SYNTHESIS AND MECHANISM OF THE FORMATION OF BIS(METHYLAMIDES) OF PYRAZOLEDICARBOXYLIC ACIDS

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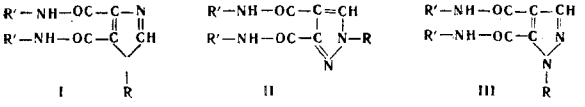
The reaction of ethoxymethyleneoxaloacetic ester with phenylhydrazine and methylhydrazine has been studied. It has been established that the addition of phenylhydrazine takes place to the ethoxy group through the β-nitrogen atom, and the addition of methylhydrazine to the ethoxy group predominantly through the α-nitrogen atom. Several derivatives of β-alkyl(aryl)hydrazinomethyleneoxaloacetic esters have been obtained. A series of bis(methylamides) and several diamides of 1-alkyl(aryl)pyrazoledicarboxylic acids have been synthesized. Their structure has been determined on the basis of their UV spectra and their breakdown by hydrolysis to known acids. It has been found that in the alkylation of an ester of 3,4-pyrazoledicarboxylic acid with alkyl halides followed by amidation, two isomeric bis(methylamide)s are formed, apparently with the predominance of derivatives of 1-alkyl-3,4-pyrazoledicarboxylic acids. It has been established that the bis(methylamide)s of 1-alkyl-3,4-pyrazoledicarboxylic and of 1-alkyl-4,5-pyrazoledicarboxylic acids have characteristic UV spectra differing from one another. The bis(methylamide)s obtained are pharmacologically active substances.

In 1961, we synthesized a series of alkylated amides of 4,5-imidazoledicarboxylic acids, or "antifeines" (I) [1–4], which can be regarded as peculiar open-structure analogs of xanthine derivatives. Pharmacological studies have shown that the antifeines possess a pronounced action on the central nervous system [3, 5, 6]. These compounds have consequently found use in clinical practice [7–9]. It is known that the diamides and some bis(alkylamide)s of 1-alkyl-3,5-pyrazoledicarboxylic acids possess sedative and narcotic properties [10, 11].

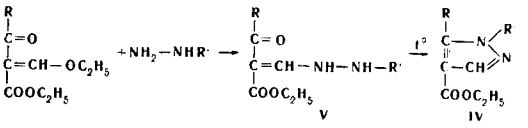
The object of the present work was to synthesize pyrazole derivatives corresponding to the antifeines: bis(methylamide)s of 1-alkyl-3,4-pyrazoledicarboxylic acids (II) and bis(methylamide)s of 1-alkyl-4,5-pyrazoledicarboxylic acids (III) and also some diamides of this type.



I II III

a $R=C_6H_5$, $R'=CH_3$; b $R=R'=CH_3$; c $R=C_2H_5$, $R'=CH_3$; d $R=i\text{-}C_3H_7$, $R'=CH_3$; e $R=CH_2=CHCH_2$, $R'=CH_3$; f $R=H$, $R'=CH_3$; g $R=R'=H$; h $R=CH_3$, $R'=H$

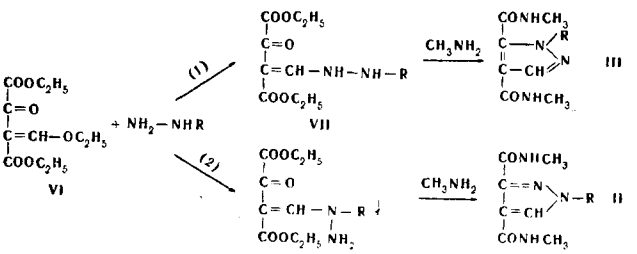
Esters of pyrazolecarboxylic acids (IV) can be obtained by the reaction of esters of ethoxymethylene-β-keto acids with hydrazines [12, 13]. Thus, in a study of the reaction of ethoxymethyleneoxaloacetic ester with phenylhydrazine [13] the hydrazine Va was isolated as an intermediate and it was shown that the addition of the phenylhydrazine takes place first at the ethoxy group and not at the keto group of the initial ester. In the reaction of ethoxymethyleneoxaloacetic ester (VI) with phenylhydrazine [12], an ester was isolated directly to which, without proof, the structure of 1-phenyl-4,5-pyrazoledicarboxylic ester was ascribed. In studying the reaction of the ester VI with some hydrazines, we repeated this synthesis and isolated an intermediate reaction product the composition of which corresponded to formula Vb. This substance was converted into 1-phenyl-4,5-pyrazoledicarboxylic acid bis(methylamide) (IIIa) without the isolation of the ester (see the experimental section, method A). We obtained the same amide with a yield of 77% without the intermediate isolation of the hydrazine Vb (see method B). The absence of traces of substance IIa isomeric with IIIa, even in the mother liquor after the separation of the bis(methylamide) (IIIa) shows that the addition of the phenylhydrazine takes place only at the ethoxy group through the β-nitrogen atom.



