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SYNTHESIS AND STUDY OF 5a,6-DIHYDRO-12H-INDOLO[2,1-b][1,3]-BENZOXAZINES

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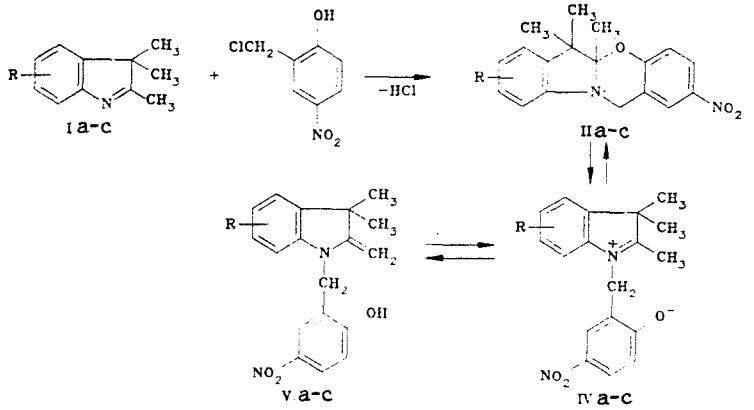
Reaction of 2,3,3-trimethyl-, 2,3,3,5- and 2,3,3,7-tetramethyl-3H-indoles with 4-nitro-2-chloromethylphenol has given the 5a,6-dihydro-12H-indolo-[2,1-b][1,3]-benzoxazines, which have been examined for ring-chain interconversion by NMR spectroscopy. Treatment of 5a,6-dihydro-12H-indolo[2,1-b][1,3]benzoxazines with either perchloric acid or potassium hydroxide results in opening of the dihydro-oxazine ring with the formation of indole derivatives.

Methods have been reported for the annelation of heterocycles to 3-H-indole, by reacting 2,3,3-trimethyl-3H-indole or its salts with a variety of bifunctional compounds [1-4], and by reacting 2,3-dimethyl-1H-indole with 2-chloromethylphenols to give 2,3-dimethyl-3-(2-hydroxybenzyl)-3H-indolium salts, which undergo ready cyclization to benzypyranol[2,3-b]indoles [5].

We have now examined the reaction of the 3H indoles (Ia-c) with 4-nitro-2-chloromethyl-phenol.

It was found that 2,3,3-trimethyl-3H-indole (Ia) reacts with 4-nitro-2-chloromethylphenol to give the 5a,6-dihydro-12H-indolo[2,1-b][1,3]benzoxazine (IIa) in 60% yield, while the methylated indoles (Ib) and (Ic) gave (IIb) and (IIc) in yields of 27 and 15% respectively.



I IV, V a R=H; b R=5-CH_3; c R=7-CH_3; II a R=H; b R=8-CH_3; c R=10-CH_3

The ^1H NMR spectrum of (IIa) (in CCl_4) showed signals for the diastereotopic geminal methyl groups at 1.13 and 1.47 ppm (Fig. 1a), together with a singlet for the 5a-CH_3 at 1.52 ppm, situated in the cis-position with respect to the lone pair of the nitrogen [6]. When the ^1H NMR spectrum of (IIa) was recorded in $CDCl_3$, the signals for the geminal methyl groups underwent considerable broadening (Fig. 1b), and when 5-10% of methanol was added to the solution, they coalesced. Similar broadening of the signal for the carbon atoms of the geminal methyl groups was seen in the ^{13}C NMR spectrum (in $CDCl_3$), obtained with full

