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Pyrazolo-N-hydroxyuracils from the Modified Lossen Rearrangement of *vicinal* Pyrazoledicarbohydroxamates

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The reaction of 1-phenyl-3,4- and 4,5-pyrazoledicarbohydroxamates, II and VIII, with benzene- and methanesulfonyl chlorides is reported. Each hydroxamate yielded two isomeric N-phenyl-N-hydroxypyrimidinediones whose structures were established. The NMR spectra of a number of isomeric pyrazole derivatives are discussed.

The synthesis of condensed heteroaromatic N-hydroxyuracils as potential antimetabolites has been the subject of a continuing study in this Laboratory (1—3). The general approach in the past had been to react a *vicinal bis*-hydroxamate with an excess of a sulfonyl halide, usually in a non-hydroxylic solvent which formed the sulfonate ester of a condensed N-hydroxyuracil (4,5). Brief alkaline hydrolysis of these esters furnished the corresponding N-hydroxyuracil. Although these series of reactions appeared to proceed well in tetrahydrofuran, it was of interest to ascertain if these transformations could be carried out in water. It had already been demonstrated that this modified Lossen degradation can take place in an aqueous medium as evidenced by the conversion of potassium sodium α-carboxy-β-phenylpropionohydroxamate to poly-*d,l*-phenylalanine by benzenesulfonyl chloride in water (6).

This paper reports a study of the modified Lossen rearrangement of 1-phenyl-3,4- and 4,5-pyrazoledicarbohydroxamates (II and VIII) with a sulfonyl halide in an aqueous basic solution and also under the previously employed conditions in tetrahydrofuran. Starting with the unsymmetrical hydroxamates, II and VIII, their reaction with a sulfonyl chloride produced, as expected, from each, two isomeric N-phenylpyrazolo-N-hydroxyuracils. A part of this study was devoted to a comparison of the yields and isomer ratios from these reactions of II and VIII under different experimental conditions. Furthermore, since only aromatic sulfonyl halides had been employed previously, it was of interest to determine how methanesulfonyl chloride would effect the course of these reactions. In one of the series, starting from II, little change in yield and isomer ratio was observed when methanesulfonyl was substituted for benzenesulfonyl chloride, but for some of the other starting hydroxamates, the yield and isomer distribution changed markedly.

The previously studied rearrangements in organic milieus suffered from the drawback that the starting hy-

droxamate, the postulated intermediates and the final product possessed limited solubility in the solvent and for the most part, the reactions proceeded in heterogeneous phases. From such reactions, one might have expected some variations in yields and distribution of isomers (when two products were expected). It was felt that these reactions would proceed more uniformly if at least the starting materials and intermediates remained in solution and water appeared to be the solvent of choice, particularly
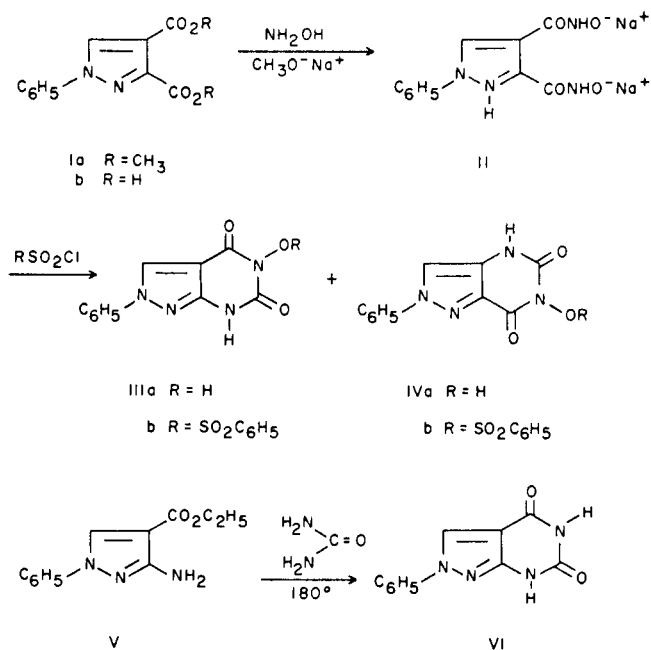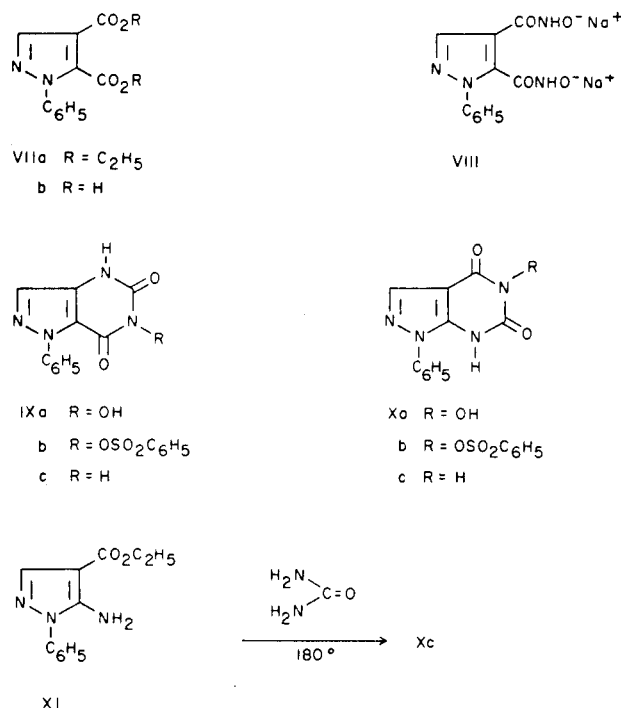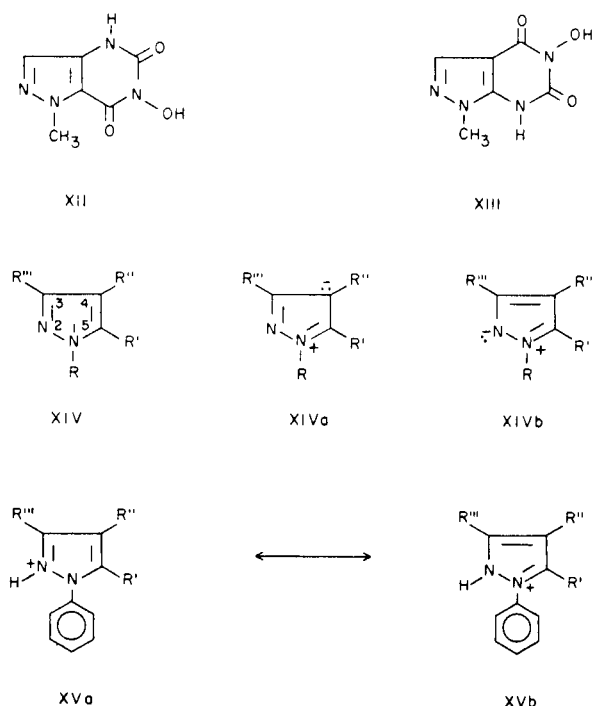
Chart I

Ia R = CH₃
b R = H

IIIa R = H
b R = SO₂C₆H₅

IVa R = H
b R = SO₂C₆H₅

V

VI

Chart II

VIIa R = C$_2$H$_5$
b R = H

VIII

IXa R = OH
b R = OSO$_2$C$_6$H$_5$
c R = H

Xa R = OH
b R = OSO$_2$C$_6$H$_5$
c R = H

XI

Xc

Chart III

XII

XIII

XIV

XIVa

XIVb

XVa

XVb

more readily. The general procedure which was developed consisted of adding the sulfonyl halide to a stirred alkaline solution of the hydroxamates, taking care to maintain the pH about 8. Sometimes, a part of the final product did precipitate at pH 7–8, but it was readily redissolved by the addition of more base.

