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DIAZO CARBONYL DERIVATIVES OF HETEROCYCLES. 2.* REACTION OF ANHYDRIDES OF PYRIDINE- AND QUINOLINEDICARBOXYLIC ACIDS WITH DIAZOMETHANE

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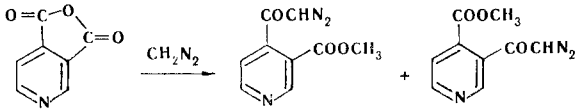
The reaction of anhydrides of cinchomeronic, quinolinic, and acridinic acids with diazomethane was studied. The reaction pathway that they have in common is acylation of diazomethane with opening of the anhydride ring, accompanied by the formation of the corresponding diazo ketones. It is shown that the nature of the heterocyclic part of the anhydride molecule has a substantial effect on the character of the parallel reactions.

One of the traditional methods for the preparation of α-diazo ketones is acylation of diazoalkanes by means of carboxylic acid chlorides or anhydrides [2-5]. In order to develop a convenient method for the production of heterocyclic diazo ketones from the corresponding acid anhydrides we investigated the reactions of pyridine- and quinolinedicarboxylic acid anhydrides with diazomethane.

Isomeric o-carbomethoxydiazoacetylpyridines can be obtained from the chlorides of the corresponding acids [1]. We found that the reaction of cinchomeronic anhydride (I) with diazomethane also leads to the formation of two isomeric o-carbomethoxydiazoacetylpyridines II and III.



I II III

The approximately identical yields of diazo ketones II and III indicate the absence of a marked difference in the electrophilicities of the carbonyl groups of anhydride I.

It is known that the reaction of phthalic anhydride with diazomethane leads, in addition to the formation of the corresponding diazo ketone, to isochroman-1,4-dione [6, 7]. However, in the case of cinchomeronic anhydride compounds with an isochroman ring could not be obtained. On the other hand, in addition to diazo ketone VII, two compounds, to which structures IX and X were assigned on the basis of the results of physicochemical and elementary analyses, were obtained in the acylation of diazomethane with quinolinic acid anhydride (IV).

Thus an intense absorption band at 1725 cm^{-1}, which is characteristic for the vibrations of the C=O group in the ester fragment of a δ-lactone [7], is observed in the IR spectra of IX, and a weak band of stretching vibrations of C=N and C=C bonds appears at 1580 cm^{-1}. In addition, the intense band at 1680 cm^{-1} that is characteristic for the keto group of isochroman-1,4-diones [6, 7] is absent. In addition to the characteristic (for 2,3-disubstituted pyridines) signals at 7.4-8.8 ppm, which correspond to three protons of the AMX type, a

*See [1] for communication 1.

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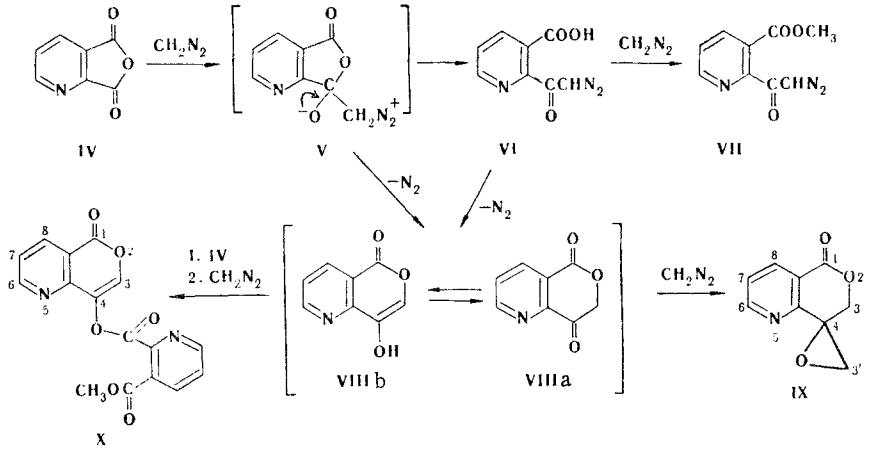
group of signals of two AB systems of spin–spin coupling shows up on the PMR spectrum of IX. Two symmetrical doublets at 3.26 and 3.95 ppm with geminal constant J_{AB} = 5.4 Hz are characteristic for the protons of the oxirane ring [8], whereas symmetrical doublets at 4.58 and 4.70 ppm with J_{AB} = 12.6 Hz are characteristic for the protons of the methylene group in δ-lactones. The $^{13}C-\{^1H\}$ NMR spectrum confirms the reality of the IX structure. In addition to signals that are characteristic for 2,3-disubstituted pyridines, the spectrum contains signals of an oxirane ring at 50.2 (carbon atom of the methylene group) and at 52.0 ppm (quaternary carbon atom). The signal at 70.3 ppm corresponds to the carbon atom of a methylene group of δ-lactone, whereas the signal at 162.6 ppm corresponds to the carbonyl atom of a carbonyl group [9]. In addition to a molecular-ion peak, intense peaks of $(M - CO\cdot)^+$, $(M - CHO\cdot - CO_2)^+$, and $(M - CHO\cdot - CHO\cdot)^{+\cdot}$ ions are noted in the mass spectrum of IX; the maximum peak corresponds to the $(M - CO_2)^{+\cdot}$ ion.

