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DIAZO CARBONYL DERIVATIVES OF HETEROCYCLES.

1. DIAZOACETYL DERIVATIVES OF PYRIDINE AND THEIR TRANSFORMATIONS

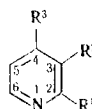
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Isomeric o-carbomethoxydiazoacetylpyridines were obtained. It is shown that, under the influence of acids on β -diazoacetyl derivatives of pyridine, the corresponding azaisochroman-1,4-diones are formed. The formation of azaisochroman-1,4-diones does not occur in the case of α - and γ -diazoacetylpyridines.

Reactions involving intramolecular cyclization of α -diazo ketones, which take place under the influence of acids, are finding application in the preparation of many heterocyclic systems that are difficult to obtain [1]. Reactions of this type proceed most readily in the case of o-substituted diazoacetophenones [2]. Thus, for example, o-carbomethoxydiazoacetophenone is readily converted to isochroman-1,4-dione under the influence of mineral acids [3, 4]. Such reactions have not yet been described for heterocyclic analogs.

In order to study the possibility and peculiarities of intramolecular cyclization of heterocyclic diazo ketones under the influence of acidic agents we obtained four isomeric o-carbomethoxydiazoacetylpyridines Ia-g and studied their acidic transformations.



Ia-d

a $R^1 = \text{COCHN}_2$, $R^2 = \text{COOCH}_3$, $R^3 = \text{H}$; b $R^1 = \text{COOCH}_3$, $R^2 = \text{COCHN}_2$, $R^3 = \text{H}$; c $R^1 = \text{H}$, $R^2 = \text{COCHN}_2$, $R^3 = \text{COOCH}_3$; d $R^1 = \text{H}$, $R^2 = \text{COOCH}_3$, $R^3 = \text{COCHN}_2$

Isomeric diazo ketones Ia-d were obtained by acylation of diazomethane by means of the chlorides of the corresponding acids. Intense absorption bands at 2084-2110 of an $\text{N} \equiv \text{N}$ group and at 1725-1735 and 1600-1625 cm^{-1} (ester and keto groups, respectively) are observed in the IR spectra of the diazo ketones (Table 1). Weak bands of stretching vibrations of $\text{C}=\text{N}$ and $\text{C}=\text{C}$ bonds of the pyridine ring are observed at 1555-1600 cm^{-1} . Singlets of three protons of a methyl group at 3.93-4.08 ppm and singlets of methylidyne protons at 5.6-6.08 ppm, as well as signals of three protons at 7.3-9.1 ppm, which are characteristic for 2,3- and 3,4-disubstituted pyridines, show up in the PMR spectra. The mass spectra of diazo ketones Ia-d (Table 2) do not contain M^{+} molecular-ion peaks, but intense ion peaks* are observed at 177 $[(\text{M} - \text{N}_2)^+]$ and 164 $[(\text{M} - \text{CHN}_2)^+]$. The subsequent fragmentation pathway is elimination of CH_3 , COOCH_3 , and $(\text{CO} + \text{CH}_3)$ fragments, which leads to the appearance of ions at

*Here and subsequently, the m/z values are given for the ion peaks.

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TABLE 1. Physicochemical Characteristics of Ia-d, II, and III

