HETARYLATION OF PYRAZOLONES BY SALTS OF N-ACYLHETEROAROMATIC CATIONS*

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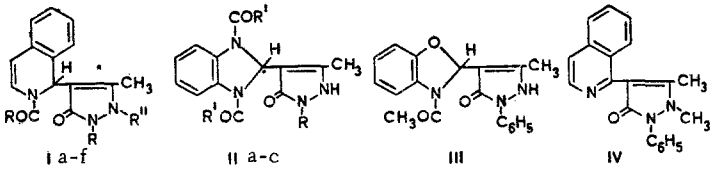
UDC 547.833.835.775

Isoquinoline, acridine, benzimidazole, and benzoxazole residues were introduced into the pyrazolone ring by reaction of N-heteroaromatic compounds with pyrazolones in the presence of acylating agents.

The hetarylation of thiazolidones proceeds readily under the influence of N-heteroaromatic systems in the presence of acylating agents [2]. Pyridylation of oxazolones takes place similarly in the Dakin–West synthesis [3]. In the present research we used the same method to introduce isoquinoline, benzimidazole, and benzoxazole residues into the pyrazolone ring. The reaction of the corresponding heteroring with pyrazolones was carried out in an inert solvent in the presence of acylating agents (acetic anhydride and acyl halides) until the pyrazolone was no longer present in the reaction medium [as monitored by thin-layer chromatography (TLC)]. In this case we obtained hetarylation products I, II, and III:



I a-f II a-c III IV

I a $R=R'=C_6H_5$, $R''=H$; b $R=C_6H_5$, $R'=o\text{-}BrC_6H_4$, $R''=H$; c $R=C_6H_5$, $R'=o\text{-}CH_3C_6H_4$, $R''=H$; d $R=C_6H_5$, R' = 2-thienyl, $R''=H$; e $R=C_6H_5$, R' = 5-benzyl-2-furyl, $R''=H$; f $R=R'=C_6H_5$, $R=CH_3$;

II a $R=C_6H_5$, $R'=CH_3$; b $R=C_3H_7$, $R'=CH_3$; c $R=C_4H_9$, $R'=CH_3$

We proved the structures of the synthesized compounds by conversion of one of them (If) by alkaline hydrolysis to the previously described [4] IV. The structures of the remaining compounds were confirmed by the presence in their IR spectra of intense bands at 1660-1710 cm^{-1}, which corresponds to the stretching vibrations of the carbonyl group of the acyl residue and the pyrazolone ring, bands of stretching vibrations of the NH group at 3200-3500 cm^{-1}, and by the similarity between their UV spectra and the spectrum of If. Characteristic signals of the methyl group of the acetyl residue, the methyl group in the 3 position, a multiplet of 10 protons of the aromatic ring of benzoxazole and the phenyl group of pyrazolone and the proton in the 2 position of the benzoxazole ring, and a singlet of the proton of the NH group are observed in the PMR spectrum of benzoxazole derivative III.

The high-resolution mass spectrum indicates the composition $C_{19}H_{17}N_3O_3$. The molecular ion of the compound has a stability of 4.8% with respect to electron impact. This W_M value lies within the same limits as those observed for most of the previously investigated N-acetyl derivatives of 1,2-dihydroquinoline, 1,2-dihydroisoquinoline, etc. [5]. The fragmentation of the molecular ion in the case of compounds of this type is accompanied in the first step by detachment of a molecule of ketene. In our case this process is responsible for the appearance of an ion peak at 293,† to which a number of isomeric structures may correspond:

*See [1] for our preliminary communication [1].

†Here and subsequently, the m/e values (intensities in percent of the maximum ion peak) are presented for the ion peaks.