Rearrangements in Water.

The reactions starting from methyl 1-phenyl-3,4-pyrazoledicarboxylate, Ia, are discussed first (Chart I). The ester was converted to hydroxamate, II, in the usual manner. The reaction of II with one equivalent of either benzenesulfonyl or methanesulfonyl chloride in aqueous alkaline solution at 20–25° furnished comparable yields of a mixture of the two isomers, IIIa and IVa, in almost equal amounts (see Table I). However, from a similar reaction at lower temperature (0–5°) for a shorter period (0.5 hour), there was obtained a mixture of IIIa and IVa, which was somewhat richer in IVa, which would indicate that the overall sequence of reactions commencing with the hydroxamate at C-4 proceeded faster. One would tend to rule out steric factors in the first step involving the reaction of either hydroxamate group in II with the sulfonyl halide which initiates the Lossen degradation to the isocyanate, the intermediate prior to cyclization with the adjacent hydroxamic acid to form either IIIa or IVa.

This then raises the question if an inductive effect exerts itself sufficiently at either the 3- or 4-hydroxamate group to impart a difference in the relative rate in the overall series of reactions. It has been postulated that in the ground state of the pyrazole ring C-4 is more nucleophilic (7), as indicated by hybrid XIVa, and thus the hydroxamate at C-4 might well react somewhat faster with the sulfonyl halide than that at C-3. Another factor which might account for the slightly faster rate at C-4 might be attributed to the fact that the more nucleophilic center at C-4 might migrate faster in the Lossen rearrangement (8). Thus, both of these effects may reinforce each other to form IVa somewhat faster than IIIa (in water).

The isomers, IIIa and IVa, were separated and IIIa was reduced relatively easily with zinc and dilute hydrochloric acid to compound VI, which in turn was synthesized independently from the fusion of ethyl 1-phenyl-3-amino-4-pyrazolecarboxylate, V, with urea. Once the structure of IIIa was established, that of the other members of the series became known.

An analogous reaction of 1-methyl-3,4-pyrazoledicarboxylate with benzenesulfonyl chloride in water gave a mixture of the N-methyl analogs of IIIa and IVa (35%) in the ratio of 40:60. The isomer distribution is quite comparable to those from a similar reaction of II and, except for the yield, the N-methyl or N-phenyl substituent did not exert a noticeable influence in changing the isomer ratio.

A cognate study (Chart II) of sodium 1-phenyl-4,5-pyrazoledicarbohydroxamate, VIII, with benzenesulfonyl

since a number of the steps involve ionic reactions. In this study, it was found that an aqueous basic medium was more satisfactory and this afforded us the opportunity to compare the results of the rearrangements from II and VIII

TABLE I

Yields and Isomer Ratios from the Reactions of the Hydroxamates and Sulfonyl Halides (a)

Starting Hydroxamate	Sulfonyl Halide (Medium)		Temp. °C (Times, hr.)		Yield (b)	Products (Ratio) (c)		
II	$C_6H_5SO_2Cl$	(H_2O)	20–25°	(2)	64	IIIa,	IVa	(45:55)
	$C_6H_5SO_2Cl$	(H_2O)	0–5°	(0.5)	55	IIIa,	IVa	(35:65)
	CH_3SO_2Cl	(H_2O)	20–25°	(2)	63	IIIa,	IVa	(50:50)
	$C_6H_5SO_2Cl$	(THF)	20–25°	(3)	72	IIIb,	IVb	(30:70)
VIII	$C_6H_5SO_2Cl$	(H_2O)	20–25°	(2)	66	IXa,	Xa	(74:26)
	$C_6H_5SO_2Cl$	(H_2O)	0–5°	(1)	44	IXa,	Xa	(92:8)
	CH_3SO_2Cl	(H_2O)	20–25°	(2)	63	IXa,	Xa	(50:50)
	$C_6H_5SO_2Cl$	(THF)	20–25°	(3)	70	IXb,	Xb	(35:65)
N-Methyl Analog of VIII	$C_6H_5SO_2Cl$	(H_2O)	32–35°	(5)	38	XII,	XIII	(92:8)
	$C_6H_5SO_2Cl$	(H_2O)	0–5°	(2)	30	XII,	XIII	(100:0)
	CH_3SO_2Cl	(H_2O)	20–25°	(2)	18	XII,	XIII	(61:39)

(a) All experiments were conducted on about 0.01 molar scale of hydroxamate and sulfonyl chloride. (b) Since the hydroxamates, II and VIII, could not be purified or analyzed, all the yields here are calculated actually on the corresponding starting ester, Ia and VIIIa, respectively. (c) These ratios were computed from the NMR spectra.

chloride in water gave a mixture of IXa and Xa. The major product of this reaction arose from the degradation of the hydroxamate at C-4, as evidenced by the large proportion of IXa in the product (Table I). After separation, the structure of the isomers was proved in the following manner. Reduction of IXa and Xa furnished the N-deoxy derivatives (IXc, Xc), one of which (Xc) was known (9,10) and was synthesized unequivocally from ethyl 1-phenyl-4-amino-5-pyrazolecarboxylate (9).

The reaction of VIII and its methyl analog was studied in a number of different environments. Again, in an analogous reaction of VIII (at lower temperature), IXa was formed faster. Now, if the same considerations as presented above apply, then the preferred rearrangement of the group at C-4 in VIII could account for some of this difference. But, in this particular system the N-substituent might offer some steric hindrance in the reaction of the hydroxamate at C-5 with benzenesulfonyl chloride. This point was investigated in the reaction of 1-phenyl and also for 1-methyl-4,5-pyrazoledicarbohydroxamates by changing from benzene- to methanesulfonyl chloride, and the results tend to substantiate such an assumption, at least for the experiments in water. The substitution of methanesulfonyl for benzenesulfonyl chloride in the reaction with VIII did not affect the yield of the products but markedly increased the quantity of Xa due to rearrangement of the hydroxamate at C-5. The prime consideration for this change might be attributed to a decrease in the bulk when switching from a

phenyl to a methyl group in the acid halide. A smaller factor which might influence the rate of reaction of the hydroxamate at C-5 with benzenesulfonyl chloride might be due to electrostatic repulsion of the two aryl groups in VIII and benzenesulfonyl chloride. Such an effect is eliminated when methanesulfonyl chloride is used and this might also contribute to the formation of the large amount of Xa.

