HETEROCYCLIC ANALOGS OF XANTHONES

II.* C-ACYLATION OF 5-PYRAZOLONES AND SYNTHESIS OF CHROMONO[3,2-d]PYRAZOLES

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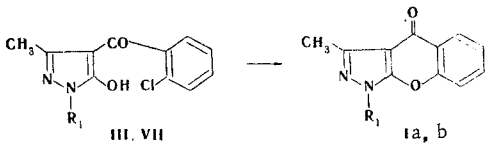
The acylation of 5-pyrazolones with carboxylic acid chlorides gave the C- and O-acyl derivatives, the ratio of which depends on the nature of the solvent and the neutralizing agent. Spectral methods demonstrated that the 4-acyl derivatives of 5-pyrazolones are enolized completely and exist primarily as 4-acyl-5-hydroxypyrazoles, which are stabilized by intramolecular hydrogen bonding. Intramolecular nucleophilic substitution of chlorine in 4-(o-chlorobenzoyl) and 5-chloropyrazoloyl derivatives of 5-hydroxypyrazole leads to xanthone analogs, which readily undergo reaction with Grignard reagents.

It has been demonstrated [1] that chromonopyrazoles (I), which are formed in the cyclization of 5-aryloxy-1-phenyl-3-methylpyrazole-4-carboxylic acid chlorides, like xanthones [2], can be used for the synthesis of psychotropic medicinal substances. This route to the synthesis of chromonopyrazoles does not give good results in all cases, and we therefore studied the cyclization of 4-(o-chlorobenzoyl)-1,3-disubstituted 5-pyrazolones, during which I can also form.



III, VII — Ia, b

III $R_1=CH_3$; VII $R_1=C_6H_5$; I $R_1=CH_3$, b $R_1=C_6H_5$

The most convenient method for the synthesis of 4-acyl derivatives of 5-pyrazolone is the action of a carboxylic acid chloride on the appropriate pyrazolone in the presence of neutralizing agents [3]. In this case, both C-acylation in the 4 position and O-acylation are possible. The ratio of the products formed depends markedly on the nature of the solvent and the base (Table 1).

*See [1] for communication I.

TABLE 1. Ratio of the Products of the Acylation of 1,3-Dimethyl-5-pyrazolone with Benzoyl Chloride

Solvent	Yield of acylation product, %			
	calcium oxide		triethylamine	
	C-acylation	O-acylation	C-acylation	O-acylation
Dioxane	73	15	39	45,0
Pyridine	62	24	38	47,0
Dimethylformamide	48	36	29	59,0
Benzene	18	64	14	70,0

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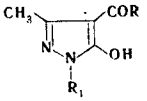
TABLE 2



Compound	R	R_1	mp, °C (crystallization solvent)	Empirical formula
II	C_6H_5	CH_3	148—149 (acetone)	$C_{12}H_{12}N_2O_2$
III	o-ClC_6H_4	CH_3	144—146 (acetone)	$C_{12}H_{11}ClN_2O_2$
IV	p-$NO_2C_6H_4$	CH_3	228—230 (ethanol)	$C_{12}H_{11}N_3O_4$
V	1,3-Dimethyl-5-chloropyrazolyl	C_6H_5	156—158 (acetone)	$C_{16}H_{15}ClN_4O_2$
VI	C_6H_5	C_6H_5	118—120[3] (ethanol–water)	—
VII	o-ClC_6H_4	C_6H_5	150—152 (acetone)	$C_{17}H_{13}ClN_2O_2$
VIII	p-$NO_2C_6H_4$	C_6H_5	195—197[3] (water – dioxane)	—
IX	p-$NH_2C_6H_4$	C_6H_5	171—173 (alcohol)	$C_{17}H_{15}N_3O_2$
X	CH_3	C_6H_5	58—59[3] (ethanol — water)	—
XI	CH_2Cl	C_6H_5	139—140[3] (ethanol – water)	—
XII	$CH_2OC_2H_5$	C_6H_5	97—98 (ethanol – water)	$C_{14}H_{16}N_2O_3$
XIII	1-Phenyl-3-methyl-5-chloropyrazolyl	C_6H_5	219—220 (acetone)	$C_{21}H_{17}ClN_4O_2$

