SYNTHESIS OF PYRROLO[2,1-a]ISOQUINOLINES

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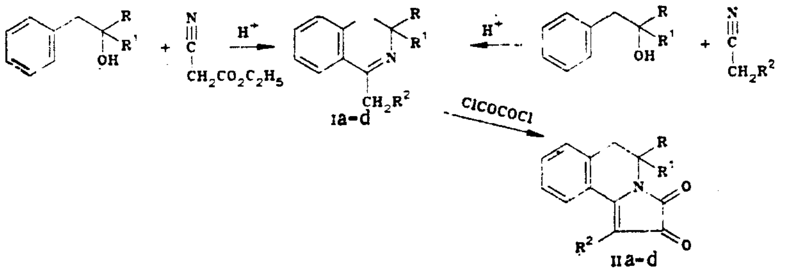
UDC 547.833.3'745'75

Enamine derivatives of 3,4-dihydroisoquinoline obtained by the Ritter reaction form 2,3-dioxo-5,5-RR^1-1-R^2-2,3,5,6-tetrahydropyrrolo[2,1-a]isoquinolines with oxalyl chloride.

Tricyclic derivatives of isoquinoline are biologically active compounds [1]. Among them pyrrolo[2,1-a]isoquinolines have up to the present time been difficult to obtain and comparatively little studied. Individual methods for synthesizing these compounds, as described in [2, 3], are protracted and give low yields.

The aim of the present work is the development of a simple general method for the synthesis of derivatives of pyrrolo[2,1-a]isoquinoline. For this purpose we investigated the reaction of enamines with oxalyl chloride [4] in relation to 3,4-dihydroisoquinoline derivatives. The initial compounds — 3,4-dihydroisoquinoline derivatives (Ia-d) — were synthesized according to the Ritter reaction by interaction of dialkylbenzylcarbinol with appropriate nitriles in a heterophase benzene—sulfuric acid medium [5].

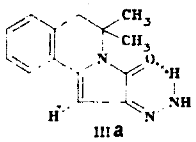
The PMR and IR spectra of compounds Ia-d correspond to the azomethine form, which is in agreement with previously obtained data [5, 6]. However, when reacting with electrophilic reagents compounds Ia-d behave as enamines with reaction taking place on the β-carbon atom of the enamine group. When 3,4-dihydroisoquinoline derivatives Ia-d react with oxalyl chloride in dioxane at 20°C in the presence of triethylamine, 2,3-dioxo-5,5-RR^1-1-R^2-2,3,5,6-tetrahydropyrrolo[2,1-a]isoquinolines (IIa-d) are formed.



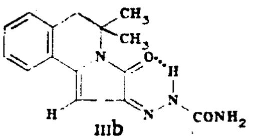
I, II a $R=R^1=CH_3$, $R^2=H$; b $R=CH_3$, $R^1=C_2H_5$, $R^2=H$; c $R+R^1=(CH_2)_5$, $R^2=H$; d $R=R^1=CH_3$, $R^2=C_6H_5$

The structure of compounds IIa-d obtained is proved by the data of PMR and IR spectroscopy. In the IR spectra of pyrralediones IIa-d there are absorption bands from stretching vibrations of lactam carbonyl in the region 1700-1705 cm^{-1}, ketone carbonyl conjugated with a double bond (1735-1742 cm^{-1}), and also an absorption band in the region 1610-1630 cm^{-1} due to the presence of a C=C bond conjugated with CO. The PMR spectra presented in Table 1 also lend positive support to the proposed structures.

When the dicarbonyl derivative IIa is reacted with hydrazine hydrate and semicarbazide, compounds IIIa, b are obtained. In their IR spectra there are absorption bands due to bonded CO (1630 cm^{-1}) and NH (3120-3130 cm^{-1}) groups, which indicates the presence of an intramolecular bond.



IIIa



IIIb

Institute of Organic Chemistry, Ural Scientific Center, Academy of Sciences of the USSR, Perm' 614600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 963-965, July, 1987. Original article submitted February 17, 1986.