In a similar series of experiments, the reaction of the N-methyl analog of VIII in water with benzenesulfonyl chloride furnished a mixture of XII and XIII with XII, due to rearrangement at C-4 as the major product (Chart II). And, again, the N-hydroxy derivative due to rearrangement at C-5, XIII, increased considerably when methanesulfonyl was substituted for benzenesulfonyl chloride (Table I), which does tend to point to a steric effect in the reaction in water of the 1-substituted 4,5-pyrazoledihydroxamates.

Rearrangements in Tetrahydrofuran.

The rearrangements described above in water were conducted with one equivalent of a sulfonyl chloride and the reaction stopped when the N-hydroxy compounds were formed. In tetrahydrofuran, the reaction could not be stopped satisfactorily at such a stage with one equivalent of acid chloride and it was best to use excess acid chloride and then isolate the sulfonates. Thus, starting from II and VIII, reproducible results were obtained in both series, but quite unexpectedly, the isomer mixture contained a larger proportion of the product due to rearrangement at C-3

TABLE II

Spectral Data

Compound	Solvent (d)	NMR Parameters (a)			Infrared Absorption Bands (b) ν C=O 1800–1600 cm^{-1} (Strong Bands in Spectrum)	Ultraviolet Spectra (c) λ max in mμ (log ϵ max)
		Pyrazole Proton (All Singlets)	N-C$_6$H$_5$	Other		
Ia	DMSO	9.15	8.17–7.40	OCH$_3$ at δ 3.95, 3.87	1770, 1725	257 (4.20)
	CDCl$_3$	8.47	7.92–7.30	OCH$_3$ at δ 3.96, 3.83		
	TFAA	8.57	7.83–7.33 (f)	OCH$_3$ at δ 4.10, 4.05		
Ib	DMSO	9.17	8.12–7.40	CO$_2$H at δ 9.96	1720	224 (4.20); 262 (4.16)
V	DMSO	8.72	8.09–7.00	NH$_2$ at δ 5.70; CH$_2$ at δ 4.30; CH$_3$ at δ 1.33	1710	234 (4.39); 301 (4.28)
V	CDCl$_3$	8.30	7.93–7.30	NH$_2$ at δ 5.07; CH$_2$ at δ 4.40; CH$_3$ at δ 1.36		
V	TFAA	8.52	7.65	CH$_2$ at δ 4.57; CH$_3$ at δ 1.50		
IIIa	DMSO	9.22	8.10–7.33		1770, 1730sh, 1675	293 (4.22)
IIIb	DMSO	9.30	8.20–7.38 (g)		1770, 1725	292.5 (4.38)
VI	DMSO	9.13	8.10–7.30		1725, 1640	294 (4.19)
IVa	DMSO	8.40	8.10–7.33		1720, 1660	261 (4.00); 303 (4.07)
IVb	DMSO	8.48	8.20–7.30 (g)		1765, 1745	266sh (4.01); 299 (4.08)
VIIa	DMSO	8.15	7.50	CH$_2$ at δ 4.28, 4.25; CH$_3$ at δ 1.27, 1.18	1725	249 (4.20)
VIIa	CDCl$_3$	8.04	7.44	CH$_2$ at δ 4.31; CH$_3$ at δ 1.32, 1.20		
VIIa	CCl$_4$	7.96	7.60–7.20	CH$_2$ at δ 4.26; CH$_3$ at δ 1.27, 1.18		
VIIa	C$_6$D$_6$	8.05	7.57–6.90	CH$_2$ at δ 4.05; CH$_3$ at δ 1.02, 0.90		
VIIa	N(C$_2$H$_5$)$_3$	7.93	7.67–7.10	CH$_2$ at δ 4.22		
VIIa	TFAA	8.50	7.60	CH$_2$ at δ 4.58, 4.46; CH$_3$ at δ 1.47, 1.22		

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TABLE II (Continued)

Compound	Solvent (d)	NMR Parameters (a)			Infrared Absorption Bands (b) ν C=O 1800–1600 cm^{-1} (Strong Bands in Spectrum)	Ultraviolet Spectra (c) λ max in mμ (log ϵ max)
		Pyrazole Proton (All Singlets)	N-C$_6$H$_5$	Other		
VIIb	DMSO	8.20	7.58	CO$_2$H at δ 11.45	1730, 1750sh	243.5 (4.02)
XI	DMSO	7.80	7.55	NH$_2$ at δ 6.30; CH$_2$ at δ 4.23; CH$_3$ at δ 1.27	1695	235 (4.35)
XI	CDCl$_3$	7.66	7.60—7.20 (h)	NH$_2$ at δ 5.47; CH$_2$ at δ 4.24; CH$_3$ at δ 1.30		
XI	CCl$_4$	7.55	7.52—7.20	NH$_2$ at δ 5.33; CH$_2$ at δ 4.20; CH$_3$ at δ 1.30		
XI	C$_6$D$_6$	7.97	7.52—6.83	NH$_2$ at δ 5.00; CH$_2$ at δ 4.12; CH$_3$ at δ 1.30		
XI	N(C$_2$H$_5$)$_3$	7.74—7.15		NH$_2$ at δ 5.95; CH$_2$ at δ 4.51		
XI	TFAA	8.47	7.69	CH$_2$ at δ 4.51; CH$_3$ at δ 1.47		
IXa	DMSO	7.77	7.75—7.40		1745, 1715	236 (4.05), 297 (3.95)
IXb	DMSO	8.20—7.50 (g)			1760, 1700	221 (4.38), 307sh (3.50)
IXc	DMSO	7.75	7.70—7.35		1775, 1730	299 (4.03)
Xa	DMSO	8.15	7.57		1755, 1700	230 (4.34)
Xb	DMSO	8.20—7.60 (g,i)			1770, 1740	223 (4.48)
Xc	DMSO	8.09	7.57		1735, 1695	231 (4.33)
XII (j)	DMSO	7.39		N-CH$_3$ at δ 4.08	1730, 1675, 1660	243 (3.90), 284 (3.79)
XIII	DMSO	7.85		N-CH$_3$ at δ 3.80	1740, 1690	250 (3.93)

(a) Recorded at 60 Mc by means of the Varian A-60 Spectrometer and δ recorded in p.p.m. downfield from TMS as internal standard. All spectra were recorded on a 500 c.p.s. sweep width and each spectrum was calibrated by a sample of chloroform (δ 7.27) in TMS (δ = 0). All compounds exhibited the number of lines expected; a range for the N-phenyl resonances denotes a complex multiplet. (b) Determined as a film or Nujol mull between salt plates using a Perkin-Elmer 337 Spectrophotometer. (c) Obtained in 95% ethanol by means of the Beckman DK-1 Spectrophotometer. (d) The following abbreviations are used: Dimethyl sulfoxide (DMSO), trifluoroacetic acid (TFAA). (e) Exchangeable (NH, OH) protons in this series sometimes gave rise to broad signals in the range δ 10 to 12, but there was considerable variation. These are not recorded here. (f) Narrow multiplet with two intense peaks at δ 7.62, 7.60. (g) Includes also the benzenesulfonyl proton resonances. (h) Narrow multiplet with an intense sharp signal at δ 7.4. (i) The two sharp signals at δ 8.20 and 7.60 do suggest that they are due to the pyrazole and N-phenyl protons by analogy with similar ones in this series. (j) Reported originally in Reference 3.

