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1,2,3,9a-TETRAHYDRO-9H-IMIDAZO[1,2-a]INDOLES

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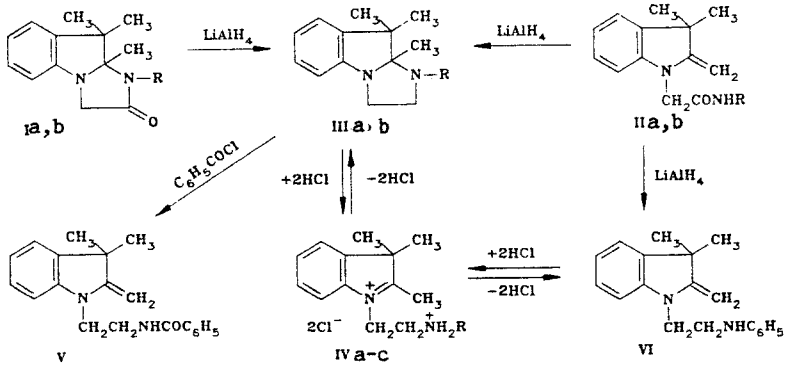
When derivatives of 1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indol-2-one or 1-carbamoylmethyl-2-methylene-2,3-dihydroindole are reacted with lithium aluminum hydride, derivatives of 1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indole are formed. Under the same conditions 1-(N-phenylcarbamoylmethyl)-2-methylene-2,3-dihydroindole is not cyclized to an imidazo[1,2-a]indole. When treated with proton acids imidazo[1,2-a]indoles are converted to 3H-indolium salts. Opening of the imidazolidine ring is also found when imidazo[1,2-a]indole is acylated with benzoyl chloride.

It has been reported previously [1] that when 1-carbamoylmethyl-2,3,3-trimethyl-3H-indolium chloride is treated with bases an intramolecular nucleophilic addition of the amide nitrogen to the α-carbon atom of the indole ring takes place with the formation of 1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indol-2-one (Ia). In this reaction a certain fraction of the initial salt does not undergo cyclization but is converted to the methylene base IIa. It was of interest to carry out the reduction of the carbonyl group of imidazolidines Ia,b and 1-carbamoylmethyl-2-methylene-2,3-dihydroindoles IIa,b to a methylene group using lithium aluminum hydride and to study the cyclic chain conversions of the hydrogenated compounds obtained when they were treated with acids and bases.

The tricyclic compounds Ia,b react with lithium aluminum hydride extremely slowly and the yields of imidazolidines IIIa,b after heating for 36 h in tetrahydrofuran do not exceed 20%. Under similar conditions reduction of the carbonyl group of the methylene base IIa is complete within 1.5-2 h.



I, III, IV a R=H, b R=$CH_2C_6H_5$; II a R=H, b R=C_6H_5; IV c R=C_6H_5

In this case addition of the nitrogen atom to the enamine double bond takes place and the final reaction product is imidazolidine IIIa. This cyclization can be grouped with those reactions typical of enamine compounds [2, 3].

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In the PMR spectrum (in $CDCl_3$) of compound IIIa the methylene protons of the imidazolidin ring form a complex multiplet in the region 2.85-3.55 ppm. Absorption maxima in the UV spectrum of compound IIIa (in ethanol) are observed at 210, 241, and 285 nm (log ε: 4.00, 3.76, 3.28).

When treated with HCl 1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indoles IIIa,b decyclize and are converted to dichlorides IVa,b. In the UV spectrum of compound IVa (in ethanol) when compared with the spectrum of compound IIIa there is a hypsochromic displacement of the absorption bands (λ_{max}: 208, 234, 278 nm; log ε: 3.91, 3.75, 3.30), indicating that 3H-indolium salts are formed [4, 5]. In the PMR spectrum (in D_2O) of dichloride IVa the methylene protons give two triplets at 3.45 and 4.16 ppm (J = 7 Hz). The presence of a triplet at 4.16 ppm (J = 4.5 Hz) from the methylene protons of the benzyl group in the spectrum of dichloride IVb (in CF_3COOH) is due to their spin–spin coupling with the protons on the nitrogen atom. When aqueous solutions of salts IVa,b are treated with bases, only the initial 1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indoles IIIa,b are formed.

Opening of the imidazolidine ring also occurs when compound IIIa is acylated with benzoyl chloride. The structure of the 1-(2-benzamidoethyl)-2-methylene-2,3-dihydroindole (V) obtained in this way is confirmed by the presence in its PMR spectrum (in $CDCl_3$) of an AB quadruplet from the protons of the terminal methylene group with its center at 3.91 ppm and a geminal spin–spin coupling constant equal to 2.5 Hz.

