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AUTOXIDATION OF 2-AMINOINDOLES TO 3-OXO-DERIVATIVES.

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2-Ethoxy-, 2-ethylthio- and 2-piperidino-3-methylindoles (I,X=OEt, SEt and piperidino) have shown to be autoxidized to afford the 3-hydroxyindolenine, while 2-ethoxy- and 2-ethylthioindoles (II; a,X=OEt; b, X=SEt) are stable towards autoxidation[1,2].

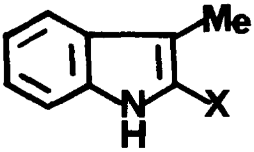
We now find that the 2-aminoindoles (IIc,X=piperidino, IIIa,b,c) having NH group undergo facil autoxidation to 3-oxo-derivatives.

Reaction of 1-methyl-2-indolinethione[3] with an excess of ethanolamine under a stream of nitrogen gave IIIa, which was purified as the hydrochloride, m.p. 235-238°. λ_{max}^{EtOH} mμ (ε); 238^{sh}(8,400), 266(11,600), 280^{sh} (7,400). Nmr (ppm from TMS in F_3CCOOH); 3.63(s,3H, N-Me), 4.12 (q, 2H, NCH_2-), 4.30 (s, 2H,3-CH_2), 4.80 (t, 2H, CH_2-O), 8.3 (s,broad, NH). ν_{max}^{KBr} cm^{-1}; 3310,3260 (OH), 1660 (C=N). When the hydrochloride was treated with $NaHCO_3$ and extracted with methylene chloride, then left overnight, IVa(R=CH_2CH_2OH) was obtained as orange red crystals, m.p. 98-99°. λ_{max}^{EtOH} mμ (ε); 232 (18,600), 257 (25,800), 263 (25,200), 300^{sh}(3,630), 470(1,300). Nmr(ppm from TMS in $CDCl_3$); 3.20(s, 3H, N-Me), 3.82(t, 2H, N-CH_2-), 4.20 (t, 2H, CH_2-O). ν_{max}^{KBr} cm^{-1}; 1710, 1650, 1610. Mass; m/e 204 (M^+, 44%). The structure of IVa was further confirmed by hydrolysis of IVa to 1-methylisatin on treatment with alumina. Presence of the free base (IIIa) was proved by the nmr spectrum taken immediately after basification of

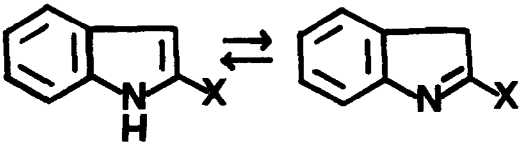
IIIa-HCl in $CDCl_3$ with aqueous NaOH, which showed an equilibrium mixture of III and III'.

Similarly 1-methyl-2-indolinethione gave IIIb and IIIc on heating with an excess of propylamine and iso-propylamine in butanol under a stream of nitrogen, respectively, and they were purified as the hydrobromides. IIIb-HBr, m.p. 244.5-245.5°. λ_{max}^{EtOH} mμ(ε); 238^{sh}(11,000), 264 (11,000). Nmr(ppm from TMS in $CDCl_3$); 1.00(t, 3H, C-Me), 1.92(m, 2H,C-CH_2-C), 3.50(q, 2H, N-CH_2-). IIIc-HBr, m.p. 286°. λ_{max}^{EtOH} mμ(ε); 238^{sh}(10,000), 267(10,400). On treatment with base, both IIIb-HBr and IIIc-HBr gave reddish semi-solid having λ_{max} 470 mμ, which was unable to crystallize. However, acid hydrolysis of these reddish semisolid provided 1-methylisatin in 76% and 56% yields respectively. These results clearly indicated that IIIb and IIIc had been autoxidized to 3-oxo-derivatives (IV) by the similar manner as in the case of IIIa.

The compound (IIc, X=piperidino) has been prepared by the reaction of IIa[2,4] or 2-indolinethione with piperidine. The hydrobromide (IIc-HBr), m.p. 269-270°, gave a dark red oil which showed λ_{max} 520 mμ and ν_{max} 1720 and 1570 cm^{-1} on treatment with triethylamine in dichloroethane in an atmosphere of oxygen. This oil could not be induced to crystallize but upon acid hydrolysis, 48% of isatin and piperidine-HCl were obtained. This result suggested that IIc was very susceptible to aereal oxidation in comparison with IIa[5] and IIb, and converted to V. Therefore, it is conceivable that the nitrogen atom at 2-position is the most effective to facilitate the autoxidation at 3-position of II probably due to the electron donating power of the nitrogen. The prominent effect of the substituent at 2-position in II also appeared in the indole-indolenine tautomerism in nmr spectra. In $CDCl_3$ IIa is shown to be an equilibrium mixture of indole-indolenine[6], whereas IIb is present as the indolic form[2]. However, the nmr spectrum of IIc in $CDCl_3$ taken immediately after basification of its hydrobromide showed only the indolenine form. (1.65(s,broad, 6H, β- and γ-H in piperidine), 3.57(s,broad, 6H, α-H in piperidine and 3-CH_2- of the indole ring), no indolic NH and 3-H signal)



I

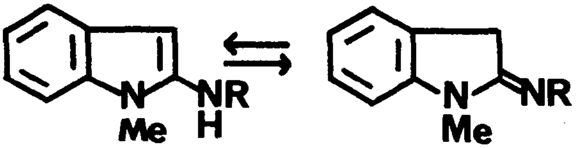


II

a: X=EtO

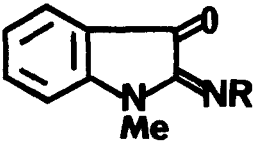
b: X=EtS

c: X=piperidino



III

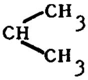
III'

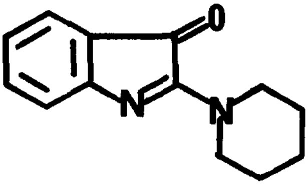


IV

a: R=CH_2CH_2OH

b: R=$CH_2CH_2CH_3$

c: R= 
$CH(CH_3)_2$



V

2-Aminoindole has been reported to be unstable towards air[7], but no characterization of the product has been made.

Details of the preparation of 2-aminoindoles from 2-indolinethiones and amines will be published in the near future.

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