ALKYLATION OF 1,2,3,4,10,10a-HEXAHYDROPYRIMIDO[1,2-a]INDOL-2-ONE

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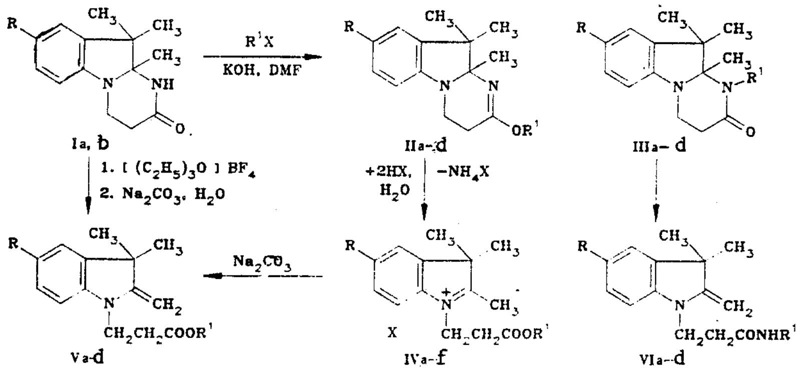
A mixture of N- and O-alkylation products is formed in the reaction of 1,2,3,4,10,10a-hexahydropyrimido[1,2-a]indol-2-ones with ethyl iodide, allyl bromide, or benzyl chloride in DMFA (dimethylformamide) in the presence of potassium hydroxide. In the presence of aqueous solutions of acids with subsequent treatment with bases, the alkylation products are converted to 1-[2-(alkoxycarbonyl)-ethyl]-2-methylene-2,3-dehydro-1H-indoles. The reaction of 1,2,3,4,10,10a-hexahydropyrimido[1,2-a]indol-2-one with triethyloxonium fluoroborate gives 1-[2-(ethoxycarbonyl)ethyl]-2-methylene-2,3-dihydro-1H-indole.

Derivatives of 1-(alkoxycarbonylalkyl)-2-methylene-2,3-dihydro-1H-indole or the corresponding 3H-indolium salts are intermediates in the synthesis of substances used in information-recording processes [1-3]. 1-(Alkoxycarbonylmethyl)-2-methylindoles can be obtained by the reaction of 2,3,3-trimethyl-3H-indole with α-bromocarboxylic acid esters [1, 4] or by alkylation of imidazo[1, 2-a]indol-2-ones with subsequent decyclization and hydrolysis of the O-substituted compounds [5]. However, methods for preparation of the corresponding 2-methyleneindoles containing a 2-(alkoxycarbonyl)ethyl group at the nitrogen atom have not been described in the literature. In the present paper, we investigated the synthesis of these compounds by alkylation of 1,2,3,4,10,10a-hexahydropyrimido[1,2-a]indol-2-one derivatives.

A mixture of the O- and N-alkylation products IIa-d and IIIa-d is formed in the reaction of pyrimido[1,2-a]indol-2-ones Ia and Ib with ethyl iodide, allyl bromide, and benzyl chloride in DMFA in the presence of potassium hydroxide. In this case, unlike in alkylation of 1,2,3,9a tetrahydro-9H-imidazo[1,2-a]indol-2-one derivatives under similar conditions [5], predominantly O-substituted compounds are obtained, with their proportion in the mixture being 75-80% according to data of PMR spectra. During treatment of compounds IIa-d with hydrochloric acid or 30% perchloric acid, the dihydropyrimidine ring is cleaved with subsequent hydrolysis of the imino ether group to an alkoxycarbonyl one, and the final reaction products are 3H-indolium salts IVa-f.