TABLE 2 (continued)

Compound	Found, %		Calc., %		ν_{CO}, cm^{-1}, in	λ_{max}, nm (lg ε)		Yield, %
	Cl	N	Cl	N	chloroform	cyclohexane	alcohol	
II	—	13,3[a]	—	13,0	1618[d]	275 (4,50)	320 (4,70)	72
III	14,0	11,9[b]	14,2	11,2	1630	265 (4,58)	310 (4,87)	74
IV	—	16,3[b]	—	16,1	1600	280 (4,46)	275 (4,62)	71
V	10,8	16,7	10,7	16,9	1604[d]	290 (4,18)	275 (4,31)	76
VI	—	—	—	—	1610[d]	290 (4,20)	277 (4,40)	77
VII	11,4	8,8	11,4	9,0	1618		266 (4,30)	80
VIII	—	—	—	—	1603	300 (4,10)	268 (4,43)	82
IX	—	14,3	—	14,3	1642	320 (4,14)	276 (4,38)	86
X	—	—	—	—	1620	270 (4,34)	264 (4,45)	60
XI	—	—	—	—	1628	280 (4,16)	265 (4,28)	45
XII	—	10,6[c]	—	10,8	1622	272 (4,26)	260 (4,34)	81
XIII	9,3	14,0	9,1	14,3	—	—	—	75

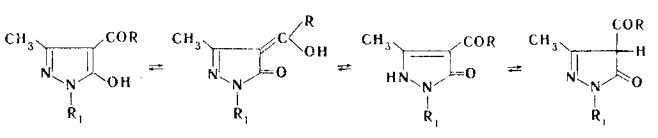
[a] Found: C 67.1; H 5.8%. Calculated: C 66.7; H 5.6%. [b] Found: C 55.6; H 4.2%. Calculated: C 55.2; H 4.2%. [c] Found: C 64.7; H 6.3%. Calculated: C 64.6; H 6.2%. [d] For 1,3-dimethyl-5-pyrazolone ν_{CO} is 1695 cm^{-1} compared with 1704 cm^{-1} for 1-phenyl-3-methyl-5-pyrazolone [4].

The best conditions for C-acylation involve the use of dioxane in the presence of calcium oxide, while the best conditions for O-acylation call for the use of benzene in the presence of triethylamine. Taking this into account, we accomplished the synthesis of a number of 4-acyl derivatives of 5-pyrazolones (II-XIII, Table 2).

The acylation of 1-phenyl-3-methyl-5-pyrazolone with benzoyl chloride in benzene gives, instead of the O-benzoyl derivative, the diacyl derivative – 1-phenyl-3-methyl-5-benzoyloxy-4-benzoylpyrazole (XIV) – the structure of which was confirmed by the IR spectrum (ν_{CO} 1768 and 1647 cm^{-1}) and the results of elementary analysis.

The introduction of an acyl group into the 4 position of 5-pyrazolones shifts the absorption band of the carbonyl group by 65-100 cm^{-1} (Table 2), and only one band, which is usually characteristic for α,β-unsaturated compounds [5], is observed in the IR spectra in the region of CO group absorption.

4-Acyl-5-pyrazolones can exist in several tautomeric forms:



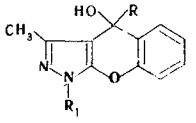
A B C D

Judging from the IR spectra (Table 2), the existence of the 4-acyl derivatives of 5-pyrazolones as structures C and D is unlikely. One band of a carbonyl group, under the condition of complete enolization

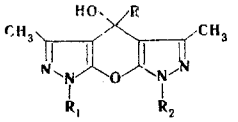
TABLE 3. Heterocyclic Analogs of Xanthones