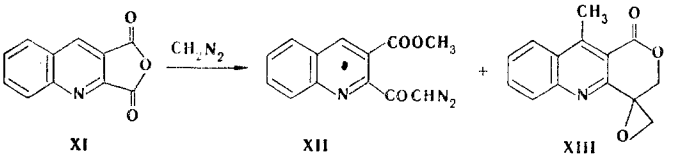


Three intense bands of stretching vibrations of C=O groups at 1725 ($COOCH_3$), 1740 (δ-lactone ester group), and 1770 cm^{-1} (the COOC=CH– fragment) are observed in the IR spectrum of X. Weak bands of stretching vibrations of pyridine C=N and C=C bonds appear at 1575 and 1585 cm^{-1}. Signals of six protons of two 2,3-disubstituted pyridine rings are found in the PMR spectrum of X at 7.2-9.1 ppm. The singlet at 7.92 ppm corresponds to one vinyl proton of the isochromene ring, while the singlet at 3.97 ppm belongs to three protons of a methyl group. The $^{13}C-\{^1H\}$ NMR spectrum of X contains 15 signals at 117.6-165.2 ppm. Seven of them, with appreciably greater intensities in the "off"-resonance spectrum, are split into a characteristic doublet and, consequently, correspond to the carbon atoms of the CH fragment, whereas the other eight are not split in the "off"-resonance spectrum and correspond to the quaternary carbon atoms of the carbonyl groups of the disubstituted pyridine rings and the isochromene ring. The signal at 52.8 ppm corresponds to the OCH_3 group.

The formation of IX and X along with diazo ketone VII is evidently explained by the fact that the unstable betaine V formed as a result of attack on the diazomethane at the α-carbonyl group of the anhydride undergoes further transformation via two pathways. Opening of the anhydride ring to give 2-diazoacetylnicotinic acid and its subsequent esterification by diazomethane lead to the formation of diazo ketone VII. Intramolecular nucleophilic substitution of the diazonium group by the oxygen atom of the anhydride ring to give the aza analog of isochroman-1,4-dione (VIIIa) and subsequent reaction of the excess diazomethane with the carbonyl group of intermediate VIIIa lead to the formation of IX. Side reactions to give an oxirane ring are characteristic for α-carbonyl compounds of the pyridine and quinoline series [10, 11]. Compound X is formed in the acylation of enol VIIIb by means of the starting quinolinic anhydride. When the reaction is carried out in excess starting quinolinic anhydride, it is possible to double the yield of X.

As in the case of quinolinic anhydride, the reaction of acridinic anhydride XI with diazomethane proceeds selectively at the α-carbonyl group to give diazo ketone XII and XIII (see scheme at top of next page).

An unusual fact in this case is the C-methylation by diazomethane of the 4 position of the quinoline ring to give XIII. Side reactions of mild C-methylation are known only for compounds with an ethylene component that contains two electron-acceptor groups in the β position relative to the site of methylation [12-14]. The formation of XIII serves as the first example of mild C-methylation of an aromatic ring by means of diazomethane. The increased



XI XII XIII

electrophilicity of the 4 position of the quinoline ring, which is due to the electron-acceptor effect of the rigidly fixed ester group in the 3 position, as well as the ability of the system to undergo significant delocalization of the negative charge of the resulting σ complex, promote nucleophilic attack of diazomethane.

The PMR-spectroscopic data constitute evidence for the presence of a methyl group in the 4 position of the quinoline ring of XIII: In addition to signals from four protons of the AA'BB' type at 7.5-8.3 ppm and signals of two AB systems that are identical to the signals of the two AB systems in the PMR spectrum of IX, a singlet from three protons at 3.15 ppm is present, but the singlet at 8.8-9.2 ppm that is characteristic for 4-unsubstituted quinolines and is present in the spectrum of XII, is absent. In addition to the molecular-ion peak, peaks of $(M - CO_2)^{+\cdot}$, $(M - CHO^{\cdot})^{+}$, and $(M - CHO^{\cdot} - CHO^{\cdot})^{+\circ}$ ions are noted in the mass spectrum of XIII; the maximum peak corresponds to the $(M - CO_2 - CHO^{\cdot})^{+}$ ion, which basically resembles the pattern of the mass-spectral fragmentation of IX. The UV spectroscopic data confirm the quinoline structure of XIII.

