A CONVENIENT METHOD FOR THE SYNTHESES OF 4-OXO-4, 5, 6, 7-TETRAHYDROINDOLE AND BENZOFURAN DERIVATIVES

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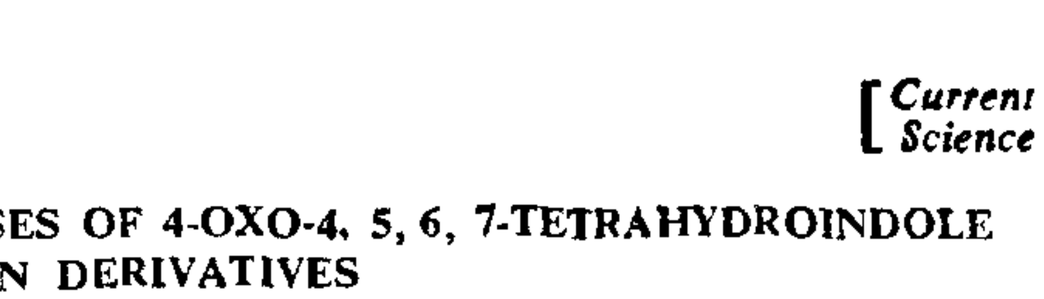
WE wish to report here a simple and convenient procedure for the synthesis of hitherto unknown heterocyclic compounds such as 2, 6, 6-trimethyl-4-oxo-4, 5, 6, 7-tetrahydroindole derivatives (2, 3 and 4) and also 2, 6, 6-trimethyl-4-oxo-4, 5, 6, 7-tetrahydrobenzofuran (5) (Chart I), starting with the easily available 2-acetonyldimedone.

2-Acetonyldimedone (1), prepared according to the procedure reported by Nagarajan and Shah[1] or by Stetter and Lauterbach[2] was treated with anhydrous ammonium acetate in boiling acetic acid to furnish after the usual work-up a pale brown solid (2) which on recrystallization from benzene-methylene chloride gave the analytical sample of 2, 6, 6-trimethyl-4-oxo-4, 5, 6, 7-tetrahydroindole (2) as a white crystalline solid, m.p. 181–182°, in 60% yield. Earlier procedure reported for the synthesis of such tetrahydroindole system with no substituent at position 1 consists in heating the 1, 4-diketone with liquor ammonia in an autoclave. But the present modification appears quite simple and furnishes the desired heterocyclic ketone (2) in high yield.

Similarly, condensation of 2-acetonyldimedone (1) with freshly distilled aniline and benzyl amine in boiling acetic acid afforded the anticipated heterocyclic ketones (3 and 4) in good yields. Cyclodehydration of 2-acetonyldimedone under the influence of anhydrous formic acid in boiling glacial acetic acid at 140° C furnished the desired tetrahydrobenzofuran derivative (5) as a thick gum which on trituration with hexane followed by recrystallization from hexane-methylene chloride gave the analytical sample of 2, 6, 6-trimethyl-4-oxo-4, 5, 6, 7-tetrahydrobenzofuran (5) as almost white solid, m.p. 74–75°, in *Ca* 50% yield. It may be quite relevant here to state that the conventional cyclodehydrating agents such as conc. sulphuric acid[4], P_2O_5,[5] etc., furnished the expected heterocyclic ketone (5) in low yield and also in a low order of purity. The use of a mixture of anhydrous formic and acetic acids at 140° appears to be the best cyclodehydrating agent for such 1, 4-diketones in furnishing the corresponding tetrahydrobenzofuran derivatives in high yields and also in greater purity.

The structures assigned to the four heterocyclic ketones (2–5) mentioned above are based on IR, NMR, mass spectral and analytical data (*vide* Experimental). The mass spectral fragmentations involving some interesting rearrangements reported in the case of these heterocyclic ketones (2–4) mentioned above are quite similar to those observed in the mass spectra of a series of 1, 2-diaryl-4-oxo-4, 5, 6, 7-tetrahydroindoles synthesized earlier in this laboratory. The details of these mass spectral fragmentations and the observed rearrangements have already been communicated in detail elsewhere[6].



(2) R = H
(3) R = C_6H_5
(4) R = CH_2-C_6H_5

CHART I

EXPERIMENTAL

I. *Preparation of 2-acetonyldimedone* (1):

This was prepared according to the procedure reported by Nagarajan and Shah[1]. Thus 14 g of dimedone, 13·7 g of freshly distilled bromoacetone and 45 g of anhydrous K_2CO_3 in 200 ml chloroform furnished (1) (14·8 g) in 76% yield, m.p. 133–134° (reported[1] m.p. 134°).

II. *Preparation of 2, 6, 6-trimethyl-4-oxo-4, 5, 6, 7-tetrahydroindole* (2):

2-Acetonyldimedone (1·96 g) and anhydrous ammonium acetate (4·5 g) (washed repeatedly with dry acetone and then dried under vacuo) were mixed with 30 ml of glacial acetic acid. The resulting mixture was heated under reflux to a temperature of 140° for 3 hours under anhydrous conditions. The hot reaction mixture was poured into 100 ml of ice-cold water. The aqueous solution is carefully neutralized with solid Na_2CO_3. The resulting neutral solution was extracted with ethyl acetate (3 × 25 ml). The organic layer, dried over anhydrous Na_2SO_4, was evaporated to furnish (2) as a pale brown solid which on recrystallization from benzene-methylene chloride (using a

little norit) gave the analytical sample of the ketone (2) (1·25 g) as a white crystalline solid, m.p. 181–182° in 60% yield. IR ($CHCl_3$) bands at 2960, 2920 and 2880 (NH and CH stretching), 1620 cm^{-1} (conjugated CO); NMR ($CDCl_3$) signals at δ1·1 (s, 6H, gem-dimethyl at C_6) 2·2 (s, 3H, methyl at C_2) 2·3 (s, 2H, methylene at C_5), 2·65 (s, 2H, methylene at C_7), 6·1 (s, 1H, proton at C_3) and 11·0 (s, 1H broad, NH); mass peaks at m/e 177 (M^+; 42%), 122 (11% r.D.A. + hydrogen transfer), 121 (100%, r.D.A. fragment) 93 (78%) and 42 (22%). (Found: C, 74·39, H, 8·42 and N 7·78%. $C_{11}H_{13}NO$ requires C, 74·58, H, 8·47 and N, 7·91%).

