ALKYLATION OF 1,2,3,9a-TETRAHYDRO-9H-IMIDAZO[1,2-a]INDOL-2-ONES

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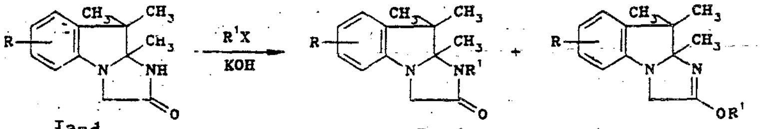
Reaction of 1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indol-2-ones with dimethyl sulfate and haloalkanes in DMF or DMSO in the presence of potassium hydroxide gives the 1-substituted 1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indol-2-ones (N-substituted products) and 9,9a-dihydro-3H-imidazo[1,2-a]indoles (O-substituted products). The latter, on treatment with acids and bases, are converted into 1-alkoxycarbonylmethyl-2,3-dihydro-1H-indoles. 1-Ethoxycarbonylmethyl-2,3-dihydro-1H-indoles on treatment with lithium aluminohydride undergoes cyclization to 2,3,9,9a-tetrahydrooxazolo[3,2-a]indole.

The reaction of 2,3,3-trimethyl-3H-indole with N-substituted chloroacetamides to give 1-substituted 1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indol-2-ones has been reported previously [1]. The aim of the present investigation was to obtain these compounds by alkylating 1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indol-2-ones (Ia-d) with dimethyl sulfate and other alkylating agents.

Direct alkylation of compounds containing the NHCO grouping, in particular amides and lactams, under neutral conditions is known to rarely give exclusively the N-substituted products. Usually, a mixture of O- and N- substituted, or the O-substituted products only, are obtained [2]. N-Alkylation may be accomplished by treating amides or lactams with dialkyl sulfates or haloalkanes in the presence of sodium hydride or sodamide [2, 3], or in systems containing alkali metal fluorides [4, 5]. A convenient method for the N-alkylation of amides by reaction with haloalkanes in polar aprotic solvents in the presence of potassium hydroxide has recently been developed [6, 7].



Ia-d IIa-ℓ IIa-1

Ia, IIa-h, IIIa-h R=H; Ib, IIi, j IIIi, j R=7-CH_3; Ic, IIk, IIIk R=7-Br; Id, IIℓ, IIIℓ R=5-CH_3; II, IIIa $R^1=CH_3$, b, i, k $R^1=C_2H_5$, c R^1=p-C_3H_7, d R^1=p-C_4H_9, e, j, ℓ $R^1=CH_2C_6H_5$, f $R^1=CH_2CH=CH_2$, g $R^1=CH_2C\equiv CH$, h $R^1=\alpha\text{-}CH_2C_{10}H_7$

Reaction of (Ia-d) with dimethylsulfate, the lower haloalkanes, benzyl or allyl chlorides, propargyl bromide, or 1-chloromethylnaphthalene in DMF or DMSO in the presence of potassium hydroxide gives a mixture of N- and O- substituted products (IIa-l) and (IIIa-l). According to the PMR spectra, the proportion of N-substituted product formed on reaction with iodomethane or dimethylsulfate is at least 95%, and with the other compounds, 72-80%. The O-alkylated product can readily be separated from the reaction mixture by treating it with an 0.5% solution of hydrochloric acid in ether or benzene.

Strong proton acids convert 1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indol-2-ones into 1-carbamoylmethyl-3H-indolium salts [1, 8]. Treatment of 9,9-dihydro-3H-imidazo[1,2-a]-indoles (IIIb, e) with acids such as hydrochloric or trifluoroacetic results in fission of the imidazoline ring with the formation of the iminoester salts (IVb, e, m, n). For example, in the PMR spectrum of (IIIb) in trifluoroacetic acid, signals are present which may be assigned to protons of the dication of salt (IVm): 2.61 (3H, s, 2-CH_3), 4.34 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$), 5.69 ppm (2H, s, CH_2CO), etc. The salts of the iminoesters (IVb, e, m, n) are hydrolyzed on treatment with water to the esters (Vb, e, m, n). Addition of 3-5% of water to a solution of (IIIb) in trifluoroacetic acid results in the slow disappearance from the PMR spectrum of the signals for the dication of salt (IVm) and the appearance of signals