Thus the overall pathway of the reaction of the anhydrides of pyridine- and quinolinedicarboxylic acids with diazomethane is acylation of diazomethane with opening of the anhydride ring to give the corresponding diazo ketones; however, the nature of the heterocyclic part of the anhydride molecule has a substantial effect on the character of the parallel reactions.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with Specord 75-IR and UR-20 spectrometers. The UV spectra of solutions in methanol were obtained with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in $CDCl_3$ were measured with Tesla BS-467 and BS-497 spectrometers (60 and 100 MHz); the spectra of IX and XIII were obtained with Varian CFT-20 and FT-80A spectrometers [the internal standard was tetramethylsilane (TMS) in all cases]. The mass spectra were recorded with a Finnigan-4021 mass spectrometer with direct introduction of the substances into the ion source; the ionizing-electron energy was 70 eV, and the emission current was 0.3 μA. For column chromatography we used L 40/100 silica gel and neutral activity II Brockmann Al_2O_3. The purity of the substances was monitored by TLC in an ethyl acetate–benzene system on Silufol UV-254 plates. The starting anhydrides were obtained by the following methods: quinolinic anhydride by the method in [15], cinchomeronic anhydride by the method in [16], and acridinic anhydride by the method in [17].

Reaction of Cinchomeronic Anhydride (I) with Diazomethane. General Method. A solution of 6.5 g (44 mmole) of cinchomeronic anhydride in 120 ml of THF was added dropwise with stirring to 720 ml of an ether solution of diazomethane (from 80 g of nitrosomethylurea) and the reaction was carried out at −15°C for 40 min. After this, the reaction mixture temperature was raised to room temperature, and the excess diazomethane was removed by purging with nitrogen. The reaction mixture was then chromatographed with a column packed with silica gel [elution with ethyl acetate–benzene (4:1)] to give a single chromatographically pure product [3.1 g (33%)] in the form of an uncrystallizable oil with R_f 0.3. A comparison of the PMR spectra of the isolated substance and diazo ketones II and III [1] made it possible to establish that the aforementioned product is a mixture of diazo ketones II and III in a ratio of 52:48, respectively.

Reaction of Quinolinic Anhydride (IV) with Diazomethane. A) The reaction was carried out by the general method, and the reaction products were separated by column chromatography [elution with benzene–ethyl acetate (1:2)]. The following products were obtained. 3-Carbomethoxy-2-diazoacetylpyridine (VII) was obtained in a yield of 2.15 g (24%) and was identical to the diazo ketone obtained by the reaction of 3-carbomethoxypicolinic acid chloride with diazomethane [1]. 1-Oxo-5-azaisochroman-4-spiro-2'-oxirane (IX), with R_f 0.52 and mp 90°C, was obtained in a yield of 1.47 g (19%). IR spectrum: 1725 (C=O) and 1580 cm^{-1} (C=C, C=N). UV spectrum, λ_{max} (log ε): 207 (4.09), 225 (3.99), and 272 nm (3.48). PMR spectrum: 8.85 (1H, q, 6-H, J_{67} = 4.5 Hz, J_{68} = 1.5 Hz); 8.45 (1H, q, 8-H, J_{87} = 7.5 Hz, J_{86} = 1.5 Hz);

