1,2,3,6,7,11b-HEXAHYDRO-4H-PYRIMIDO[2,1-a]ISOQUINOLINE-2-ONES

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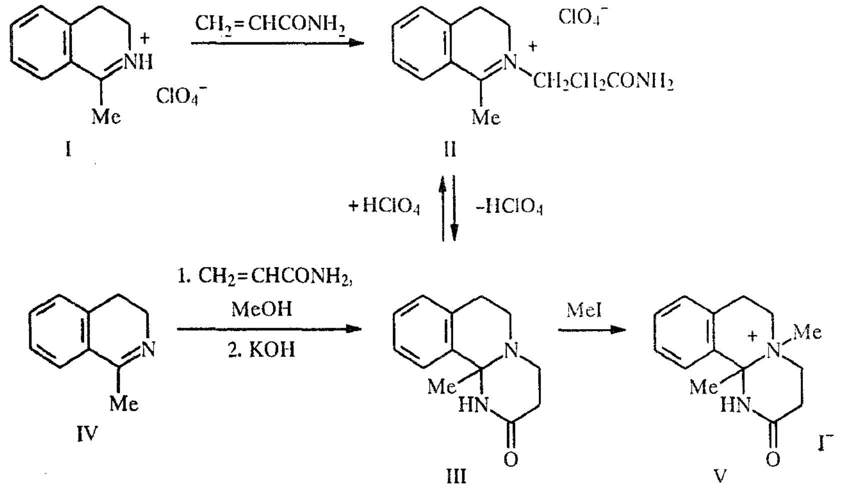
The reaction of 1-methyl-3,4-dihydroisoquinolinium salts with acrylamide forms 2-(2-carbamoylethyl)-1-methyl-3,4-dihydroisoquinolinium salts, which are cyclized by the action of bases to form 11b-methyl-1,2,3,6,7,11b-hexahydro-4H-pyrimido[2,1-a]isoquinolin-2-one. Treatment of this compound with iodomethane yields 5,11b-dimethyl-2-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrimido[2,1-a]isoquinolinium iodide. The 11b-methyl-pyrimido[2,1-a]isoquinolin-2-one enters into condensation with aromatic aldehydes, forming the corresponding styryl compounds.

It was shown in [1] that when a mixture of 1-methyl-3,4-dihydroisoquinoline and acrylamide is heated at 100°C, one or two molecules of the unsaturated compound add to the methyl group of the isoquinoline, with subsequent cyclization of the adduct to form derivatives of 2,3,6,7-tetrahydro-4H-benz[a]quinolizine. However, in the reaction of 2,3,3-trimethyl-3H-indolinium salts with amides of 2,3-unsaturated carboxylic acids, the nitrogen atom of the azomethine grouping enters into addition to the activated carbon—carbon double bond [2, 3].

We have found that upon refluxing an alcohol solution of a mixture of 1-methyl-3,4-dihydroisoquinolinium perchlorate (I) with acrylamide, the main reaction product is 1-methyl-2-(2-carbamoylethyl)isoquinolinium perchlorate (II). The structure of the salt II was confirmed by the PMR spectrum (CH_3COOH), in which we observed at 2.64 ppm a singlet of protons of the methyl group, and at 3.80 and 4.16 ppm two triplets of protons of methylene groups at the positively charged nitrogen atom. The IR spectrum of this salt exhibited absorption bands that are characteristic for primary amides: 3440 (N—H), 3345 (N–H), and 1680 cm^{-1} (C=O) [4].



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The interaction of 1-methyl-2-(2-carbamoylethyl)isoquinolinium perchlorate II with bases results in nucleophilic addition of the nitrogen atom of the carbamoyl grouping to the carbon atom of the azomethine grouping to form a derivative of pyrimido[2,1-a]isoquinolin-2-one (III). (See scheme at the bottom of the previous page.)