V IV

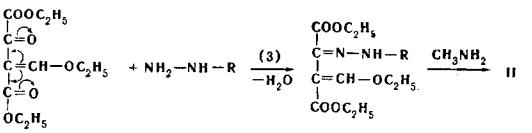
a $R=CH_3$, $R'=C_6H_5$; b $R=COOC_2H_5$; $R'=C_6H_5$; c $R=COOC_2H_5$, $R'=i\text{-}C_3H_7$

While in phenylhydrazine the reactivity of the α-nitrogen atom is greatly weakened by the influence of the phenyl group and therefore the course of the reaction by scheme (1) is completely understandable, for methylhydrazine, in which a higher electron density is concentrated on the α-atom, one would rather expect the reaction to take place by scheme (2). The same difference in the reactivities of phenylhydrazine and methylhydrazine is observed in their acylation [14–16].



VI VII III II

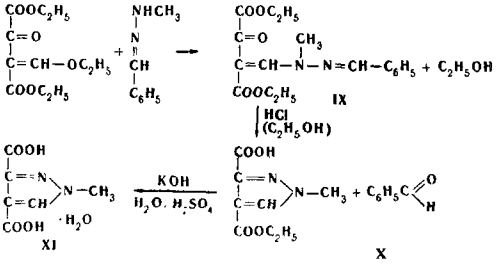
It must be emphasized that the isolation of compounds VII excludes the possibility of the reaction's taking place by scheme (3), since in this case the composition of the intermediate reaction products would be different.



We have shown that it is not the ketone but the ethoxymethylene group of compound VI that takes part in the reaction not only in the case of phenylhydrazine but also in the case of α,α-dimethylhydrazine (substance VIII, Table 1). Ethoxymethylene β-keto esters react similarly with ammonia and amines [17, 18]. Apparently, the lowered reactivity of the keto groups is explained in this case by their conjugation with the C=C bond, as a result of which the methine carbon acquires the greatest positive charge.

The reaction of VI with methylhydrazine did not lead to the formation of crystalline hydrazine derivatives. Because of this, the reaction mixture was heated to 40–50° C, whereupon cyclization took place. The pyrazoledicarboxylic acid formed was not isolated but was converted directly into the bis(methylamide) by the action of methylamine. The isolation of substance IIb shows that VI reacts with methylhydrazine by scheme (2). The structure of substance IIb was established by comparing the melting point and a mixed melting point of the acid obtained on its hydrolysis (Table 4) with authentic 1-methyl-3,4- and 1-methyl-4,5-pyrazoledicarboxylic acids which we had synthesized. The identity of the acid obtained on the hydrolysis of the bis(methylamide) IIb with 1-methyl-3,4-pyrazoledicarboxylic acid was also confirmed by comparing their UV spectra in dioxane (Fig. 1).*

The authentic 1-methyl-4,5-pyrazoledicarboxylic and 1-methyl-3,4-pyrazoledicarboxylic acids were synthesized by oxidizing the two different trimethylpyrazoles obtained by the method of Auwers and Cauer [20]. No one had succeeded in oxidizing them previously and it was achieved by us on the basis of a described example of the stability of a methyl group on a nitrogen atom of the pyrazole ring with respect to permanganate [19]. 1-Methyl-3,4-pyrazoledicarboxylic acid (XI) was previously unknown, and therefore we synthesized it by another method, as well:



The reaction of VI with benzaldehyde methylhydrazone [21] first gave the hydrazine derivative IX, and the reaction of this with dry HCl in anhydrous ethanol led simultaneously to cyclization and the acidolysis of one of the ethoxycarbonyl groups with the formation of 4(3)-ethoxycarbonyl-1-methyl-3(4)-pyrazolecarboxylic acid (X) (the position of the carboxy group in substance X was not established), which was then converted by hydrolysis into the acid XI.