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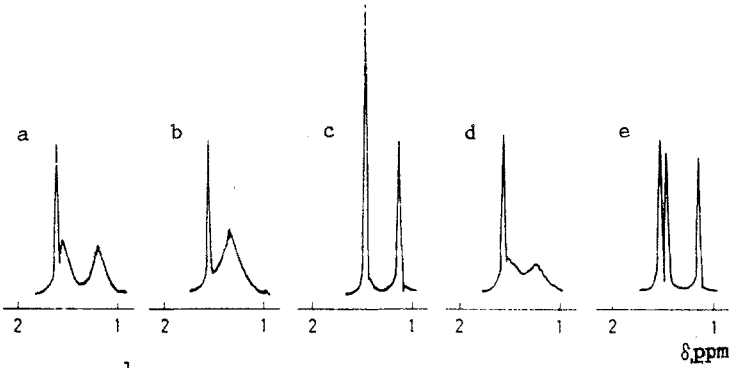
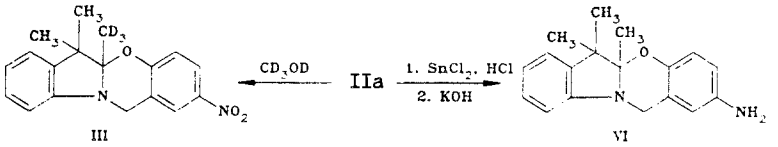
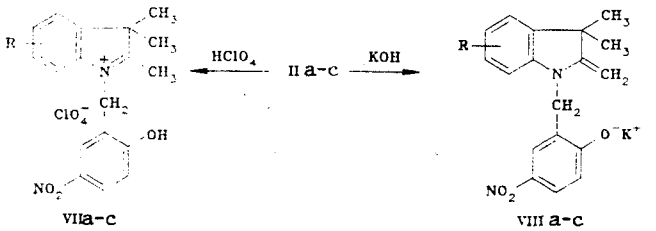


Fig. 1. ^1H NMR spectrum of methyl groups in positions 5a, 5, and 6 in indolo[2,1-b][1,3]benzoxazines, obtained in CCl_4 (a) and $CDCl_3$ (b-e): a, b) (IIa), c) (VI), d) (IIb), e) (IIc).

decoupling from protons. When deuteromethanol was added to the solution of (IIa) in $CDCl_3$, the signal for the protons of the 5a-CH_3 group in the ^1H NMR spectrum disappeared, indicating the formation of the deuterated compound (III).



It is assumed that in solution in polar solvents (IIa) exists in equilibrium with the open-chain form (IVa), which can isomerize to the methylene base (Va). The proportion of the open-chain form in the mixture is, however, extremely small, since no characteristic absorption for (IVa) or (Va) was seen in either the electronic or IR spectra (in alcohol and chloroform respectively), within the sensitivity limits of the instruments used. The observed broadening and shift of the signals for the atoms of the diastereotopic methyl groups in the NMR spectra of (IIa) is due to inversion of the chiral center at $C_{(5a)}$, since addition of the phenolic oxygen to the α-carbon of the indole nucleus during recyclization can occur from either side of the chiral center with the same probability [7, 8]. In this case, changes in the stability of the ring form of (IIa) will affect the signals for these atoms. Examination of ring-chain interconversions in a number of compounds has shown that electron-donor substituents sited close to the electrophilic center destabilize the ring form, but conversely when present in the nucleophilic moiety of the molecule they favor closure of the ring [9, 10]. In fact, no marked changes were seen in the shape and positions of the signals in the ^1H NMR spectrum of (VI) (Fig. 1, c), which contains an amino-group in the 2-position, when CCl_4 was replaced by $CDCl_3$, showing that the equilibrium is shifted towards the ring form as compared with the original compound (IIa). The ^1H NMR spectrum of (IIb) in $CDCl_3$ shows coalescence of the signals for the geminal methyl groups (Fig. 1d) as a result of a shift in the equilibrium towards the open-chain form under the influence of the methyl group in the 8-position, which increases the electron density at the α-carbon of the indole ring. However (as will be seen from Fig. 1e) the methyl group in the 10-position, on the other hand, stabilizes the ring form, owing to the steric effect of this methyl group, which is essentially similar to the so-called steric compound effect [10].