Compound	Name	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
Ia	1,3-Dimethylchromono[3,2-d]pyrazole	181—182	$C_{12}H_{10}N_2O_2$	67,3	4,5	13,2	67,3	4,7	13,1	52
Ib	1-Phenyl-3-methylchromono[3,2-d]pyrazole	172—173	$C_{17}H_{12}N_2O_2$	73,4	4,8	10,3	73,9	4,3	10,1	58
XXII	1,3,5-Trimethyl-7-phenylpyrazolo[4,5-d]-4-pyrono[2,3-d]-pyrazole	200—201	$C_{16}H_{14}N_4O_2$	65,3	4,8	18,3	65,3	4,8	19,0	65
XXIII	1,7-Diphenyl-3,5-dimethylpyrazolo[4,5-d]-4-pyrono[2,3-d]-pyrazole	240—241	$C_{21}H_{16}N_4O_2$	71,0	4,8	15,7	70,8	4,5	15,7	66

TABLE 4. Hydrols



XXIV, XXV, XXVIII, XXX

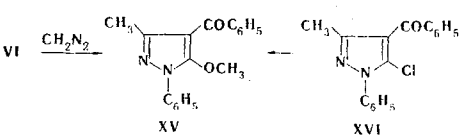


XXVI, XXVII, XXXII

Compound	R	R_1	R_2	mp, °C (crystallization solvent)	Empirical formula	Found, %			Calc., %		
						C	H	N	C	H	N
XXIV	C_2H_5	CH_3	—	90—92 (alcohol)	$C_{14}H_{16}N_2O_2$	68,9	6,7	11,1	68,8	6,6	11,8
XXV	C_2H_5	C_6H_5	—	117—120 (acetone)	$C_{19}H_{18}N_2O_2$	74,4	5,8	9,2	74,5	5,9	9,1
XXVI	C_2H_5	CH_3	C_6H_5	108—112 (alcohol)	$C_{18}H_{20}N_4O_2$	66,8	6,2	17,8	66,7	6,7	17,8
XXVII	C_2H_5	C_6H_5	C_6H_5	116—119 (alcohol)	$C_{23}H_{22}N_4O_2$	72,1	5,7	14,4	71,5	5,7	14,7
XXVIII	$(CH_3)_2N(CH_2)_3 \cdot C_2H_2O_4$	CH_3	—	159—163 (ether)	$C_{17}H_{23}N_3O_2 \cdot C_2H_2O_4$	58,2	6,4	11,0	58,3	6,9	10,7
XXX	$(CH_3)_2N(CH_2)_3$	C_6H_5	—	119—120 (acetone)	$C_{22}H_{25}N_3O_2$	73,9	7,1	11,7	72,7	6,9	11,6
XXXII	$(CH_3)_2N(CH_2)_3$	C_6H_5	C_6H_5	148—150 (acetone)	$C_{26}H_{29}N_5O_2$	70,3	6,6	16,0	70,4	6,5	15,8

of the other, can be observed in the spectra of structures A and B. The presence of an absorption band at 1550-1580 cm^{-1}, which is characteristic for the pyrazole ring [4, 6], in the IR spectra of the compounds is evidence that the carbonyl group in the 5 position is enolized. The considerable shift of the absorption bands of the CO group in II-XII is associated with the formation of a strong intramolecular hydrogen bond. Thus a broad band of low intensity that depends only slightly on the concentration is observed at 2500-3660 cm^{-1}. In some cases, for example, in the case of VIII, X, and XI, cleavage of the intramolecular hydrogen bond to form an intermolecular hydrogen bond with dioxane is observed when chloroform is replaced by dioxane (ν_{OH} 2910 cm^{-1} in chloroform, ν_{OH} 3477 cm^{-1} in dioxane).