1-Methyl-3,4-pyrazoledicarboxylic acid bis(methylamide) (IIb), the synthesis of which has been described above, possesses an extremely characteristic UV spectrum (see Fig. 2). By using these data, we

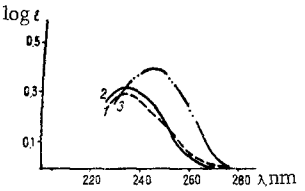
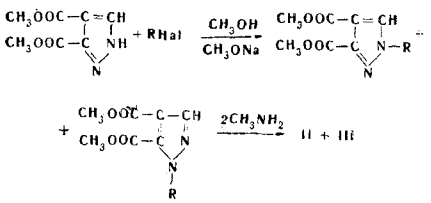


Fig. 1. UV spectra of 1-methyl-pyrazoledicarboxylic acids: 1) authentic 1-methyl-3,4-pyrazoledicarboxylic acid; 2) the 1-methyl-3,4-pyrazoledicarboxylic acid studied; 3) 1-methyl-4,5-pyrazoledicarboxylic acid.

decided to investigate what substances are formed by the alkylation of dimethyl 3,4-pyrazoledicarboxylate with methyl iodide or ethyl bromide and with allyl bromide with subsequent amidation with methylamine, when the simultaneous formation of two types of isomeric bis(methylamide)s could be expected:



The results of the production of bis(methylamide)s by this method (method C) are given in Table 2. When the reaction was carried out with methyl iodide, as also in the reaction of VI with methylhydrazine, the bis(methylamide) IIb was obtained. In both cases the mother liquors after the separation of the main mass of this substance contained a mixture with the composition $C_8H_{12}N_4O_2$ (mp 120–135° C) apparently consisting of a mixture of isomers undergoing further separation with difficulty.

Similarly, we obtained 1-ethyl-3,4-pyrazoledicarboxylic acid bis(methylamide) IIc, with a characteristic UV spectrum very similar to that of the corresponding methyl derivative (Fig. 2), which confirms its structure. From the mother liquors after the recrystallization of IIc we isolated a mixture of the isomers IIc and IIIc with the composition $C_9H_{14}N_4O_2$. From this, by separating the substances in a solution with a definite density gradient* we isolated the bis(methylamide) IIIc, possessing a UV spectrum with a maximum (Fig. 3). The difference of this spectrum from the spectrum of substance IIc shows the structure of the amide under consideration as a derivative of 1-methyl-4,5-pyrazoledicarboxylic acid.

*According to the literature [19], the UV spectrum of 1-methyl-4,5-pyrazoledicarboxylic acid has a maximum at 250 mμ.

*This method of separating isomers was developed by S. P. Kozhevnikov; details of the separation will be published later. He also took all the UV spectra.

The reaction of ethoxymethyleneoxaloacetic ester with isopropylhydrazine gave a 29% yield of the intermediate hydrazine Vc. This substance was characterized by its composition, which shows the addition of the isopropylhydrazine at the ethoxy group; from Vc we obtained the bis(methylamide) IIId, which was also synthesized without the intermediate isolation of Vc. In this synthesis, in addition to the formation of the crystalline reaction product IIId, a considerable amount of a dark resin was formed from which it was impossible to isolate an individual substance. The UV spectrum of IIId confirms its structure (see Fig. 3).

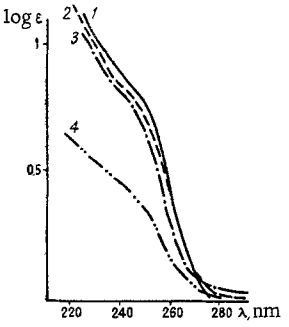


Fig. 2. UV spectra of amides of 1-alkyl-3,4-pyrazoledicarboxylic acids: 1) IIIc; 2) IIc; 3) IIh; 4) IIe.

