SYNTHESES BASED ON DIMETHYLPYRAZOLES.

9.* SYNTHESIS AND SPECTRAL PECULIARITIES OF ISOMERIC PYRAZOLO[3',4'-5,6]- AND -[5',4'-5,6]-PYRIMIDO[1,2-b]BENZO[d,e]ISOQUINOLINE-4,12-DIONES

V. P. Perevalov, M. A. Andreeva,
L. I. Baryshnenkova, V. Ya. Gurvich,
and B. I. Stepanov

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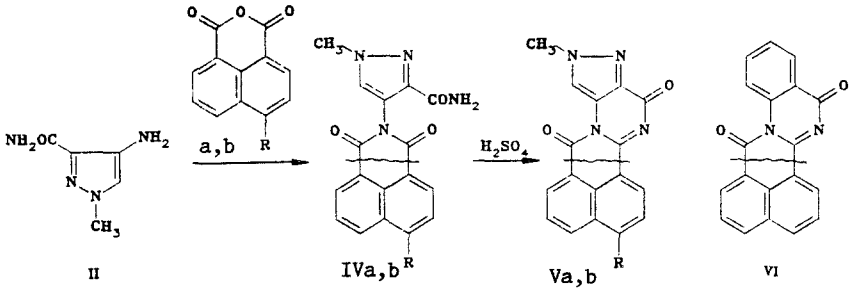
2-Methyl-2,4,12,13H-pyrazolo[3',4'-5,6]pyrimido[1,2-b]benzo[d,e]isoquinoline-4,12-dione and its 8-nitro- and 8-amino-substituted derivatives were obtained starting from 4-amino-3-carbamoyl-1-methylpyrazole and naphthalic and 4-nitronaphthalic anhydrides. The spectral properties of the synthesized compounds were studied.

The products of monoacylation of 3,4-diamino-1,5-dimethyl- and 4,5-diamino-1-methylpyrazole with 4-nitronaphthalic anhydride do not undergo cyclization to pyrazole analogs of naphthoylenebenzimidazole [1]. However, the synthesis of 3-methyl-3,4,12,13H-pyrazolo[5',4'-5,6]pyrimido[1,2-b]benzo[d,e]isoquinoline-4,12-dione (I) and its 8-nitro and 8-amino derivatives on the basis of 4-amino-5-carbamoyl-1-methylpyrazole demonstrated the possibility of heterocyclization with the formation of a pyrimidinone ring [2], as in the case of 5,13,14H-benzo[d,e]isoquinolino[2',3']quinazoline-5,13-dione [3].

In order to study the effect of the nature of the ring annelated to the pyrimidine fragment on the spectral properties of such compounds we synthesized the isomeric (with respect to I) 2-methyl-2,4,12,13H-pyrazolo[3',4'-5,6]pyrimido[1,2-b]benzo[d,e]isoquinoline-4,12-dione (Va), as well as some of its derivatives that contain a strong electron-acceptor (Vb) or electron-donor (Vc) substituent, starting from 4-amino-3-carbamoyl-1-methylpyrazole (II) and naphthalic and 4-nitronaphthalic anhydride (IIIa, b).



IIIa, IVa, Va R=H; IIIb IVb, Vb R=NO_2

In contrast to 4-amino-5-carbamoylpyrazole, 4-amino-3-carbamoylpyrazole reacts with naphthalic anhydride (IIIa) at 185-190°C in acetic acid only with the formation of an acylation product – 2-(3-carbamoyl-1-methyl-4-pyrazolyl)-1,3H-benzo[d,e]isoquinoline-1,3-dione (IVa), which does not undergo cyclization under these conditions to Va, even when the reaction time is increased to 25 h. Carrying out the reaction in water at 180-190°C under pressure makes it possible to increase the yield of IVa to 89%; this is evidently associated with exclusion of acetylation of aminopyrazole II.

The reaction of aminopyrazole II with anhydride IIIb, which has a greater acylating ability than anhydride IIIa, takes place on refluxing in 50% acetic acid with the formation of 2-(3-carbamoyl-1-methyl-4-pyrazolyl)-6-nitro-1,3H-benzo[d,e]isoquinoline-1,3-dione (IVb).

*See [1] for Communication 8.