III. *Preparation of* 1-*phenyl*-2, 6, 6-*trimethyl*-4-*oxo*-4, 5, 6, 7-*tetrahydroindole* (3):

2-Acetonyldimedone (1·96 g) and freshly distilled aniline (1·38 g) were dissolved in 30 ml of glacial acetic acid. The mixture was heated to a temperature of 140° under reflux in anhydrous conditions. The resulting reaction mixture was worked up as detailed in Expt. No. II. The gummy material (3) on trituration with hexane solidified. Recrystallization of this solid from hexane-methylene chloride gave the analytical sample of the heterocyclic ketone (3) as a pale yellow crystalline solid (2·1 g), m.p. 81–82°, in 82% yield. IR ($CHCl_3$) bands at 2960 and 2920 (CH stretching), 1625 (conjugated CO), 1580, 1500 and 1480 cm^{-1} (aromatic skeletal vibrations), NMR ($CDCl_3$) signals at δ1·05 (s, 6H, gem-dimethyl at C_6), 2·02 (s, 3H, methyl at C_2); 2·35 (s, 2H, methylene at C_5), 2·45 (s, 2H, methylene at C_7), 6·3 (s, 1H, proton at C_3) and 7·1–7·6 (m, 5H, phenyl at N); mass peaks at m/e 253 (M^+; 38%); m/e 198 (12%; retro D.A. + hydrogen transfer), m/e 197 (100%; retro D.A. fragment), 169 (46%), m/e 168 (24%) and m/e 118 (22%). (Found: C, 80·38 H, 7·26 and N, 5·34%. $C_{17}H_{19}NO$ requires C, 80·63, H 7·51 and N, 5·53%).

IV. *Preparation of* 1-*benzyl*-2, 6, 6-*trimethyl*-4-*oxo*-4, 5, 6, 7-*tetrahydroindole* (4):

2-Acetonyldimedone (1·96 g) and benzylamine (1·62 g) were dissolved in glacial acetic acid (25 ml) and the mixture was heated to 140° under reflux. The resulting reaction mixture was worked up as described in Expt. No. III. The expected ketone (4) obtained as a gum was chromatographed over basic Brockmann alumina (50 g). Benzene eluates on evaporation yielded the purified sample of the ketone (4) which on trituration with hexane solidified. Recystallization from hexane-methylene chloride furnished the analytical sample of the heterocyclic ketone (4) as a white crystalline solid, (1·89 g), m.p. 85–86° in 70% yield. IR ($CHCl_3$) bands at 3020, 2960, 2920 and 2840 (CH stretching), 1640 (conjugated CO), 1510, 1460 and 1430 (aromatic skeletal vibrations); NMR ($CDCl_3$) signals at δ1·05 (s, 6H, gem-dimethyl at C_6), 2·05 (s, 3H, CH_3 at C_2), 2·35 (s, 2H, CH_2 at C_5), 2·60 (s, 2H, CH_2 at C_7), 5·02 (s, 2H, benzylic CH_2), 6·3 (s, 1H, proton at C_3) and 6·9–7·2 (m, 5H, aromatic); mass peaks at m/e 267 (M^+; 30%), m/e 212 (7%; retro D.A. + hydrogen transfer), m/e 211 (38%; retro D.A. fragment); m/e 183 (25%); ,m/e 182 (8%) and 91 (100%); (Found C, 80·68, H, 7·58 and N, 4·97%. $C_{18}H_{21}NO$ requires C, 80·91, H, 7·87 and N, 5·24%).

V. *Preparation of* 2, 6, 6-*trimethyl*-4-*oxo*-4, 5, 6, 7-*tetrahydrobenzofuran* (5):

2-Acetonyldimedone (1·96 g) is dissolved in a mixture of glacial acetic acid and anhydrous formic acid (80%) (2 : 1) (30 ml) and the mixture heated to 140° C under reflux. The reaction mixture was worked up as described in Expt. No. II. to furnish the expected ketone as a white solid which on recrystallization from benzene afforded the analytical sample of the heterocyclic ketone (5) (0·9 g) as dirty white flakes, m.p. 74–75°, in 50% yield. IR ($CHCl_3$) bands at 2900, 2920, 2880 (CH stretching), 1660 (conjugated C = 0), 1580 and 1550 cm^{-1} (C = C stretching of the furan ring); NMR ($CDCl_3$) δ1·1 (s, 6H, gem-dimethyl at C_6), 2·2 (s, 3H, CH_3 at C_2), 2·3 (s, 2H, CH_2 at C_6), 2·65 (s, 2H, CH_2 at C_7), 6·3 (s, 1H, H at C_2); mass peaks at m/e 178 (M^+; 60%), m/e 123 (5%; retro D.A. + hydrogen transfer), m/e 122 (100%; retro D.A. fragment), m/e 43 (60%). (Found: C, 74·19, H, 7·30%. $C_{11}H_{14}O_2$ requires C, 74·15, and H, 7·76%).

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