(IIIa) and C-5 (Xa) respectively, which would tend to contradict the explanation of the results in the water experiments. In these reactions, only the sulfonyl halide remains in solution, no control over pH can be exercised, nor can one judge the solubility of any intermediates, and no attempt is made to interpret these results. What is even more difficult to understand is why the reaction of 1-methyl-4,5-pyrazoledicarbohydroxamate in tetrahydrofuran did originally (3) give more of the isomer due to initial rearrangement at the less hindered position (the benzenesulfonate of XII) while the N-phenyl analog, VIII, gave the opposite result (Table I).

All the sulfonate esters were hydrolyzed to the corresponding N-hydroxy compounds on relatively short exposure to hot dilute sodium hydroxide solution. It was found that these N-hydroxyuracil derivatives decomposed on prolonged heating in base, but appeared to be quite stable in hot dilute mineral acids.

NMR Spectra.

In view of the many recent papers (7, 11–18) dealing with some aspects of the NMR spectra of pyrazoles, it seems reasonable to comment more fully on the NMR data obtained during this and our previous work (3) in this area. In general, the chemical shifts of the pyrazole protons of the compounds in hand are in the range expected in terms of the substituents on the ring (Table II). The unique combination of a pyridine and pyrrole type of sp^2 nitrogen atoms vicinal to each other in pyrazole, does suggest that its structure (XIV in general terms, Chart III) is stabilized to a considerable degree by resonance hybrids XIVa, XIVb. On such an assumption one would expect that protons attached to C-5 (XIV, $R' = H$) would be more deshielded than those at C-3 (XIV, $R''' = H$) provided for both systems, R'' remains the same. Such a premise is upheld in our series when it was found that in DMSO the 5-H pyrazole proton of each member of the 1-phenyl-3,4-disubstituted pyrazole series (Ia to VI) was more deshielded than the 3-H pyrazole proton of the corresponding member in the 1-phenyl-4,5-disubstituted pyrazole series (VIIa to Xc). This difference in chemical shift was of the order of 0.7 to 1.0 p.p.m. A similar correlation was found to be true for similar shifts in the N-methyl series of DMSO (3).

One of the most useful observations emerging from this study was that one could use the chemical shift of the pyrazole proton in these pyrazolouracils to predict the structure of each isomer, provided both isomers were formed. The distinguishing feature in the NMR spectra of these isomers was that a C=O group flanking the lone pyrazole proton shifted that proton resonance, as expected, considerably further downfield than did an adjoining NH group. This effect increased with conjugation, being about 0.3–0.5 p.p.m. (Xc vs. IXc; Xa vs. IXa; XIII vs. XII), and 0.8 p.p.m. (IIIa vs. IVa; IIIb vs. IVb). Such a difference permitted estimation of concentration of each isomer when

both were present (from the integration curve) since these shifts were usually sufficiently apart in both the N-methyl and N-phenyl series. In several sulfonate esters (IXb, Xb) the pyrazole proton resonances were not clearly discernible and the ratio of isomers was estimated after hydrolysis to the N-hydroxy compounds (IXa, Xa).

The nature of the NMR signals for an N-phenyl group has received much attention (11,19). Two principal types of patterns have been observed, one in which the 5-protons have identical chemical shifts and give rise to a singlet (A_5) and one in which a multiplet is seen characteristic of such a complex spin system (A_2B_2C). It has been suggested that the free-electron pair on nitrogen influences the chemical shifts on the o-, m- and p-protons and protonation may equalize the chemical shifts, thus giving rise to a singlet (19). For example, the signal arising from the arene protons of diphenylamine was a multiplet in deuteriochloroform, but a singlet in trifluoroacetic acid (19). However, the two arene signals in N-methyl-N-benzylaniline appeared as a singlet and a multiplet in deuteriochloroform and yet in trifluoroacetic acid the spectrum did not simplify and still consisted of a complex multiplet (19). The authors (19) have suggested that an anisotropic effect exerted by the second arene in close proximity to the N-aryl group (now an N-aryl-ammonium cation in the acidic medium) polarizes these ring protons to an extent that their chemical shifts remain different. One other pertinent generalization appeared in the literature that bears on this problem. From an extensive NMR study of N-phenylpyrazoles, it was observed that the arene resonances of such a group consist of a multiplet unless there is a substituent on the pyrazole ring next to the N-phenyl group, when the arene resonance becomes a singlet (11). Although, in many instances this generalization is obeyed (13–15), the N-phenyl resonances in 1-phenyl-3-methoxy-5-methyl-, 1-phenyl-3-methyl-5-ethoxy- and 1-phenyl-3,4-dimethyl-5-ethoxypyrazoles each of which had a substituent next to the N-phenyl group, all appeared as complex multiplets (18).

In examining our data for the N-phenyl resonances (Table II) we find that in DMSO all of the samples in the 3,4-disubstituted pyrazole series (I–VI) having a proton on the carbon adjacent to the N-phenyl group, were recorded as complex multiplets. Similarly, in the 4,5-disubstituted pyrazole series, the N-phenyl proton resonances for compounds VIIa, VIIb, Xa, Xb, Xc, XI gave rise to clearly discernible singlets, but those for IXa and IXc (in DMSO) appeared as complex multiplets. In comparing the structure of IXa and IXc with their isomeric counterparts, Xa, Xc, it becomes apparent that in the former, the N-phenyl group is flanked by a C=O group, in the latter by an NH group. It is suggested that the anisotropic effect of the C=O group influences the chemical shifts of the neighboring N-phenyl protons in IXa and IXc sufficiently to produce the multiplet rather than a singlet.

There is one other observation regarding the singlet *vs.* multiplet structure of the *N*-phenyl NMR signals. Solvents have been known to influence chemical shifts frequently and this could change a singlet to a multiplet (or *vice versa*). For example, in DMSO both VIIa and XI showed the *N*-phenyl resonances as singlets while in perdeuteriobenzene and symmetrical polar carbon tetrachloride, triethylamine a complex pattern arose. It is then apparent that solvent interaction, particularly dipolar solvents may greatly influence the chemical shifts of the *N*-arene protons. According to the literature (11), both VII and XI, in having substituents (even different types) on the carbon next to the *N*-phenyl group, should have shown a singlet, but in fact show either a singlet or multiplet, depending on the solvent.

