20-3.70 (4H, m), 6.34, 7.64, 8.01 (3x1H d), 7.12-7.52 (3H, m), 8.28 (1H, br)	354 (M^+, 2), 339 (8), 294 (45), 261 (100), 206 (29), 205 (29)
5	1635	2.22, 3.96 (2x3H s), 3.04, 4.44 (2x2H t), 3.16-3.28 (4H, m), 6.50, 7.58, 7.98 (3x1H d), 7.12-7.20 (3H, m)	368 (M^+, 3), 353 (9), 310 (57), 308 (40), 276 (100), 205 (43)
6	1670, 1640	2.72, 3.96 (2x3H s), 3.08, 4.48 (2x2H t), 6.62, 7.64, 8.22 (3x1H d), 7.12-7.50 (3H, m)	292 (M^+, 49), 277 (100), 249 (18), 219 (51), 206 (52), 205 (73)
7	1650	3.02, 4.38 (2x2H t), 3.92 (3H, s), 6.40-6.56 (2H, m), 7.12-7.60 (5H, m)	250 (M^+, 87), 249 (100), 235 (40), 221 (51), 220 (42), 206 (81), 205 (71)
8	1720, 1665, 1650	1.44 (3H, t), 2.74 (3H, s), 3.04, 4.56 (2x2H t), 4.50 (2H, q), 6.42, 8.12, 8.16 (3x1H d), 7.20-7.64 (3H, m)	350 (M^+, 57), 335 (52), 262 (66), 206 (100)
9	1720, 1650	1.22 (3H, t), 2.96, 4.46 (2x2H t), 4.44 (2H, q), 6.32, 6.54 (2x1H dd), 7.20-7.44 (4H, m), 8.10 (1H, d)	308 (M^+, 45), 235 (100), 206 (93)
10	1705, 1655, 1645	2.62, 2.72 (2x3H s), 3.10, 4.56 (2x2H t), 6.28, 8.10, 8.18 (3x 1H d), 7.24-7.70 (3H, m)	320 (M^+, 16), 305 (2), 278 (33), 277 (38), 263 (96), 235 (40), 206 (99), 205 (100)
11	1690, 1655, 1645	2.64 (3H, s), 3.08, 4.56 (2x2H t), 5.98 (1H, d), 7.20-8.00 (10H, m)	382 (M^+, 63), 369 (19), 277 (15), 261 (21), 235 (23), 205 (100)
12	1705, 1645	1.80, 2.56 (2x3H s), 2.96, 4.48 (2x2H t), 3.84-4.18, 7.20-7.60 (2x4H m), 6.08, 8.04 (2x1H d)	364 (M^+, 12), 349 (100), 321 (96), 306 (91), 278 (75), 277 (66), 263 (92), 235 (88), 205 (97)
13	1690, 1645	1.78 (3H, s), 3.04, 4.52 (2x2H t), 3.74-4.08 (4H, m), 5.90 (1H, d), 7.20-7.92 (10H, m)	426 (M^+, 1), 411 (21), 383 (21), 321 (16), 306 (96), 278 (42), 261 (90), 249 (56), 205 (100)
14	3280, 1645	1.84 (3H, s), 3.08, 4.28 (2x2H t), 3.84-4.12 (4H, m), 6.32, 7.58 (2x1H d), 7.04-7.30 (4H, m), 8.40 (1H, br)	322 (M^+, 6), 307 (90), 278 (56), 263 (100), 206 (93), 205 (93)
15	1655, 1640	1.20 (3H, t), 3.08, 4.26 (2x2H t), 3.22 (2H, q), 3.92 (3H, s), 6.58, 7.60, 8.20 (3x1H d), 7.20-7.40 (3H, m)	306 (M^+, 22), 291 (4), 277 (94), 206 (99), 205 (100)

*All the compounds purified by repeated crystallisation from petroleum ether-$CHCl_3$

MeI-NaH in DMF afforded 15 (90%, mp 192-193°C) by concomittant C-alkylation. Similarly, the N-ethoxycarbonyl derivative 8 (93%, mp 166-168°C from 1 with ClCOOEt and NaH in DMF at room temp.) gave the deacylated compound 9, though in reduced yield (51%). Substitution of the indole NH with more powerful electron withdrawing groups, however, resulted in complete suppression of deacetylation leading to the exclusive formation of ketal. For example, the N-acetyl 10, mp 194-195°C, and the N-benzoyl 11, mp 183-184°C, derivatives respectively furnished 12 (58%) and 13 (64%) which when passed through basic Al_2O_3 regenerated the desired ketal 14 (86%, mp 247-248°C). Such deacylation has rarely been observed[3,4]. In fact, pyrrole is the only other system studied in some details that has been reported[5,6] after the completion of our work. Nevertheless, while our findings corroborate the essentiality of ethylene glycol and the role of nitrogen lone pair for the reaction, the suggested intermediacy of the ketal itself remains a moot point at least in our system for the following reasons: (i) Refluxing the ketal 14 in benzene (30 min) with TsOH (0.2 eqv.) led to almost quantitative regeneration of the ketone 1. Though prolonged reflux (12 h) yielded 3 (30%), this was also the case when 1 was similarly treated with ethylene glycol (1 eqv.). (ii) When the ketal 14 was refluxed with TsOH (0.2 eqv.) in benzene and ethylene glycol (5 eqv.) monitoring every 30 min by TLC showed the existence of the ketal in the reaction mixture for at least 1.5 h, implying that direct deacylation of ketal cannot be a fast process. (iii) The ketal could not be detected (TLC) at any time during the deacylation reaction of ketone 1.

On the other hand, the thioketal 4 smoothly underwent deacylation when refluxed with TsOH in benzene. The reaction rate was, however, slower in presence of ethanedithiol either with 4 or ketone 1, thereby allowing the isolation of the thioketal 4.

Further work is in progress to ascertain the exact methanism though protonation at C-3 (16) at some stage appears to be involved in the process.

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