0009-3122/87/2307-0790$12.50

TABLE 1. PMR Spectra of Compounds IIa-d and IIIa, b

Compound	Chemical shifts, ppm					Solvent
	1H $(C_{(1)})$ (s)	$>\overset{5}{C}<{R \atop R^1}$	2H $(C_{(6)})$ (s)	4H (Ar) (m)	2H (NH_2) (s)	
IIa	5,76	1,47, s, 6H	2,84	7,48	—	$CDCl_3$
IIb	5,68	1,23, s, 3H; 1,03, t, 3H; 1,36, q, 4H	2,84	7,45	—	$CDCl_3$
IIc	5,72	1,50, s, 10H	2,87	7,44	—	$CDCl_3$
IId	—	1,47, s, 6H	2,85	7,17 (8H)	3,90	$CDCl_3$
IIIa	6,37	1,34, s, 6H	2,80	7,12	3,90; 11,3	$CDCl_3$
IIIb*	6,50	1,37, s, 6H	2,80	7,15	6,80	DMSO-d_6

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*For compound IIIb chemical shift at 10.3 ppm [1H (NH), s].

TABLE 2. Properties of Compounds Synthesized

Compound	mp, °C*	Found, %			Empirical formula	Calculated, %			Yield, %
			H	N (Cl)		C	H	N (Cl)	
Id	208—209	75,6	7,0	4,7 (12,3)	$C_{18}H_{10}ClN$	75,6	7,1	4,9 (12,4)	87
IIa	127—128	73,8	5,7	6,3	$C_{14}H_{13}NO_2$	74,0	5,8	6,2	81
IIb	196—197	74,6	6,2	5,9	$C_{15}H_{15}NO_2$	74,7	6.3	5,8	67
IIc	165—166	76,2	6,3	5,2	$C_{17}H_{17}NO_2$	76,4	6.4	5,2	92
IId	223—224	79,0	5,5	4,5	$C_{20}H_{17}NO_2$	79,19	5,7	4,6	91
IIIa	243—245	69,5	6,2	17,5	$C_{14}H_{15}N_3O$	69,7	6,3	17,4	48
IIIb	200—202	63,1	5,6	19,9	$C_{15}H_{16}N_4O_2$	63,4	5,7	19,7	52

*Compounds Id (hydrochloride), IIa, b, and IIIb were crystallized from isopropanol; IIc from heptane; IId from acetone; IIIa from acetonitrile.

In the IR spectra of these compounds absorption bands occur in the regions 1620 (C=N) and 1605 cm^{-1} (C=C). There are also bands from NH groups — in compound IIIa at 3390 and 3295 cm^{-1} (free NH_2), in compound IIIb at 3420 and 3345 cm^{-1} as well as an adsorption band from semicarbazone CO (1685 cm^{-1}). The presence of an intramolecular hydrogen bond is confirmed by the fact that the signals from the protons of the NH groups occur at low field — 11.3 and 10.3 ppm (Table 1).

EXPERIMENTAL

PMR spectra were recorded on a PC-60 (60 MHz) instrument with HMDS as internal standard. IR spectra of solutions (0.01 moles/liter) were recorded in $CHCl_3$ on a UR-20 spectrophotometer. Compounds Ia-c have been described previously [5]. The properties of compounds Id, IIa-d, and IIIa, b are given in Table 2.

1-Benzyl-3,3-dimethyl-3,4-dihydroisoquinoline (Id). To 1.15 ml (10 mmole) of benzyl cyanide in 20 ml of benzene at a temperature not exceeding 5°C was added dropwise 4 ml of concentrated H_2SO_4. The cooling was removed and 1.50 ml (10 mmole) of dimethylbenzylcarbinol in 20 ml of benzene was rapidly introduced. The temperature was increased to 80°C, the mixture was boiled for 2 h and 30 min with vigorous agitation and cooled, the reaction mass was poured on to 30 g of ice, and the benzene layer was separated. The aqueous phase was neutralized with a 25% solution of ammonia. The base that separated out was extracted with ether and dried with NaOH. The extraction agent was distilled off, the residue was dissolved in ethyl acetate, and after gaseous HCl was passed through the hydrochloride was obtained (Table 2). IR spectrum of base (CCl_4): 1620 cm^{-1} (C=N). PMR spectrum of base (CCl_4): 1.18 (6H, s, $2CH_3$—$C_{(3)}$); 2.57 (2H, s, CH_2—$C_{(4)}$); 3.83 (2H, s, CH_2—$C_{(1)}$); 7.10 ppm (4H, m, Ar).