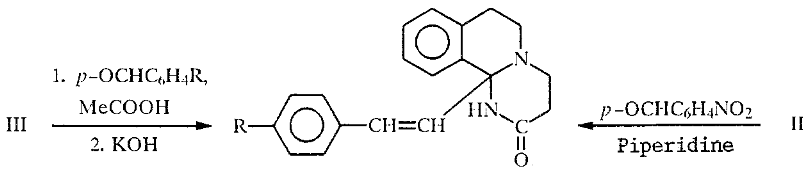
An identical product is obtained by reaction of 1-methyl-3,4-dihydroisoquinoline (IV) with acrylamide in acetic acid, with subsequent treatment of the reaction mixture with caustic.

In the PMR spectrum ($CDCl_3$) of the tricyclic compound III, the signal of the methyl-group protons is observed at 1.75 ppm; in the ^{13}C NMR spectrum ($CDCl_3$), the signal of the sp^3-hybridized nodal atom $C_{(11b)}$ is observed at 71.9 ppm. In the mass spectrum of the pyrimido[2,1-a]isoquinolin-2-one III, peaks are observed for ions with m/z 216 $(M)^{+\cdot}$, 201 $(M - CH_3)^+$, 173 $(M - CH_3 - CO)^+$ or 173 $(M - NHCO)^{+\cdot}$, 159 $(M - CH_2NHCO)^{+\cdot}$, 144 $(M - CH_3 - CH_2NHCO)^+$, and 130 $(M - CH_3 - CH_2CH_2NHCO)^+$, indicating decomposition of the hexahydropyrimidine ring.

Upon taking the PMR spectrum of compound III in CF_3COOH, we observed a downfield shift of the signal of the methyl-group protons amounting to 0.89 ppm, related to opening of the hexahydropyrimidine ring and the formation of a 2-(2-carbamoylethyl)-1-methyl-3,4-dihydroisoquinolinium cation. Treatment of the pyrimido[2,1-a]isoquinolin-2-one III with perchloric acid gives the original perchlorate II.

Alkylation of the pyrimido[2,1-a]isoquinolin-2-one (III) with iodomethane in acetone takes place at the $N_{(5)}$ atom, and the main reaction product is 5,11b-dimethyl-2-oxo-pyrimido[2,1-a]isoquinolinium iodide (V). A similar reaction of alkylation of derivatives of oxazolo-[2,3-a]isoquinoline was described in [5]. When compound V is exposed to the action of protic acids, the tricyclic structure is preserved, as evidenced by its PMR spectrum (CF_3COOH), with a signal of protons of the 11b-CH_3 group at 1.82 ppm.

By condensation of the 11b-methyl-pyrimido[2,1-a]isoquinolin-2-one III with 4-dimethylamino- and 4-chlorobenzaldehydes in acetic acid in the presence of acetic anhydride, followed by treatment of the reaction mixture with bases, the styryl compounds VIa,b are obtained.



VIa-c

VIa)R = NMe2; b)R = Cl; c)R = NO2

In contrast, 4-nitrobenzaldehyde does not enter into condensation with the active methyl group of compound III under analogous conditions. The 11b-(4-nitrostyryl)pyrimido[2,1-a]isoquinolin-2-one (VIc) has been synthesized by refluxing a mixture of the aldehyde with the perchlorate II in alcohol in the presence of piperidine.

EXPERIMENTAL

The IR spectra were taken in a Specord IR-75 instrument, in KBr tablets. The PMR spectra were obtained in Tesla BS-487C (80 MHz) and Bruker WH-360 (360 MHz) spectrometers, with HMDS internal standard. The ^{13}NMR spectra were recorded in a Bruker WH-360 spectrometer (90.5 MHz). The mass spectra were taken in a Hitachi M-80A instrument (12.2 eV) with direct introduction of the sample into the ion source, at temperatures of 150-180°C. The course of the reaction and the individuality of the compounds were monitored by means of TLC on Al_2O_3 (level II activity) in an acetone—hexane system (2:3); development by iodine vapor.

The elemental analyses were in agreement with the calculated values.