VII, VIII a R=H; b R=5-CH_3; c R=7-CH_3

On treatment with perchloric acid, the benzoxazines (IIa-c) are converted into the perchlorates (VIIa-c), the IR spectra of which show OH absorption for the phenolic OH at 3220-3300 cm^{-1}. When potassium hydroxide is added to an aqueous-ethanolic solution of (IIa-c) to pH 9, absorption is seen in the visible region of the electronic spectrum at 408-410 nm characteristic of the phenoxide anion, indicating that the dihydrooxazine ring has been cleaved with the formation of (VIIIa-c).

EXPERIMENTAL

IR spectra were obtained on a Perkin-Elmer 325 in KBr disks or chloroform. ^1H NMR spectra were obtained on a Tesla BS-487C (80 MHz) at 25°C, internal standard HMDS. ^{13}C NMR spectra were recorded on a Tesla BS-567 (25.14 MHz). The signals were assigned by using different impulse methods for recording the spectra [11], and the data given in [4, 6]. Mass spectra were obtained on a Riber-1010 (100 eV), with direct introduction of the compounds into the ion source and temperatures of 150-190°C. Electronic absorption spectra were obtained with a Specord UV-VIS. The reactions were followed and the purities of the products established by TLC on grade II alumina in the system acetone—hexane, 3:5, visualized with iodine vapor.

The elemental analysis of (IIa-c), (III), and (VI) for C, H, and N, and of (VIIa-c) for Cl, were in agreement with the calculated values.

2-Nitro-5a,6,6-trimethyl-5a,6-dihydro-12H-indolo[2,1-b][1,3]benzoxazine (IIa, $C_{18}H_{18}N_2O_3$). To a solution of 9.55 g (60 mmole) of the indole (Ia) in 5 ml of nitromethane was added a solution of 12.38 g (66 mole) of 4-nitro-2-chloromethylphenol in 20 ml of nitromethane. The mixture was kept for 2 h at room temperature, and 20 h at 0-3°C. The crystals of (IIa) which separated were filtered off, the filtrate poured into 120 ml of water, treated with 5% aqueous potassium hydroxide until alkaline, and extracted with 20 ml of ether. After 2 h, 8.30 g of solid had separated from the solution. This was filtered off, and washed with 10 ml of ether. The ether layer was separated, washed with water, dried over calcium chloride, and 4/5 by volume of the solvent distilled off. The residue was kept for 24 h at −5°C, to give a further 1.10 g of crystalline (IIc). The overall yield of (IIa) was 11.3 g (61%), mp 176-177°C (from acetone). UV spectrum (in alcohol), λ_{max} (log ε): 212 (4.12), 236 (4.15), 318 nm (4.07). ^1H NMR spectrum (CCl_4): 1.13 (3H, s, 6-CH_3), 1.47 (3H, s, 6-CH_3), 1.52 (3H, s, 5a-CH_3), 4.58 (2H, s, CH_2), 6.31-8.06 ppm (7H, m, Ar). ^{13}C NMR spectrum ($CDCl_3$): 16.3 (5a-CH_3), 18.8 (br, 6-CH_3), 25.5 (br, 6—CH_3), 39.8 ($C_{(12)}$); 47.8 ($C_{(6)}$); 102.7 ($C_{(5a)}$); 108.2, 117.9, 120.3, 122.1, 123.1, 123.7, 127.4 ($C_{(1)}$, $C_{(3)}$, $C_{(4)}$, $C_{(7-10)}$); 118.7, 137.9, 140.4, 146.5, 159.0 ppm ($C_{(2)}$, $C_{(4a)}$, $C_{(6a)}$, $C_{(10a)}$, $C_{(12a)}$). Found: M+ 310. Calculated: M 310.