We also examined the NMR spectra of the bis-esters, Ia, VIIa and amino esters, V, XI in trifluoroacetic acid. There was a remarkable consistence in the chemical shifts of the *N*-phenyl resonance (δ 7.60 − 7.69) and that of the pyrazole protons (δ 8.47 − 8.57). The *N*-phenyl signals were either singlets or very narrow multiplets, but the chemical shifts were not so different from those in non-acidic media. One might have expected that in trifluoroacetic acid the pyrazole molecule is protonated and is presented by XVa and XVb (Chart III) and the chemical shifts might substantiate such an assumption and perhaps give an insight into the distribution of the positive charge. In the 4,5-disubstituted series, the bis-ester, VIIa and the amino ester, XI, the chemical shift of H-3 is shifted considerably downfield in trifluoroacetic acid (0.35 to 0.92 p.p.m.), but the *N*-phenyl signals experienced a considerably lesser shift. This would indicate that the positive charge on the pyridine type nitrogen in XVa is felt more at the 3-position than by the *N*-phenyl protons (see XVa, R''' = H and R' = R'' = carbethoxy and R' = amino, R'' = carbethoxy respectively).

However, in the 3,4-disubstituted counterparts, Ia, V, trifluoroacetic acid exerts almost an opposite effect; these signals moved upfield compared to those in DMSO and were little different from those in deuteriochloroform. Thus, if Ia and V are protonated (XVa, R' = H with R'' = R''' = carbomethoxy and R''' = amino, R'' = carbethoxy), the effect on H-5 is felt very little. However, before drawing any further conclusions, it would be imperative to know if Ia and V were indeed protonated in trifluoroacetic acid. It might be plausible that with the aid of spectra in DMSO and trifluoroacetic acid, the NMR spectra in these solvents might distinguish readily between 3,4- and 4,5-substituted pyrazoles bearing similar substituents. However, this point remains to be checked out vigorously and requires a detailed examination on the effect of all types of substituents on these chemical shifts.

EXPERIMENTAL

All melting points and boiling points are uncorrected. Analyses were performed by Dr. Kurt Eder, Geneva, Switzerland and Micro-Tech Laboratories, Inc., Skokie, Illinois. Petroleum-ether refers to the fraction, b.p. 30—60°. Pure acetone was used for crystallizations and chromatographic work.

(A) Reaction Starting from Methyl 1-Phenyl-3,4-pyrazoledicarboxylate.

Methyl 1-phenyl-3,4-pyrazoledicarboxylate, Ia, b.p. 180—185° at 1 mm., m.p. 95—97° was prepared in 90% yield from *N*-phenylsydnone and methyl acetylenedicarboxylate (20). Alkaline hydrolysis yielded 1-phenyl-3,4-pyrazoledicarboxylic acid, Ib, m.p. 234—235°, lit. m.p. 234° (21).

Sodium 1-phenyl-3,4-pyrazoledicarbohydroxamate, II, was prepared as follows: A solution of hydroxylamine in methanol was prepared by neutralizing a stirred suspension of finely-powdered dry hydroxylammonium chloride in methanol (6.12 g. in 50 ml.) at 5° by the slow addition (0.5 hour) of a solution of sodium methoxide in methanol (2.03 g. sodium in 100 ml.). Sodium chloride was filtered off and the ester (10.4 g.) was added to the methanolic hydroxylamine solution, followed by a sodium methoxide solution (2 g. sodium in 200 ml. methanol) and the mixture stirred at 25° for 15 hours. The salt, II (11 g.), was filtered off, washed with ice-cold methanol, ether and dried *in vacuo* at 25° (over sulfuric acid), and used within a few days.

Reaction of Sodium 1-Phenyl-3,4-pyrazoledicarbohydroxamate, II, to Form 2-Phenyl-5-hydroxy-2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6-[5*H*,7*H*]-dione, IIIa, and 2-Phenyl-6-hydroxy-2*H*-pyrazolo[4,3-*d*]-pyrimidine-5,7[4*H*,6*H*]-dione, IVa.

(1) With Benzenesulfonyl Chloride in Water.

Benzenesulfonyl chloride (1.7 g., 0.0098 mole) was added dropwise to a well-stirred cold aqueous solution of II (3.06 g. in 50 ml.) keeping the temperature between 20-25°. It was observed that as the reaction proceeded the *p*H of the solution decreased and after some time, 5 *N* sodium hydroxide was added as needed to maintain the *p*H between 7.5 and 8.5. After 2 hours, enough sodium hydroxide solution was added to obtain a solution which was filtered. The filtrate was acidified to *p*H 3, cooled to 5° for 10 hours, and the product (1.6 g.) collected, m.p. 280—285° (dec.). The NMR spectrum clearly indicated two signals expected from the pyrazole protons of IIIa and IVa (Table II). The total height of the integration curve for these two signals and those of the *N*-phenyl protons was taken to represent 6 protons and hence the height per proton was known. From the relative height of the integration curve over the downfield resonance (due to IIIa), the percentage of that isomer was calculated and the result showed IIIa and IVa to be present in the ratio of 4:5. Concentration of the acid filtrate to about 10 ml. afforded an additional quantity (0.15 g.), m.p. 280—285° (dec.) which consisted of a mixture (1:1) of IIIa and IVa (NMR). The total yield (1.75 g.) represents a 64% conversion from Ia. The ratio of the isomers in both fractions was then compiled to give the values in Table I.

Separation of the two isomers was effected in the following manner: The first product (1.6 g.) was extracted once with boiling dilute acetic acid (100 ml., 1:2), and the insoluble product (0.5 g., m.p. 330—335°) subsequently recrystallized from ethanol-acetone (1:1) until the NMR spectrum showed it to be the pure isomer, IVa. In a sealed capillary it began to shrink and decompose over 335° and melt by 348°.

Anal. Calcd. for C$_{11}$H$_8$N$_4$O$_3$: C, 54.10; H, 3.28; N, 22.95. Found: C, 54.16; H, 3.50; N, 22.91.

The hot dilute acetic acid filtrate from above on cooling gave

an additional batch of almost pure IVa (0.2 g.). At this stage, the 1.5 g.-sample obtained above (IIIa, IVa in the ratio of 1:1) was dissolved in this acetic acid mother liquor and the solution concentrated *in vacuo* to 25 ml. There were obtained fractions composed of IIIa and IVa in various proportions as evidenced from their NMR spectra. Those rich in isomer IIIa were combined and recrystallized repeatedly from dilute acetic acid until pure IIIa was obtained, m.p. 304–305°.