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TABLE 1. Characteristics of I, IVa, b, Va-c, and VI

Compound	Empirical formula	mp, °C (solvent)	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	Mass spectrum, m/z (I_{rel}, %)	Yield, %
I	—	—	—	364 (4,47), 342 (4,31), 248 (5,02)	M^+ 302 (69), 301 (100), 273 (16), 220 (10), 207 (9), 180 (28), 153 (12), 152 (51), 149 (11, 125 (13)	—
IVa	$C_{17}H_{12}N_4O_3$	344...346	1650, 1665, 1695 (C=O)	347 (4,04), 331 (4,09)*	M^+ 320	89
IVb	$C_{17}H_{11}N_5O_5$	283...284 (AcOH+ water)	1685, 1725 (C=O), 1337, 1542 (NO_2)	350 (4,07), 232 (4,63)	—	92
Va	$C_{17}H_{10}N_4O_2$	341...343 (AcOH)	1665, 1680 (C=O), 1485 (C=N)	366 (4,17), 344 (4,14), 250 (4,80)	M^+ 302 (100), 261 (10), 260 (56), 245 (9), 232 (13), 180 (10), 153 (19), 152 (39), 151 (10), 126 (8), 125 (15)	30
Vb	$C_{17}H_9N_5O_4$	336...338 (Ac_2O)	1670, 1695 (C=O), 1490 (C=N)	375 (4,25)	M^+ 347	91
Vc	$C_{17}H_{11}N_5O_2$	>360 (DMF)	1675, 1705 (C=O), 1480 (C=N)	485 (4,27)**	M^+ 317	79
VI	—	214...216***	—	389 (4,05), 332 (3,83), 300 (3,77), 243 (4,78)	M^+ 298 (100), 297 (7), 271 (15), 270 (12), 269 (7), 244 (7), 242 (10), 241 (8), 180 (9), 152 (33), 125 (12)	25

*The spectrum was recorded with DMF as the solvent.
**The spectrum was recorded with dioxane as the solvent.
***According to the data in [3], this compound had mp 214-216°C.

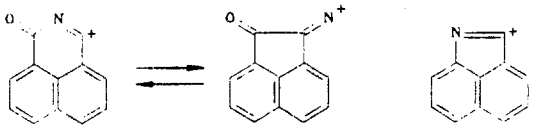
The best method for the cyclization of IVa, b, as well as 2-(5-carbamoyl-1-methyl-4-pyrazolyl)-6-nitro-1,3H-benzo[d,e]isoquinoline-1,3-dione, which was previously obtained by acylation of 4-amino-5-carbamoylpyrazole with anhydride IIIb [2], to the corresponding pyrazole diones Va, b is heating in monohydrate at 120°C for 30 min. The sharp melting point of nitro dione Vb and the data from TLC and the IR spectrum, in which sharp bands of stretching vibrations of C=O and C=N groups are present [2], make it possible to assume that one isomer is formed in the cyclization of IVb as a consequence of the different effect of the nitro group on the carbonyl groups [4].

Compounds I and Va are pyrazole analogs of 5,13,14H-benzo[d,e]isoquinolino[2',3'-a]-quinazoline-5,13-dione (VI), which was obtained by fusing anhydride IIIa with anthranilic acid amide at 240°C by the method in [3].

Amino dione Vc (R = NH_2) was obtained from Vb by the action of hydrazine hydrate in the presence of ferric chloride in acetic acid at 100°C.

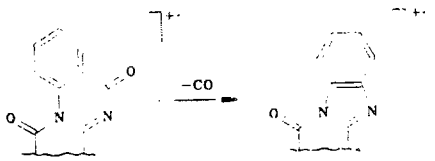
The structures of the synthesized compounds were confirmed by data from the IR, electronic absorption, and mass spectra. As a result of a study of the spectral peculiarities of pyrazole diones I and Va and benzene dione VI, which are due to the difference in the nature of the ring annelated with the pyrimidinone fragment of the molecules, it was established that these peculiarities show up most clearly in the mass spectra.

Intense molecular-ion peaks (M^+, Table 1), the profound transformation of which upon electron impact leads to the formation of F_1 and F_2 ions with m/z 180 and 152, are characteristic for all three compounds. However, the initial acts of fragmentation that are associated with the peculiarities of the structures of the benzene (VI) and pyrazole (I and Va) diones differ substantially.



