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REACTIONS OF 2,3-DIOXOPYRROLO[2,1-a]ISOQUINOLINES WITH SODIUM BOROHYDRIDE AND THE PROPERTIES OF ITS PRODUCTS

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The reaction of 2,3-dioxopyrrolo[2,1-a]isoquinolines with sodium borohydride, depending on the conditions under which it is carried out, can proceed by the route of hydrogenation or by the opening of the pyrrole ring. In the latter case, ketoesters, for which examples of reactions at the dicarbonyl and enamine fragments are presented, are formed.

We previously synthesized and investigated 2,3-dioxopyrrolo[2,1-a]isoquinolines [1-5] – compounds having two reaction centers in their structure: the dicarbonyl fragment, and the electron-deficient double bond [6]. One of the possible reactions of both centers is hydrogenation, the products of which present interest as synthons and biologically active compounds. The aim of the given work is to investigate the hydrogenation reaction of 2,3-dioxopyrrolo[2,1-a]isoquinolines using sodium borohydride.

Initial reagents utilized were the dicarbonyl compounds (IIa-d) (Table 1), two of which (IIa,b) were previously synthesized in the works [1, 3]. The substances (IIc,d) were synthesized from the spiro compound (Ic) [7] and the Noshp base [8] correspondingly. Investigations of the reaction of the dioxopyrrolines (IIa-d) with sodium borohydride showed that the structure of its products depends on the character of the solvent and the percentage content of water in it. Syntheses were initially carried out in solvents not rendered absolute, or not tested for moisture content. Experiments showed that, in the case of solvents containing 5-10% of water, sodium borohydride does not exhibit its reducing action. Instead of that, the ring opening of the pyrrolediones (IIa-d) occurs with the formation of the corresponding enaminoketoesters (IVa-f). The radicals R^4, presented in Table 1, correspond to the selected alcohol. The analogous effect is observed when 5-10% v/v of water is added to the corresponding absolute alcohol. It is evident that the alkali formed by the ready hydrolysis of sodium borohydride in the given case catalyzes the opening of the pyrroledione ring. The reaction for the formation of ketoesters of the type (IVa-f), previously described by us [9], proceeds similarly by the action of the corresponding sodium alkoxides. Testing showed that compounds (IVb,c), synthesized by the method described in the work [9], can also be obtained in the corresponding alcoholic medium containing 10% of water by the action of sodium borohydride with yields of 63 and 67%. Experiments showed that the method of [9] also gives good results: it can be seen by the comparison of the yields of the substances (IVa,e) obtained by both methods (Table 1) that both methods are preparatively acceptable.

In the case of the absolute solvent (ethanol, methanol, isopropanol, tert-butanol, dioxane), the normal reduction of the ketone group to the alcohol group is noted. Reduction is also observed in the case of aqueous dioxane, but it is true that the yield thereby decreases to 35%. The reaction was not observed in the solution of absolute or 85% acetonitrile (using monitoring by TLC), possibly on account of the poor solubility of sodium borohydride. It should be noted that the hydrogenation of the electron-deficient double bond in the pyrrole ring occurs in this reaction besides the reduction of the carbonyl ketone. It was previously communicated that the double bond in a similar type of structure is not affected by sodium borohydride [10]. Attention is drawn to the fact that the initial substances were obtained instead of the expected reduction products in the case of the electron-donor groups OCH_3 and OC_2H_5 at the positions 8, 9 [compounds (IIb,d)]. At the same time, the opening of the pyrrole ring of these compounds in the corresponding alcoholic solutions by the action of sodium borohydride with added water proceeds smoothly with normal yields (Table 1).