When 1-(N-phenylcarbamoylmethyl)-2-methylene-2,3-dihydroindole is reacted with lithium aluminum hydride, intramolecular cyclization does not occur and the reaction product is compound VI. When treated with HCl compound VI is converted to salt IVb, which in turn forms the initial base VI when treated with sodium carbonate.

EXPERIMENTAL

PMR spectra were recorded on a Tesla BS-487C instrument (80 MHz). IR spectra were obtained on a UR-20 spectrometer (KBr pellets or thin layer); electronic absorption spectra were obtained on a Specord UV-vis instrument. Mass spectra were obtained on a Riber-1010 instrument with direct introduction of material into the ion source at a temperature of 150-200°C and with ionizing potential 100 eV. The course of the reaction and the purity of the materials were monitored by means of TLC on alumina (activity grade II) in the system acetone–hexane (3:5) with development using iodine vapor.

9,9,9a-Trimethyl-1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indole (IIIa) and 1-(2-Ethylammonium)-2,3,3-trimethyl-3H-indolium Dichloride (IVa). A. To a solution of 0.52 g (15 mmole) of lithium aluminum hydride in 80 ml of absolute tetrahydrofuran was added 3.24 g (15 mmole) of imidazo[1,2-a]indol-2-one (Ia) and the mixture was agitated for 36 h at 55°C. Excess lithium aluminum hydride was decomposed with 0.5 ml of water and the precipitate was filtered off. After 4/5 of the solvent had been distilled off the solution was cooled to 5°C, the unreacted initial material was filtered off, and the filtrate was poured into 150 ml of water and extracted with petroleum ether (2 × 20 ml). The extract was washed with 20 ml of water and dried over calcium chloride. The solvent was distilled off and the residue chromatographed on an Al_2O_3 column (600 × 25 mm) (R_f 0.57, eluent: acetone–hexane, 3:5). A yield of 0.90 g (20%) of the oily compound IIIa was obtained. IR spectrum (thin layer): 3300 cm^{-1} (N–H). PMR spectrum ($CDCl_3$): 1.16 (3H, s, CH_3); 1.26 (3H, s, CH_3); 1.35 (3H, s, CH_3); 1.98 (1H, br. s, NH); 2.85-3.55 (4H, m, CH_2CH_2); 6.50-7.33 ppm (4H, m, H_{arom}). Mass spectrum, m/z (%): 51 (13), 63 (12), 65 (13), 77 (26), 91 (23), 103 (13), 115 (24), 117 (19), 118 (20), 130 (23), 131 (18), 144 (28), 146 (25), 158 (39), 171 (26), 172 (35), 187 (100), 188 (32), 201 (80), 202 (63). Found: C 77.4; H 8.9; N 13.8%. $C_{13}H_{18}N_2$. Calculated: C 77.2; H 9.0; N 13.8%.

A 0.90-g (4.5 mmole) portion of compound IIIa was dissolved in 5 ml of alcohol and the solution was saturated with gaseous HCl. The precipitate was filtered off and recrystallized from alcohol. A yield of 1.0 g (82%) of dichloride IVa was obtained, mp 273-274°C (from alcohol). IR spectrum (KBr): 3100-2900 ($\overset{+}{N}H_3$), 1625 cm^{-1} ($C{=}\overset{+}{N}$). PMR spectrum (CF_3COOH): 1.24 (6H, s, 3,3-CH_3); 2.56 (3H, s, 2-CH_3); 3.30-3.85 (2H, m, CH_2); 4.55-4.95 (2H, m, CH_2), 7.05-7.80 ppm (4H, m, H_{arom}). Found: Cl 25.4; N 10.5%. $C_{13}H_{20}Cl_2N_2$. Calculated: Cl 25.8; N 10.2%.

B. To a solution of 2.08 g (60 mmole) of lithium aluminum hydride in 200 ml of absolute tetrahydrofuran was added 8.65 g (40 mmole) of methylene compound IIa and the mixture was agitated for 2 h at 55°C. Excess lithium aluminum hydride was decomposed with 1 ml of water

and the precipitate was filtered off. After 4/5 of the solvent had been distilled off from the filtrate, the mixture was poured into 200 ml of water and extracted with ether (3 × 20 ml). The extract was washed with 30 ml of water, dried over sodium sulfate, and the solvent was distilled off. Then 20 ml of ethanol was added to the residue and the solution was saturated with gaseous HCl. The precipitate was filtered off and recrystallized from alcohol Dichloride IVa (7.70 g) obtained was dissolved in 100 ml of water and treated with 6.0 g dry sodium carbonate. The substance that separated out was extracted with ether (2 × 25 ml) and the extract was dried over sodium sulfate and the solvent was distilled off. 5.0 g (62%) of compound IIIa was obtained; its TLC data and PMR spectrum matched that of the sample obtained according to method A.