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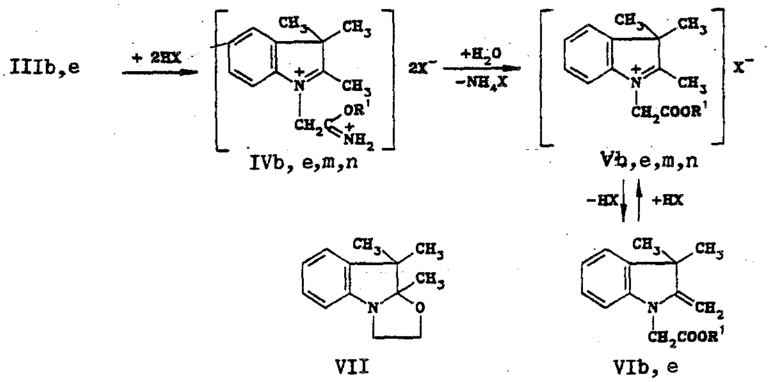
TABLE 1. 1,2,3,9a-Tetrahydro-9H- and 9,9a-dihydro-3H-imidazo[1,2-a]indoles

Compound	T_{mp}*, °C	Found, N, %	Empirical formula	Calculated, N, %	Yield, %
I d	191—192	12,5	$C_{14}H_{18}N_2O$	12,2	12
II g	92—93	11,0	$C_{16}H_{18}N_2O$	11,0	37
II h	176—177	8,0	$C_{24}H_{24}N_2O$	7,9	51
II i	94—95	11,0	$C_{16}H_{22}N_2O$	10,8	62
II j	135—136	9,0	$C_{21}H_{24}N_2O$	8,8	58
II k	137—138	8,8	$C_{15}H_{19}BrN_2O$	8,7	62
II l	144—145	9,1	$C_{21}H_{24}N_2O$	8,7	53
III b	39—40	11,7	$C_{16}H_{22}N_2O$	11,5	11
III e	69—70	9,4	$C_{20}H_{22}N_2O$	9,1	8

*Compounds (Id) and (IIℓ) were crystallized from alcohol, (IIg, h, i) from acetone, (IIi, k) from acetone—hexane, and (IIIe) from hexane.

characteristic of (VIb) in the same solvent: 2.48 (3H, s, 2-CH_3), 4.04 (2H, q, J = 7 Hz, $\underline{CH_2}CH_3$), 5.03 ppm (2H, s, CH_2CO), etc. The shift of the signals for the protons of salt (Vm) to higher field as compared with the signals of the same protons in the iminoester salt (IVm) is due to the fact that the carbonyl group is less electronegative than the $C{=}\overset{+}{N}H_2$ group. Treatment of hydrochloric acid solutions of (IIIb, e) with sodium carbonate gives the esters (VIb, e). The synthesis of (VIb) by reaction of the 3H-indole (Ia) with ethyl bromoacetate has been reported [9].



IV—VI b $R^1{=}C_2H_5$; e $R^1{=}CH_2C_6H_5$, IV, V m $R^1{=}C_2H_5$, n $R^1{=}CH_2C_6H_5$; IV, V b, e, $X{=}Cl$; m, n $X{=}CF_3COO$

It has already been shown [10] that 1-carbamoylmethyl-2-methylene-2,3-dihydro-1H-indole cyclizes on treatment with lithium aluminohydride to 1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]-indole. 1-Ethoxycarbonylmethyl-2-methylene-2,3-dihydro-1H-indole (VIb) is converted under similar conditions into 2,3,9,9a-tetrahydrooxazolo[3,2-a]indole (VII). The preparation of (VII) by the reaction of 3H-indole (Ia) with ethylene oxide or 2-bromoethanol has been reported [13, 14].

EXPERIMENTAL

PMR spectra were obtained on a Tesla BS 487C instrument (80 MHz), internal standard HMDS. IR spectra were obtained on a UR-20 spectrometer (KBr disks), and UV spectra (in alcohol) on a Specord UV-VIS. The progress of the reactions and the purity of the products were checked by TLC on grade II alumina in the system acetone—hexane (2:5), visualized with iodine vapor.

The properties of the new imidazo[1,2-a]indoles are given in Tables 1 and 2.

5,9,9,9a-Tetramethylene-1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indol-2-one (Id). A mixture of 8.66 g (50 mmole) of 2,3,3,7-tetramethyl-3H-indole and 9.35 g (100 mmole) of α-chloroacetamide was heated for 12 h at 140°C. The mixture was dissolved in 200 ml of 3% sulfuric acid, and extracted with ether (2 × 30 ml). The acid layer was basified with 5% potassium hydroxide, and extracted with ether (2 × 30 ml). The solvent was removed, and the residue crystallized from alcohol.