Anal. Calcd. for $C_{11}H_8N_4O_3$: C, 54.10; H, 3.28; N, 22.95. Found: C, 54.27; H, 3.46; N, 23.05.

(2) With Methanesulfonyl Chloride in Water.

When the rearrangement was carried out (on the same scale) as described under A–1 using methanesulfonyl chloride (1.1 g., 0.0098 mole), there was obtained a mixture (1.7 g., 63%), m.p. 270–280° whose NMR spectrum revealed it to be a mixture of IIIa and IVa (Table I).

(3) With Benzenesulfonyl Chloride in Tetrahydrofuran To Form 2-Phenyl-5-benzenesulfonyloxy-2H-pyrazolo[3,4-d]pyrimidine-4,6-[5H,7H]-dione, IIIb, and 2-Phenyl-6-benzenesulfonyloxy-2H-pyrazolo[4,3-d]pyrimidine-5,7[4H,6H]-dione, IVb.

A solution of benzenesulfonyl chloride in tetrahydrofuran (8.8 g., 0.05 mole in 25 ml.) was added dropwise to a well stirred ice-cold suspension of II (6.12 g.) in tetrahydrofuran (70 ml.) at a rate that the temperature remained between 10–15°. The addition took about 0.25 hour and the mixture was then stirred 2 hours at 25°. Sodium acetate trihydrate (2 g.) was then added and the mixture stirred 1 hour longer at 25°. The mixture was filtered, the insoluble solids washed with tetrahydrofuran (25 ml.) and the two phases processed separately. The tetrahydrofuran insoluble material was suspended in water (100 ml.) and petroleum ether (50 ml.), and the insoluble material filtered off after 15 hours. This product (3.6 g.) consisted of a mixture of IIIb and IVb (8:1), m.p. 270–272° (dec.). The original tetrahydrofuran filtrate was concentrated *in vacuo* to 25 ml. and diluted with water (200 ml.) and petroleum ether (50 ml.). After 15 hours, the solid (2.0 g.) so obtained was shown to consist of a mixture of IIIb and IVb (2:3), m.p. 255–260° (dec.). The combined yield was 5.6 g. (72% yield based on the ester).

The isomers were separated in the following manner. Recrystallization of the 3.6 g.-sample from above from warm dimethyl sulfoxide (60–70°) gave on cooling pure IIIb (2.5 g.), m.p. 284–286° (dec.).

Anal. Calcd. for $C_{17}H_{12}N_4O_5S$: C, 53.12; H, 3.13; N, 14.55. Found: C, 53.21; H, 3.20; N, 14.67.

The other isomer could not be obtained pure by fractional crystallization. Successive addition of ethanol to the above dimethyl sulfoxide filtrate produced initially more pure IIIb, then a mixture of IIIb and IVb in various proportions. A more satisfactory procedure was as follows. The 2.0 g.-sample obtained above was crystallized from a mixture of hot acetone-methanol (1:1) which yielded on cooling some more pure IIIb. The mother liquors from this crystallization were removed *in vacuo* and the residue dissolved in acetone. This acetone solution was placed on a column of silicic acid (25 g., prepared in benzene) and elution with acetone-benzene (1:5) gave the pure isomer, IVb (0.3 g.) m.p. 271–273° (dec.). Recrystallization from acetone-methanol (1:2) raised the m.p. to 273–275° (dec.).

Anal. Calcd. for $C_{17}H_{12}N_4O_5S$: C, 53.12; H, 3.13; N, 14.55. Found: C, 53.03; H, 3.30; N, 14.47.

Hydrolysis of IIIb.

A solution of IIIb (1 g.) in 5% sodium hydroxide solution (15 ml.) was heated on the steam bath for 7 minutes and then filtered

hot. The filtrate was cooled, acidified to pH 3 and the product (0.54 g., 85%) collected after 10 hours. After crystallization from aqueous acetic acid (1:1), it melted at 300–302° (dec.) and was identical to IIIa prepared in A–1.

Hydrolysis of IVb.

The hydrolysis of IVb (0.2 g.) as described for IIIb afforded IVa (0.008 g., 63%) identical to that prepared in A–1.

2-Phenyl-2H-pyrazolo[3,4-d]pyrimidine-4,6[5H,7H]-dione, VI.

(i) From the Reduction of IIIa.

A suspension of IIIa (0.5 g.) in 1 N hydrochloric acid (75 ml.) was boiled under reflux while zinc dust (0.8 g.) was added in three portions (over 0.75 hour) and the mixture boiled for 6 hours. Solids were filtered off, the filtrate concentrated *in vacuo* to 25 ml. The product, VI (0.08 g., 17%) crystallized after 20 hours and was recrystallized first from ethanol, then from dilute acetic acid (1:1), m.p. 310–312° (dec.).

Anal. Calcd. for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.50; N, 24.55. Found: C, 57.47; H, 3.51; N, 24.89.

(ii) By Total Synthesis via Ethyl 1-Phenyl-3-amino-4-pyrazolecarboxylate.

Ethyl β-(N^2-benzal-N'-phenyl)hydrazino-α-cyanoacrylate [$C_6H_5CH=N-N(C_6H_5)-CH=C(CN)CO_2C_2H_5$].

The preparation essentially followed that described in the patent literature (22). A solution of ethyl ethoxymethylenecyanoacetate (17.0 g., 0.1 mole) in benzene (50 ml.) was added to a solution of benzaldehyde phenylhydrazone (19.5 g., 0.1 mole) in benzene (50 ml.). After 1 hour solvents were removed at 100° and xylene (100 ml., b.p. 130–137°) added and the mixture boiled for 5 hours. After cooling, petroleum ether (25 ml.) was added and the product (12 g.) was collected. Recrystallization from ethanol furnished the pure product (10 g.), m.p. 179–180°, lit. m.p. 180° (22). Its NMR spectrum (deuteriochloroform) showed a triplet at δ 1.33 (CH_3), a quartet at δ 4.37 (CH_2) and a complex multiplet between δ 7.25 and 8.50 (CH and C_6H_5).

Ethyl 1-Phenyl-3-amino-4-pyrazolecarboxylate, V.

A solution of the above hydrazino ester (6.4 g., 0.02 mole) in ethanol (20 ml.) and concentrated hydrochloric acid (6 ml.) was boiled for 2 hours. Solvents were removed *in vacuo* and anhydrous ether (100 ml.) was added to the residual oil and the mixture allowed to stand at 5° for 15 hours. The hydrochloride was filtered, washed with ether (25 ml.) and added to 1 N sodium hydroxide solution. The free base was extracted by chloroform, solvent distilled off, and the residue recrystallized from methanol to give V (1.5 g., 32%) m.p. 98–100°, lit. m.p. 105° (22).

Reaction of V with Urea to give VI.