2,3-Dioxo-5,5-RR^1-1-R^2-2,3,5,6-tetrahydropyrrolo[2,1-a]isoquinolines (IIa-d). To 0.86 ml (10 mmole) of oxalyl chloride in 20 ml of dioxane was added over the course of 30 min with agitation a solution of 10 mmole of base Ia-d mixed with 2.76 ml (20 mmole) of triethylamine in 30 ml of dioxane. The mixture was agitated for a further 1 h, diluted with 300 ml of water, and the precipitate formed was filtered off, dried, and recrystallized.

2-Hydrazono-3-oxo-5,5-dimethyl-2,3,5,6-tetrahydropyrrolo[2,1-a]isoquinoline (IIIa). A mixture of 2.27 g (10 mmole) of compound IIa and 0.68 ml (15 mmole) of hydrazine hydrate was boiled in ethanol for 3 h. On cooling, hydrazone IIIa formed a precipitate, which was filtered off, dried, and recrystallized.

2-Semicarbazono-3-oxo-5,5-dimethyl-2,3,5,6-tetrahydropyrrolo[2,1-a]isoquinoline (IIIb). A 2.27-g (10 mmole) portion of pyrroledione IIa was dissolved on heating in 30 ml of 70% ethanol; 1.12 g (10 mmole) of semicarbazide hydrochloride was dissolved in 20 ml of water and 1.5 g of sodium acetate and the aqueous alcoholic solution of compound IIa were added. The mixture was agitated and boiled for 2 h. On cooling, substance IIIb precipitated out, and it was filtered off, dried, and recrystallized.

LITERATURE CITED

1. W. J. Houligan, US Patent No. 4100165; Ref. Zh. Khim., 40187P (1979).
2. S. G. Agbalyan and R. D. Khachikyan, Khim. Geterotsikl. Soedin., No. 7, 943 (1979).
3. S. G. Agbalyan, R. D. Khachikyan, and K. K. Lulukyan, Arm. Khim. Zh., 29, 527 (1976).
4. T. Sano, I. Holiguchi, and Y. Tsuda, Heterocycles, 3, 65 (1973).
5. V. S. Shklyaev, B. B. Aleksandrov, M. I. Vakhrin, and G. I. Legotkina, Khim. Geterotsikl. Soedin., No. 11, 1560 (1983).
6. Yu. S. Andreichikov, V. S. Shklyaev, B. B. Aleksandrov, and Yu. V. Ionov, Khim. Geterotsikl. Soedin., No. 3, 420 (1982).

DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN BRIDGEHEAD POSITIONS.

15.* REACTIONS OF BENZO[b]-1,4-DIAZABICYCLO[2.2.2]OCTENE MONOQUATERNARY SALT DERIVATIVES WITH NUCLEOPHILIC REAGENTS

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UDC 547.863.13'895:543.878:541.127

Monoquaternary salt derivatives of benzo[b]-1,4-diazabicyclo[2.2.2]octene react with piperidine and sodium methoxide or 4-tert-butylthiophenoxide to give primarily N,N-disubstituted tetrahydroquinoxalines. Rate constants have been measured for these bimolecular reactions. Based on their levels of reactivity, these quaternary salts behave as typical alkylating agents.

Methyl iodide salts of cyclic amines can react via three pathways with sodium methoxide: demethylation, ring opening via a Hofmann reaction, and ring opening via nucleophilic substitution [2, 3]. The third pathway predominates as the ring strain of the cyclic amine increases [2]. Quaternary salt derivatives of benzo[b]-1,4-diazabicyclo[2.2.2]octene contain strained bicyclic diamine fragments, and thus would be expected to react with nucleophilic reagents primarily via the ring opening pathways. This is indicated indirectly by the earlier observation [4] that an equilibrium mixture of 1-(2-bromoethyl)-1,2,3,4-tetrahydroquinoxaline and benzo[b]-1,4-diazabicyclo[2.2.2]octene (I) is formed when the latter is heated in concentrated hydrobromic acid.

Our goal in the present paper was to determine the main reaction pathway and obtain a quantitative estimate of the reactivities of quaternary salt derivatives of benzo[b]-1,4-diazabicyclo[2.2.2]octene with nucleophilic reagents.

Methyl iodide, benzyl bromide and 4-nitrobenzyl bromide derivatives of benzo[b]-1,4-diazabicyclo[2.2.2]octene (compounds II, IV, and V) were prepared by treatment of compound

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*For communication 14, see [1].

Novosibirsk Institute of Bioorganic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 966-972, July, 1987. Original article submitted January 24, 1986.

0009-3122/87/2307-0792$12.50