REACTION OF 2,3,3-TRIMETHYL-3H-INDOLIUM SALTS WITH CROTONALDEHYDE

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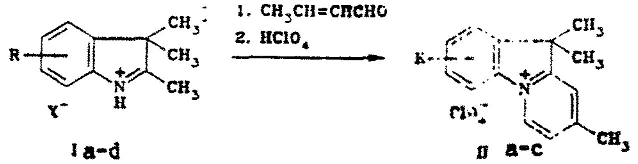
Reaction of 2,3,3-trimethyl-3H-indolium salts with crotonaldehyde leads to 8-methyl-10H-pyrido[1,2-a]indolium salts. Condensation of the latter with aromatic aldehydes gave 8-styryl-10H-pyrido[1,2-a]indolium derivatives.

We have previously shown that reaction of 2,3,3-trimethyl-3H-indolium salts with cinnamaldehyde leads to 8-phenyl-10H-pyrido[1,2-*a*]indolium chlorides [1]. The synthesis of 10H-pyrido[1,2-*a*]indolium derivatives by reaction of 2,3,3-trimethyl-3H-indolium salts with α,β-unsaturated ketones has been reported in [2-4]. The products of treating 2,3,3-trimethyl-3H-indolium perchlorate with dibenzylideneacetophenones are 6-styryl-8-phenyl-10H-pyrido[1,2-*a*]indolium perchlorates [5].

In this work we have studied the reaction of 2,3,3-trimethyl-3H-indolium salts with crotonaldehyde.



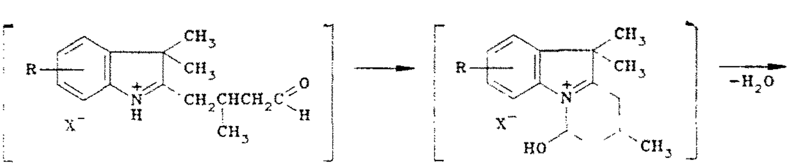
I a-d II a-c

Ia,b IIa R=H; I c R=5-CH_3, d R=7-CH_3; II b R=2-CH_3, c R=4-CH_3; Ia,c,d X=Cl, b X=Br

Heating 2,3,3-trimethyl-3H-indolium chloride (Ia) with crotonaldehyde in DMF, ethanol, or methanol and subsequent workup with perchloric acid gives 8-methyl-10H-pyrido[1,2-*a*]indolium perchlorate in 10-12% yields. There was also separated from the reaction mixture a significant amount of oily material, apparently the product of polymerization of the unsaturated aldehyde. When the reaction is carried out in alcohol in the presence of hydroquinone the yield of perchlorate IIa is increased to 26%.

Similar results were obtained for synthesis of perchlorate IIa from 2,3,3-trimethyl-3H-indolium bromide (Ib). Reaction of the salts Ic,d with crotonaldehyde gave the 2,8,10,10- and 4,8,10,10-tetramethyl-10H-pyrido[1,2-*a*]indolium perchlorates (IIb,c). As in the perchlorate IIa, the PMR spectra in acetone-D_6 show characteristic proton doublets for 6-H in the region 9.51-9.67 ppm with an ortho $J_{6\text{-H},7\text{-H}}$ coupling of 6.5 Hz.

The reaction of 2,3,3-trimethyl-3H-indolium salts Ia-d with crotonaldehyde apparently occurs in several stages. Although individual intermediates were not isolated, it is possible to propose a first stage of addition of the carbon of the 2-CH_3 group of the 3H-indolium salts to the activated carbon-carbon double bond of the unsaturated aldehyde. The formed Michael adducts IIIa-d then cyclize to 6-hydroxy-6,7,8,9-tetrahydro-10H-pyrido[1,2-*a*]indolium salts (IVa-d). The solvent takes part in the reaction via proton transfer.