7.51 (1H, q, 7-H, J_{78} = 7.5 Hz, J_{76} = 4.5 Hz); 4.70 and 4.58 (2H, dd, 3-H^1, 3-H^2, J_{3-CH_2} = 12.6 Hz); 3.95 and 3.26 ppm (2H, dd, 3'-H^1, 3'-H^2, $J_{3'-CH_2}$ = 5.4 Hz). $^{13}C-\{^1H\}$ NMR spectrum: 162.6 s; 154.3 d; 153.8 s; 137.5 d, 124.3 d, 123.0 s, 70.3 t; 52.0 s; 50.2 ppm. Mass spectrum I/I_{max}, %: 177, (5) M^+; 148 (7), 134 (10), 133 (100), 132 (24), 119 (7), 105 (34), 104 (54), 103 (23), 92 (14), 91 (30), 78 (22); 77 (33), 76 (30), 64 (30), 63 (26), 51 (29), 50 (41). 4-Hydroxy(pyridyl-3-carbomethoxy-2-carboxyl)-5-aza-3,4-isochromen-1-one, with mp 161-162°C, was obtained in a yield of 0.45 g (6%). IR spectrum: 1775, 1740, 1720 (C=O); 1585 and 1570 cm^{-1} (C=N, C=C). UV spectrum, λ_{max} (log ε): 208 (3.99) shoulder, 266 (3.60) shoulder, 270 (3.61), and 310 nm (3.22). PMR spectrum: 9.05 and 8.93 (2H, dq, 6-H, 6'-H, $J_{67} = J_{6'5'}$ = 4.5 Hz, $J_{6'4'} = J_{68}$ = 1.5 Hz); 8.59 and 8.29 (2H, dq, 8-H, 4'-H, $J_{87} = J_{4'5'}$ = 7.5 Hz, $J_{86} = J_{4'6'}$ = 1.5 Hz); 7.62 and 7.56 (2H, dq, 7-H, 5'-H, $J_{78} = J_{5'4'}$ = 7.5 Hz, $J_{76} = J_{5'6'}$ = 4.5 Hz); 7.91 (1H, s, 3-CH); 3.97 ppm (3H, s, $COOCH_3$). $^{13}C\{^1H\}$ NMR spectrum: 165.2 s, 163.4 s, 160.3 s, 156.0 d, 152.0 d 149.0 s, 141.5 d, 137.9 d, 137.5 d, 133.3 s, 126.6 s, 125.4 d, 125.1 s, 123.8 d, 117.6 s, 52.8 ppm. Mass spectrum, m/z (I/I_{max}, %): 326 (5) $M^{+\cdot}$, 295 (10), 267 (10), 239 (5), 165 (53), 164 (100), 163 (6), 137 (24), 136 (94), 123 (11), 106 (92), 105 (22), 93 (13), 80 (24), 79 (19), 78 (53), 77 (36), 76 (12), 65 (8), 51 (24), 50 (22).

B) A 280-ml sample of an ether solution of diazomethane (from 29 g of nitrosomethylurea) was added dropwise with stirring in the course of 40 min to a solution of 3 g (20 mmole) of quinolinic anhydride in 40 ml of THF, after which the reaction was carried out at −15°C. Compounds VII, IX, and X were isolated as in the case of method A. This procedure gave 0.62 g (15%) of diazo ketone VII, 0.71 g (20%) of IX, and 0.50 g (15%) of X.

Reaction of Acridinic Anhydride (XI) with Diazomethane. The reaction was carried out by the general method but at room temperature for 4 h. The products were chromatographed with a column packed with Al_2O_3 [ethyl acetate–benzene (1:5)] to give the following products. 3-Carbethoxy-2-diazoacetylquinoline (XII), was obtained in 31% yield an oil with R_f 0.44. IR spectrum: 2100 (N≡N); 1730, 1630 (C=O); 1590, 1565 cm^{-1} (C=N, C=C). UV spectrum, λ_{max} (log ε): 208 (4.11), 243 (4.27), 288 (3.67), 294 (3.66) shoulder, and 313 nm shoulder (3.55). PMR spectrum: 8.38 (1H, s, 4-H); 8.14-7.69 (4H, m, 5-H, 7-H, 8-H); 6.61 (1H, s, CH); 3.98 ppm (3H, s, $COOCH_3$). Mass spectrum: 227 (46), 214 (8), 199 (5), 184 (9), 169 (60), 156 (41), 141 (31), 140 (39), 128 (100), 114 (20), 113 (20), 101 (37). 8-Methyl-1-oxobenzo[g]-5-azaisochroman-4-spiro-2'-oxirane (XIII), with mp 155°C and R_f 0.32, was obtained in 17% yield. IR spectrum: 1740 (C=O); 1565, 1590 cm^{-1} (C=N and C=C). UV spectrum, λ_{max} (log ε): 220 (4.38), 245 (4.91), and 294 (3.81). PMR spectrum: 7.5-8.3 (4H, arom., 4.70 and 4.58 (2H, dd, 3-H^1, 3-H^2, J_{3-CH_2} = 12.6 Hz); 3.95 and 3.36 (2H, dd, 3'-H^1, 3'-H^2, $J_{3'-CH_2}$ = 5.4 Hz); 3.15 ppm (3H, s, CH_3). Mass spectrum: 242 (12), $(M + 1)^{+\cdot}$, 241 (72) $M^{+\cdot}$, 240 (26), 213 (8), 212 (25), 211 (19), 198 (13), 197 (92), 196 (9), 185 (8), 183 (13), 183 (17), 169 (62), 168 (100), 167 (72), 166 (33), 156 (17), 155 (16), 154 (63), 143 (38), 141 (88), 140 (72), 128 (43), 127 (35), 115 (43), 114 (37), 113 (25), 101 (15), 100 (6).

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