Ia, IIa—c—VIa—c, IVe-f R=H; Ib, IId—VId R=CH_3; IIa—VIa, IVe R¹=C_2H_5; IIb—VIb R¹=$CH_2CH=CH_2$; IIc,d-VIc,d, IVf R¹=$CH_2C_6H_5$; IVa—d X=Cl; e,f X=ClO_4

An absorption band of a C=O ester group is present in the IR spectra of perchlorates IVe and IVf at 1740 cm^{-1} [6]. 1-[2-(Alkoxycarbonyl)ethyl]-2,3-dihydro-1H-indoles Va-d were obtained by treating hydrochloric acid solutions of compounds IIa-d with sodium carbonate.

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In an attempt to recover N-substituted pyrimido[1,2-a]indol-2-ones IIIa-d in pure form by chromatography of a mixture of alkylation products on a column with silica gel or aluminum oxide, IIIa-d were isomerized to methylene bases VIa-d. The structure of the thus-recovered compounds VIa and VIc was confirmed by the IR spectra, which contained absorption bands in the regions of 3265-3260 (N—H), 1650 (C=O), and 1565-1560 cm^{-1} (amide II), characteristic of secondary amides [6].

It is known that trialkyloxonium salts are selective reagents for O-alkylation of lactams and related compounds [7]. Only O-ethylation of the amide group occurs in the reaction of pyrimido[1,2-a]indol-2-one Ia with triethyloxonium fluoroborate, and the final reactions product after treatment of the alkylation product with the base is ester Va.

EXPERIMENTAL

The IR spectra were obtained on a UR-20 spectrometer (in KBr tablets or in a thin layer). The PMR spectra were recorded on a Tesla BS-487C instrument (80 MHz), and the internal standard was HMDS. Mass spectra were recorded on a Riber-1010 instrument with direct introduction of the substance into the ion source, and the ionizing voltage was 100 eV. The reactions and the purity of the substances were monitored by thin-layer chromatography (TLC) on aluminum oxide of second activity grade in the 1:6 acetone—hexane system with development by iodine vapor. The data of elemental analysis for C, H, N, and Cl corresponded to the calculated values.

10,10,10a-Trimethyl-2-ethoxy-3,4,10,10a-tetrahydropyrimido-[1,2-a]indole (IIa, $C_{16}H_{22}N_2O$) and 3,3-Dimethyl-2-methylene-1-[2-(N-ethylcarbamoyl)ethyl]-2,3-dihydro-1H-indole (VIa, $C_{16}H_{22}N_2O$). To a solution of 2.30 g (10 mmoles) of compound Ia in 12 ml of DMFA was added 1.68 g (30 mmoles) of finely ground potassium hydroxide, and 3.90 g (2.02 ml, 25 mmoles) of ethyl iodide was added dropwise. The mixture was stirred for 2 h at 20°C, poured into 70 ml of water, and extracted with ether (3 × 20 ml). The extract was washed with water (3 × 20 ml) and dried with magnesium sulfate, the solvent was driven off, and the residue was chromatographed on a column (350 × 25 mm) with Al_2O_3 (eluent methyl ethyl ketone—hexane, 1:2). From the first fraction, with R_f 0.96, after the solvent had been driven off, oily compound IIa was obtained, which crystallized during storage at −5°C. The yield was 1.27 g (49%), mp 33-34°C. IR spectrum (KBr): 1680 cm^{-1} (C=N). PMR spectrum ($CDCl_3$): 1.11 (3H, triplet, J = 7.0 CH_2CH_3); 1.16 (3H, singlet, 10-CH_3); 1.35 (6H, singlet, 10-CH_3, 10a-CH_3); 1.56-4.21 (4H, multiplet, CH_3CH_2); 3.96 (2H, triplet, J = 7.0 Hz, OCH_2); 6.53-7.21 ppm (4H, multiplet, Ar). M^+ 258.

