ACTA CHEMICA SCANDINAVICA 22 (1968) 1063–1066

A Simple Synthesis of 3-Acetoacetylindoles

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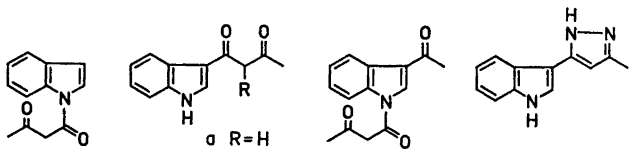
A facile method for the preparation of 3-acetoacetylindoles from indoles and diketene is described. These compounds are partly enolized and are easily alkylated to products which on hydrolysis give 3-acylindoles.

The reaction between indole and diketene has been investigated by several authors. Harley-Mason [1] and Treibs [2] obtained 1-acetoacetylindole (I) in unspecified yield by heating indole and diketene without a solvent. Perekalin and Slavachevskaya [3] obtained the same compound in 44 % yield by heating these components in a mixture of toluene and benzene, a tertiary aromatic amine being added to catalyse the reaction.

It has now been found that 3-acetoacetylindole (IIa) is obtained when an acetic acid solution of indole and diketene is heated to 120° for 3 h. At lower temperatures (100°) a mixture of both isomers (I and IIa) was obtained. When acetic anhydride was used as solvent, 1-acetoacetylindole (I) was obtained in excellent yield at 90° but on prolonged (24 h) boiling under reflux 1-acetoacetyl-3-acetylindole (III) was obtained in low yield. 3-Acetoacetylindole could not be detected in the reaction mixture. When dioxan (100°) or diethylene glycol dimethyl ether (130°) was used as solvent 1-acetoacetylindole (I) was obtained. The latter could not be transformed into IIa by refluxing with acetic acid.

1-Methylindole and 2-methylindole reacted with diketene in acetic acid solution (120°) with formation of 1-methyl-3-acetoacetylindole and 2-methyl-3-acetoacetylindole respectively, but with 3-methylindole a brownish product was obtained from which only unchanged 3-methylindole could be isolated.



I II III IV

Alkaline hydrolysis of the 3-acetoacetylindoles furnished the corresponding 3-acetylindoles; no indole-3-carboxylic acids could be detected in the reaction mixtures.

3-Acetoacetylindole (IIa) reacted readily with hydrazine with formation of the 1,2-diazole derivative IV, and it was reduced by excess lithium aluminium hydride in tetrahydrofuran to 3-butylindole. (Ether was found to be less suitable as a solvent owing to the formation of increased amounts of by-products' (3-butyrylindole and a compound with the same R_F-value as 3-(3-hydroxybutyl)indole, prepared by borohydride reduction of 3-(3-oxobutyl)-indole).

The potassium salt of 3-acetoacetylindole reacted with ethyl iodide yielding 3-(ethylacetoacetyl)indole (IIb). Other alkyl halides reacted similarly.

The diketo compounds are partly enolized and the composition of the equilibrium mixture was determined by NMR spectroscopy at 41° in deutero-chloroform and hexadeuterodimethyl sulphoxide. These relevant data are given in Table 1.

Table 1.

Compound	Percent enol	
	$DMSO_{d_6}$	$CDCl_3$
1-Methyl-3-acetoacetylindole	49	52
3-Acetoacetylindole (IIa)	47	—
1-Acetoacetylindole (I)	15	37
2-Methyl-3-acetoacetylindole	62	—
3-(Methylacetoacetyl)indole (IIc)	Not detectable	
3-(Ethylacetoacetyl)indole (IIb)	Not detectable	

EXPERIMENTAL

Melting points were determined on a micro hot stage and are uncorrected. Infrared spectra from potassium bromide discs were recorded using a Perkin Elmer No 237 instrument. The NMR spectra were determined with a Varian A60 spectrometer at concentrations in the range 120—130 mg/ml and using TMS as internal standard.

Chemicals. Schuchardt technical grade diketene (85—97 %) was used. Freshly distilled diketene gave slightly higher yields (0—5 %) of 3-acetoacetylindoles. 1-Methylindole was prepared according to Gray and Archer [4] and was purified by refluxing over potassium for 36 h and distilled. The product did not contain any 3-methylindole or indole as shown by TLC and IR.