Compound	mp, °C	UV spectrum, λ_{\max} , nm (log ϵ)	IR spectrum, ν , cm ⁻¹			PMR spectrum, δ , ppm (τ , Hz)	Found, %			Empirical formula	Calc., %			Yield, %
			N \equiv N	C=O	C=N, C=C		C	H	N		C	H	N	
Ia	51	308 (3,93)	2085	1725, 1600	1550	8,70 (1H, q, 6-H, $J_{66}=4,5$, $J_{64}=1,5$); 7,92 (1H, q, 4-H, $J_{45}=7,5$, $J_{46}=1,5$); 7,53 (1H, q, 5-H, $J_{54}=7,5$, $J_{56}=4,6$); 6,06 (1H, s, CH), 4,03 (3H, s, COOCH ₃)	52,6	3,5	20,6	C ₉ H ₇ N ₃ O ₃	52,7	3,4	20,5	78
Ib	68	248 (4,01) sh ^a , 297 (3,98)	2097	1725, 1600	1555	8,81 (1H, q, 6-H, $J_{66}=4,5$, $J_{64}=1,5$); 7,92 (1H, q, 4-H, $J_{45}=7,5$, $J_{46}=1,5$); 7,59 (1H, q, 5-H, $J_{54}=7,5$, $J_{56}=4,5$); 5,82 (1H, s, CH); 4,08 (3H, s, COOCH ₃)	52,8	3,5	20,6	C ₉ H ₇ N ₃ O ₃	52,7	3,4	20,5	67
Ic	—	248 (3,85) sh, 292 (4,00)	2105	1735, 1620	1585, 1555	8,80 (1H, d, 6-H, $J_{66}=4,5$); 8,77 (1H, s, 2-H); 7,60 (1H, d, 5-H, $J_{56}=4,5$); 5,80 (1H, s, CH); 3,93 (3H, s, COOCH ₃)	52,8	3,4	20,5	C ₉ H ₇ N ₃ O ₃	52,7	3,4	20,5	65
Id	—	248 (3,90), 295 (3,96), 302 (3,94) sh	2110	1730, 1625	1590, 1535	9,09 (1H, s, 2-H); 8,80 (1H, d, 6-H, $J_{66}=4,5$); 7,32 (1H, d, 5-H, $J_{56}=4,5$); 5,63 (1H, s, CH), 3,93 (3H, s, COOCH ₃)	52,8	3,5	20,5	C ₉ H ₇ N ₃ O ₃	52,7	3,4	20,5	37
II	144—146	246 (3,59), 344 (3,19)	—	1733, 1700	1580	9,36 (1H, d, 7-H, $J_{78}=7,2$); 9,17 (1H, d, 5-H, $J_{56}=12,6$); 8,64 (1H, q, 6-H, $J_{68}=12,6$, $J_{67}=7,2$); 5,28 and 5,14 (2H, dd, CH ₂ , $J_{ab}=12,6$)	59,0	3,2	8,6	C ₈ H ₅ NO ₃	58,9	3,1	8,6	75
III	197—198	263 (3,55), 281 (3,63), 365 (3,15)	—	1740, 1703	1600	9,60 (1H, d, 5-H, $J_{56}=10$); 9,19 (1H, q, 7-H, $J_{76}=10,0$, $J_{78}=6,0$); 8,86 (1H, d, 8-H, $J_{87}=6,0$); 5,28 and 5,14 (2H, dd, CH ₂ , $J_{ab}=12,6$)	58,8	3,2	8,6	C ₈ H ₅ NO ₃	58,9	3,1	8,6	49

^aThe abbreviation "sh" denotes a shoulder.

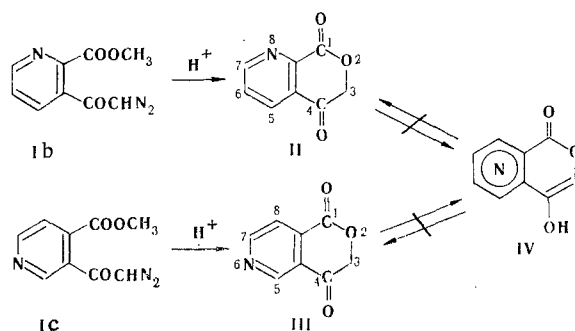
TABLE 2. Mass Spectra of Ia-d, II, and III

