ISOMERIZING RECYCLIZATION OF QUATERNARY SALTS OF ETHYL 3-(2-PYRIDYL)BUTYRATE AND DIETHYL 2-(2-PYRIDYL)ETHYLMALONATE

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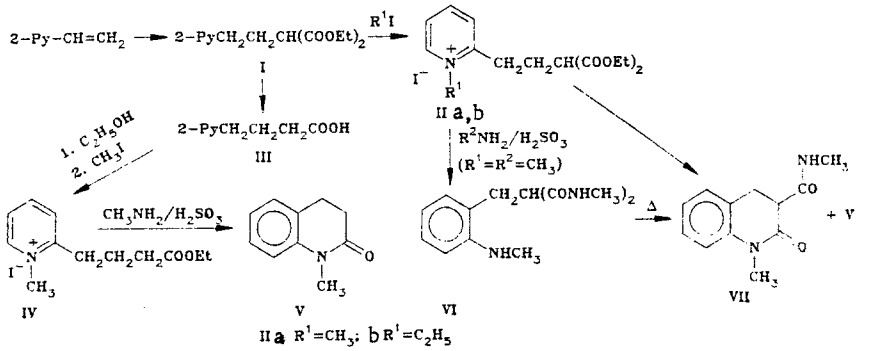
A number of quaternary salts of ethyl γ-pyridylbutyrate and diethyl β-pyridylethylmalonate undergo the Kost—Sagitullin reaction to give N-methyl-2-quinolone and 3-methylaminocarbamoyl-N-methyl-2-quinolone. Rearrangement in the presence of excess aliphatic amines is accompanied by an efficiently proceeding transamination.

We have shown previously that the isomerizing recyclization of quaternary salts of pyridylethylated ketones can give substituted 1,4-dihydroquinolines, 9,10-dihydroacridines, or their tetrahydro analogs in good yield [1-3]. We suggested that when pyridylethylated esters of carboxylic acids undergo the Kost—Sagitullin reaction in similar manner [4] it would be possible to obtain 2-quinolone and its derivatives.

Starting from diethyl malonate and 2-vinylpyridine we synthesized ethyl 3-(2-pyridyl)-butyrate methiodide (IV) in three stages, prolonged heating of this compound (40 h, 140-150°C sealed ampul) with an aqueous solution of methylamine sulfite giving a very tarry reaction mass, from which 1-methyl-2-quinolone (V) was isolated in 14% yield, this nevertheless being the main reaction product. In its IR spectrum there was a band due to carbonyl group stretching vibrations characteristic of benzolactams [5] at 1685 cm^{-1} and a band at 755 cm^{-1}, which indicated an ortho-disubstituted benzene ring. In the mass spectrum the molecular ion peak (m/z 161) was observed, decomposing with the loss of CHO (132) or C_2H_3O (118), which was noted previously in the mass spectra of other benzolactams [6]



IIa $R^1=CH_3$; b $R^1=C_2H_5$

Finally, in the PMR spectrum of compound V, there was a singlet from the three protons of the N—CH_3 group (3.2 ppm), a multiplet from the four methylene protons in the region 2.3-3.0 ppm, and a multiplet from the four aromatic protons in the region 7.0-7.5 ppm. Attempts to increase the yield of 2-quinolone V by prolonging the time of heating to 90 h or varying the methods for its isolation did not give favorable results.

The recyclization reaction carried out (70 h, 130-150°C) on quaternary salt II, which contained two carbethoxy groups at the end of a propyl residue, made it possible to isolate from the very tarry reaction mass two products, one of which (yield 7%) proved to be 1-methyl-3-(n-methylcarbamoyl)-1,2,3,4-tetrahydro-2-quinolone (VII), and the other to be an initial rearrangement product — N-methyl-2-[2,2-bis(N-methylcarbamoyl)ethyl]aniline (VI). On heating this to 130°C for 10 min the substituted tetrahydroquinolone VII was obtained. In the IR spectrum of the latter, absorption bands for amide-I (1650 and 1675 cm^{-1}) and