3-Acetoacetylindole (IIa). Indole (58.5 g, 0.5 mole), diketene (60 ml) and acetic acid (300 ml) were boiled under reflux for 3 h. The brown solution was allowed to cool and poured into ice-water. The mixture was extracted with ether. After washing with water, the ether solution was dried. The ether was distilled off and the brown residue was triturated with carbon tetrachloride. The solid obtained was collected by filtration and recrystallized from ethanol:water (2:1) (norite). (Yield 40 g, 40 %). M.p. 146—148°. (Found: N 6.9. Calc. for $C_{12}H_{11}NO_2$: N 7.0).

3-Acetylindole. 3-Acetoacetylindole (1.0 g) was heated on the steam-bath with a mixture of 1 N sodium hydroxide and ethanol (1:1) (50 ml) for ten minutes. On cooling and addition of water, crystals separated, which were identified as 3-acetylindole (IR and mixed m.p.). (Yield 0.7 g, 88 %). M.p. 190—191° (Lit.[5] 191°).

1-Methyl-3-acetoacetylindole. 1-Methylindole (13.1 g, 0.1 mole), diketene (12 ml), and acetic acid (75 ml) were boiled under reflux for 3 h. The brown solution was allowed to

cool and poured into ice-water. The solid formed was dried and recrystallized from toluene. (Yield 10.5 g, 45 %). M.p. 117—118°. (Found: N 6.5. Calc. for $C_{13}H_{13}NO_2$: N 6.5).

2-Methyl-3-acetoacetylindole. 2-Methylindole (13.1 g, 0.1 mole), diketene (12 ml), and acetic acid (75 ml) were boiled under reflux for 3 h. The crystals which separated upon cooling were collected, washed with ethanol, dried and recrystallized from ethanol. (Yield 12 g, 51 %). M.p. 164—166°. (Found: N 6.4. Calc. for $C_{13}H_{13}NO_2$: N 6.5).

1-Methyl-3-acetylindole. 1-Methyl-3-acetoacetylindole was hydrolysed using the same conditions as for 3-acetoacetylindole. (Yield 90 %). M.p. 108—108.5° (Lit.[6] 109—110°).

3-Butylindole. 3-Acetoacetylindole (4.0 g) in 0.4 g portions was added to lithium aluminium hydride (8.0 g) in tetrahydrofuran (100 ml). The mixture was boiled under reflux for 8 h. Excess of the hydride was destroyed by careful addition of water under stirring. The mixture was then poured into water and ether. The ether phase was washed with water and dried. The ether was evaporated and the residue distilled, b.p. 145—148°/12 mm. (Yield 2.2 g, 65 %). The picrate melted at 102—103° (Lit.[8] 102—103°). The infrared spectrum (CCl_4) showed the following bands above 1600 cm^{-1}, 3490 (s) (free NH), 3410 (w) (associated NH), 3060 (w), 2940 (m) and 2860 cm^{-1} (w).

2-Methyl-3-acetylindole. 2-Methyl-3-acetoacetylindole (1.0 g) was refluxed with 1 N sodium hydroxide (50 ml) for 1 h. On cooling crystals separated. (Yield 0.8 g, 90 %). M.p. 201—202° (Lit.[7] 204°).

1-Acetoacetylindole (I). Indole (11.7 g, 0.1 mole), diketene (12 ml), and acetic anhydride (70 ml) were heated on the steam-bath for 2 h. The cooled solution was poured into water (300 ml). The brown solid formed was recrystallized from ethanol. On cooling colourless crystals separated. (Yield 17 g, 85 %). M.p. 94—95° (Lit.[1] m.p. 95—96°). When 1-acetoacetylindole was heated in boiling acetic acid for 3 h, a mixture was obtained from which unchanged starting material could be recovered in a 20 % yield. No 3-isomer could be detected by TLC.

1-Acetoacetyl-3-acetylindole (III). Indole (11.7 g), diketene (12 ml), and acetic anhydride (70 ml) were boiled under reflux for 24 h. The cooled solution was poured into water. The brown solid formed was recrystallized twice from ethanol. (Yield 5.5 g, 20 %). M.p. 179—180° (Lit.[3] 179—180°).