From the second fraction, with R_f 0.68, compound VIa was obtained. The yield was 0.46 g (18%), mp 66-67°C (from an acetone—hexane mixture). PMR spectrum ($CDCl_3$); 0.93 (3H, triplet, J = 7.0 Hz, CH_2CH_3); 1.29 (6H, singlet, 3,3-CH_3); 2.43 (2H, triplet, J = 7.0 Hz, CH_2CO); 3.05-3.30 (2H, multiplet, CH_2CH_3); 3.68 (2H, triplet, J = 7.0 Hz, NCH_2CH_2); 3.86 (2H, singlet, C=CH_2); 5.90 (1H, broadened singlet, NH); 6.55-7.28 ppm (4H, multiplet, Ar).

2-(Allyloxy)-10,10,10a-trimethyl-3,4,10,10a-tetrahydropyrimido-[1,2-a]indole (IIb, $C_{17}H_{22}N_2O$). This compound was obtained similarly to compound IIa from 2.30 g (10 mmoles) of pyrimido[1,2-a]indol-2-one (Ia) and 3.02 g (2.16 ml, 25 mmoles) of allyl bromide, with collection, during chromatography, of a fraction with R_f 0.83 (eluent methyl ethyl ketone, 2:7). The yield was 1.03 g (38%), mp 38-39°C. IR spectrum (KBr): 1680 cm^{-1} (C=N). PMR spectrum ($CDCl_3$): 1.16 (3H, singlet, 10-CH_3); 1.38 (6H, singlet, 10-CH_3, 10a-CH_3); 1.71-3.98 (4H, multiplet, CH_2CH_2); 4.21-6.25 (5H, multiplet, $CH_2CH{=}CH_2$); 6.56-7.28 ppm (4H, multiplet, Ar).

2-(Benzyloxy)-10,10,10a-trimethyl-3,4,10,10a-tetrahydropyrimido-[1,2-a]indole (IIc, $C_{21}H_{24}N_2O$) and 1-[2-(N-Benzylcarbamoyl)-ethyl]-3,3-dimethyl-2-methyl-2,3-dihydro-1H-indole (VIc, $C_{21}H_{24}N_2O$). To a solution of 4.60 g (20 mmoles) of compound Ia in 25 ml of DMFA was added 3.36 g (60 mmoles) of finely ground potassium hydroxide, and 5.06 g (4.60 ml, 40 mmoles) of benzyl chloride was added dropwise. The mixture was held for 2 h at 20°C, poured into 150 ml of water, and extracted with ether (3 × 25 ml). The extract was washed with water (3 × 25 ml) and dried with calcium chloride, the ether was driven off, and the residue was crystallized from acetone. The crystalline material was filtered, washed with 10 ml of ether, and dried. Obtained: 2.50 g of compound IIc. The filtrate was chromatographed on a column (550 × 25 mm) with silica gel L40/100 (eluent methyl ethyl ketone—hexane, 1:1). From the first fraction, with R_f 0.95, 0.70 g more of compound IIc was obtained. The total yield was 50%, mp 95-96°C (from acetone). IR spectrum (KBr): 1675 cm^{-1} (C=N). PMR spectrum ($CDCl_3$): 1.13 (3H, singlet, 10-CH_3); 1.36 (6H, singlet, 10-CH_3, 10a-CH_3); 1.63-3.88 (4H, multiplet, CH_2CH_2); 4.83; 5.10 (2H, AB system, J_{AB} = 12.5 Hz, OCH_2); 6.45-7.58 ppm (9H, multiplet, Ar). M^+ 320.

From the second fraction, with R_f 0.43, compound VIc was obtained. The yield was 0.50 g (8%), mp 99-100°C (from an acetone–hexane mixture). PMR spectrum ($CDCl_3$): 1.25 (6H, singlet, 3,3-CH_3); 2.48 (2H, triplet, J = 7.0 Hz, CH_2CO); 3.89 (2H, triplet, J = 7.0 Hz, NCH_2CH_2); 3.89 (2H, singlet, $C{=}CH_2$); 4.30 (2H, doublet, J = 3.0 Hz, $NHCH_2$); 5.90 (1H, broadened singlet, NH); 6.55-7.30 ppm (9H, multiplet, Ar). M^+ 320.