The possibility of the existence of 4-acyl-5-pyrazolones primarily in form A, which is stabilized by hydrogen bonding, is also confirmed by the IR and UV spectra of a compound with a fixed structure, for example, 1-phenyl-3-methyl-4-benzoyl-5-methoxypyrazole (XV). Compound XV was obtained via two routes:



XV XVI

In the IR spectra of XV, ν_{CO} is situated at 1650 cm^{-1}, just as in the spectrum of XIV (1647 cm^{-1}), and $\Delta\nu_{CO}$, which is caused by the formation of an intramolecular hydrogen bond, is consequently 40 cm^{-1} (Table 2). A similar pattern is also observed for other model compounds of 1-phenyl-3-methyl-4-acetyl-, 4-chloroacetyl-, and 4-ethoxyacetyl-5-methoxypyrazoles (XVII-XIX), which are obtained on treatment of X-XII with diazomethane. The IR spectra of the O-acyl derivatives (XIV, XX) contain the absorption bands of an ester group at 1750-1783 cm^{-1} and of the pyrazole ring at 1550-1580 cm^{-1}, and the character of the curves is close to that of 5-methoxy derivatives.

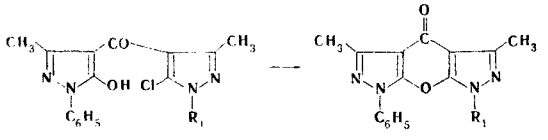
An increase in color on passing from a nonpolar solvent to a polar solvent (6-38 nm, Table 2) is primarily observed in the electronic spectra of 4-acyl-5-pyrazolones.

The introduction of a chlorine atom into the ortho position relative to the ketone group (III, VII) leads to a shift in ν_{CO} of ~12 cm^{-1} and somewhat increases the color (Table 2), which is apparently due to the steric hindrance to the formation of a hydrogen-bonded ring.

The 4-acyl derivatives of 5-pyrazolones are stronger acids than the starting compounds. The pK_a values, measured potentiometrically in 60% dioxane, are 5.12, 4.12, 6.0, 4.9, 4.02, and 4.55, respectively, for VI and VIII-XII. The high acidity of 4-acyl-5-pyrazolones made it possible to hope for successful intramolecular cyclization in the case of the o-chlorobenzoyl and 5-chloropyrazoloyl derivatives. In fact, intramolecular substitution of the halogen to form chromonopyrazoles (I) occurs when III and VII are heated for 12 h with an equimolar amount of alcoholic potassium hydroxide in dimethylformamide.

Simultaneous hydrolytic cleavage of an acyl group which is of a type with the acid cleavage of β-diketones, is observed along with the cyclization. This reaction proceeds especially readily in the case of III.

Under the conditions indicated above, the 4-pyrazoloyl derivatives (V and XIII) could not be cyclized, since the cyclic compounds corresponding to them undergo opening of the pyrone ring in 1% potassium hydroxide. The replacement of chlorine in these compounds, which is facilitated by the considerable electron-acceptor effect of the pyrazoloyl group, occurs in the presence of pyridine on heating in dimethylformamide. Since this effect is more significant in XIII than in V, heating for 6 h is required for the ring closing of XIII, while V closes in 24 h under comparable conditions.



V, XIII — XXII, XXIII

V $R_1 = CH_3$; XIII $R_1 = C_6H_5$; XXII $R_1 = CH_3$; XXIII $R_1 = C_6H_5$

The structures of the cyclization products were confirmed by spectral data and alternative synthesis [1]. The xanthone analogs (which contain a pyrazole ring), their melting points, and the results of elementary analysis are presented in Table 3.

Compounds Ia, Ib, XXII, and XXIII readily react with organomagnesium compounds obtained from ethyl bromide and dimethylaminopropyl chloride to give the corresponding hydrols (XXIV-XXVIII, XXX, and XXXII, Table 4) under the conditions previously described in [1]. Compounds XXIX and XXXI with presumable psychotropic action were obtained by dehydration of the latter by heating in 2 N hydrochloric acid.

The heterocyclic analogs of xanthones react with phosphorus pentasulfide to give thiones XXXII-XXXV, which, in contrast to the thione of xanthone, do not react with hydroxylamine.

EXPERIMENTAL

4-Acyl-1,3-Disubstituted 5-Pyrazolones (II-XIII). Calcium oxide (0.4 mole) was added at 85-90° in the course of 2 h to 0.1 mole of the 1,3-disubstituted 5-pyrazolone in 150 ml of dioxane and 0.1 mole of a carboxylic acid chloride, and the mixture was held at this temperature for 2 h. The mass was cooled and poured into 200 ml of 3 N hydrochloric acid, and the resulting oil was extracted with chloroform. The solvent was removed, and the residue was crystallized (Table 2).