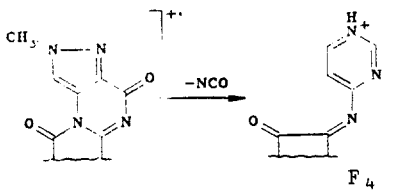
F_1 F_2

The first most likely pathway of the fragmentation of VI is the detachment of a carbonyl group from the pyrimidinone ring, which leads, under mass-spectrometric conditions, to the formation of the 1,8-naphthoylene-1',2'-benzimidazole ion F_3.



F_3

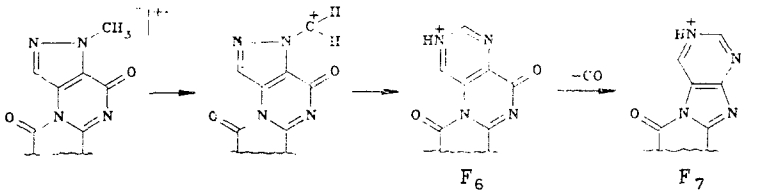
Disruption of the pyrimidinone ring [5], which is associated with the detachment of an NCO fragment from M^+, occurs in the case of Va. This process probably gives rise to complex transformations that lead to the F_4 ion, migration of a hydrogen of the N-methyl group of the pyrazole ring after cleavage of the C(Pz)—CO bond, expansion of the pyrazole ring to a pyrimidine ring [6], and isomerization of the remainder of the imide fragment.



F_4

A distinctive feature of the mass spectrum of I is the presence of peaks of $[M - H]^+$ ions, the intensity of which surpasses that of the M^+ peak. The detachment of hydrogen evidently takes place from the N-methyl group of the pyrazole fragment of the molecule, which is characteristic for 1-methylpyrazole and some substituted 1-methylpyrazoles [7]. The possi-

bility of the detachment of hydrogen from the M^+ ions of pyrazole diones is due to the relative orientation of the N-methyl group and the C=O group of the pyrimidine ring, as well as to stabilization of the initially formed F_5 ion due to interaction of the CH_2^+ ion and the C=O group, which is confirmed by the absence of this sort of fragmentation pathway for isomer Va. Subsequent expansion of the pyrazole ring to a pyrimidine ring ensures the formation of the more stable (than M^+) F_6 ion, which then undergoes fragmentation to the F_7 ion – evidently in analogy with benzene dione VI.



F_6 F_7

Thus, the peculiarities of the fragmentation of I and Va are in agreement with the previously drawn conclusion of the impossibility of obtaining pyrazole analogs of naphthoylenebenzimidazole from 2-(amino-1-methylpyrazolyl)-1,3H-benzo[d,e]isoquinoline-1,3-diones [1].

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The electronic absorption spectra of solutions in ethanol were obtained with a Specord UV-vis spectrophotometer. The mass spectra were obtained with an MAT-311 spectrometer at an ionizing voltage of 70 eV; the temperature of the ionization chamber was 210°C.

The results of elementary analysis of the compounds obtained were in agreement with the calculated values.

4-Amino-3-carbamoyl-1-methylpyrazole (II), the 1-methyl-4-nitropyrazole-3-carboxylic acid and 3-carbamoyl-1-methyl-4-nitropyrazole necessary for its synthesis, and 2-(5-carbamoyl-1-methyl-4-pyrazolyl)-6-nitro-1,3H-benzo[d,e]isoquinoline-1,3-dione (VII) were obtained by the methods described in [2, 8, 9].

2-(3-Carbamoyl-1-methyl-4-pyrazolyl)-1,3H-benzo[d,e]isoquinoline-1,3-dione (IVa). A mixture of 1.1 g (7.9 mmole) of II and 1.5 g (7.7 mmole) of anhydride IIIa in 30 ml of water was heated in an autoclave to 180-190°C (the bath temperature) and maintained at this temperature for 5 h, after which it was cooled, and the precipitate was removed by filtration. The yield was 2.2 g.

2-(3-Carbamoyl-1-methyl-4-pyrazolyl)-6-nitro-1,3H-benzo[d,e]isoquinoline-1,3-dione (IVb). A solution of 0.84 g (6 mmole) of aminocarbamoylpyrazole II in 15 ml of water was added to a refluxing solution of 1.22 g (5 mmole) of anhydride IIIb in 30 ml of acetic acid, and the mixture was refluxed for 5 h until anhydride IIIb had vanished. The mixture was then cooled, and the precipitate was removed by filtration, washed with water, and dried. The yield was 1.65 g.