TABLE 2. PMR spectra (in $CDCl_3$) of 1,2,3,9a-tetrahydro-9H- and 9,9a-dihydro-3H-imidazo[1,2-a]indoles

Compound	δ, ppm				
	9,9-CH_3 (two s)	9a-CH_3 (s)	NCH_2CO (AB system)*	Ar (m)	NH, R, R' (in addition to Ar)
Id	1,16; 1,26	1,45	3,74; 3,94 (16,0)	6,75—7,03	2,24 (3H, s, 5-CH_3); 8,61 (1H, s, NH)
IIg	1,18; 1,38	1,55	3,75; 3,99 (15,5)	6,60—7,26	2,14—2,26 (1H, m, CH); 3,75—4,38 (2H, m, CH_2)
IIh	1,01; 1,28	1,34	3,89; 4,16 (15,5)	6,70—8,18	4,88; 5,11 (2H, AB-system, $J_{AB}=16$ Hz, CH_2)
IIi	1,01; 1,38	1,44	3,63; 3,98 (15,0)	6,55—7,05	1,27 (3H, t, $J=7$ Hz, CH_2CH_3); 2,26 (3H, s, 7-CH_3); 2,83—3,88 (2H, m, CH_2)
IIj	1,01; 1,25	1,37	3,75; 4,13 (15,0)	6,58—7,43	2,24 (3H, s, 7-CH_3); 4,16; 4,93 (2H, AB-system, $J_{AB}=15{,}5$ Hz, CH_2)
IIk	1,02; 1,38	1,43	3,62; 3,99 (15,5)	6,49—7,33	1,26 (3H, t, $J=7$ Hz, CH_3); 2,75—3,86 (2H, m, CH_2)
IIℓ	0,98; 1,18	1,41	3,68; 4,24 (15,5)	6.76—7.50	2,19 (3H, t, 5-CH_3): 4,06; 5,14 (2H, AB system $J_{AB}=15{,}5$ Hz, CH_2)
IIIb	1,19; 1,36	1,34	3,76; 3,95 (15,7)	6,50—7,18	1,17 (3H, t, $J=7$ Hz., CH_3), 4,09 (2H, q., CH_2)
IIIe	1,24; 1,40	1,38	3,86; 4,03 (15,5)	6,58—7,43	5,04; 5,12 (2H, AB-system $J_{AB}=12$ Hz., CH_2)

*Parameters of the AB-system: δ_A, δ_B (J_{AB}, Hz).

1,9,9,9a-Tetramethyl-1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indol-2-one (IIa). A. To a solution of 4.32 g (20 mmole) of (Ia) in 20 ml of DMF was added 3.37 g (60 mmole) of finely ground potassium hydroxide, followed by the dropwise addition of 5.05 g (3.79 ml, 40 mmole) of dimethylsulfate. The mixture was kept at 20°C for 1 h, poured into 150 ml of water, and extracted with ether (3 × 25 ml). The extract was washed with 0.5% hydrochloric acid until all the O-methyl compound (IIIa) had been removed from the mixture (TLC, R_f of (IIa) 0.52 and of (IIIa) 0.90, eluent acetone—hexane, 2:5). The ether solution was washed with 20 ml of 3% sodium carbonate, water (2 × 20 ml), dried over calcium chloride, and the solvent removed to give 3.30 g (72%) of (IIa), mp 42-43°C; lit. 42-43°C [1]).

B. The reaction of 2.16 g (10 mmole) of (Ia) with 2.84 g (1.25 ml, 20 mmole) of iodomethane in 10 ml of DMSO in the presence of 1.40 g (25 mmole) of potassium hydroxide, and the isolation of the product were carried out as in method A. Yield of (IIa), 1.70 g (74%); mp and R_f identical with those of material obtained by method A.

9,9,9a-Trimethyl-1-ethyl-1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indol-2-one (IIb). To a solution of 6.49 g (30 mmole) of (Ia) in 35 ml of DMF was added 4.49 g (80 mmole) of finely ground potassium hydroxide, followed by the dropwise addition of 9.36 g (4.84 ml, 60 mmole) of iodoethane. The mixture was kept at 20°C for 1 h, poured into 200 ml of water, and extracted with ether (3 × 25 ml). The extract was washed with water (3 × 20 ml) and dried over calcium chloride. The solvent was removed, and the residue crystallized from a mixture of acetone and hexane. Yield of (IIb), 4.16 g (57%), mp 82-83°C; lit. mp 82-83°C [1]. IR spectrum: 1650 cm^{-1} (C=N). UV spectrum, λ_{max} (log ε): 209 (4.08), 235 (3.79), 283 nm (3.32).