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amide-II (1570 cm^{-1}) are present. In its mass spectrum the molecular ion (218) is observed, which readily eliminates a methyl isocyanate molecule (McLafferty rearrangement) to give the enol form of the pseudomolecular ion of N-methyl-2-quinolone (161), further fragmentation of which corresponds to that observed for compound V. In the PMR spectrum of amide VII, a three-proton doublet from the N-methylcarbamoyl group (2.7 ppm), a three-proton singlet from the 1-methyl group (3.45 ppm), a multiplet from the three protons of the tetrahydro ring (3.2-3.8 ppm), and a multiplet from the four aromatic protons (7.0-7.8 ppm) were observed. The mass spectrometric behavior of compound VI also supported the proposed structure. Its molecular ion (249) lost a methylamine molecule (218), a methylcarbamoyl residue (191) with subsequent elimination of methylamine (160), or split off a malonic acid bismethylamide fragment completely (ion 120). Such a type of decomposition in combination with the thermal conversion to quinolone VII referred to above definitely proved the noncyclic structure of compound VI. Chromatographic-mass spectrometric analysis of an ether extract of the residue after isolation of these products indicated the presence of traces of 2-quinolone V and 2-ethylpyridine in them. The latter was formed evidently as a result of a similarly occurring dealkylation and reductive cleavage of salt II.

Using a chromatographic-mass spectrometric method, we investigated the recyclization reaction of methiodide II in the presence of isobutylamine and benzylamine sulfites. It was established in this case that the main components of the reaction mixture were transamination products — N-isobutyl-2-quinolone (VIII) (M = 203) and N-benzyl-2-quinolone (IX) (M = 237), respectively. Together with them, small quantities of quinolone V and ethylpyridine were always present in the reaction masses. We failed to detect substituted amides corresponding to VI and VII in the reaction mixture. In the case of the reaction with benzylamine, chromatography-mass spectrometry made it possible to detect the secondary formation of benzal benzylamine. On the other hand, when ethiodide II was heated with methylamine sulfite (63 h, 130-150°C), the reaction mass formed, according to the data from chromatographic-mass spectrometric analysis, contained only methylamide VII (main product, M = 218) and small quantities of quinolone V and ethylpyridine.

Thus, the data obtained show that when a number of alkiodides of γ-pyridylbutyrate esters undergo the Kost—Sagitullin reaction there is almost complete accompanying transamination, which probably occurs at the first stage of the opened form of the pyridine ring; whereas previously [7-9] when using functionally unsubstituted 2-alkylpyridines as models only partial transamination was noted. The fact that in the experiments with isobutylamine and benzylamine suitably substituted anilines of type VI or amides of type VII were not found in the reaction mass is a positive indication that amination with methylamine occurs at the more advanced stages of rearrangement, with the 'bulkiness' of the amine playing a significant part in the formation of the final reaction products.

EXPERIMENTAL

TLC analysis was performed on Silufol-UV-254 plates in the system benzene—methanol (9:1). Preparative separation on plates was carried out on silica gel with grain size 40/100 μm and thickness of layer 1 mm in the same system; chromatograms were developed under UV light. IR spectra were obtained on a UR-20 instrument in petrolatum oil or as a film. PMR spectra were recorded on a Varian T-60 instrument in $CDCl_3$ solution (TMS standard). Chromatographic-mass spectrometric analysis of the reaction mixtures was performed on a MAT-112 instrument with a capillary column (l = 40 m, d = 0.25 mm) containing 5% SE-30 on Chromosorb, and ionization energy 70 eV. Mass spectra of individual compounds were recorded on a MX-1303 instrument at an ionization energy of 50 eV.

