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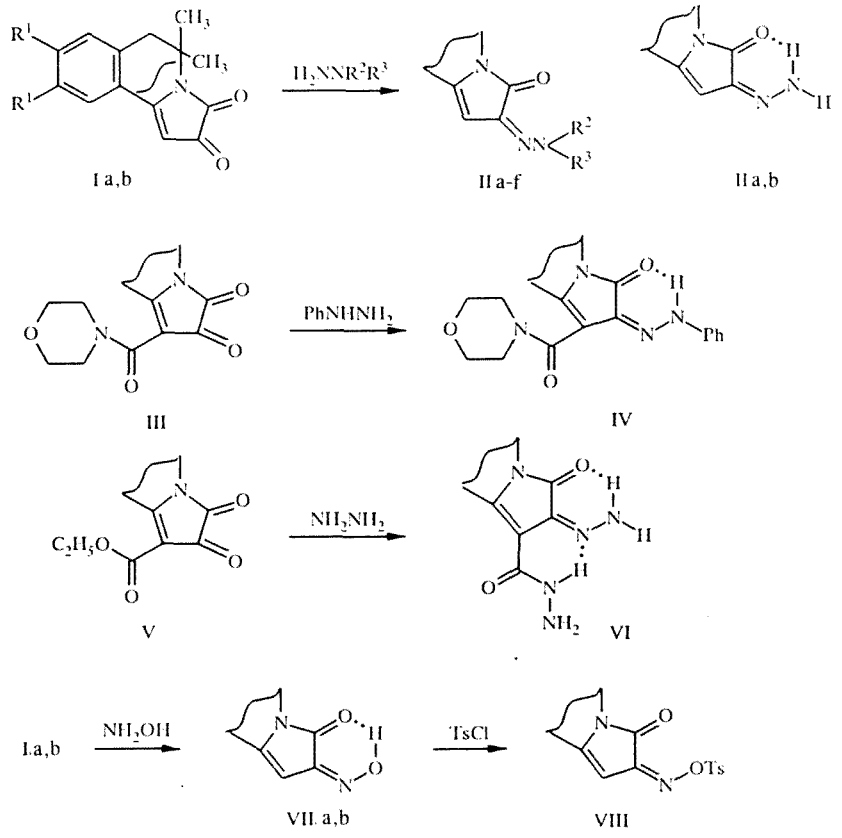
SYNTHESIS OF PYRROLO[2,1-*a*]ISOQUINOLINE HYDRAZONES AND OXIMES

A. G. Mikhailovskii, V. S. Shklyaev, A. V. Ignatenko, and M. I. Vakhrin

Reactions between 2,3-dioxopyrrolo[2,1-a]isoquinolines and hydrazines and hydroxylamine afforded the corresponding hydrazones and oximes.

We have previously obtained 2,3-dioxopyrrolo[2,1-*a*]isoquinolines and studied their reaction with o-phenylenediamine [1-5]. The reactions of these compounds with other nucleophiles have not been studied up to the present time. The reactions of 2,3-dioxopyrrolines with nucleophiles are known to take place not only on the carbonyl residue but also on the electron-deficient carbon–carbon double bond [6], so an investigation of the structure of the products of these reactions is of definite interest. In this study the reactions between 2,3-dioxopyrrolo[2,1-*a*]isoquinolines and the strongest N-nucleophiles — hydrazines and hydroxylamine — are described.



I a R^1 = H, b OCH_3; II R^2 = R^3 = H, a R^1 = H, b OCH_3, R^2 = R^3 = CH_3, c R^1 = H, d OCH_3, R^2 = H, R^3 = Ph, e R^1 = H, f OCH_3; VII a R^1 = H, b OCH_3; VIII R^1 = H