Its formation is possible only if the isopropylhydrazine adds by the β-nitrogen atom at the ethoxy group of the initial ester VI.

The reaction of the ester VI with allylhydrazine (after cyclization and amidation with methylamine) gave a crystalline mixture of the isomeric bis(methylamides) IIe and IIIe, with the composition $C_{10}H_{14}N_4O_2$ and mp 80–95° C. The same mixture, with mp 85–102° C, was obtained by alkylating dimethyl 3,4-pyrazoledicarboxylate with allyl bromide and subsequent amidation with methylamine. The repeated crystallization of this mixture from cyclohexane gave a 29% yield of the bis(methylamide) IIe. After additional treatment with solvents,* the isomeric bis(methylamide) IIIe was obtained from the mother liquors with a yield of 4.5%. The two amides IIe and IIIe possess characteristic UV spectra differing markedly from one another. On the basis of these spectra (see Fig. 2 and 3), substance IIe was ascribed the structure of a derivative of 1-allyl-3,4-pyrazoledicarboxylic acid and substance IIIe the structure of a derivative of 1-allyl-4,5-pyrazoledicarboxylic acid.

The amidation of both methyl and ethyl 3,4-pyrazoledicarboxylates with methylamine gave the bis(methylamide) IIf. A comparison of its UV spectrum with the spectra of the bis(methylamide)s of the alkylated 3,4-pyrazoledicarboxylic acids II and the 4,5-pyrazoledicarboxylic acids III confirms that this substance had the structure of a 3,4-derivative.

3,4-Pyrazoledicarbonamide (IIg) was obtained from the dimethyl ester of this acid and aqueous ammonia at room temperature, while it had previously been synthesized from the acid chloride and liquid ammonia [22], since it had not been possible to obtain it from the diethyl ester and ethanolic ammonia [12]. The initial pyrazoledicarboxylic ester was obtained by oxidizing 4,5-pyrazolinedicarboxylic ester [23] with chlorine, while the previously-known method used bromine as oxidizing agent [24], which gives very poor results. We observed that in the case of prolonged contact of dimethyl-3,4-pyrazoledicarboxylate with a chloroformic solution of HCl, the ester underwent acidolysis with the formation of 4(5)-methoxycarbonyl-5(4)-pyrazolecarboxylic acid XII (the position of the carboxy group in this compound was not established).

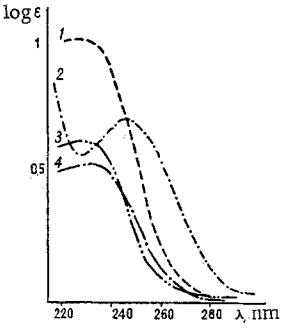
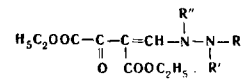


Fig. 3. UV spectra of 1-alkyl-4,5-pyrazoledicarboxylic acid bis(methylamide)s: 1) IIIc; 2) IIIa; 3) IId; 4) IIIe.

We have described a similar case of acidolysis above (conversion of IX into X). The structure of substance XII was shown by its conversion into the previously-known 4,5-pyrazoledicarboxylic acid hydrate [24]. 1-Methyl-3,4-pyrazoledicarbonamide (IIh) was obtained

*The method of separating the isomers was developed by S. P. Kozhevnikov.

Table 1



Compound	R	R′	R″	Mp, °C	Empirical formula	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N	Yield, %
Vb	C_6H_5	H	H	104–104.5	$C_{15}H_{18}N_2O_5$	58.72 58.89	5.96 6.03	9.07 9.39	58.81	5.92	9.15	70
VIII	CH_3	CH_3	H	78–79	$C_{11}H_{18}N_2O_5$	51.38 51.41	7.08 7.03	10.71 10.45	51.15	7.02	10.84	72
Vc	*i*-C_3H_7	H	H	64–65	$C_{12}H_{20}N_2O_5$	52.67 52.67	7.06 7.12	10.50 10.52	52.92	7.40	10.29	29
IX	=CH—C_6H_5		CH_3	81–82	$C_{17}H_{20}N_2O_5$	60.37 60.23	6.24 6.26	8.96 8.97	61.42	6.07	8.43	89.5