2-[3,3-Bis(ethoxycarbonyl)propyl]pyridine (I). To a boiling solution of 105 g (1 mole) of 2-vinylpyridine in 175 ml of absolute ethanol was added a solution of 375 g (2.35 mole) of diethyl malonate and 23 g (1 mole) of metallic sodium in 225 ml of absolute ethanol. The mixture was boiled for 2 h, the alcohol was distilled off, the residue was acidified with 10% hydrochloric acid until pH 5 was reached, the unreacted diethyl malonate was extracted with ether; the aqueous phase was made alkaline with a 10% sodium carbonate solution until pH 8-9 was reached, extracted with ether, the extract was dried with anhydrous magnesium sulfate, the solvent removed, and the residue distilled under vacuum. Yield 92 g (31%), bp 175-180°C (7 mm), n_D^{20} 1.4848; picrate, mp 83-85°C; according to [10], picrate, mp 85-85.5°C. Methiodide IIa, mp 82-84°C (ethanol). Ethiodide IIb, mp 40-42° (ethanol).

2-(3-Hydroxycarbonylpropyl)pyridine (III). A mixture of 71 g (0.28 mole) of ester I was boiled with 200 ml of a 5 N solution of caustic soda, extracted with ether, and the aqueous extract acidified with 10% hydrochloric acid until pH 3 was reached; this was cooled and 18.3 g of precipitated dicarboxylic acid was separated out and boiled in 150 ml of mesitylene for 1 h 30 min. 10.5 g (22%) of acid III was obtained, mp 86-87°C. According to the data of [11], mp 84-85°C.

2-(3-Ethoxycarbonylpropyl)pyridine. This was obtained by boiling 10 g (50 mmole) of acid III in 15 ml of ethyl alcohol in the presence of 1 ml of concentrated HCl. Yield 7.5 g (65%), bp 145-150°C (18 mm), n_D^{20} 1.4809. According to the data of [11], bp 145-150°C (18 mm). Methiodide IV, mp 78-82,C (methanol).

Recyclization of Ester Methiodide IV. To a solution of 6.2 g (20 mmole) of ester methiodide IV in 5 ml of water was added 10 ml of a 20% aqueous solution of methylamine and 6 ml of the same solution saturated with sulfur dioxide; the solution obtained was heated in a sealed ampul for 90 h at 150°C. The solution was cooled, extracted repeatedly with ether, the extract was dried with anhydrous magnesium sulfate, the solvent distilled off, and the residue was separated by preparative chromatography on a plate. From the band with R_f 0.7-0.9 was isolated 0.45 g (14%) of 2-quinolone V (oil). According to the GLC data, the purity of the product was 99.9%. IR spectrum: 755, 1680, 3045, 3075 cm^{-1}. PMR spectrum: 2.3-3.0 (4H, m, 3, 4-H); 3.2 (3H, s, NCH_3); 7.0-7.5 ppm (4H, m, C_6H_4). Mass spectrum: 161 (32), 132 (14), 118 (100), 91 (16). $C_{10}H_{11}NO$. Calculated: M 161.

Recyclization of Salt IIa. This was carried out in a similar manner using 8.0 g (20 mmole) of quaternary salt with heating at 130-140°C for 70 h. After similar treatment, amide VII precipitated on standing from an ether extract. Yield 0.32 mg (7%), mp 148-150°C (ethanol). IR spectrum: 750, 1613, 1650, 1675, 3325 cm^{-1}. PMR spectrum: 2.9 (3H, d, NCH_3); 3.2-3.8 (1H, d. d, 3-H); 3.45 (3H, s, 1-CH_3); 3.4-3.5 (2H, d. d, 4-H); 7.0-7.9 ppm (5H, m, C_6H_4 + NH). Mass spectrum: 218 (12), 161 (74), 160 (100), 145 (10), 132 (10), 130 (20), 118 (32), 103 (36), 91 (20). Found, %: C 66.2, H 6.4, M 218 (by mass spectrometry). $C_{12}H_{14}N_2O_2$. Calculated, %: C 66.0, H 6.5, M 218.