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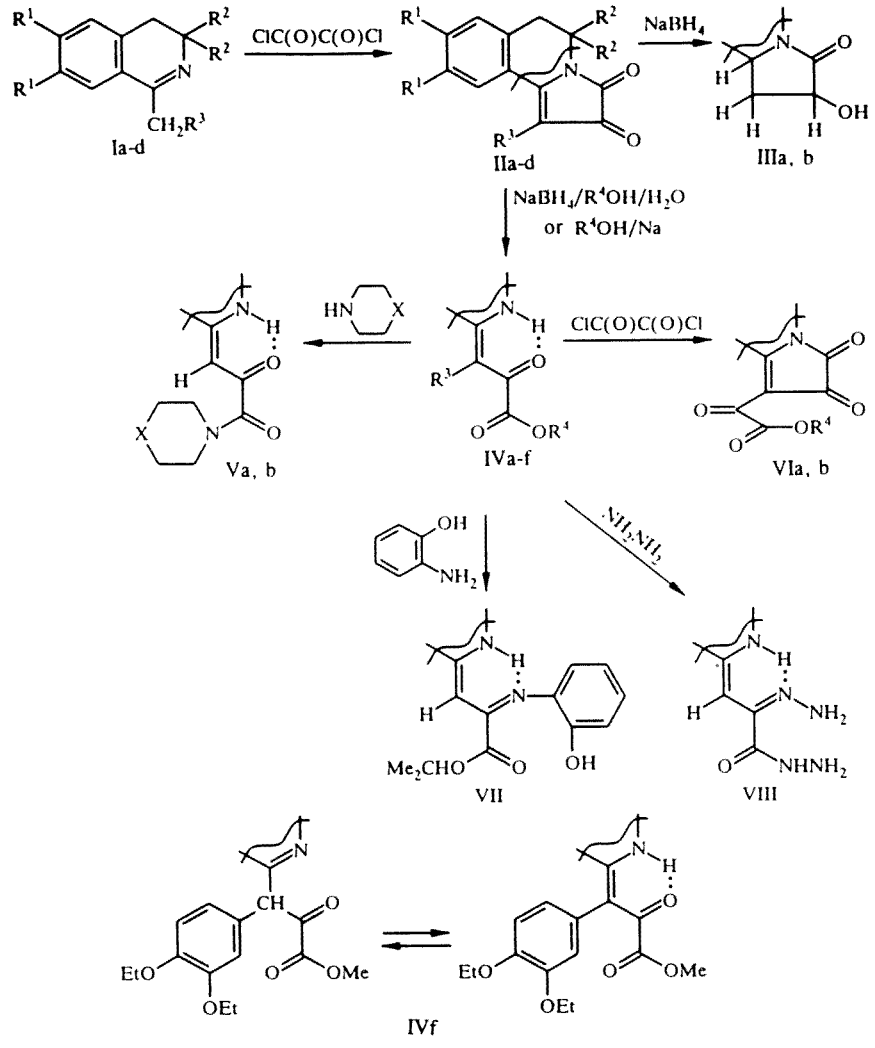

The presence of the two fragments – dicarbonyl and enamine – in the structure of the ketoesters (IVa-f) makes them valuable synthons. The conversions presented in the scheme confirm the structure of these compounds and indicate some of their synthetic possibilities. Thus, when the compound (IVa) is boiled in piperidine or morpholine, the corresponding enaminoketoamides (Va,b) are formed instantly. The interaction of the esters (IVa,c) with oxalyl chloride results in the formation of the tetracarbonyl compounds (VIa,b), colored bright red, which confirms the fact that the initial substances occur in the form of the enamine. The reaction of the ester (IVc) with o-aminophenol leads to the azomethine (VII), the phenolic structure of which is confirmed by its solubility in the aqueous solution of alkali, besides spectral data. The same initial enamine (IVc) gives the hydrazone (VIII) with hydrazine hydrate; (VIII) is the product of the reaction at both carbonyl groups – the ketonic and the ester.

It can be seen from the scheme considered that the compounds (IIa-d), being electrophiles, change their properties in the course of the conversions, acquiring nucleophilic character due to the enamine group [the substances (IVa-f)], i.e., the inversion of chemical properties takes place. At the same time, the normal properties of carbonyl groups are preserved in the enamines (IVa-f). The corresponding changes in the electronic structure are accompanied by sharp changes in the color of the substances. Thus, the initial compounds (IIa-d) are colored bright red, and the products of their hydrogenation (IIIa,b) are completely colorless; the enamines (IVa-f) are slightly yellowish. The amides (Va,b) are yellow crystalline substances; the compounds (VII) and (VIII) are also yellow, with a deep coloration typical of Schiff bases and hydrazones. The characteristics of the compounds obtained are given in Table 1.