Compound	m/z (I/I _{max} , %) ^a
Ia	177 (33), 164 (25), 163 (10), 150 (7), 149 (64), 146 (6), 137 (7), 136 (7), 135 (7), 134 (57), 120 (9), 119 (85), 118 (6), 107 (7), 106 (87), 105 (9), 93 (6), 92 (12), 91 (100), 90 (67), 79 (19), 78 (72), 77 (20), 76 (11), 65 (20), 64 (90), 63 (95), 62 (46), 61 (20), 52 (31), 51 (69), 50 (51)
Ib	177 (97), 164 (10), 163 (6), 149 (57), 148 (7), 134 (40), 133 (15), 120 (10), 119 (41), 118 (15), 106 (49), 105 (29), 91 (100), 90 (17), 78 (77), 77 (30), 64 (21), 63 (40), 51 (44), 50 (33)
Ic	177 (18), 164 (29), 149 (9), 134 (31), 119 (5), 106 (20), 105 (12), 91 (9), 90 (14), 79 (10), 78 (78), 77 (20), 64 (15), 63 (77), 62 (40), 51 (68), 50 (100)
Id	177 (97), 165 (8), 164 (72), 149 (20), 135 (7), 134 (100), 119 (9), 106 (49), 105 (23), 91 (16), 90 (33), 79 (9), 78 (98), 77 (23), 64 (15), 63 (85), 51 (50), 50 (77)
II	163 (14), 135 (23), 134 (7), 133 (74), 106 (8), 105 (100), 78 (10), 77 (93), 76 (27), 75 (10), 64 (6), 63 (6), 51 (21), 50 (51)
III	163 (63), 134 (14), 133 (98), 106 (53), 105 (100), 78 (17), 77 (48), 50 (57)

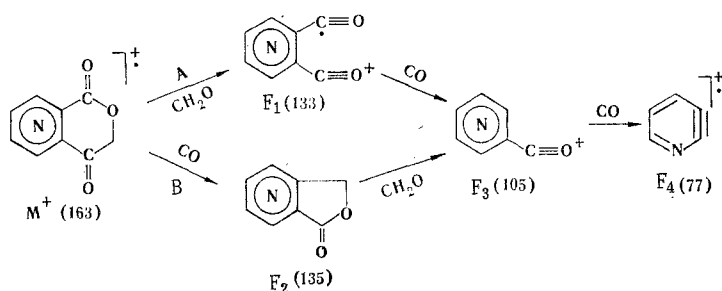
^aPeaks with intensities less than 5% and with m/z values less than 50 are not presented.

149, 105, and 134, respectively. In contrast to 2,3-disubstituted diazo ketones Ia,b, 3,4-disubstituted analogs Ic,d are unstable at room temperature and are obtained as uncrystallizable colored oils.

We found that only β -diazoacetyl derivatives Ib,c are converted to the corresponding 8-azaisochroman-1,4-dione (II) and 6-azaisochroman-1,4-dione (III) by the action of acids (20% H₂SO₄, 20% HClO₄, and 10% HCl) on the resulting isomeric diazo ketones Ia-d. The conversion of diazo ketones to azaisochromandiones takes place at room temperature in aqueous or aqueous organic solutions under the influence of various mineral acids and is virtually complete after 30-40 min. The reaction includes protonation of the diazocarbonyl fragment and subsequent intramolecular alkylation of the oxygen atom of the COOCH₃ group with the simultaneous elimination of nitrogen and methanol molecules. Both azaisochroman-1,4-diones II and III exist in the keto form, as evidenced by the spectral data (Table 1), which excludes the possibility of enolization and the existence of the IV structure.