from dimethyl 3,4-pyrazoledicarboxylate in a similar manner to the synthesis of the corresponding bis(methylamide) (see Table 2). The structure of the diamide was shown by its hydrolysis to 1-methyl-3,4-pyrazoledicarboxylic acid (Table 3). It was found that this acid can form a molecular compound with one molecule of its monopotassium salt which crystallizes from water without decomposition (similar salts are known for acetic acid [25]). From the aqueous solution, the addition of H_2SO_4 liberated the free 1-methyl-3,4-pyrazoledicarboxylic acid. The monopotassium salt of this acid is stable in an acid medium. 1-Phenyl-4,5-pyrazoledicarboxylic acid possesses similar properties [13].

We have also synthesized 1-methyl-3,5-pyrazoledicarboxylic acid bis(methylamide) (XIII) starting from the corresponding ester [26], methyl iodide, and aqueous methylamine.

A pharmacological study of the substances II, III, and XIII obtained has shown that they possess a pronounced central activity consisting in the supression of cortical sections with the simultaneous excitation of a series of formations of the diencephalon. The sedative action of these substances is somewhat greater than of the antifeines while at the same time there is a weakening of the stimulating influence on the subcortical formations. The latter property is most strongly developed in substance XIII [27].* In addition, substance IId was found to have an antiphlogistic action and an exciting influence on the hypophyseal-adrenal system [28].

EXPERIMENTAL

β-Alkyl(aryl)hydrazinomethyleneoxaloacetic esters. With cooling (+ 5° C) and stirring, 0.055 mole of an alkyl(aryl)hydrazine was added dropwise to 12.2 g (0.05 mole) of the ester VI in 25 ml of absolute ethanol. The precipitate that deposited was filtered off and dried in vacuum. It was purified by reprecipitation from ethanol with water (Table 1).

1-Alkyl(aryl)pyrazoledicarboxylic acid bis(methylamide) and diamides (Table 2).

A. With cooling and stirring, 0.11 mole of an alkyl- or arylhydrazine was added dropwise to 24.4 g (0.1 mole) of the ester VI in 50 ml of absolute ethanol. Then the solution was heated at 40–50° C for 1 hr, cooled, and treated with 38 ml of 33% aqueous methylamine or the corresponding amount of ammonia. After a day, 100 ml of water was added and the mixture was extracted with chloroform four times with heating. In the case of IIIa, no extraction was carried out. In the case of IIId, after the evaporation of the $CHCl_3$ the oil was treated with benzene and cooled for crystallization. After the elimination of the chloroform, the substance was crystallized several times: IIb from ethanol, IIIa from water, IIId from cyclohexane, and IIc from a mixture of benzene and petroleum ether.

B. With heating to 50–60° C, 6 g of substance Vb or Vc was dissolved in 10 ml of absolute ethanol, and the solution was cooled and treated with 9 ml of 33% aqueous methylamine. In the case of Vb, the white precipitate of IIIa was filtered off after 12 hr, yield 70%, mp 199–200° C (from water). In the case of Vc, substance IIId was extracted with $CHCl_3$, and after the evaporation of the solvent the small amount of C_6H_6 was added and the mixture was cooled for crystallization. Mp 100–101.5° C (from cyclohexane). In both cases, mixed melting points were taken with the substances obtained by method A.

C. A solution of sodium methoxide prepared from 7.8 g (0.34 g-atom) of sodium in 225 ml of methanol and then a 100% excess of alkyl halide were added to a solution of 60 g (0.32 mole) of dimethyl pyrazoledicarboxylate in 1800 ml of methanol that had been cooled to 25° C. The reaction mixture was boiled gently under reflux—for 10 hr in the case of CH_3I and for 16 hr in the case of C_3H_5Br; in the case of C_2H_5Br the mixture was boiled for 7 hr and cooled, half the amount of C_2H_5Br first taken was added, and it was boiled in the same way for another 7 hr. Then the methanol was distilled off and 90 ml of 33% aqueous methylamine or the corresponding amount of aqueous methylamine or the corresponding amount of aqueous ammonia was added. The further operations for the isolation of the bis(methylamide)s II were similar to those of method A. The mother solutions after the crystallization of the bis(methylamide)s from an appropriate solvent yielded a mixture of the two isomers: IIb + IIb—yield 31%; IIc + IIIc—36.4%; IIe + IIIe—40.6%.