IIIa-d IV a-d

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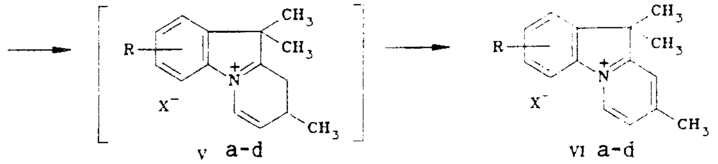
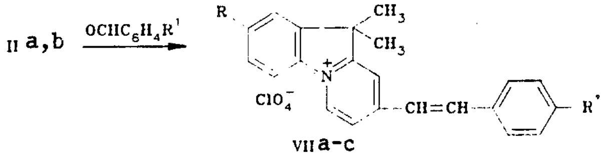


V a-d VI a-d

III—VI a,b R=H; III c R=5-CH_3, d, R=7-CH_3; IV—VI c R=2-CH_3, d R=4-CH_3;
III—VI a,c,d X=Cl, b X=Br

Subsequent elimination of water from IVa-d gives Va-d which contains a dihydropyridine ring and these then dehydrogenate to the 10H-pyrido[1,2-*a*]indolium salts VIa-d.

Like other pyridinium salts which contain a γ-oriented methyl group [6], the 8-methyl-10H-pyrido[1,2-*a*]indolium perchlorates IIa,b undergo condensation with aromatic aldehydes.



VII a-c

VIIa R=H, R^1=Cl; b R=H, R^1=NO_2; c R=CH_3, R^1=Cl

Heating IIa,b with 4-chloro- and 4-nitrobenzaldehydes in alcohol in the presence of piperidine gives the 8-styryl-10H-pyrido[1,2-*a*]indolium perchlorates VIIa-c.

EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 instrument for KBr tablets. PMR spectra were obtained on a Hitachi-Perkin–Elmer R-22 (90 MHz) instrument with HMDS internal standard. ^{13}C NMR spectra were taken on a Tesla BS-567 (25.14 MHz) spectrometer. Signal assignments were made from a series of different pulse methods [7] and using reported data [8, 9].

8,10,10-Trimethyl-10-pyrido[1,2-*a*]indolium Perchlorate (IIa, $C_{15}H_{16}ClNO_4$). **A.** Hydroquinone (0.05 g) was added to a solution of Ia (3.91 g, 20 mmoles) and crotonaldehyde (1.68 g, 1.96 ml, 24 mmoles) in alcohol (4.0 ml) and heated for 2 h at 70°C. The mixture was poured into water (40 ml), the solution filtered, and perchloric acid (48%, 4.19 g, 20 mmoles) added with stirring to the filtrate. The precipitate was filtered off, washed with water (20 ml), and dried. The product was dissolved in refluxing alcohol (12 ml), cooled to 20°C, held at this temperature for 30 min, and filtered. The filtrate was left at 20°C for 24 h and the crystallized material filtered and recrystallized from alcohol to give product (1.61 g, 26%) with mp 207-208°C (according to [2], mp = 206°C (from alcohol)). IR spectrum: 1640 ($C=N^+$); 1616, 1600 (C=C); 1460 (CH_3); 1098, 622 cm^{-1} (ClO_4^-). PMR spectrum (acetone-D_6): 1.79 (6H, s, 10,10-CH_3), 2.82 (3H, s, 8-CH_3,; 7.63-8.41 (4H, m, 1- to 4-H), 8.01-8.16 (1H, m, 7-H), 8.44-8.52 (1H, m, 9-H), 9.60 ppm (1H, d, J = 6.5 Hz, 6-H). ^{13}C NMR spectrum (DMSO-D_6): 21.9 (10-CH_3), 21.9 (10-CH_3), 25.0 (8-CH_3), 47.5 (C_{10}), 114.7 (C_4), 123.6 (C_1), 124.2 (C_9), 126.7 (C_7), 129.1, 130.8 (C_2, C_3), 134.6 (C_6), 138.8 (C_{10a}), 141.6 (C_{4a}), 159.3 (C_8), 162.6 ppm (C_{9a}).

B. Compound Ib (2.40 g, 10 mmoles) and crotonaldehyde (0.84 g, 0.98 ml, 12 mmoles) in alcohol (2.5 ml) containing hydroquinone (0.03 g) were used and the product separated as described in method **A**. The yield of IIa was 0.53 g (17%) and the melting point and PMR spectra were identical to those of the sample obtained by method **A**.