2-(Benzyloxy)-8,10,10,10a-tetramethyl-3,4,10,10a-tetrahydropyrimido-[1,2-a]indole (IId, $C_{22}H_{26}N_2O$). This compound was obtained similarly to compound IIc from 2.44 g (10 mmoles) of pyrimido[1,2-a]indol-2-one Ib and 2.53 g (2.30 ml, 20 mmoles) of benzyl chloride and was recovered by crystallization of the mixture from acetone. The yield was 1.20 g (36%), mp 91-92°C. PMR spectrum ($CDCl_3$): 1.14 (3H, singlet, 10CH_3); 1.34 (6H, singlet, 10-CH_3, 10a-CH_3); 1.88-3.78 (4H, multiplet, CH_2CH_2); 2.27 (3H, singlet, 8-CH_3); 4.84; 5.11 (2H AB system, J = 12.5 Hz, OCH_2); 6.46-7.38 ppm (8H, multiplet, Ar). M^+ 334.

2,3,3-Trimethyl-1-[2-(ethoxycarbonyl)ethyl]-3H-indolium Perchlorate (IVe, $C_{16}H_{22}ClNO_6$). A solution of 0.26 g (1 mmole) of compound IIa in 4 ml of alcohol was treated with 30% perchloric acid to pH 1. The mixture was held for 24 h at 5°C, and the precipitated crystalline material was filtered and recrystallized from alcohol. The yield was 0.25 g (70%), mp 160-161°C. PMR spectrum (CF_3COOH): 0.88 (3H, triplet, J = 7.0 Hz, CH_2CH_3); 1.25 (6H, singlet, 3,3-CH_3); 2.58 (3H, singlet, 2-CH_3); 2.91 (2H, triplet, J = 7.0 Hz, CH_2CO); 2.93 (2H, quartet, J = 7.0 Hz, OCH_2); 4.56 (2H, triplet, J = 7.0 Hz, NCH_2); 7.25-7.45 ppm (4H, multiplet, Ar).

1-[2-(Benzyloxycarbonyl)ethyl]-2,3,3,-trimethyl-3H-indolium Perchlorate (IVf, $C_{21}H_{24}ClNO_6$). This compound was obtained similarly to compound IVe from 0.32 g (1 mmole) of compound IIc. The yield was 0.21 g (51%), mp 127-128°C (from alcohol). PMR spectrum (CF_3COOH): 1.09 (6H, singlet, 3,3-CH_3); 2.37 (3H, singlet, 2-CH_3); 2.96 (2H, triplet, J = 7.0 Hz, CH_2CO); 4.53 (2H, triplet, J = 7.0 Hz, NCH_2); 4.87 (2H, singlet, OCH_2); 6.85-7.35 ppm (9H, multiplet, Ar).

3,3-Dimethyl-2-methylene-1-[2-(ethoxycarbonyl)ethyl]-2,3-dihydro-1H-indole (Va, $C_{16}H_{21}NO_2$). A. The reaction of 5.07 g (22 mmoles) of compound Ia with 8.58 g (4.44 ml, 55 mmoles) of ethyl iodide in 25 ml of DMFA containing 3.70 g (66 mmoles) of potassium hydroxide was carried out as described in the procedure for the preparation of compounds IIa and VIa. The obtained mixture of alkylation products was dissolved in 15 ml of acetone and poured into 5% HCl (150 ml). The solution was held for 30 min at 20°C and treated with sodium carbonate to pH 9. The recovered material was extracted with ether (2 × 25 ml), and the extract was washed with water (20 ml) and dried with calcium chloride. The solvent was driven off, and the residue was distilled in vacuo at 3.33 hPa, with collection of a fraction with bp 139-142°C. The yield of oily compound Va was 2.60 g (46%), R_f 0.85 (Al_2O_3 and acetone–hexane, 1:6). IR spectrum (thin layer): 1740 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 1.19 (3H, triplet, J = 7.0 Hz, CH_2CH_3); 1.32 (6H, singlet, 3.3-CH_3); 2.51-2.76 (2H, multiplet, CH_2CO); 3.77-4.02 (4H, multiplet, NCH_2, $C{=}CH_2$); 4.14 (2H, quartet, J = 7.0 Hz, OCH_2); 6.56-7.31 ppm (4H, multiplet, Ar).