2-Methyl-2,4,12,13H-pyrazolo[3',4'-5,6]pyrimido[1,2-b]benzo[d,e]isoquinoline-4,12-dione (Va), 2-Methyl-8-nitro-2,4,12,13H-pyrazolo[3',4'-5,6]pyrimido[1,2-b]benzo[d,e]isoquinoline-4,12-dione (Vb), and 3-Methyl-8-nitro-3,4,12,13H-pyrazolo[5',4'-5,6]pyrimido[1,2-b]benzo[d,e]-isoquinoline-4,12-dione (VIII). Finely powdered IVa (IVb) or VII (6.88 mmole) was added to 22 ml of heated (to 120°C) monohydrate, and the mixture was stirred for 30 min at 120°C. It was then cooled and poured over 200 g of ice, and the precipitate was removed by filtration, washed with water until the wash water was neutral, and dried. The yield of VIII, with mp 304-305°C (dilute acetic acid) (mp 303-305°C [2]), was 93%.

8-Amino-2-methyl-2,4,12,13H-pyrazolo[3',4'-5,6]pyrimido[1,2-b]benzo[d,e]isoquinoline-4,12-dione (Vc). A 1.04-g (3 mmole) sample of Vb was heated in 50 ml of acetic acid to the boiling point; the bulk of the substance dissolved. A 0.2-g sample of ferric chloride was added at 95-100°C, and 3 ml of hydrazine hydrate was added dropwise in the course of 1 h. At the end of the reaction the mixture was refluxed for 10 min, after which it was cooled, and the precipitate was removed by filtration, washed with water to remove inorganic impurities, and dried. The yield was 0.75 g.

5,13,14H-Benzo[d,e]isoquinolino[2',3'-a]quinazoline-5,13-dione (VI). A mixture of 0.4 g (2 mmole) of anhydride IIIa and 0.42 g (3.2 mmole) of anthranilic acid amide was triturated until a homogeneous mass was obtained, and the mass was then heated to 240°C and maintained at this temperature for 1.5 h. The mixture was dissolved in the minimum amount of chloroform and chromatographed with a column (silica gel 100/250, chloroform) with collection of the fraction containing a substance with yellow luminescence (R_f 0.6). The solvent was removed by distillation to give 0.15 g of VI.

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CONFORMATION OF 4,5,6-SUBSTITUTED 2-ISOPROPYL-1,3,2-OXATHIOBORINANES

V. A. Bacherikov, A. I. Gren', V. Ya. Gorbatyuk, and O. S. Timofeev

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The configuration and predominant conformations of 2-isopropyl-4,5,6-alkylsubstituted 1,3,2-oxathioborinanes have been studied by ^{1}H-NMR spectroscopy. 2,4- and 2,6-Dialkylsubstituted derivatives exist in near half-chair conformations, while 6,6-dimethyl-2-isopropyl-1,3,2-oxathioborinane exists in two energetically equivalent inverting forms. 2,5,6- and 2,4,6-Trialkylsubstituted 1,3,2-oxathioborinanes consist of mixtures of stereoisomers differing in the orientations of the alkyl groups at the $C_{(6)}$ and $C_{(4)}$ ring atoms.

2-Isopropyl-5-alkylsubstituted 1,3,2-oxathioborinane molecules exist predominantly in half-chair conformations [1]. The present paper deals with an examination of the conformations of 2-isopropyl-1,3,2-oxathioborinanes (I-VI), containing alkyl substituents in the 4,5, and 6-ring positions.

Analysis of the signal multiplicities in the ^{1}H-NMR spectra (Table 1) of compounds I and II reveals that they exist primarily in chair-like conformations with an equatorial methyl group at the $C_{(4)}$ and $C_{(6)}$ atoms, respectively. A distinguishing feature of the spectrum of compound II relative to that of compound I are the lower values of the vicinal spin-spin coupling constants (SSCC) $^3J_{H_AH_a}$ and $^3J_{H_CH_a}$. This is apparently due to the fact that introduction of a methyl group in the 6-position of the 1,3,2-oxathioborinane ring results in greater distortion of the ring than does introduction of the same group at the $C_{(4)}$ atom.

A. V. Bogatskii Physical Chemical Institute, Academy of Sciences of the Ukrainian SSR, Odessa.

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