An intimate mixture of V (0.5 g.) and urea (1 g.) was gently heated at 160–180° for 10 minutes until the melt commenced to solidify. After cooling, the product was washed with hot water (50 ml.) and then dissolved in 1 N sodium hydroxide solution (50 ml.). Solids were filtered off, the filtrate extracted with chloroform and the basic aqueous solution acidified to pH 3. After 10 hours at 5°, the product, VI (0.2 g., 41%) was filtered, crystallized from dilute acetic acid, m.p. 310–312°, identical to VI prepared from the reduction described in part (i).

(B) Reactions Starting from Ethyl 1-Phenyl-4,5-pyrazoledicarboxylate.

Ethyl 1-phenyl-4,5-pyrazoledicarboxylate (VIIa) was prepared from phenylhydrazine and ethyl ethoxymethyleneoxalacetate (23). Alkaline hydrolysis gave the corresponding acid, VIIb, m.p. 215–

216° (dec.), lit. m.p. 214–215° (dec.) (23). The hydroxamate, VIII, was prepared from the ester as described under A, except for the use of absolute ethanol for methanol. It is also advisable to use the dry salt as soon as possible.

Reaction of Sodium 1-Phenyl-4,5-pyrazoledicarbohydroxamate, VIII, to form 1-Phenyl-5-hydroxy-1H-pyrazolo[3,4-*d*]pyrimidine-4,6[5H,7H]-dione, Xa, and 1-Phenyl-6-hydroxy-1H-pyrazolo[4,3-*d*]pyrimidine-5,7[4H,6H]-dione, IXa.

(1) With Benzenesulfonyl Chloride in Water.

The reaction was carried out on the same scale and under the same conditions described under A–1. After acidification of the basic filtrate from the reaction, the first product (1.5 g.) was proved to be a mixture of Xa and IXa (1:5 by NMR), m.p. 235–250° (dec.). On concentrating the acidic filtrate to about 25 ml., an additional quantity (0.3 g.) of this mixture (IXa and Xa, 1:1), m.p. 235–265° (dec.) was collected after 10 hours at 5°. The combined yield (1.8 g.) represents a 66% conversion from VIIa. Repeated recrystallization of the first sample (1.5 g.) from aqueous acetic acid (1:1) afforded 1.2 g. of pure IXa, m.p. 264–266°.

Anal. Calcd. for $C_{11}H_8N_4O_3$: C, 54.10; H, 3.28; N, 22.95. Found: C, 54.15; H, 3.36; N, 22.70.

The second product (0.3 g., m.p. 235–265°) was dissolved in the mother liquors from these crystallizations and the solution concentrated to 20 ml. Fractional crystallization (7–8 times) from dilute acetic acid (1:1) furnished pure isomer, Xa, m.p. 290–293°.

Anal. Calcd. for $C_{11}H_8N_4O_3$: C, 54.10; H, 3.28; N, 22.95. Found: C, 54.18; H, 3.32; N, 23.10.

(2) With Methanesulfonyl Chloride in Water.

Rearrangement of VIII (3.06 g.) with methanesulfonyl chloride (1.1 g., 0.0098 mole) at 20° for 2 hours gave after the work-up as described under A–1, a mixture of IXa and Xa (1.7 g., 63%), m.p. 220–235° (dec.) in the ratio listed in Table I.

(3) With Benzenesulfonyl Chloride in Tetrahydrofuran to form 1-Phenyl-5-benzenesulfonyloxy-1H-pyrazolo[3,4-*d*]pyrimidine-4,6-[5H,7H]-dione, Xb, and 1-Phenyl-6-benzenesulfonyloxy-1H-pyrazolo[4,3-*d*]pyrimidine-5,7[4H,6H]-dione, IXb.

The reaction was carried out on the same scale and under identical conditions as described in A–3. The tetrahydrofuran insoluble precipitate yielded a solid (2.0 g.) m.p. 230–232°, and that from the filtrates, 3.4 g., m.p. 205–215°. The yield of 5.4 g. represented a 70% conversion from VIIa.

Since the resonances of the pyrazole protons of IXb and Xb were buried amongst those of the phenyl proton multiplets, it was impossible to ascertain the proportions of the two isomers in these mixtures. This problem was resolved by hydrolyzing these mixtures (see below) in better than 90% if the mother liquors were worked for a second crop. The mixture of IXa and Xa possessed well separated pyrazole proton signals and the proportion of the isomers was estimated (Table I) by the method listed under A–1.

To separate the two isomers, the following procedure proved satisfactory. The 2.0 g.-sample (m.p. 230–232°, which after hydrolysis was shown by NMR to consist predominantly of only one isomer) was extracted with boiling acetone to leave the pure isomer, Xb, m.p. 234–235° which was then crystallized from ethanol, m.p. 235–237° (dec.).

Anal. Calcd. for $C_{17}H_{12}N_4O_5S$: C, 53.12; H, 3.13; N, 14.55. Found: C, 52.98; H, 3.25; N, 14.19.

To obtain the other isomer, the hot acetone extract from the 2 g.-sample as well as that of the 3.4 g.-sample were combined and concentrated to 10 ml., filtered and the filtrate chromatographed over silicic acid as in B–1. The initial eluates with acetone-benzene (1:4) gave a product, m.p. 203–208° which proved to be almost

pure IXb. Recrystallization from acetone-ethanol gave colorless needles, m.p. 205–207°.

Anal. Calcd. for $C_{17}H_{12}N_4O_5S$: C, 53.12; H, 3.13; N, 14.55. Found: C, 53.03; H, 3.34; N, 14.43.

Further elution with the same solvent gave mixtures of IXb and Xb, then finally some pure IXa, m.p. 235–237°.

Hydrolysis of Xb.

Hydrolysis of a 1 g.-sample of Xb by the method described for IIIb gave 0.6 g. (94%) of pure Xa, m.p. 290–293° (dec.), identical to that prepared in B–1.

Hydrolysis of IXb.

Similarly, IXb (1 g.) was hydrolyzed as described for IIIb to give IXa (0.55 g., 86%), identical to that prepared in B–1.

1-Phenyl-1H-pyrazolo[3,4-*d*]pyrimidine-4,6[5H,7H]-dione, Xc.

(i) From the Reduction of Xa.

A suspension of Xa (0.5 g.) in 2 N hydrochloric acid (50 ml.) was heated at 100° while zinc dust (1 g.) was added in three portions at 15 minute intervals. The mixture was filtered after 2 hours, the pH adjusted to 5 by the addition of sodium acetate and the product (0.2 g., 43%) collected after 15 hours at 5°. It was crystallized from water, m.p. 342–345° (dec.), lit. m.p. 298° (9), 320° (10). Its ultraviolet spectrum at pH 11 showed λ max 240, (log ε 4.40), 268 mμ (log ε 4.15), lit. (10) λ max at pH 11, 239 mμ (log ε 4.40).

Anal. Calcd. for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.50; N, 24.55. Found: C, 57.99; H, 3.63; N, 24.90.