Intense absorption bands at 1733-1740 and 1703 cm⁻¹ of the C=O groups of δ -lactones and ketones, respectively, are observed in the IR spectra of II and III [3, 5]. In addition to signals of three protons of the pyridine ring (spin-spin coupling of the protons in the α position with the proton attached to the quaternized nitrogen atom), signals of an AB system of spin-spin coupling, viz., symmetrical doublets at 5.11 and 5.31 ppm with geminal constant J_{AB} = 12.6 Hz, which is characteristic for the methylene protons of δ -lactones [6], appear in the PMR spectra (CF₃COOH). Intense M⁺ molecular-ion peaks (163) appear in the mass spectra of azaisochromandiones II and III (Table 2). In the case of III subsequent fragmentation includes two pathways: pathway A, viz., the loss of a molecule of formaldehyde to give the F₁ ion (133), which subsequently loses two CO molecules to give the F₄ ion, and pathway B, viz., the initial loss of a CO molecule to give the F₂ ion (135) with subsequent splitting out of a CH₂O molecule (the F₃ ion) and a CO molecule (the F₄ ion). The fragmentation of azaisochromandione III is realized primarily in conformity with pathway A; moreover, in contrast to the spectrum of II, one observes ions at 164, 134, 106, and 78, which correspond to fragmentation of the (M + 1)⁺ ion via pathway A.



Under similar acidic-decomposition conditions diazo ketones Ia,d are not converted to the corresponding cyclic compounds but rather give solvolysis and polymerization products. Thus in the case of treatment of diazo ketone Ia with 10% aqueous HCl solution the principal reaction product is the corresponding α -chloro ketone, whereas diazo ketone Ib under the same conditions gives II in 75% yield.

Thus the introduction of a nitrogen atom into the aromatic ring leads to selectivity of heterocyclization of o-carbomethoxydiazoacetylpyridines, which proceeds readily in the case of β -diazoacetyl derivatives but does not take place in the case of α - and γ -diazoacetylpyridines.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil 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 of diazo ketones Ia-d in $CDCl_3$ and of II and III in CF_3COOH were recorded with Tesla BS-467 and BS-497 spectrometers (60 and 100 MHz) with tetramethylsilane as the internal standard. The mass spectra were obtained 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. The purity of the substances was monitored by TLC on Silufol UV-254 plates. The starting reagents were obtained by the following methods: quinolinic acid anhydride by the method in [7], cinchomeric anhydride by the method in [8], and the o-carbomethoxy pyridinecarboxylic acids by the methods in [9, 10].

o-Carbomethoxydiazoacetylpyridines (Ia-d). A twofold excess of $SOCl_2$ was added to 4.5 g (25 mmole) of the o-carbomethoxy pyridinecarboxylic acid, and the reaction mixture was refluxed for 4 h. The excess thionyl chloride was then removed by vacuum distillation, and the residue was dissolved or suspended in ether. This solution or suspension was then added with vigorous stirring at $-15^\circ C$ in the course of 40 min to 225 ml of an ether solution of diazomethane (from 25 g of nitrosomethylurea), and the resulting mixture was stirred for another 20 min while the temperature was raised to room temperature. The diazomethane was then eliminated from the mixture by purging with air. The diazo ketones were isolated from the reaction mixtures by column chromatography [elution with ethyl acetate-benzene (2:1) in the case of Ia,b and with the same solvent mixture (4:1) in the case of Ic,d].

8- and 6-Azachroman-1,4-diones (II and III). A solution of 1 g (5 mmole) of the diazo ketone in 2 ml of water was treated with 5-10 drops of 20% H_2SO_4 (or 20% $HClO_4$ or 10% HCl), during which vigorous evolution of nitrogen was observed. The mixture was then maintained at room temperature for 30-40 min, after which it was neutralized with sodium bicarbonate and allowed to stand at $0-5^\circ C$ for 10 h. The resulting crystals were removed by filtration and recrystallized from methanol.

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DIAZO CARBONYL DERIVATIVES OF HETEROCYCLES.

2.* REACTION OF ANHYDRIDES OF PYRIDINE- AND QUINOLINEDICARBOXYLIC ACIDS WITH DIAZOMETHANE

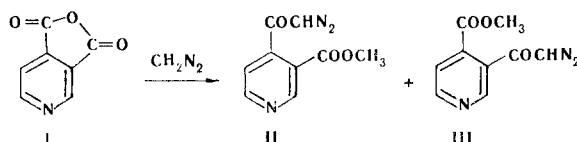
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1'837.1:542.951.1:543.422

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 -diazoketones 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.



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.