The acylation of 5-pyrazolones, in which benzene, pyridine, and dimethylformamide were used as solvents and calcium oxide or triethylamine were used as neutralizing agents, was carried out similarly. In addition to the C-acyl derivatives (II-XIII) indicated in Table 2, O-acyl derivatives XIV, XX, and XXI were obtained.

1-Phenyl-3-methyl-4-benzoyl-5-benzoyloxypyrazole (XIV). This compound was obtained in 87% yield using benzene and calcium oxide and had mp 158-159° (from aqueous alcohol) and ν_{CO} 1768 and 1647 cm^{-1}. Found: C 75.2; H 5.1; N 7.2%. $C_{24}H_{18}N_2O_3$. Calculated: C 75.1; H 4.7; N 7.3%.

1,3-Dimethyl-5-benzoyloxypyrazole. This compound was isolated in the acylation of 1,3-dimethyl-5-pyrazolone with benzoyl chloride (Table 1) and was characterized as the hydrochloride (XX) with mp 152° (from alcohol) and ν_{CO} 1750 cm^{-1}. Found: Cl 14.2; N 11.1%. $C_{12}H_{12}N_2O_2 \cdot HCl$. Calculated: Cl 14.0; N 11.1%.

TABLE 5. Thiones of Heterocyclic Analogs of Xanthone

Compound	Starting compound	mp, °C (crystallization solvent)	Empirical formula	Found, %		Calc., %	
				N	S	N	S
XXXII	Ia	167—169 (alcohol)	$C_{12}H_{10}N_2OS$	12,1	14,2	12,2	13,9
XXXIII	Ib	189—190 (acetone)	$C_{17}H_{12}N_2OS$	—	10,7	—	10,9
XXXIV	XXII	226—227 (alcohol)	$C_{16}H_{14}N_4OS$	17,9	10,6	18,1	10,3
XXXV	XXIII	285—286 (benzene)	$C_{21}H_{16}N_4OS$	15,0	8,7	15,1	8,6

1,3-Dimethyl-5-(1',3'-dimethyl-5'-chloro-4'-carboxypyrazolyl)pyrazole (XXI). This compound was obtained in 77% yield by the general method of acylation from 1,3-dimethyl-5-pyrazolone and 1,3-dimethyl-5-chloropyrazole-4-carboxylic acid chloride and had mp 119-120° (from acetone) and ν_{CO} 1750 cm^{-1}. Found: C 49.6; H 5.0%. $C_{11}H_{13}N_4O_2$. Calculated: C 49.2; H 4.8%.

1-Phenyl-3-methyl-4-benzoyl-5-methoxypyrazole (XV). A. A 1.42-g sample of 1-phenyl-3-methyl-4-benzoyl-5-chloropyrazole (XVI) was dissolved in 3 ml of absolute methanol, and a solution of sodium oxide, prepared from 0.1 g of sodium metal in 4 ml of absolute methanol, was added, and the mixture was refluxed for 7 h. The alcohol was removed by distillation, and the oily residue was washed with water, sodium carbonate solution, and ether to give 0.68 g (47%) of XV with mp 74-75° (from aqueous ethanol). Found: C 73.2; H 5.7; N 9.7%. $C_{18}H_{16}N_2O_2$. Calculated: C 74.0; H 5.5; N 9.6%.

B. A total of 0.008 mole of an ether solution of diazomethane was added to a suspension of 0.008 mole of 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone in ether, during which the solid dissolved. The mixture was allowed to stand overnight, after which the ether was removed by distillation, and the residue was washed with water to give 85% of XV with mp 74° (from aqueous alcohol). The product did not depress the melting point of a sample obtained by method A.

Similarly, treatment of X-XII with diazomethane gave the corresponding XVII-XIX.