(ii) By Synthesis from Ethyl 1-Phenyl-5-amino-4-pyrazolecarboxylate, XI.

This synthesis was mentioned (9) without actual experimental details and the one described below was fashioned after an analogous one where formamide was used instead of urea (9) and the one from 1-phenyl-5-amino-4-pyrazolecarboxamide and urea (10). A mixture of XI (1 g.) (9) and urea (1 g.) were fused at 180–190° for 5 minutes. The cooled solid was washed with hot water (50 ml.) and dissolved in 10% sodium hydroxide solution (30 ml.). The mixture was filtered, the filtrate acidified to pH 3 and the product recrystallized several times from water, m.p. 345–346°, identical to that made in (i).

1-Phenyl-1H-pyrazolo[4,3-*d*]pyrimidine-5,7[4H,6H]-dione, IXc.

To a boiling solution of IXa (0.4 g.) in aqueous acetic acid (50 ml., 1:2) was added zinc dust (0.8 g.) in three portions and heating continued for 2 hours. The mixture was filtered, concentrated *in vacuo* to 25 ml. and allowed to stand at 5° for 15 hours. The product, IXc (0.1 g., 27%) was recrystallized from water, m.p. 334–335°.

Anal. Calcd. for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.50; N, 24.55. Found: C, 57.61; H, 3.52; N, 24.43.

(c) Reaction of Sodium 1-Methyl-4,5-pyrazoledicarbohydroxamate (3) to form 1-Methyl-5-hydroxy-1H-pyrazolo[3,4-*d*]pyrimidine-4,6[5H,7H]-dione, XIII, and 1-Methyl-6-hydroxy-1H-pyrazolo-[4,3-*d*]pyrimidine-5,7[4H,6H]-dione, XII.

(1) With Benzenesulfonyl Chloride in Water.

A stirred solution of sodium 1-methyl-4,5-pyrazoledicarbohydroxamate (4.88 g.) in water (50 ml.) was treated dropwise with benzenesulfonyl chloride (3.35 g.) at 35–40°, while maintaining the pH between 7.5 and 8.5 by adding 2 N sodium hydroxide solution as necessary. After 5 hours at 32–35°, the mixture was acidified to pH 3 and the product (1.2 g.) isolated. It melted at 300–309° (dec.) and consisted of a mixture of XII and XIII (15:1).

Concentration of the acidic filtrate yielded another 0.2 g. (XII and XIII, 4:1). The combined yield (1.4 g.) represented a 38% conversion from the starting ester. Three recrystallizations of 1.4 g. from aqueous acetic acid (1:3) gave XII (0.6 g.), m.p. 309–310° (dec.), lit. m.p. 310–312° (dec.) (3).

The mother liquors from various crystallizations were combined and concentrated to 25 ml. to yield a solid (0.6 g.) which was crystallized from aqueous acetic acid (1:5) until pure XIII (0.1 g.) was obtained, m.p. 342–344° (dec.).

Anal. Calcd. for $C_6H_6N_4O_3$: C, 39.56; H, 3.32; N, 30.77. Found: C, 39.77; H, 3.34; N, 30.63.

The structure of XIII was confirmed by reducing it with zinc dust and hot 2 N hydrochloric acid to the known 1-methyl-1H-pyrazolo[3,4-d]pyrimidine-4,6[5H,7H]-dione, m.p. > 400°, lit. m.p. > 300° (10), λ max (pH 11) 247 (log ε 4.02), 270 mμ (log ε 3.95), lit. λ max (pH 11) 247 (log ε 4.10), 269 mμ (log ε 3.97) (10).

(2) With Methanesulfonyl Chloride in Water.

Reaction of the hydroxamate as above with methanesulfonyl chloride (2.21 g.) at 20–25° for 2 hours as in C–1 gave a mixture (see Table I) of XII and XIII (0.65 g., 18%).

REFERENCES

(1) L. Bauer, C. N. V. Nambury and D. Dhawan, *J. Heterocyclic Chem.*, **1**, 275 (1964); *ibid.*, **2**, 220 (1965).

(2) L. Bauer, C. N. V. Nambury and F. M. Hershenson, *ibid.*, **3**, 224 (1966).

(3) L. Bauer, D. Dhawan and C. S. Mahajanshetti, *J. Org.*

Chem., **31**, 2491 (1966).

(4) C. D. Hurd and L. Bauer, *J. Am. Chem. Soc.*, **76**, 2791 (1954).

(5) C. M. Buess and L. Bauer, *J. Org. Chem.*, **20**, 33 (1955).

(6) L. Bauer, *ibid.*, **21**, 1182 (1956).

(7) I. L. Finar and E. F. Mooney, *Spectrochim. Acta*, **20**, 1269 (1964).

(8) D. C. Berndt and H. Schechter, *J. Org. Chem.*, **29**, 916 (1964).

(9) P. Schmidt and J. Druey, *Helv. Chim. Acta*, **39**, 986 (1956).

(10) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **23**, 852 (1958).

(11) L. G. Tensmeyer and C. Ainsworth, *ibid.*, **31**, 1878 (1966) and references quoted therein.

(12) M. Bertrand, J. Elguero, R. Jacquier and J. LeGras, *Compt. Rend., Ser. C*, **262**, 785 (1966).

(13a) R. Jacquier, *et al.*, *Bull. Soc. Chim. France*, **619**, 775 3727 (1966) and papers quoted therein. (b) P. Bouchet, J. Elguero and R. Jacquier, *Tetrahedron*, **22**, 2461 (1966).

(14) W. E. Parham and J. F. Dooley, *J. Am. Chem. Soc.*, **89**, 985 (1967).

(15) D. F. O'Brien and J. W. Gates, Jr., *J. Org. Chem.*, **31**, 1538 (1966).

(16) M. Ochiai and T. Kamikado, *Chem. Pharm. Bull., Tokyo*, **14**, 628 (1966).

(17) V. F. Bystrov, I. I. Grandberg and G. I. Sharova, *J. Gen. Chem. USSR (Engl. Transl.)*, **35**, 294 (1965).

(18a) A. R. Katritzky and F. W. Maine, *Tetrahedron*, **20**, 299 (1964). (b) A. R. Katritzky and F. W. Maine, *ibid.*, **20**, 315 (1964).

(19) R. J. Warren, W. E. Thompson, J. E. Zarembo and I. B. Eisdorfer, *J. Pharm. Sci.*, **55**, 524 (1966).

(20) R. Huisgen and R. Grashey, *Angew. Chem.*, **74**, 29 (1962).

(21) R. Fusco, S. Rossi and S. Maiorana, *Gazz. Chim. Ital.*, **95**, 286 (1965).

(22) Ciba Ltd., British Patent, 884,841, Dec. 20, 1961, *Chem. Abstr.*, **61**, 3116 (1964).

(23) R. G. Jones and C. W. Whitehead, *J. Org. Chem.*, **20**, 1342 (1955).