2,8,10,10-Tetramethyl-10H-pyrido[1,2-*a*]indolium perchlorate (IIb, $C_{16}H_{18}ClNO_4$) was obtained from Ic (2.10 g, 10 mmoles) and crotonaldehyde (0.84 g, 0.98 ml, 12 mmoles) as described for IIa (method **A**) in 0.50 g (15%) yield with mp 234-235°C (from alcohol). PMR spectrum (acetone-D_6): 1.77 (6H, s, 10,10-CH_3); 2.51 (3H, s, 2-CH_3), 2.80 (3H, s, 8-CH_3), 7.42-7.59 (1H, m, 3-H), 7.68-7.76 (1H, m, 1-H), 7.97-8.12 (1H, m, 7-H), 8.18 (1H, d, J = 8.3 Hz, 4-H), 8.40-8.48 (1H, m, 9-H), 9.51 ppm (1H, d, J = 6.5 Hz, 6-H).

4,8,10,10-Tetramethyl-10H-pyrido[1,2-*a*]indolium perchlorate (IIc, $C_{16}H_{18}ClNO_4$) was obtained from Id (4.19 g, 20 mmoles) and crotonaldehyde (1.68 g, 1.96 ml, 24 mmoles) similarly to IIa (method **A**) in 1.55 g (24%) yield with mp 241-242°C (from alcohol). PMR spectrum (acetone-D_6): 1.76 (6H, s, 10,10-CH_3), 2.78 (3H, s, 8-CH_3), 2.96 (3H, s, 4-CH_3), 7.48-8.28 (3H, m, 1- to 3-H), 8.01-8.16 (1H, m, 7-H), 8.43-8.52 (1H, m, 9-H), 9.67 ppm (1H, d, J = 6.5 Hz, 6-H).

10,10-Dimethyl-8-(4-chlorostyryl)-10H-pyrido[1,2-*a*]indolium Perchlorate (VIIa, $C_{22}H_{19}Cl_2NO_4$). Piperidine was added dropwise to a solution of IIa (0.62 g, 2 mmoles) and 4-chlorobenzaldehyde (0.28 g, 2 mmoles) in alcohol (6 ml) and refluxed for 4 h. The precipitate was filtered off and recrystallized from acetonitrile to give 0.50 g (58%) with mp 300-301°C. IR spectrum: 1636 ($C=N^+$), 1616, 1598 (C=C), 1460 (CH_3), 1092, 622 cm^{-1} (ClO_4^-). PMR spectrum ($DMSO-D_6$): 1.73 (6H, s, 10,10-CH_3), 7.19-8.46 (11H, m, CH=CH, Ar except 6-H, 9-H), 8.71 (1H, br.s, 9-H), 9.71 ppm (1H, d, J = 6.5 Hz, 6-H).

10,10-Dimethyl-8-(4-chlorostyryl)-10H-pyrido[1,2-*a*]indolium perchlorate (VIIb, $C_{22}H_{19}ClN_2O_6$) was obtained from IIa (0.62 g, 2 mmoles) and 4-nitrobenzaldehyde (0.30 g, 2 mmoles) similarly to VIIa in 0.39 g (44%) yield with mp 288-289°C (from acetonitrile). IR spectrum: 1640 ($C=N^+$); 1614, 1602, 1594 (C=C), 1516 (NO_2), 1454 (CH_3), 1096, 624 cm^{-1} (ClO_4^-). PMR spectrum ($DMSO-D_6$): 1.73 (6H, s, 10,10-CH_3), 7.61-8.46 (11H, m, CH=CH, Ar except 6-H, 9-H), 8.79 (1H, br.s, 9-H), 9.79 ppm (1H, d, J = 6.5 Hz, 6-H).

2,10,10-Trimethyl-8-(4-chlorostyryl)-10H-pyrido[1,2-*a*]indolium Perchlorate (VIIc, $C_{23}H_{21}Cl_{21}NO_4$). Piperidine was added dropwise to a solution of IIb (0.65 g, 2 mmoles) and 4-chlorobenzaldehyde (0.28 g, 2 mmoles) in alcohol (6 ml) and refluxed for 5 h. The solvent was evaporated and the residue crystallized from acetone to give 0.70 g (78%) with mp 281-282°C. PMR spectrum ($DMSO-D_6$): 1.72 (6H, s, 10,10-CH_3), 2.50 (3H, s, 2-CH_3), 7.38-8.34 (10H, m, CH=CH, Ar except 6-H, 9-H), 8.67 (1H, br.s, 9-H), 9.64 ppm (1H, d, J = 6.5 Hz, 6-H).

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