2-(2-Carbamomylethyl)-1-methyl-3,4-dihydroisoquinolinium Perchlorate (IIa, $C_{13}H_{17}ClN_2O_5$). A. A solution of 4.91 g (20 mmoles) of 1-methyl-3,4-dihydroisoquinolinium perchlorate (I) and 2.13 g (30 mmoles) of acrylamide in 15 ml of ethanol was refluxed for 10 h. The mixture was cooled to 20°C, and the precipitate was filtered off and recrystallized from ethanol. Yield 4.49 g (71%); mp 202-204°C. PMR spectrum (CH_3COOH): 2.64 (3H, s, CH_3); 2.68-3.15 (4H, m, CH_2CO, CH_2Ph); 3.80 (2H, t, J = 5.0 Hz, NCH_2); 4.16 (2H, t, J = 7.5 Hz, NCH_2); 6.96-7.78 ppm (4H, m, Ar).

B. To a solution of 0.43 g (2 mmoles) of compound III in 5 ml of ethanol, 30% perchloric acid was added to bring the pH to 1. The mixture was held for 24 h at 3°C; the precipitate was filtered off, washed with 1 ml of ethanol, and dried. Yield 0.51 g (81%). According to IR and PMR spectra and melting point, the product was identical to that obtained by method A.

11b-Methyl-1,2,3,6,7,11b-hexahydro-4H-pyrimido[2,1-a]isoquinolin-2-one (III, $C_{13}H_{16}N_2O$). A. A solution of 1.51 g (5 mmoles) of the perchlorate IIa in 100 ml of 10% acetic acid was treated with a sodium carbonate solution to pH 9. The precipitated substance was extracted with ether (3 × 25 ml), the extract was dried with sodium sulfate, the solvent was driven off, and the residue was crystallized from ethanol. Yield 0.52 g (50%); mp 131-132°C. IR spectrum: 3195 (N—H), 1655 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 1.75 (3H, s, CH_3); 2.35-2.60 (2H, m, CH_2CO); 2.81-2.91 (2H, m, CH_2Ar); 3.03-3.13 (2H, m, $N\underline{CH_2}CH_2Ar$); 3.03-3.13; 3.39-3.49 (2H, m, $N\underline{CH_2}CH_2CO$); 7.09-7.53 (4H, m, Ar); 7.96 ppm (1H, bs, NH). ^{13}C NMR spectrum ($CDCl_3$): 27.4 (t, $C_{(3)}$; 28.1 (t, $C_{(7)}$); 30.6 (q, CH_3); 44.6 (t, $C_{(6)}$); 45.4 (t, $C_{(4)}$); 71.9 (s, $C_{(11b)}$); 125.6; 126.6; 127.1; 128.6 (4 × d, $C_{(8-11)}$); 132.9 (s, $C_{(11a)}$); 139.4 (s, $C_{(7a)}$); 169.5 ppm (s, C=O).

B. A solution of 10.81 g (50 mmoles) of 1-methyl-3,4-dihydroisoquinoline (IV) and 5.33 g (75 mmoles) of acrylamide in 30 ml of acetic acid was heated for 7 h at 105-110°C. The mixture was poured into 150 ml of water, treated with a 10% sodium hydroxide solution until an alkaline reaction was obtained, and extracted with ether (4 × 100 ml). The extract was dried with sodium sulfate, the solvent was driven off down to a volume of 8 ml, and the residue was held for 24 h at 3°C. The precipitated crystalline substance was filtered off, washed with 3 ml of ether, and dried. Obtained 2.35 g of compound III. The aqueous phase was extracted repeatedly with chloroform (2 × 50 ml), the extract was dried with sodium sulfate, and the solvent was driven off. The residue was chromatographed in a column (100 × 25 mm) with Al_2O_3 L 40/100 (eluent acetone—hexane, 2:5). From the fraction with R_f 0.26, obtained another 1.0 g of compound III. Total yield 21%. According to the PMR spectrum and melting point, the product was identical to that obtained by method A.

5,11b-Dimethyl-2-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrimido[2,1-a]isoquinolinium Iodide (V, $C_{14}H_{19}IN_2O$). To a solution of 1.08 g (5 mmoles) of compound III in 12 ml of acetone, 2.13 g (0.93 ml, 15 mmoles) of iodomethane was added, and the mixture was refluxed for 0.5 h. The solution was cooled, and the precipitate was filtered off and recrystallized from alcohol. Yield 0.84 g (47%); mp 226-227°C. IR spectrum: 3170 (N—H), 1670 cm^{-1} (C=O). PMR spectrum (CF_3COOH): 1.82 (3H, s, 11*b*-CH_3); 2.64-4.31 (8H, m, 4 × CH_2); 3.26 (3H, s, N^+CH_3); 6.93-7.31 ppm (4H, m, Ar).