To isolate the isomer IIIe, 17 g of the mixture, with mp 85–102° C, was boiled with a mixture of 50 ml of water and 50 ml of CCl_4. The aqueous layer, on evaporation and crystallization, gave a precipitate which was treated with the mixture of solvents once or twice more and was crystallized several times from water. To isolate IIIb from its mixture with IIb (mp 112–137° C) the same method was used, with final crystallization from ethanol (in this case, according to the UV spectra, it was impossible to achieve complete separation). The isolation of IIIc from its mixture with IIc (mp 83–100° C) was carried out by the repeated treatment of the finely-ground powder with a mixture of cyclohexane and CCl_4 (n_D 1.445) in a centrifuge with subsequent isolation of the ring of substance formed. Thirteen grams of the mixture yielded 0.65 g of IIIc.

Substance IIf was obtained both from dimethyl and from diethyl pyrazoledicarboxylates and aqueous methylamine. In the synthesis of IIh, a mixture of the isomers II and III was formed from which the IIh was isolated by repeated crystallization from water.

1-Methyl-3,5-pyrazoledicarboxylic acid bis(methylamide) (XIII) was obtained by the same method with a yield of 78%, mp 234–236° C (from water). Found, %: C 48.76, 48.99; H 6.24, 6.47; N 28.54, 28.32%. Calculated for $C_8H_{12}N_4O_3$, %: C 48.97; H 6.17; N 28.55.

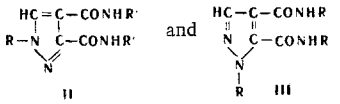
4(3)-Ethoxycarbonyl-1-methyl-3(4)pyrazolecarboxylic acid (X). A current of dry HCl was passed into a solution of 14.37 g (0.043 mole) of substance IX in 100 ml of absolute ethanol for 2 hr. Then the methanol was distilled off at 40–60° C in a vacuum of 40 mm. The residue crystallized on cooling. Yield 52.3%, mp 182–183° C after two crystallizations from ethanol. Found, %: C 48.69, 48.99; H 5.36, 5.02; N 14.23, 14.21; equiv. 193.3, 193.6. Calculated for $C_8H_{10}N_2O_4$, %: C 48.49; H 5.09; N 14.14; equiv. 198.2.

Pyrazoledicarboxylic acids and their salts (see Table 3). Method 1A. A mixture of 2 g (0.01 mole) of the bis(methylamide) IIb and 11.4 g of 30% KOH solution and a mixture of 2 g (0.008 mole) of the bis(methylamide) IIIa and 8.6 g of the same solution were boiled for 4-6 hr. After cooling, the mixtures were immediately acidified with 11 (or in the second case 22) ml of H_2SO_4 (1 : 2 by volume). The acids were crystallized from water. Method 1B. If to the product of hydrolysis of IIb the same H_2SO_4 was added in drops until the mixture was acid to Congo Red, the monopotassium salt of the acid XI was obtained in the form of colorless crystals. Method 1C. A mixture of 2 g of the diamide IIh and 13.6 g of 30% KOH solution was boiled for 5 hr. After cooling, the mixture was immediately acidified with 13 ml of H_2SO_4 (1 : 2 by volume). Colorless crystals of the double salt were obtained and these were crystallized several times from water. A 1.4 g amount of the double salt was dissolved in 12 ml of water with heating, and the solution was cooled and acidified with 11 ml of H_2SO_4 (1 : 2 by volume). On stirring, a precipitate of the acid XI deposited.