The ether extract remaining after precipitation of amide VII was concentrated by evaporation and chromatographed on a plate. From the band with R_f 0.6-0.7 was isolated 10 mg of aniline VI. Mass spectrum: 249 (40), 218 (5), 192 (6), 191 (6), 161 (30), 160 (100), 147 (25), 120 (52), 93 (55), $C_{13}H_{19}N_3O_2$. Calculated: M 249. On heating compound VI at 130°C for 10 min amide VII was obtained (mp 146-148°C, depression of the melting point with a previously obtained sample not given). Its mass spectrum agreed with the data given above. Chromatographic-mass spectrometric analysis of the same ether extract showed the presence of traces of 2-ethylpyridine and quinolone V in it; the mass spectra of these products matched the spectra of known samples.

Recyclization of Salt IIb. Using the same conditions and the same quantities of methylamine sulfite, 0.77 g (18%) of quinolone VII was isolated after similar treatment. Chromatographic-mass spectrometric analysis of the ether extract made identification possible of traces of quinolone V and 2-ethylpyridine in it.

Recyclization of Salt IIa in the Presence of Benzylamine Sulfite. To a solution of 8.0 g (20 mmole) of salt IIa in 5 ml of water was added 9 ml of a 20% aqueous solution of benzylamine and 6 ml of the same solution saturated with sulfur dioxide. The solution obtained (pH 9) was heated in a sealed ampul at 150°C for 14 h. After treatment analogous to the first experiment, chromatography-mass spectrometry was used to detect the following in the ether extract: 2-quinolone V, 2-ethylpyridine, N-benzyl-2-quinolone IX [mass spectrum: 237 (80), 160 (30), 132 (27), 131 (12), 130 (31), 118 (30), 91 (100), 77 (18)] and benzal benzylamine [mass spectrum: 195 (30), 194 (28), 167 (6), 165 (5), 118 (16), 92 (40), 91 (100), 77 (7)]; these being in the ratio 1:3:15:2. Isolation of compound IX in a pure form was not achieved. When the analogous reaction was carried out in the presence of isobutylamine sulfite, compounds V and VIII [mass spectrum: 203 (100), 161 (70), 160 (97), 147 (90), 148 (75), 135 (95), 119 (60), 118 (58), 117 (56), 105 (15), 91 (70), 77 (35)] were identified in the ether extract by chromatography-mass spectrometry; these compounds being in the ratio 1:7.

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STUDIES IN THE QUINOXALINE SERIES.

17.* PREPARATION AND PROPERTIES OF SOME DERIVATIVES OF 2-SULFONYLMETHYLQUINOXALINE

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Ketimines of 2-methylthiomethyl- and 2-methylsulfonylmethyl-3-oxodihydroquinoxaline have been prepared with the object of studying their tautomeric forms. The enaminoester of 1,3-bis(ethoxycarbonyl)-4,9-dihydrothienol[3,4-b]-quinoxaline-2,2-dioxide is very stable: it does not eliminate sulfur dioxide on boiling in diphenyl ether, under UV irradiation, or under electron bombardment. Reductive decomposition does not lead to the expected dienaminoester.

In preceding communications [1-3], the preparation and properties of several derivatives of 2-carbonylmethylene- and 2-cyanomethylene-3-oxo-1,2,3,4-tetrahydroquinoxaline (I) have been described. The present paper is concerned with methods for the preparation of analogs containing sulfonyl groups and a study of their properties. Among derivatives of this type only 2-phenylsulfonylmethyl-3,4-dihydro-3-oxoquinoxaline (II) is described in the literature [4] as having a ketimine structure. It was prepared by condensation of phenylmethylsulfone with diethyloxalate under the influence of sodium hydride, and subsequent reaction of the product with o-phenylenediamine.

In view of the fact that a similar reaction does not occur with dimethylsulfone, we used a more effective basic catalyst for ester condensations — sodium dimsylate in tetrahydrofuran [5]. The ethyl 2-methylsulfonyl-pyruvate which we prepared was reacted with o-phenylenediamine to give 2-methylsulfonylmethyl-3,4-dihydro-3-oxoquinoxaline (III) which possesses the ketimine structure B similar to the phenylene analog II. The lactim structure C does not seem to occur in compounds of this type [6].

*For Communication 16, see [1].

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