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TABLE 1. Properties of Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	IR spectrum, cm^{-1}	Yield, %
		C	H	N			
IIb	$C_{16}H_{19}N_3O_3$	63.6 63.8	6.2 6.4	13.9 13.9	187...188	1685 (C=O), 3120, 3430 (NH)	82
IIc	$C_{16}H_{19}N_3O$	71.3 71.4	7.0 7.1	15.7 15.6	168...169	1695 (C=O)	35
IId	$C_{18}H_{23}N_3O_3$	65.5 65.6	6.8 7.0	12.9 12.8	175...176	1695 (C=O)	43
IIe	$C_{20}H_{19}N_3O$	75.6 75.7	5.9 6.0	13.2 13.2	195...197	1690 (C=O), 3200 (NH)	57
IIf	$C_{22}H_{23}N_3O_3$	69.8 70.0	5.9 6.1	11.0 11.1	190...191	1680 (C=O), 3250 (NH)	77
IV	$C_{25}H_{26}N_4O_3$	69.7 69.8	5.9 6.1	13.1 13.0	188...190	1670, 1630 (C=O), 3200 (NH)	73
VI	$C_{15}H_{17}N_4O_2$	63.0 63.1	5.9 6.0	19.7 19.6	183...184	1648, 1720 (C=O), 3000, 3248 (NH), 3216, 3280 (NH_2, ν_s, ν_{as})	83
VIIa	$C_{14}H_{14}N_2O_2$	69.3 69.4	5.7 5.8	11.5 11.6	153...154	1670 (C=O), 3150 (OH)	53
VIIb	$C_{16}H_{18}N_2O_4$	63.4 63.6	5.8 6.0	9.4 9.3	189...190	1670 (C=O), 3200 (OH)	58
VIII*	$C_{21}H_{20}N_2O_4S$	63.5 63.6	5.0 5.1	7.2 7.1	145...147	1700 (C=O)	72

*Found: S 8.0%: Calculated: S 8.1%.

TABLE 2. PMR Spectral Parameters for Compounds IIb-f, IV, VI, VIIa,b, and VIII

Compound	PMR spectrum, δ, ppm						
	5-$(CH_3)_2$, s	6-$(CH_2)_2$, s	aromatic protons	$(CH_3O)_2$, d	1-H, s	HN, s	other signals
IIb	1,23	2,73	6,60, 7,17	3,78	6,47	8,67, 11,57	—
IIc	1,27	2,84	7,03...8,27	—	6,70	—	2,57 s ($2CH_3$—N)
IId	1,50	2,90	6,57, 6,90	3,77	6,02	—	2,90 s ($2CH_3$—N)
IIe	1,28	2,70	6,72...7,47	—	6,43	11,47	—
IIf	1,30	2,73	6,67...7,40	3,73	6,53	10,57	—
IV	1,47	2,80	6,85...7,60	—	—	12,87	3,67 br.s ($4CH_2$)
VI	1,28	2,95	7,30...8,20	—	—	4,85, 10,70	—
VIIa	1,13	2,80	6,28...7,31	—	6,28	—	11,35 s (OH)
VIIb	1,17	2,78	6,87, 7,17	3,80	6,23	—	11,60 s (OH)
VIII	1,40	2,76	7,00...8,10	—	6,13	—	2,33 s (CH_3—Ar)

Studies showed that the reactions of compound Ia, b with hydrazine hydrate, asymmetric dimethylhydrazine and phenylhydrazine take place in a normal manner to give the corresponding hydrazones IIa-f. In a similar manner amide III reacts with phenylhydrazine to give hydrazone IV. The formation of a pyrazolone derivative is feasible by reaction of ester V with hydrazine hydrate. However, this reaction does not occur, and the product of simple hydrazinolysis VI is formed. The reaction of ketones Ia, b with hydroxylamine leads to the corresponding oximes VIIa, b. It is known [7] that isatin oxime on treatment with toluenesulfonyl chloride decomposes to form a nitrile. We have found that under the reported conditions [7] oxime VIIa does not decompose and the tosylation product VIII is formed.

All the reactions with N-nucleophiles described here were carried out by boiling in ethanol. It was shown on monitoring the course of the reactions by means of TLC that in all cases the reactions with hydrazine hydrate, N,N-dimethylhydrazine, and hydroxylamine were completed more rapidly (within 10-15 min) while the reaction with phenylhydrazine required boiling for 30-40 min.