Method 2A. With stirring, a hot solution of 31.5 g (0.199 mole) of $KMnO_4$ was added to a solution of 5.5 g (0.05 mole) of 1,3,4-trimethylpyrazole [20] in 70 ml of water. Method 2B. In the oxidation of 1,4,5-trimethylpyrazole [20], we used 3.1 g (0.028 mole) of it in

*In this paper, 1-methyl-, 1-ethyl-, and 1-allyl-3,4-pyrazoledicarbonylic acid bis(methylamides)s were erroneously ascribed the structures of the corresponding 1-alkyl-4,5-pyrazoledicarbonylic acid derivatives.

Table 2



Compound	R	R′	Method of synthesis	Mp, °C	Empirical formula	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N	Yield, %
IIIa	C_6H_5	CH_3	A	199—200	$C_{13}H_{14}N_4O_2$	60.84 60.73	5.59 5.69	21.62 21.71	60.45	5.46	21.69	76.8
IIb	CH_3	CH_3	A	192—193	$C_8H_{12}N_4O_2$	48.53 48.63	6.76 6.50	28.31 28.34	48.97	6.17	28.55	33.5*
			B	192—193**		—	—	—				25.7
IIIb	CH_3	CH_3	B	136—138	$C_8H_{12}N_4O_2$	—	—	28.72 28.71			28.55	
IIId	i-C_3H_7	CH_3	A	100—101.5	$C_{10}H_{16}N_4O_2$	53.40 53.62	7.23 7.22	25.42 25.56	53.55	7.19	24.98	40
IIд+IIIe	CH_2=$CHCH_2$	CH_3	A	80—95		—	—	25.05 25.49			25.21	
IIe	CH_2=$CHCH_2$	CH_3	B	117—118**	$C_{10}H_{14}N_4O_2$	54.53 54.28	6.64 6.73	25.10 24.83	54.03	6.34	25.21	29
IIIe	CH_2=$CHCH_2$	CH_3	B	122—123.5		54.23 54.21	6.29 6.59	24.90 25.11	54.03	6.34	25.24	4.5
IIc	C_2H_5	CH_3	B	129—130	$C_9H_{14}N_4O_2$	51.43 51.44	6.69 6.89	26.91 26.40	51.41	6.71	26.65	30.4
IIIc	C_2H_5	CH_3	B	104—107	$C_9H_{14}N_4O_2$	51.85 51.66	6.60 6.96	26.82 27.01	51.41	6.71	26.65	3
IIc	H	CH_3	B***	245—246	$C_7H_{10}N_4O_2$	46.01 46.29	5.62 5.78	30.73 31.08	46.14	5.53	30.76	74
IIf	CH_3	H	B***	282—283	$C_6H_8N_4O_2$	43.04 43.25	5.17 4.86	33.45 33.31	42.85	4.79	33.32	38.7
IIg	H	H	B***	322	$C_5H_6N_4O_2$	—	—	36.72 36.81	—	—	36.35	70.6

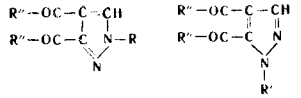
*Another 17.5% of a mixture of isomers was obtained from the ethanolic mother liquors.

**A mixture with the substance obtained by method A gave no depression.

***Extraction with chloroform was not carried out since the substance crystallized readily from the aqueous solutions.

Table 3

Pyrazoledicarboxylic Acids and Their Salts



Method of synthesis	R″	R or R′	Mp, °C	Empirical formula	Found, % C	Found, % H	Found, % N	Found, % K	Calculated, % C	Calculated, % H	Calculated, % N	Calculated, % K	Yield, %
1A	OH	R=CH_3	233b	$C_6H_6N_2O_4 \cdot H_2O$[a]	38.60 38.70	4.29 4.31	14.98 14.70	—	38.30	4.29	14.89	—	92.2
1A	OH	R=CH_3	233	$C_6H_6N_2O_4$[c]	42.29 42.47	3.29 3.28	16.58 16.54	—	42.36	3.56	16.47	—	
1B	OK OH	R=CH_3	335—335.5	$C_6H_5KN_2O_4$	34.20 34.10	2.70 2.71	13.51 13.62	18.70 18.46	34.61	2.42	13.46	18.78	98.0
1A	OH	R′=C_6H_5	211d	$C_{11}H_8N_4O_4$	—	—	12.23 12.24	—	—	—	12.06	—	67.4
1C	OK 3OH	R=CH_3	335—335.5e	$C_6H_6N_2O_4 \cdot C_6H_5KN_2O_4$	38.16 38.44	2.58 2.90	14.96 19.15	10.31 10.06	38.09	2.93	14.81	10.33	91.0
1C	OH	R=CH_3	230—231[f]	$C_6H_6N_2O_4 \cdot H_2O$									
2B	OK OH	R′=CH_3	272	$C_6H_5KN_2O_4$			13.77 13.16	18.08			13.46	18.78	76.2
2B	OH	R′=CH_3	234	$C_6H_6N_2O_4 \cdot H_2O$									
2A	OK OH	R=CH_3	322	$C_6H_5KN_2O_4$	34.32	2.44	13.78 13.38	18.45	34.61	2.42	13.46	18.78	
2A	OH	R=CH_3	234[f]	$C_6H_6N_2O_4 \cdot H_2O$									
3	OH	R=CH_3	231—232[f]	$C_6H_6N_2O_4 \cdot H_2O$									98.1