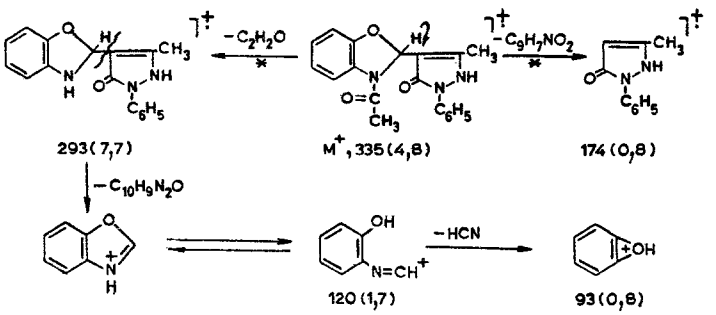
Dnepropetrovsk Construction-Engineering Institute, Dnepropetrovsk 320092. Donetsk State University, Donetsk 340055. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1394-1397, October, 1977. Original article submitted October 25, 1976; revision submitted January 31, 1977.

 0009-3122/77/1310-1118$07.50

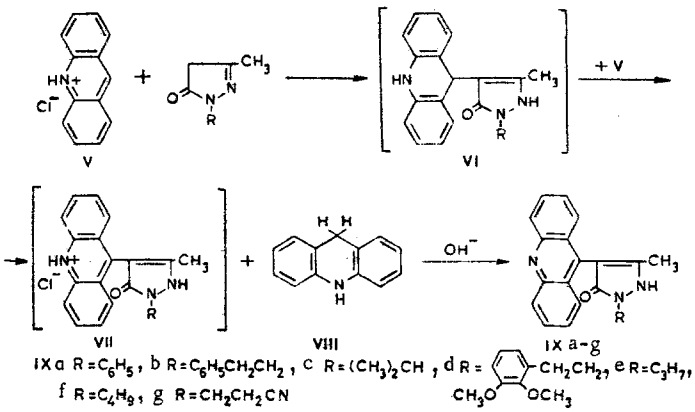
TABLE 1. Heterocyclic Derivatives of Pyrazolones

Compound	mp, °C[a]	R_f [b]	Found, %			Empirical formula	Calc., %			IR spectrum, cm^{-1} [c]		Yield, %	Picrates				Hydrochlorides			
			C	H	N		C	H	N	$\nu_{C=O}$	ν_{N-H}		mp, °C[d]	N found, %	empirical formula	N calc., %	mp, °C[d]	Cl found, %	empirical formula	Cl calc., %
Ia	125—126[f]	0,35	76,5	5,3	10,0	$C_{26}H_{21}N_2O_3$	76,7	5,2	10,3	1650, 1680	3422	65								
Ib	115—116[f]	0,24	64,0	3,8	8,6	$C_{26}H_{20}N_3O_2Br$	64,0	3,8	8,7	1657, 1692	3420	60								
Ic	70—71[f]	0,30	77,3	5,1	10,0	$C_{27}H_{22}N_3O_2$	77,1	5,2	10,0	1665, 1695	3435	68								
Id	98—99[f]	0,31	69,7	4,2	9,9	$C_{24}H_{18}N_3O_2$	70,0	4,4	10,0	1660, 1695	3428	40								
Ie	114—115[f]	0,30	73,2	5,0	10,2	$C_{31}H_{24}N_3O_3$	73,1	4,9	10,3	1665, 1690	3425	55								
IIa	177—178[f]	0,33	67,0	5,2	14,8	$C_{21}H_{20}N_4O_3$	67,0	5,3	14,9	1655, 1695	3440	83								
IIb	197—198	0,18	60,0	6,2	16,3	$C_{18}H_{21}N_4O_3$	60,4	6,1	16,4	1660, 1695	3400	90								
IIc	144—145	0,34	63,8	6,6	15,8	$C_{19}H_{24}N_4O_3$	64,0	6,7	15,7	1665, 1692	3428	90								
III	168—169	0,20	67,9	5,1	12,8	$C_{19}H_{16}N_3O_3$	68,1	4,8	12,5	1650, 1695	3440	68								
IXa	286—287	0,23 g	78,5	5,0	12,0	$C_{23}H_{17}N_3O$	78,6	4,9	12,0	1680	3435	90	295—296	14,2	$C_{29}H_{20}N_6O_8$	14,5	343—344	8,7	$C_{23}H_{18}N_3OCl$	9,0
IXb	289—290	0,25 g	79,1	5,9	10,6	$C_{25}H_{21}N_3O$	79,1	5,5	11,1	1685	3435	68	249—250	13,5	$C_{31}H_{24}N_6O_8$	13,8	195—196	7,1	$C_{25}H_{22}N_3OCl$	7,2
IXc	260—261	0,14 g	75,9	6,1	12,9	$C_{20}H_{19}N_3O$	75,7	5,5	13,2	1682	3440	65	175—176	15,1	$C_{26}H_{22}N_6O_8$	15,4	234—235	10,2	$C_{20}H_{20}N_3OCl$	10,0
IXd	283—284	0,14 g	75,8	6,0	13,1	$C_{20}H_{18}N_3O$	75,9	5,7	13,3	1680	3428	70	248—249	15,1	$C_{26}H_{21}N_6O_8$	15,2	236—237	10,1	$C_{20}H_{19}N_3OCl$	10,0
IXe	214—215	0,21 g	76,3	6,4	12,6	$C_{21}H_{21}N_3O$	76,1	6,3	12,7	1695	3427	80	226—227	15,2	$C_{27}H_{24}N_6O_8$	15,0	248—249	9,2	$C_{21}H_{22}N_3OCl$	9,5
IXf	273—274	0,18 g	73,2	4,4	17,0	$C_{20}H_{16}N_4O$	73,4	4,6	17,1	1692	3435	85	265—266	17,3	$C_{26}H_{19}N_7O_8$	17,4	305—306	5,7	$C_{20}H_{17}N_4OCl$	5,9
IXg	247—248	0,21 g	74,4	5,3	9,8	$C_{27}H_{22}N_3O$	74,3	5,0	9,6	1690	3440	70	219—220	13,2	$C_{33}H_{25}N_7O_8$	13,3	175—176	7,8	$C_{27}H_{23}NOCl$	8,0