The properties of the new compounds are given in Table 1. In contrast to the initial dioxopyrroline Ia, b, III, and V, which have a bright red color, their nitrogen derivatives are pale yellow, while compound VI is colorless. In the PMR spectra of compounds Ia-f, VIIa, b, and VIII (Table 2) there is a singlet signal due to the proton of the pyrrole ring [1, 5], which indicates that it remains unchanged during reaction. In the spectra of several compounds the formation of a hydrogen bond involving the protons of the NH group and the carbonyl group at the 3-position can be detected. Thus, for example, in the spectrum of hydrazone IIb there are two signals due to an NH group (8.67 and 11.57 ppm), corresponding to the structure of compounds IIa, b in the reaction scheme [1]. A similar pattern occurs in the spectrum of compound IV — the proton of the NH group is strongly shifted downfield (12.87 ppm). In the spectrum of hydrazide VI signals due to the free NH_2 group can be seen at 4.85 ppm as well as signals from protons participating in the formation of hydrogen bonding. Confirmation that the respective signals belong to the NH groups is obtained when they are shifted downfield on addition of CF_3COOH. The structure of compound VI is also confirmed from its ^{13}C NMR spectrum. In the PMR spectra of oximes VIIa, b the protons of the OH groups occur at 11.35 and 11.60 ppm respectively, which suggests that they participate in hydrogen bonding.

In the IR spectrum of a solution of hydrazone IIb (0.01 moles/liter, $CHCl_3$) there are bands due to chelated C=O lactam (1685 cm^{-1}) and NH (3120 cm^{-1}) groups and also a free NH group (3430 cm^{-1}). The IR spectrum of hydrazide VI has a complex pattern. Nevertheless, a band due to hydrazide carbonyl (1720 cm^{-1}) and those from three NH groups can be detected in it.

EXPERIMENTAL

The PMR and ^{13}C NMR spectra of compound VI were recorded on a Bruker AC-200P instrument, while the PMR spectra of the remaining compounds were recorded on a RYa 2310 spectrometer (60 MHz) as solutions in $CDCl_3$ (for compounds IIb, c, d and VIII) and in DMSO-d_6 for the remaining compounds. The internal standard was HMDS. The IR spectra were recorded on UR-20 and Specord M-80 instruments in $CHCl_3$ (IIb, e), as a KBr pellet (VI), in vaseline oil (for the remaining compounds). The course of the reactions was monitored by TLC on Silufol UV-254 plates in acetone–ethanol–chloroform (1:3:6), using bromine vapor for development.

The synthesis of the initial compounds Ia, b, III, and V is described in three studies [1, 4, 5]. All compounds were recrystallized from isopropanol.

The elemental analysis data for C, H, N, and S corresponded to the calculated values.

N,N-R^2,R^3 Hydrazones of 2,3-Dioxo-5,5-dimethyl-8,9-$(R^1)_2$-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolines (IIa-f), 2,3-Dioxo-5,5-dimethyl-1-morpholinocarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline Phenylhydrazone (IV), and 2-Hydrazono-3-oxo-5,5-dimethyl-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-1-carboxylic Acid Hydrazide (VI). A mixture of 15 mmole of the respective hydrazine and 10 mmole of compound Ia, b or III or 1.50 g (5 mmole) of compound V was boiled in 50 ml of ethanol for 5-10 min (IIa-d, IV, VI) or 30-40 min (IIe, f). After the reaction was complete (monitored by TLC), about 30 ml of solvent was distilled off under vacuum, and the solution was cooled. The precipitate that formed was filtered off, dried, and recrystallized. ^{13}C NMR spectrum of hydrazide VI: 26.02 ($2CH_3$), 39.78 ($C_{(6)}$), 51.16 ($C_{(5)}$), 90.13, 123.56, 126.24, 126.51, 131.82, 134.03, 137.13 (6C, Ar), 159.45 and 160.61 ($C_{(1)}$ and C=N), 170.25 (CONH), 179.03 ppm ($C_{(3)}$).

2,3-Dioxo-5,5-dimethyl-8,9-$(R^1)_2$-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline Oximes (VIIa, b) and 2,3-Dioxo-5,5-dimethyl-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline Oxime Tosylate (VIII). To a solution of 10 mmole of compound Ia, b in 30 ml of ethanol was added 1.04 g (15 mmole) of hydroxylamine hydrochloride in 5 ml of water and 0.4 g (10 mmole) of NaOH, and the mixture was boiled for 10 min. The procedure then followed that described for the above hydrazones. A mixture of 2.42 g (10 mmole) of oxime VIIa and 3.82 g (20 mmole) of p-toluenesulfonyl chloride in 20 ml of dioxane was heated to boiling, and 0.16 g (4 mmole) of NaOH in 5 ml of water was added. The mixture was stirred vigorously for 10 min, and NH_3 was added until there was an alkaline reaction. The solution was cooled to 20°C and the reaction product was precipitated by the addition of 50 ml of water. The resulting precipitate of compound VIII was filtered off, dried, and recrystallized.

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