[a]Found, %: H_2O 9.19, 9.17. Calculated, %: H_2O 9.58. [b]On being placed on a block heated to 320° C, the acid sublimed without melting and without decomposing. [c]Found, equivalent: 88.4, 87.2. Calculated, equivalent: 85.1. [d]According to the literature [13], mp 216° C. [e]The melting point of the substance coincides with that of potassium 1-methyl-4,5-dicarboxylate. However, in the melting of the two substances there is a clearly-visible difference: in the upper part of the capillary containing the double salt there is a pronounced ring of crystalline sublimed acid, which is absent from the capillary with the potassium hydrogen salt. Sublimation begins rapidly when the capillary containing the double salt is placed in a block heated to 320° C, i. e., at the same temperature at which the free acid sublimes. [f]A mixture with the acid obtained by another method gave no depression.

65 ml of water with the addition of 1.4 g of NaOH and 38.6 (0.244 mole) of $KMnO_4$. Both mixtures were boiled for 2 hr. After the usual working up and acidification of the evaporated solutions to pH 4, the potassium hydrogen salts of the methylpyrazoledicarboxylic acids were obtained. By boiling the salts with dilute H_2SO_4, the free acids were obtained: from 1,3,4-trimethylpyrazole—mp 234° C, a mixture with the acid obtained by method 1 giving no depression; from 1,4,5-trimethylpyrazole—mp 234° C, a mixture with the preceding acid giving a depression of ~ 20° C.

Method 3. A mixture of 1.45 g of substance X and a solution of 1.9 g of KOH in 4.5 ml of water was boiled for 2 hr. After cooling, it was acidified with 11 ml of H_2SO_4 (1 : 2 by volume).

Dimethyl 3,4-pyrazoledicarboxylate. A current of dry chlorine was passed into a solution of 10 g (0.63 mole) of dimethyl 3,4-pyrazolinedicarboxylic acid [23] in 40 ml of $CHCl_3$ at 0 to −5° C. The resulting solution was immediately poured into a flat dish for the evaporation of the $CHCl_3$ at room temperature. Yield 91.5%, mp 139–140° C (according to the literature [24], mp 141° C). Found, %: N 18.05, 18.09. Calculated for $C_7H_{12}NO_2$, %: N 17.93.

4(5)-Methoxycarbonyl-5(4)-pyrazolecarboxylic acid (XII). The conditions of preparation were the same as above, but after the end of the passage of chlorine the solution was left in a closed vessel overnight. A precipitate of the acid **XII**, which is insoluble in chloroform and methanol, deposited. Yield 42.9%. To obtain an analytically pure sample, the substance was boiled three times with fresh methanol. Found, %: C 42.68, 42.46; H 3.76, 3.52; N 16.54, 16.72%. Calculated for $C_6H_6N_2O_4$, %, C 42.36; H 3.55; N 16.46%.

3,4-Pyrazoledicarboxylic acid hydrate. Two grams (0.012 mole) of substance XII was boiled with 45 ml of 13% HNO_3 until it had dissolved and then for another 30 min. Yield 90.7%, mp 259° C (from water); a mixture with an authentic sample melted at 258–259° C [24].

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