[a]From n-butanol. [b]In system A. [c]In chloroform. [d]From glacial acetic acid. [e]From ethanol—ether. [f]From ethanol. [g]In system B.



It was found to be more convenient to introduce an acridine residue in the pyrazolone ring by means of protic salts of acridine rather than by means of its N-acyl salts. This sort of method for the introduction of an acridine residue in some aromatic and heteroaromatic compounds has been previously described [6, 7]. When we heated acridine hydrochloride with pyrazolones, we obtained (9-acridinyl)pyrazolones (IX) and acridan, probably through hydride transfer from the intermediately formed 9,10-dihydroacridine derivative VI to cation V, as has been previously demonstrated in the case of dialkylanilines [7]:



An intense band of stretching vibrations of the carbonyl group of the pyrazolone ring at 1665-1700 cm^{-1} is observed in the IR spectra of the IX derivatives; the mass spectra indicate molecular weights corresponding to the calculated values, and the presence in them of fragment ions corresponding to pyrazolone and acridine residues completely confirms their structures. Pyridine and quinoline hydrochlorides do not react with pyrazolones under similar conditions.

EXPERIMENTAL

The IR spectra of chloroform solutions of the compounds were recorded with a UR-20 spectrometer. Chromatography was accomplished in a loose thin layer of Al_2O_3 (activity II on the Brockmann scale) with elution by chloroform–benzene–hexane (30:6:1) (A) and chloroform–benzene–hexane–methanol (30:6:1:1) (B). The chromatograms were developed with iodine vapors and in UV light. The mass spectrum was obtained with a Varian CH-6 spectrometer; the accelerating voltage was 3 kV, the cathode emission current was 300 mA, the ionizing voltage was 70 eV, and the temperature of the ion source was 80°C. The PMR spectra of solutions of the compounds in perdeuterated dimethyl sulfoxide were recorded with a Varian XL-100 spectrometer (100 MHz) at room temperature with tetramethylsilane as the internal standard.