1-Phenyl-3-methyl-4-acetyl-5-methoxypyrazole (XVII). This compound has mp 96°. Found: C 68.0; H 6.4; N 12.1%. $C_{13}H_{14}N_2O_2$. Calculated: C 67.8; H 6.1; N 12.2%.

1-Phenyl-3-methyl-4-chloroacetyl-5-methoxypyrazole (XVIII). This compound had mp 69°. Found: C 59.0; H 5.2; N 10.5%. $C_{13}H_{13}ClN_2O_2$. Calculated: C 59.0; H 5.0; N 10.6%.

1-Phenyl-3-methyl-4-ethoxyacetyl-5-methoxypyrazole (XIX). This compound had mp 70°. Found: C 65.3; H 7.0; N 10.2%. $C_{15}N_{18}N_2O_3$. Calculated: C 65.7; H 6.6; N 10.2%.

1,3-Dimethylchromono[3,2-d]pyrazole (Ia). A solution of 5 g of III and 1.12 g of potassium hydroxide in 15 ml of water and 20 ml of dimethylformamide was heated at 100° for 12 h, and the mass was cooled and poured into 100 ml of water. The precipitated Ia was removed by filtration and crystallized from alcohol (Table 3). 1-Phenyl-3-methylchromono[3,2-d]pyrazole (Ib, Table 3) was similarly obtained from VII.

1,3,5-Trimethyl-7-phenylpyrazolo[4,5-d]-4-pyrono[2,3-d]pyrazole (XXII). A solution of 6.6 g of V in 20 ml of dimethylformamide and 1.6 g of pyridine was heated at 100° for 24 h. The mass was cooled and poured into 100 ml of water, and the precipitate was removed by filtration, washed several times with 5% sodium hydroxide solution, and crystallized from alcohol.

1,7-Diphenyl-3,5-dimethylpyrazolo[4,5-d]-4-pyrono[2,3-d]pyrazole (XXIII). This compound was similarly obtained, but the reaction time was 6 h (Table 3).

Compounds Ia, Ib, XXII, and XXIII were subjected to reaction with organomagnesium compounds, obtained from ethyl bromide and dimethylaminopropyl chloride, and with phosphorus pentasulfide via a previously described method [1]. The characteristics of the compounds obtained are presented in Tables 4 and 5.

Oxalate of 1,3-Dimethyl-4-dimethylaminopropylidenechromono[3,2-d]pyrazole (XXIX). A 1.0-g sample of XXVIII was dissolved in 10 ml of 2 N hydrochloric acid, and the solution was heated at 60° for 1 h and cooled. The cooled solution was made alkaline with 20% sodium hydroxide solution and extracted with ether. The ether solution was dried, and the oxalate of XXIX with mp 40-44° was precipitated from the ether solution. The yield was 70%. Found: N 11.1%. $C_{17}H_{21}N_3O \cdot C_2H_2O_4$. Calculated: N 11.3%.

Oxalate of 1-Phenyl-3-methyl-4-dimethylaminopropylidenechromono[3,2-d]pyrazole (XXXI). This compound was similarly obtained and had mp 128-132° (from alcohol). Found: N 9.6%. $C_{22}H_{23}N_3O \cdot C_2H_2O_4$. Calculated: N 9.6%.

LITERATURE CITED

1. A. S. Sarenko, L. S. Éfros, and I. Ya. Kvitko, Khim.-Farmats. Zh., No. 9, 23 (1970).
2. A. A. Goldberg and A. H. Wragg, J. Chem. Soc., 453 (1960); Swiss Patent No. 346,892 (1960); Chem. Abstr., 55, 16,570 (1961).
3. B. S. Jensen, Acta Chem. Scand., 13, 1668 (1959).
4. J. Elguero, R. Jacquier, and G. Tarrago, Bull. Soc. Chim. France, 3780 (1967).
5. L. Bellamy, Infrared Spectra of Complex Molecules, Methuen (1958).
6. I. I. Grandberg, V. G. Vinokurov, V. S. Troitskaya, T. A. Ivanova, and V. A. Moskalenko, Khim. Geterotsikl. Soedin., 202 (1970).