B. A solution of 2.30 g (12 mmoles) of triethyloxonium fluoroborate in 8 ml of methylene chloride was added to a solution of 2.30 g (10 mmoles) of compound Ia in 20 ml of methylene chloride. The mixture was held for 16 h at 20°C, and the crystalline material, was filtered and dissolved in water (50 ml). The solution was treated with sodium carbonate to pH 9 and extracted with ether (2 × 15 ml). The extract was washed with water (15 ml) and dried with calcium chloride, and the solvent was driven off. Obtained: 1.45 g (56%) of compound Va, identical, according to TLC data and the PMR spectrum, to the sample obtained by method A.

1-[2-(Allyloxycarbonyl)ethyl]-3,3-dimethyl-2-methylene-2,3-dihydro-1H-indole (Vb, $C_{17}H_{21}NO_2$). A solution of 0.54 g (2 mmoles) of compound IIb in 4 ml of acetone was poured, with stirring, into 12 ml of 5% HCl. The mixture was held for 30 min at 20°C and treated with sodium carbonate to pH 10. The recovered material was extracted with ether (2 × 15 ml), and the extract was washed with water (15 ml) and dried with calcium chloride. The solvent was driven off, and the residue was chromatographed on a column (300 × 10 mm) with Al_2O_3 (R_f 0.85 and eluent acetone–hexane, 1:6). Obtained: 0.36 g (66%) of oily compound Vb. IR spectrum (thin layer): 1750 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 1.29 (6H, singlet, 3.3-CH_3); 2.51-2.77 (2H, multiplet, CH_2CO); 3.76-4.00 (2H, multiplet, NCH_2); 3.91 (2H, singlet, $C{=}CH_2$): 4.46-6.18 (5H, multiplet, $Ch_2CH{=}CH_2$); 6.53-7.31 ppm (4H, multiplet, Ar).

1-[2-(Benzyloxycarbonyl)ethyl]-3,3-dimethyl-2-methylene-2,3-dihydro-1H-indole (Vc, $C_{21}H_{23}NO_2$). This compound was obtained similarly to compound Vb from 0.64 g (2 mmoles) of compound IIc. The yield of oily compound Vc was 0.54 g (84%), R_f 0.79 (Al_2O_3 and acetone–hexane, 1:6). IR spectrum (thin layer): 1730 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 1.29 (6H, singlet, 3,3-CH_3); 2.57-2.82 (2H, multiplet, CH_2CO); 3.78-4.06 (2H, multiplet, NCH_2); 3.93 (2H, singlet, C=CH_2); 5.14 (2H, singlet, OCH_2); 6.58-7.45 ppm 9H, multiplet, Ar).

1-[2-(Benzyloxycarbonyl)ethyl]-2-methylene-3,3,5-trimethyl-2,3-dihydro-1H-indole (Vd, $C_{22}H_{25}NO_2$). This compound was obtained similarly to compound Vb from 0.67 g (2 mmoles) of compound IIe. The yield of oily compound Vd was 0.42 g (63%), R_f 0.81 (Al_2O_3 and acetone–hexane, 1:6). PMR spectrum ($CDCl_3$): 1.27 (6H, singlet, 3,3-CH_3); 2.27 (3H, singlet, 5-CH_3); 2.52-2.67 (2H, multiplet, CH_2CO); 3.73-3.99 (2H, multiplet, NCH_2); 3.86 (2H, singlet, C=CH_2); 5.11 (2H, singlet, OCH_2); 6.43-7.43 ppm (8H, multiplet, Ar).

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