1-Phenyl-2,3-dimethyl-4-(2-benzoyl-1,2-dihydro-1-isoquinolinyl)pyrazol-5-one (If). A mixture of 4.7 g (25 mmole) of antipyrine, 6.4 g (50 mmole) of isoquinoline, and 3.5 g (25 mmole) of benzoyl chloride in 35 ml of dry benzene was refluxed for 20 h, after which it was subjected to steam distillation, and the residue in the distilling flask was separated and recrystallized from ethanol to give 6.3 g (60%) of a product with mp 161-161.5°C and R_f 0.66 (B). IR spectrum: $\nu_{C=O}$ 1650; ν_{N-H} 3420 cm^{-1}. Found: C 76.7; H 5.4; N 10.1%. $C_{27}H_{24}N_3O_2$. Calculated: C 77.0; H 5.5; N 10.1%.

The other iosquinolinylpyrazolones I, the principal characteristics of which are presented in Table 1, were similarly obtained.

1-Phenyl-2,3-dimethyl-4-(1-isoquinolinyl)pyrazol-5-one (IV). This compound was obtained by refluxing 8.4 g of If and 28.8 g of potassium hydroxide in 100 ml of 70% ethanol for 6 h. The yield of product with mp 170-171°C (from ethyl acetate) (mp 172-173°C [4]) was 1.8 g (29%)..

1-Phenyl-2,3-dimethyl-4-(9-acridinyl)pyrazol-5-one (IX). A mixture of 8.6 g (40 mmole) of acridine hydrochloride and 3.8 g (20 mmole) of antipyrine in 30 ml of dry dimethylformamide (DMF) was heated at 100 °C for 2 h, after which it was subjected to steam distillation, and the residue in the distilling flask was separated, washed with ether, and recrystallized from DMF to give 1.5 g (20% based on antipyrine) of a product with mp 241-242°C and R_f 0.21 (B). IR spectrum: $\nu_{C=O}$ 1685; ν_{N-H} 3418 cm^{-1}. Found: C 79.0; H 5.1; N 11.6%. $C_{24}H_{19}N_3O$. Calculated 78.8; H 5.2; N 11.5%. The picrate has mp 194-194.5°C (from glacial acetic acid). Found: N 14.2%. $C_{24}H_{19}N_3O \cdot C_6H_3N_3O_7$. Calculated: N 14.1%. The hydrochloride had mp 338-339°C (from ethanol containing ether). Found: Cl 9.0%. $C_{24}H_{19}N_3O \cdot HCl$. Calculated: Cl 8.8%.

Evaporation of the filtrate yielded 1.8 g (50%) of acridan with mp 171-172°C (from methanol). No melting-point depression was observed for a mixture of a sample of this product with a genuine sample.

1-Phenyl-3-methyl-4-(3-acetyl-2-benzoxazolinyl)pyrazol-5-one (III). A mixture of 1.2 g (10 mmole) of benzoxazole and 1.7 g (10 mmole) of 1-phenyl-3-methyl-5-pyrazolone in 10 ml of acetic anhydride was heated at 125°C for 5 h, and the resulting precipitate was removed by filtration, washed with methanol and water, and recrystallized from n-butyl alcohol to give 2 g (61%) of a product with mp 168-169°C and R_f 0.20 (A). IR spectrum: $\nu_{C=O}$ 1665, 1685; ν_{N-H} 3422 cm^{-1}. PMR spectrum: 2.45 s, 2.25 s, 7.15-8.05 m, and 8.65 s ppm. Mass spectrum: 335 (38.93); 294 (13.33); 293 (62.67); 292 (5); 276 (7.44); 186 (15.21); 185 (100); 174 (6.93); 148 (6.80); 145 (5.94); 120 (13.85); 109 (9.67); 105 (5.00); 104 (13.37); 103 (5.11); 93 (6.92); 91 (11.77); 77 (21.06); 71 (5.93); 65 (8.21); 57 (8.18); 55 (6.10); 51 (7.54); 43.9 (15.90); 42.9 (17.13); 41.8 (7.34); 34.6 (5.14). Found: C 67.9; H 5.1; N 12.8%. $C_{19}H_{16}N_3O_3$. Calculated: C 68.1; H 4.8; N 12.5%.

Benzimidazolinylpyrazolones II (see Table 1) were similarly obtained.

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