1-Benzyl-9,9,9a-trimethyl-1,2,3,9a-tetrahydro-9H-imidazo[1,2-a]indole (IIIb) and 1-[2-(Benzylammonium)ethyl]-2,3,3-trimethyl-3H-indolium Dichloride (IVb). The reaction of 4.60 g (15 mmole) of benzylimidazo[1,2-a]indol-2-one (Ib) with 0.52 g (15 mmole) of lithium aluminum hydride in 80 ml of tetrahydrofuran was carried out as in the case of the synthesis of compound IIIa (method A). The product obtained was crystallized from hexane. Yield of compound IIIb was 0.80 g (18%), mp 93.5-94°C (from hexane). UV spectrum (in alcohol), λ_{max} (log ε): 212 (4.19), 240 (3.86), 280 nm (3.78). PMR spectrum ($CDCl_3$): 1.18 (3H, s, 9-CH_3); 1.35 (3H, s, 9a-CH_3); 1.45 (3H, s, 9-CH_3); 2.23-4.23 (4H, m, CH_2CH_2); 3.24, 4.06 (2H, AB system, J_{AB} = 13.7 Hz, CH_2); 6.48-7.35 ppm (9H, m, H_{arom}). Mass spectrum, m/z (%): 51 (12), 63 (9), 67 (27), 77 (6), 89 (9), 91 (69), 103 (5), 115 (7), 117 (7), 118 (10), 130 (12), 131 (15), 144 (15), 145 (19), 158 (21), 159 (46), 161 (26), 171 (10), 173 (30), 175 (15), 187 (6), 188 (6), 202 (13), 250 (3), 264 (3), 279 (27), 292 (100). Found: C 82.4; H 8.0; N 9.8%. $C_{20}H_{24}N_2$. Calculated: C 82.1; H 8.3; N 9.6%.

Dichloride IVb was obtained from compound IIIb in the same way as dichloride IVa (method A). Yield 75%, mp 217-218°C (from alcohol). IR spectrum (KBr): 2750-2300 cm^{-1} ($\overset{+}{N}H_2$). PMR spectrum (CF_3COOH): 1.27 (6H, s, 3,3-CH_3); 2.53 (3H, s, 2-CH_3); 3.33-3.85 (2H, m, $CH_2\underline{CH_2}\overset{+}{N}H_2$) 4.16 (2H, t, J = 4.5 Hz, $CH_2C_6H_5$); 4.67 (2H, t, J = 8 Hz, $\underline{CH_2}CH_2\overset{+}{N}H_2$); 7.02-7.50 (9H, m, H_{arom} 8.06 ppm (2H, br. s, $\overset{+}{N}H_2$). Found: Cl 19.3; N 7.7%. $C_{20}H_{26}Cl_2N_2$. Calculated: Cl 19.4; N 7.7%.

1-(2-Benzamidoethyl)-3,3-dimethyl-2-methylene-2,3-dihydroindole (V). To a solution of 1.01 (5 mmole) of imidazo[1,2-a]indole IIIa in 10 ml of ether was added 5 ml of water and 2.0 g of sodium carbonate; 1.41 g (10 mmole) of benzoyl chloride was then added dropwise with agitation. The mixture was agitated for 1.5 h at 20°C; the ether layer was separated, washed with 5 ml of water, dried over calcium chloride, and mixed with 20 ml of hexane. The precipitate was filtered off and recrystallized from alcohol. Yield 1.15 g (75.1%), mp 94-95°C (from alcohol). PMR spectrum ($CDCl_3$): 1.31 (6H, s, 3,3-CH_3); 3.55-3.80 (4H, m, CH_2CH_2); 3.84, 3.9 (2H, AB system, J_{AB} = 2.5 Hz, C=CH_2); 6.49-7.80 ppm (10H, m, H_{arom}, NH). Found: N 9.4%. $C_{20}H_{22}N_2O$. Calculated: N 9.1%.