3-(3-Indolyl)-5-methyl-1,2-diazole (IV). A mixture of 3-acetoacetylindole (2.0 g), hydrazine hydrate (0.5 ml) and ethanol (25 ml) was boiled for one minute. On cooling crystals separated, which were recrystallized from ethanol. (Yield 1.4 g, 70 %). M.p. 223—224°. (Found: N 21.0. Calc. for $C_{12}H_{11}N_3$: N 21.3). The infrared spectrum showed broad absorption around 3000 cm^{-1} and bands at 3390, 1625, 1455, 1340, 1270, 1110, 1005, 935, 800, and 755 cm^{-1}. The NMR spectrum ($DMSO_{d_6}$) showed a 3H-peak at $\tau = 8.25$ (methyl group) and a 1H-peak at $\tau = 4.3$ (the aromatic proton of the 1-2-diazole ring). The indolic protons (5H) appeared between $\tau = 1.7$ and $\tau = 3.0$. A broad band appeared at $\tau = -1.5$ and a very broad at $\tau = -2.7$.

3-(Ethylacetoacetyl)indole (IIb). 3-Acetoacetylindole (2.0 g) was dissolved in ethanol (50 ml). Potassium hydroxide (0.56 g) in water (10 ml) was added followed by ethyl iodide (1.6 g) and the solution was boiled under reflux for 0.5 h. Acetic acid (1 ml) and excess water were added to the cooled solution. The solid obtained was washed with water, dried and recrystallized from benzene. (Yield 1.8 g, 78 %). M.p. 142—143°. (Found: N 6.0. Calc. for $C_{14}H_{15}NO_2$: N 6.1). Infrared bands in the carbonyl region: 1710 and 1610 cm^{-1}. The NMR spectrum ($CDCl_3$) showed triplets centered at $\tau = 9.1$ (methyl group) and $\tau = 6.1$ (methine proton). A strong signal appeared at $\tau = 8.2$ (acetyl group). The methylene protons gave a multiplet centered at $\tau = 8.0$. The aromatic protons appeared between $\tau = 1.7$ and $\tau = 3.0$.

3-(Methylacetoacetyl)indole (IIc). 3-Acetoacetylindole was alkylated as above with methyl iodide. (Yield 75 %). M.p. 140—141°. (Found: N 6.6. Calc. for $C_{13}H_{13}NO_2$: N 6.5). The NMR spectrum ($CDCl_3$) showed a doublet centered at $\tau = 9.4$ (methyl group) and a strong singlet at $\tau = 8.2$ (acetyl group). The methine proton gave a quartet centered at $\tau = 6.2$. IR: 1715 cm^{-1} (C=O), 1605 cm^{-1} (vinylog amide).

3-Butyrylindole. 3-(Ethylacetoacetyl)indole (1.0 g) was boiled with 2 N sodium hydroxide (30 ml) for 1 h. After cooling the solid was collected, dried and recrystallized from benzene. (Yield 0.5 g, 60 %). M.p. 176—178° (Lit.[9] 177—178.5°).

3-Propionylindole. 3-Propionylindole was prepared from 3-(methylacetoacetyl)indole using the method described above. (Yield 65 %). M.p. 171—173° (Lit.[10] 171—173°).

3-(3-Hydroxybutyl)indole. 3-(3-Oxobutyl)indole [11] (5.0 g) was added to a cooled (0–5°) solution of potassium borohydride (2.0 g) in ethanol (40 ml) and water (30 ml). The mixture was stored overnight without cooling and then poured into water. The crystals formed were separated and recrystallized from benzene. (Yield 3.9 g, 77 %). M.p. 58–59.5°. (Found: N 7.3. Calc. for $C_{12}H_{15}NO$: N 7.4). The infrared spectrum showed strong bands at 3520, 3210, 1075, and 695 cm^{-1}.

Acknowledgements. I thank Professor H. Erdtman for his interest in this work and for many useful suggestions. I also thank Miss G. Hammarberg for spectral assistance and Dr. P. Fredricks for kindly checking the English.

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Received November 17, 1967.