The IR and PMR spectra of the compounds obtained for the first time are presented in Table 2. The alcohols (IIIa,b) contain two chiral centers. The PMR spectra of these compounds do not allow a conclusion to be made concerning the proportion of diastereomers contained in the sample, since the hydrogenation of three atoms of carbon strongly complicates the spectral picture. The spectrum of the alcohol (IIIa), in contrast to the initial substance (IIa) [1], contains the multiplet of

TABLE 1. Characteristics of the Compounds Synthesized

Compound*	R^1	$C(R^2)_2$	R^4	Empirical formula	mp, °C	Yield,† %
IIc	H	$C(CH_2)_4$	—	$C_{16}H_{15}NO_2$	157...158	82
IId	C_2H_5O	CH_2	—	$C_{26}H_{29}NO_6$	215 (decomp.)	57
IIIa	H	$C(CH_3)_2$	—	$C_{14}H_{17}NO_2$	238...239	78
IIIb	H	$C(CH_2)_4$	—	$C_{16}H_{19}NO_2$	173...175	66
IVa	H	$C(CH_3)_2$	CH_3	$C_{15}H_{17}NO_3$	92...93	90 (70)
IVd	CH_3O	$C(CH_3)_2$	$CH(CH_3)_2$	$C_{19}H_{25}NO_5$	115...117	58
IVe	H	$C(CH_2)_4$	$CH(CH_3)_2$	$C_{19}H_{23}NO_3$	72...73	81 (67)
IVf	C_2H_5O	CH_2	CH_3	$C_{27}H_{33}N_7O_7$	208...209	60
Va	H	$C(CH_3)_2$	—	$C_{19}H_{24}N_2O_2$	105...106	56
Vb	H	$C(CH_3)_2$	—	$C_{18}H_{24}N_2O_3$	153...154	52
VIa	H	$C(CH_3)_2$	—	$C_{17}H_{15}NO_5$	185...186	76
VIb	H	$C(CH_3)_2$	—	$C_{19}H_{19}NO_5$	154...155	75
VII	H	$C(CH_3)_2$	—	$C_{23}H_{26}N_2O_3$	187 (decomp.)	43
VIII	H	$C(CH_3)_2$	—	$C_{14}H_{19}N_5O$	240 (decomp.)	47

*I, II $R^2 = CH_3$, a) $R^1 = H$; b) $R^1 = OCH_3$; c) $R^1 = H$, $C(R^2)_2 = C(CH_2)_4$; d) $R^1 = OC_2H_5$, $R^2 = H$; IV $R^1 = H$, $R^2 = CH_3$ b $R^4 = C_2H_5$; c $R^4 = CH(CH_3)_2$; V a X = CH_2, b X = O; I, IId, IVf R^3 = 3,4-diethoxyphenyl, in all remaining compounds $R^3 = H$.

†The yields of the products of direct synthesis using R^4ONa are presented in brackets.

two protons at the position 1 (4.29 ppm), the multiplet of the proton at the position 10b (5.27 ppm), and furthermore the signal of 2-H as part of the complex multiplet at 2.65-2.95 ppm. The signals of the two methyl groups at the position 6, in contrast to the initial compound (IIa) [1], appear in the form of two singlets at 1.0 and 1.50 ppm for methyl groups. The picture of the aromatic part of the PMR spectrum of compound (IIIa) is not that of a complex multiplet and is compressed to a broad singlet, which reflects the loss of general π-conjugation after hydrogenation. There is a characteristic band of the group in the IR spectrum at 3250 cm^{-1}. The spectrum of the alcohol (IIIb) is completely analogous to the spectrum of compound (IIIa).