2-Nitro-5a,6,6,8-tetramethyl-5a,6-dihydro-12H-indolo[2,1-b][1,3]benzoxazine (IIb, $C_{19}H_{20}N_2O_3$). A solution of 2.25 g (13 mmole) of 2,3,3,5-tetramethyl-3H-indole and 2.63 g (14 mmole) of 4-nitro-2-chloromethylphenol in 6 ml of nitromethane was kept for 6 h at room temperature. The mixture was poured into 20 ml of water, 5% potassium hydroxide solution added until alkaline, and extracted with ether (2 × 15 ml). The extract was washed with water (2 × 10 ml), dried over calcium chloride, the solvent removed, and the residue crystallized from 2 ml of ether at −5°C. Yield 1.15 g (27%), mp 168-169°C (from acetone). UV spectrum (in alcohol), λ_{max} (log ε): 212 (4.56), 238 (4.53), 318 nm (4.44). ^1H NMR spectrum (CCl_4): 1.13 (3H, s, 6-CH_3), 1.47 (3H, s, 6-CH_3), 1.53 (3H, s, 5a-CH_3), 2.23 (2H, s, CH_2), 6.18-8.06 ppm (6H, m, Ar). Found: M^+ 324. Calculated: M 324.

2-Nitro-5a,6,6,10-tetramethyl-5a,6-dihydro-12H-indolo[2,1-b][1,3]benzoxazine (IIc, $C_{19}H_{20}N_2O_3$). A solution of 2.43 g (14 mmole) of 2,3,3,7-tetramethyl-3H-indole and 3.0 g (16 mmole) of 4-nitro-2-chloromethylphenol in 7 ml of nitromethane was kept for 20 h at room temperature, then heated for 2 h at 60°C. The mixture was poured into 20 ml of water, basified with 5% potassium hydroxide solution, and extracted with ether (2 × 15 ml). The extract was washed with water (2 × 10 ml), dried over calcium chloride, the solvent removed, and the residue chromatographed on a column (600 × 25 mm) of alumina (R_f 0.73, eluent acetone—hexane, 3:5). Yield 0.68 g (15%), mp 148-149°C. UV spectrum (alcohol), λ_{max} (log ε): 213 (4.35), 237 (4.24), 320 nm (4.16). ^1H NMR spectrum ($CDCl_3$); 1.13 (3H, br. s, 6-CH_3), 1.49 (3H, br. s, 6-CH_3), 1.61 (3H, s, 5-aCH_3), 4.68, 5.13 (2H, br AB quadruplet, J_{AB} = 15 Hz, CH_2), 6.56-8.06 ppm (6H, m, Ar). Found: M^+ 324. Calculated: M 324.

6,6-Dimethyl-2-nitro-5a-trideuteromethyl-5a,6-dihydro-12H-indolo[2,1-b][1,3]-benzoxazine (III, $C_{18}H_{15}D_3N_2O_3$). A solution of 0.62 g (2 mmole) of (IIa) in a mixture of 8 ml of chloroform and 10 ml of methanol-D_4 was boiled for 10 min. The mixture was cooled to 0°C, and the

crystals which separated filtered off. Yield 0.39 g (62%), mp 175-176° (from methanol-D_4). The ^{1}H NMR spectrum of (III) (in CCl_4) was identical to that of (IIa) in the same solvent, except that there was no singlet for the 5a-CH_3 group at 1.52 ppm. Found: M^+ 313. Calculated: M 313.