11b-(4-Dimethylaminostyryl)-1,2,3,6,7,11b-hexahydro-4H-pyrimido[2,1-a]isoquinolin-2-one (VIa, $C_{22}H_{25}N_3O$). A solution of 2.16 g (10 mmoles) of the pyrimido[2,1-a]isoquinolin-2-one III and 1.64 g (11 mmoles) of 4-dimethylaminobenzaldehyde in a mixture of 12 ml of acetic acid and 0.5 ml of acetic anhydride was heated for 5 h at 100°C. The mixture was poured into 70 ml of water and extracted with ether (2 × 20 ml). A 10% potassium hydroxide solution was added to the aqueous phase until an alkaline reaction was obtained; the precipitate was filtered off, dried, and crystallized from acetone. Yield 1.46 g (42%); mp 187-188°C. IR spectrum: 3225 (N—H), 1650 (C=O), 1600 cm^{-1} (CH=CH). PMR spectrum ($CDCl_3$): 2.00-3.84 (8H, m, 4 × CH_2); 2.96 (6H, s, N, N—CH_3); 5.88-6.80 (2H, AB-quad, J_{AB} = 16.0 Hz, CH=CH); 6.56-7.58 ppm (9H, m, Ar, NH).

11b-(4-Chlorostyryl)-1,2,3,6,7,11b-hexahydro-4H-pyrimido[2,1-a]isoquinolin-2-one (VIb, $C_{20}H_{19}ClN_2O$). A solution of 1.08 g (5 mmoles) of compound III and 0.84 g (6 mmoles) of 4-chlorobenzaldehyde in a mixture of 6 ml of acetic acid and 0.3 ml of acetic anhydride was heated for 4 h at 100°C. The mixture was poured into 35 ml of water, and a 10% potassium hydroxide solution was added until an alkaline reaction was obtained. The precipitate was filtered off, dried, and crystallized from alcohol. Yield 0.93 g (55%); mp 186-187°C. IR spectrum: 3195 (N—H), 1640 (C=O), 1600 cm^{-1} (CH=CH). PMR spectrum ($CDCl_3$): 1.94-3.79 (8H, m, 4 × CH_2); 6.03-6.81 (2H, AB-quad, J_{AB} = 16.0 Hz, CH=CH); 6.41-7.37 ppm. (9H, m, Ar, NH).

11b-(4-Nitrostyryl)-1,2,3,6,7,11b-hexahydro-4H-pyrimido[2,1-a]isoquinolin-2-one (VIc, $C_{20}H_{19}N_3O_3$). A solution of 1.58 g (5 mmoles) of the perchlorate IIa and 0.9 g (6 mmoles) of 4-nitrobenzaldehyde in a mixture of 12 ml of alcohol and 1 ml of piperidine was refluxed for 0.5 h. The crystalline substance was filtered off and recrystallized from alcohol. Yield 1.20 g (69%); mp 184-185°C. IR spectrum: 3200 (N—H), 1640 (C=O), 1520 cm^{-1} (NO_2). PMR spectrum (DMSO): 2.00-4.30 (8H, m, 4 × CH_2); 6.35-7.00 (2H, AB-quad, J_{AB} = 16.0 Hz, CH=CH); 7.05-8.30 ppm. (9H, m, Ar, NH) .

REFERENCES

1. S. G. Agbalyan, Zh. A. Khanamiryan, and A. O. Nshanyan, Arm. Khim. Zh., **21**, 422 (1968).
2. A. A. Shachkus and R. Yu. Dyagutite, Khim. Geterotsikl. Soedin., No. 8, 1056 (1986).
3. A. A. Shachkus, R. Yu. Dyagutite, and Z. A. Stumbryavichyute, Khim. Geterotsikl. Soedin., No. 5, 625 (1990).
4. G. Sokrates, Infrared Characteristic Group Frequencies, Wiley, New York (1980), p. 74.
5. J. B. Bremner and K. N. Winzenberg, Aust. J. Chem., **307**, 1659 (1984).