The PMR spectra of compounds (IVa-e) contain singlets of the vinyl (6.32-6.43 ppm) and chelated NH (11.83-11.87 ppm) protons. The IR spectra of these compounds (0.01 M, $CHCl_3$) contain the corresponding bands of the chelated C=O (1590-1600 cm^{-1}) and NH (3110-3130 cm^{-1}) groups, as well as the absorption band of the ester group (1705-1710 cm^{-1}) which demonstrates the structure of the enaminoketoesters.

The PMR spectrum of compound (IVf) contains singlets in the region of 5.50 and 9.85 ppm, comprising approximately one proton according to the total integral. That indicates that the compound (IVf) exists as the equilibrium mixture of two forms – the enamine and the azomethine [11]. Since 1-benzyl-3,4-dihydroisoquinolines exist in the azomethine form [1, 12], then, in the given case, the appearance of the enamine form may be determined by the presence of conditions favorable for H-chelation. The IR spectrum of compound (IVf), insoluble in CCl_4 and $CHCl_3$, taken in mineral oil, indicates preference for the enamine form under these conditions.

The spectra of the enaminoketoamides (Va,b) recall the spectra of the corresponding initial esters. In contrast to the initial substances, the PMR spectra of the amides contain signals corresponding to the piperidine and morpholine rings, and the IR spectra contain the band of the amide group at 1630 cm^{-1}. The PMR spectra of the tetracarbonyl compounds (VIa,b) contain the corresponding signals of the R^4 groups, and do not contain signals of the HC= and NH groups of the initial substances. The IR spectra of the ketoesters (VIa,b) have the corresponding bands of four carbonyl groups.

The PMR spectra of compound (VII) contains signals of the isopropyl group (1.23 d and 4.92 q). That indicates that the ester group is not affected in the course of the reaction with o-aminophenol, and the reaction proceeds at the ketone carbonyl. The spectrum contains singlets of the HC= (6.18 ppm), OH, and NH (9.74 and 11.50 ppm) groups. The IR spectrum contains bands at 1700 cm^{-1} (C=O ester), 3100 cm^{-1}, and 3350 cm^{-1} (NH and OH). In contrast to the initial substance

TABLE 2. PMR and IR Spectral Parameters of the Compounds Synthesized

Compound	PMR spectrum, δ, ppm					IR spectrum, ν, cm^{-1}
	1-H(2H)	3(5)-$(R^2)_2$	4(6)-CH_2	aromatic protons, m	other signals	
1	2	3	4	5	6	7
IIc	5,83 s	1,48 (br.s, 8H)	2,83 s	7,35...8,45	–	1700, 1730 (C=O)
IId		*	*	6,83...7,22	0,82...1,34 br.t ($4CH_3CH_2$)	1700, 1735 (C=O)
IIIa	4,29 m,	1,0 c, 1,50 s	2,65...2,95	7,16	2,65...2,95 (m,2-H), 5,27 (m,10b-H)	1650 (C=O), 3250 (OH)
IIIb	4,33 m,	1,22...1,90 m,	2,60...3,05 m,	7,13	2,65...2,95 (m,2-H), 5,28 (m,10b-H)	1660 (C=O), 3300 (OH)
IVa	6,33 s	1,19 s	2,74 s	7,11...7,70	3,72 (s,CH_3O), 11,87 (s, NH)	1600, 1705 (C=O), 3110 (NH)
Ivd	6,32 s	1,27 s	2,76 s	6,61 s, 7,17 s	1,34 (d, $2CH_3$–CH), 3,88 (s,$2CH_3O$), 5,10 (q, CHO), 11,85 (s, NH)	1590, 1710 (C=O), 3130 (NH)
IVe	6,43	1,71 (br.s, 8H)	2,90 s	7,13...7,79	1,30 (d, $2CH_3$–CH), 5,30 (q, CH–O), 11,83 (s, NH)	1600, 1720 (C=O), 3120 (NH)
IVf	5,50 s	*	*	6,37...7,30	0,82...1,36 br. t, $4CH_3CH_2$), 2,62...4,12 (m, CH_3O), 9,85 (s, NH)	1600, 1710 (C=O), 3150 (NH)
Va	5,77 s	1,27 s	2,82 s	7,10...7,72	1,58 (br. s, $3CH_2$), 3,53 (m, $2CH_2$–N), 11,49 (s, NH)	1610, 1630 (C=O), 3050 (NH)
IVe	5,87 s	1,28 s	2,83 s	7,15...7,73	3,64 (br. s, $4CH_2$), 11,24 (s, NH)	1605, 1630 (C=O), 3030 (NH)
Va	–	1,52 s	2,87 s	7,28...8,51	3,84 (s, CH_3O)	1690, 1700, 1705, 1732 (C=O)
VIb	–	1,50 s	2,96 s	7,25...8,55	1,27 (d, $2CH_3$–CH), 5,14 (q, CHO)	1684, 1696, 1704, 1736 (C=O)
VII	6,18 s	1,12 s	2,88 s	6,70...8,16	1,23 (d, $2CH_3$–CH), 4,92 (q, CH–O), 9,74 s and 11,50 s (NH and OH)	1700 (C=O), 3100 (NH), 3350 (OH)
VIII	6,36 s	1,24 s	2,47 s	7,15...7,79	9,48 s, 9,81 br. s, 11,42 s (NH groups)	1630 (C=O), 3220, 3250, 3300 (NH)