2-Amino-5a,6,6,-trimethyl-5a,6-dihydro-12H-indolo[2,1-b][1,3]benzoxazine (VI, $C_{18}H_{20}N_2O$). To a solution of 0.93 g (3 mmole) of 2-nitroindolo[2,1-b][1-3]benzoxazine in 10 ml of conc. HCl was added at 80°C a solution of 1.89 g (10 mmole) of tin(II) chloride in 5 ml of the same acid. The mixture was boiled for 3 min, and cooled to 20°C. The precipitate was filtered off, dissolved in 30 ml of water, and basified with 5% potassium hydroxide solution. The compound which separated was extracted with ether (2 × 20 ml), the extract washed with water (2 × 15 ml), and dried over calcium chloride. The solvent was removed, and the residue crystallized from alcohol to give 0.30 g (36%) of product, mp 134-135°C, UV spectrum (alcohol), λ_{max} (log ε): 212 (4.00), 241 (4.05), 298 nm (3.50). IR spectrum (KBr): 3335, 3445 cm^{-1} (NH_2). ^{1}H NMR spectrum ($CDCl_3$): 1.12 (3H, s, 6-CH_3), 1.49 (3H, s, 6-CH_3), 1.49 (3H, s, 5a-CH_3), 3.26 (2H, br, s, NH_2), 4.49 (2H, s, CH_2), 6.33-7.23 ppm (7H, m, Ar). ^{13}C NMR spectrum ($CDCl_3$): 15.6 (5a-CH_3); 18.7 (6-CH_3); 25.7 (6-CH_3); 40.2 ($C_{(12)}$); 47.4 ($C_{(6)}$); 99.4 ($C_{(5a)}$); 107.8, 112.7, 115.5, 118.1, 119.3, 121.8, 127.1 ($C_{(1)}$, $C_{(3)}$, $C_{(4)}$, $C_{(7-10)}$); 191.1, 138.4, 139.0, 145.9, 147.6 ppm. ($C_{(2)}$, $C_{(4a)}$, $C_{(6a)}$, $C_{(10a)}$, $C_{(12a)}$).

1-(2-Hydroxy-4-nitrobenzyl)-2,3,3-trimethyl-3H-indolinium Perchlorate (VIIa, $C_{18}H_{19}ClN_2O_7$). To a hot solution of 0.31 g (1.0 mmole) of (IIa) in 30 ml of alcohol was added 0.3 ml of 60% perchloric acid. The mixture was cooled to 0°C, and kept for 24 h. The crystalline solid was filtered off and recrystallized from alcohol. Yield 0.35 g (85%), mp 244-245°C (decomp.). UV spectrum (alcohol), λ_{max} (log ε): 212 (4.16, 235 (4.17), 316 nm (4.10). IR spectrum (KBr): 3225 (OH), 1540 (NO_2), 1150-1040 cm^{-1} (ClO_4^-). ^{1}H NMR spectrum (CF_3COOH): 1.31 (6H, s, 3,3-CH_3), 2.64 (3H, s, 2-CH_3), 5.46 (2H, s, CH_2), 6.66-8.24 ppm (7H, m, Ar).

1-(2-Hydroxy-4-nitrobenzyl)-2,3,3,5-tetramethyl-3H-indolinium perchlorate (VIIb, $C_{19}H_{21}ClN_2O_7$) was obtained from 0.32 g (1.0 mmole) of IIb (as for the perchlorate (VIIa). Yield 0.34 g (75%), mp 240-241°C (decomp., from alcohol). IR spectrum (KBr): 3290 (OH), 1645 (NO_2), 1150-1040 cm^{-1} (ClO_4^-). ^{1}H NMR spectrum (CF_3COOH): 1.28 (6H, s, 3,3-CH_3), 2.09 (3H, s, 5-CH_3), 2.61 (3H, s, 2-CH_3), 5.39 (2H, s, CH_2), 6.67-8.16 ppm (6H, m, Ar).

1-(2-Hydroxy-4-nitrobenzyl)-2,3,3,7-tetramethyl-3H-indolinium perchlorate (VIIc, $C_{19}H_{21}ClN_2O_7$) was obtained from 0.32 g (1.0 mmole) of (IIc), as for the perchlorate (VIIa). Yield 0.30 g (71%), mp 235-236°C (decomp., from alcohol). IR spectrum (KBr): 3280 (OH), 1540 (NO_2), 1150-1140 cm^{-1} (ClO_4^-). ^{1}H NMR spectrum (CF_3COOH): 1.34 (6H, s, 3,3-CH_3), 2.19 (3H, s, 7-CH_3), 2.46 (3H, s, 2-CH_3), 5.59 (2H, s, CH_2), 6.61-8.18 ppm (6H, m, Ar).

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