Compounds (IIc, d) were obtained from (Ia) and propyl or butyl iodide, as for (IIa) (method A). Yield of (IIc) 52%, mp 90-91°C (from cyclohexane). Yield of (IId) 61%, mp 59-60°C (from a mixture of cyclohexane and hexane). Identical melting points have been reported [1] for (IIc) and (IId).

Compounds (IIe-ℓ) were obtained by reacting compounds (Ia-d) with ethyl iodide, benzyl chloride, allyl chloride, propargyl bromide, or 1-chloromethylnaphthalene as for (Ib). Yield of (IIe) 55%, mp 146-147°C (from alcohol). Yield of (IIf) 63%, mp 104-105°C (from acetone). Identical melting points have been reported [1] for (IIe, f).

9,9,9a-Trimethyl-2-ethoxy-9,9a-dihydro-3H-imidazo[1,2a]indole (IIIb). The reaction of 6.49 g (30 mmole) of (Ia) with 9.36 g (60 mmole) of ethyl iodide was carried out as for (IIb). The resulting mixture of N- and O-ethyl compounds was chromatographed on a column (600 × 32 mm) of alumina, the fraction with R_f (acetone—hexane, 1:15) being collected. Removal of the solvent gave (IIIb) as an oil, which crystallized on keeping at −5°C.

2-Benzyloxy-9,9,9a-trimethyl-9,9a-dihydro-3H-imidazo[1,2-a]indole (IIIe) was obtained from 6.49 g (30 mmole) of (Ia) and 7.59 g (6.88 ml, 60 mmole) of benzyl chloride, as for (IIIb). R_f of (IIIe) 0.55 (acetone—hexane, 1:15).

3,3-Dimethyl-2-methylene-1-ethoxycarbonylmethyl-2,3-dihydro-1H-indole (VIb). A solution of 1.22 g (5 mmole) of the indole (IIIb) in 8 ml of acetone was poured with stirring into 40 ml of 3% hydrochloric acid. The solution obtained was neutralized with sodium carbonate to pH 9, and the compound which separated was extracted with ether (2 × 20 ml). The extract was washed with 20 ml of water, dried over sodium sulfate, the solvent removed, and the residue chromatographed on a column (550 × 25 mm) of alumina (R_f 0.62, acetone–hexane, 1:15) to give 0.75 g (61%) of (VIb) as an oil. PMR spectrum ($CDCl_3$): 1.25 (2H, t, J = 7 Hz, CH_2CH_3), 1.41 (6H, s, 3,3-CH_3), 3.90, 3.95 (2H, AB system, J_{AB} = 2.3 Hz, C=CH_2), 4.19 (2H, q, CH_2CH_3), 4.38 (2H, s, NCH_2), 6.59-7.43 ppm (4H, m Ar). Found: N 6.0%. $C_{15}H_{19}NO_2$. Calculated: N 5.7%. The PMR spectrum of (VIb) was identical with that of the product obtained as described in [14].

Compound (VIe) was obtained from 1.24 g (4 mmole) of the indole (IIIe) as for (VIb). The yield of (VIe) (an oil) was 0.65 g (53%), R_f 0.55 (acetone–hexane, 1:15). PMR spectrum ($CDCl_3$): 1.32 (6H, s, 3,3-CH_3), 3.80, 3.86 (2H, AB system, J_{AB} = 2.3 Hz, C=CH_2), 4.21 (2H, s, NCH_2), 5.11 (2H, s, OCH_2), 6.34-7.38 ppm (9H, m, Ar). Found N 4.7%. $C_{20}H_{21}NO_2$. Calculated: N 4.6%.

9,9,9a-Trimethyl-2,3,9,9a-tetrahydrooxazolo[3,2-a]indole (VII). To a solution of 0.38 g (10 mmole of lithium aluminohydride in 30 ml of dry diethyl ether was added over 20 min with stirring an ether solution of 1.23 g (5 mmole) of (VIb). Excess lithium aluminohydride was destroyed with 0.5 ml of water, the solid filtered off, and the ether solution dried over calcium chloride. The solvent was distilled off, and the residue chromatographed on a column (600 × 25 mm) of alumina (R_f 0.84, acetone–hexane, 2:15), to give 0.73 g (72.2%) of (VII), mp 44-45°C, lit. mp [13] 44-46°C. Found: N 6.7%. $C_{13}H_{17}NO$. Calculated; N 6.9%.

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