*The signals of these groups, as well as the unsymmetrical quadruplet $4CH_2O$, form multiplets at 2.77-4.35 ppm [compound (IId)] and 2.62-4.12 ppm [compound (IVf)].

TABLE 3. Data of the Elemental Analysis of the Compounds Synthesized

Compound	Found, %			Empirical formula	Calculated, %		
	C	H	N		C	H	N
IIc	75,7	5,8	5,4	$C_{16}H_{15}NO_2$	75,9	6,0	5,5
IId	69,1	6,4	2,3	$C_{26}H_{29}NO_6$	69,2	6,5	2,2
IIIa	72,5	7,3	6,1	$C_{14}H_{17}NO_2$	72,7	7,4	6,1
IIIb	74,5	7,3	5,5	$C_{16}H_{19}NO_2$	74,7	7,4	5,4
IVa	69,4	6,5	5,4	$C_{15}H_{17}NO_3$	69,5	6,6	5,4
IVd	65,6	7,1	4,0	$C_{19}H_{25}NO_5$	65,7	7,3	4,0
IVe	72,8	7,4	4,5	$C_{19}H_{23}NO_3$	72,8	7,4	4,5
IVf	57,0	5,7	17,1	$C_{27}H_{33}N_7O_7$	57,1	5,8	17,3
Va	72,9	7,6	9,1	$C_{19}H_{24}N_2O_2$	73,0	7,7	9,0
Vb	68,1	7,6	8,7	$C_{18}H_{24}N_2O_3$	68,3	7,7	8,9
VIa	65,1	4,7	4,6	$C_{17}H_{15}NO_5$	65,2	4,8	4,5
VIb	66,8	5,5	4,2	$C_{19}H_{19}NO_5$	66,9	5,6	4,1
VII	72,9	6,7	7,5	$C_{23}H_{26}N_2O_3$	73,0	6,9	7,4
VIII	61,3	6,8	25,7	$C_{14}H_{19}N_5O$	61,5	7,0	25,6

(IVc), the PMR spectrum of compound (VIII) lacks signals of the isopropyl group and contains singlets of the NH groups (9.48, 9.81, and 11.42 ppm), corresponding to the structure formed by the substitution of the two groups – the ketone and the ester. The IR spectrum of the hydrazone (VIII) has absorption bands of the hydrazide carbonyl (1630 cm^{-1}) and NH groups (3230, 3250, and 3300 cm^{-1}).

EXPERIMENTAL

The PMR spectra were registered on the Tesla BS-587A instrument (80 MHz) using $CDCl_3$ for the compounds (IIc,d), (IVa-e), (Va,b), and (VIa,b), and using DMSO-D_6 for all remaining compounds. The internal standard was HMDS. The IR spectra were taken on the Specord M-82 instrument for the ketones (VIa,b) and the UR-20 for the remaining compounds in $CHCl_3$ at the concentration of 0.01 M for the compounds (IIc,d), (IVa-e), (Va,b), and (VIa,b), and in mineral oil for the remaining compounds. Monitoring of the course of reactions was accomplished by the method of TLC on plates of Silufol UV-254 in the 1:3:6 system of acetone–ethanol–chloroform. Development was effected with bromine vapor.