3,3-Dimethyl-2-methylene-1-[2-(phenylamino)ethyl]-2,3-dihydroindole (VI) and 2,3,3-Trimethyl-1-[2-(phenylammonium)ethyl]-3H-indolium Dichloride (IVb). To a solution of 0.52 g (15 mmole) of lithium aluminum hydride in 80 ml of absolute tetrahydrofuran was added 2.92 g (10 mmole) of methylene compound IIb. The mixture was agitated for 8 h at 20°C, excess lithium aluminum hydride was decomposed with 0.5 ml of water, and the precipitate was filtered off. After 4/5 of the solvent had been distilled off, the mixture was poured into 150 ml of water, extracted with ether (2 × 20 ml), and the extract dried over sodium sulfate. The solvent was distilled off, and the residue was dissolved in 8 ml of acetone and the solution was saturate with gaseous HCl. The precipitate was filtered off and recrystallized from alcohol. 1.83 g (52%) of dichloride IVb was obtained, mp 217-218°C (from alcohol). IR spectrum: 2750-2200 cm^{-1} ($\overset{+}{N}H_2$). Found: Cl 20.0; N 8.0%. $C_{19}H_{24}Cl_2N_2$. Calculated: Cl 20.2; N 8.0%.

Dichloride IVb obtained (1.83 g) was dissolved in 20 ml of water, treated with 1.0 g of dry sodium carbonate, and extracted with ether (2 × 15 ml). The extract was dried over sodium sulfate and the solvent distilled off. 1.20 g of the oily 2-methylene-2,3-dihydroindo VI was obtained (43% based on initial comopund IIb). IR spectrum (thin layer): 3310 cm^{-1} (N–H). PMR spectrum ($CDCl_3$): 1.31 (6H, s, 3,3-CH_3); 3.25-4.06 (6H, m, CH_2CH_2, C=CH_2); 3.06 (1H, br. s, NH); 6.39-7.40 ppm (9H, m, H_{arom}). Found: N 10.4%. $C_{19}H_{22}N_2$. Calculated: N 10.1%.

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NUCLEOSIDES OF 4-METHYLTHIO-1,2,3-TRIAZOL-5-YL-CARBOXYLIC ACID DERIVATIVES

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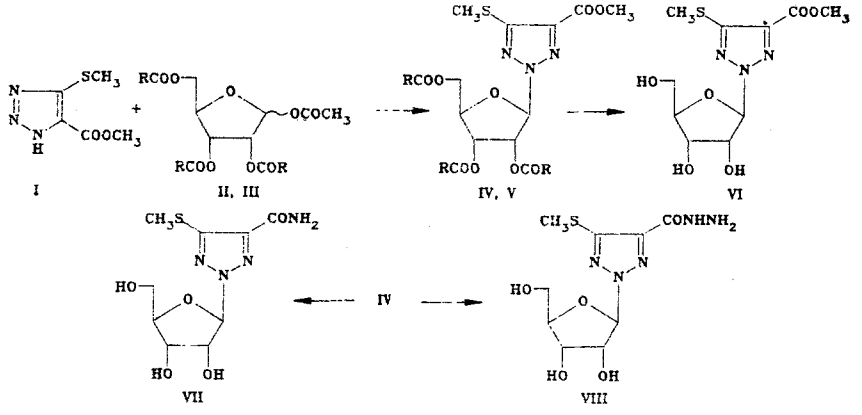
2-β-D-Ribofuranosyl-4-methylthio-5-methoxycarbonyl-1,2,3-triazole was obtained by fusing 4-methylthio-5-methoxycarbonyl-1,2,3-triazole together with tetraacyl-D-ribofuranose, followed by deacylation, and its amide and hydrazide were prepared. The structures of the new nucleosides were established by converting them into known 2-nucleosides of 1,2,3-triazol-4-yl-carboxylic acid derivatives.

Nucleosides of azoles, including 1,2,3-triazole, are of interest as potential inhibitors of nucleic acid metabolism in tumor and virus-infected cells. Among the nucleosides of 1,2,4-triazole, thiazole, pyrazole, and other azoles, compounds with pronounced antitumor or antiviral activity were discovered (for example, Virazol, pyrazofurin, thiazofurin, etc.) [1].

In the present work, we studied the ribosylation under fusion reaction conditions of 4-methylthio-5-methoxycarbonyl-1,2,3-triazole (I) obtained by T. S. Safonova et al. by rearrangement of 6-methylthio-5-diazouracil [2]. Fusion of triazole (I) with 1,2,3,5-tetra-O-acetyl-D-ribofuranose (II), or 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (III) at 120°C, in vacuo and in the presence of catalytic amounts of bis-p-nitrophenyl phosphate, led to the formation of 2-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-4-methylthio-5-methoxycarbonyl-1,2,3-triazole or to the corresponding per-O-benzoyl derivative V in yields of 89 and 96%, respectively. In a control by TLC, the formation of noticeable amounts of isomeric nucleosides was not revealed.



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