Substances were recrystallized from benzene for (IIc,d), acetonitrile for (IIIb), hexane for (IVa), petroleum ether (70-100°C) for (IVe,f) and (Va,b), and from isopropyl alcohol for all the remaining compounds.

The data of the elemental analysis for C, H, and N correspond with the calculated data.

2,3-Dioxo-5,5-(R^2)$_2$-8,9-(R^1)$_2$-1-R^3-2,3,5,6-tetrahydropyrrolo[2,1-a]isoquinolines (IIc,d) and 2,3-Dioxo-5,5-(R^2)$_2$-8,9-(R^1)$_2$-1-($COCO_2R^4$)-2,3,5,6-tetrahydropyrrolo[2,1-a]isoquinolines (VIa,b). To 0.86 ml (10 mmole) of oxalyl chloride in 50 ml of abs. ether at 0-5°C is added, in the course of 15 min, the mixture of 10 mmole of the enamine (Ic,d) or (IVa,c) and 2.76 ml (20 mmole) of triethylamine in 150 ml of ether. The reaction mixture is brought to 20°C and left at this temperature for 30 min more. The precipitated residue is filtered off, washed with water, dried, and recrystallized.

2-Hydroxy-3-oxo-5,5-(R^2)$_2$-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolines (IIIa,b). To the boiling solution of 10 mmole of compound (IIa,c) in 50 ml of abs. methanol is added 0.95 g (25 mmole) of sodium borohydride. The solution having a dark cherry color is thereby instantly decolorized. A residue is precipitated when the mixture is cooled to 20°C. The mixture is diluted with 100 ml of water, and the residue is filtered off, dried, and recrystallized. The yields presented in Table 1 were obtained in methanol. In the remaining solvents, indicated in the paper, the yields are close to the yield in methanol (the difference not greater than 10%).

Esters (IVa-f) and Amides (Va,b) of [3,3-(R^2)$_2$-6,7-(R^1)$_2$-1,2,3,4-Tetrahydroisoquinolinidene-1]-β-R^3-pyruvic Acid. A. To the boiling solution of 10 mmole of compound (IIa-c) in 30 ml of the corresponding alcohol R^4OH, containing 5-10% of water, is added 0.95 g (25 mmole) of sodium borohydride. After the boiling of the mixture for 15-20 min, the dark cherry color disappears. The solution is cooled to 20°C and is further treated as in the case of the compounds (IIIa,b).

B. To the boiling solution of 10 mmole of the compound (IIa,c) in the corresponding abs. alcohol is added 0.23 g (10 mmole) of sodium, whereby the solution is instantly decolorized. The mixture is further treated by analogy with the method for the synthesis of the compounds (IIIa,b).

For the isolation of the amides (Va,b), 10 mmole of compound (IVa) are added to 5 ml of boiling piperidine or morpholine, and the reaction is completed after 3 min (monitoring by TLC). The mixture is cooled to 20°C, and is further treated as in the case of the compounds (IIIa,b).

The o-Hydroxyanil of Isopropyl (3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolinidene-1)pyruvate (VII). To the solution of 2.87 g (10 mmole) of the enamine (IVc) in 15 ml of glacial acetic acid are added 1.09 g (10 mmole) of o-aminophenol. The mixture is boiled for 15 min, and is further treated as in the case of the compounds (IIIa,b).

The Hydrazone of (3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolinidene-1)pyruvic Hydrazide (VIII). To the solution of 2.87 g (10 mmole) of compound (IVc) in 15 ml of ethanol are added 2 ml (40 mmole) of the 70% solution of hydrazine hydrate, and the mixture is boiled for 2 h. The precipitated residue is filtered off, dried, and recrystallized.

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