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SYNTHESIS AND ALKYLATION OF CYCLIC AZOMETHINES — 3-SPIRO- AND 3,3-DIMETHYL-3,4-DIHYDROISOQUINOLINES

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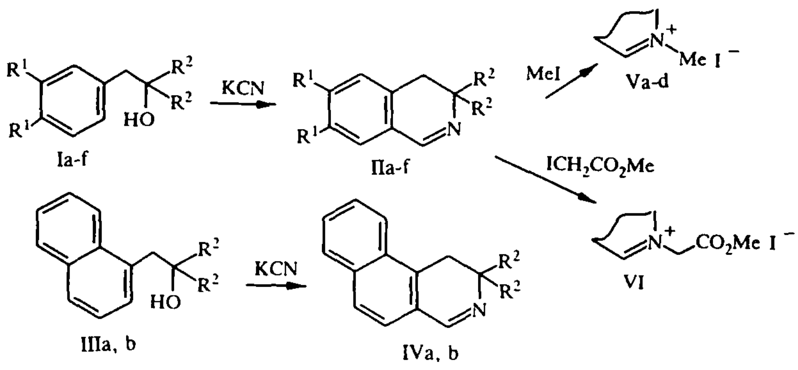
The cyclic imines 3,3-dimethyl-, 3-spiro-3,4-dihydro-, and benzo[f]isoquinolines were synthesized, and their quaternary salts were obtained.

Earlier we obtained and investigated cyclic imines of the 3,3-dimethyl-3,4-dihydroisoquinoline series [1-3]. The method for the production of these compounds based on the Ritter reaction has wide possibilities. In particular, it makes it possible to obtain spiroannelated [4, 5] and benzo[*f*]isoquinolines [6], which are of undoubted interest as biologically active compounds. Until now, 3,4-dihydroisoquinolines with such structures have been unknown. The aim of the present work was to study the possibility of synthesizing these compounds.

Cyclization to an isoquinoline ring by the Ritter reaction with hydrocyanic acid as nitrile component was first realized by Wollweber and Hiltmann [7]. In [1] we proposed a method of cyclization suitable for preparative purposes. Here the alcohols (Ia) (R^1 = H, R^2 = Me) and (Ib) (R^1 = OMe, R^2 = Me), which give the respective isoquinolines (IIa, b) during cyclization, were used as starting compounds.



Investigations showed that the reaction of the tertiary carbinols (Ia-c) with potassium cyanide in the presence of sulfuric acid also leads to the corresponding isoquinolines (IIc-f).

The characteristics of the compounds obtained for the first time are given in Table 1. As seen from the data in the table, the yield of the cyclization product depends on the nature of the aromatic ring; in the case of activation by methoxy groups [carbinols (Id, f)] the yield is increased by approximately 1.5 times compared with the inactivated ring [carbinols (Ic, e)].

As expected, analogous cyclization with the naphthalene-containing carbinols (IIIa, b) takes place smoothly with the formation of benzo[*f*]isoquinolines (IVa, b) (Table 1). The yields of the products reflect the increased activity of the naphthalene ring compared with the inactivated benzene ring [compounds (IIc, e)] in substitution reactions.

It should be noted that in the case of an inactivated aromatic ring the reactions of the respective carbinols with other nitrile components, such as benzyl cyanides [8, 9] and the esters [10] or amides [5, 11] of cyanoacetic acid, lead to larger preparative yields than in the case of hydrocyanic acid, where lesser stabilization of the nitrile intermediate evidently occurs [12].

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	R^1	$C(R^2)_2$	Found, %				Molecular formula	Calculated, %				mp, °C	Yield, %
			C	H	N	Cl(S)		C	H	N	Cl(S)		
IIc	H	$C(CH_2)_4$	70,3	7,1	6,4	15,8	$C_{13}H_{15}N \cdot HCl$	70,4	7,3	6,3	16,0	183...184	37
IId	OCH_3	$C(CH_2)_4$	63,7	7,1	5,1	12,4	$C_{15}H_{19}NO_2 \cdot HCl$	63,9	7,2	5,0	12,6	191...192	63
IIe	H	$C(CH_2)_5$	71,1	7,6	6,0	14,8	$C_{14}H_{17}N \cdot HCl$	71,3	7,7	5,9	15,0	210...211	41
IIf	OCH_3	$C(CH_2)_5$	64,8	7,8	4,8	11,8	$C_{16}H_{21}NO_2 \cdot HCl$	65,0	7,9	4,7	12,0	186...187	62
IVa	–	$C(CH_3)_2$	58,5	5,5	4,6	10,3	$C_{15}H_{15}N \cdot H_2SO_4$	58,6	5,6	4,6	10,3	181...183	73
IVb	–	$C(CH_2)_4$	75,0	6,6	5,3	12,9	$C_{17}H_{17}N \cdot HCl$	75,1	6,6	5,1	13,0	203...205	64
Va	H	$C(CH_3)_2$	47,7	5,3	4,8	–	$C_{12}H_{16}IN$	47,9	5,4	4,7	–	116...118	90
Vb	OCH_3	$C(CH_3)_2$	46,5	5,4	3,8	–	$C_{14}H_{20}INO_2$	46,6	5,6	3,9	–	217...218	95
Vc	H	$C(CH_2)_4$	51,2	5,3	3,8	–	$C_{14}H_{18}IN$	51,4	5,5	3,9	–	167...168	38
Vd	H	$C(CH_2)_5$	52,7	5,8	3,9	–	$C_{15}H_{20}IN$	52,8	5,9	4,1	–	200...201	51
VI	OCH_3	$C(CH_3)_2$	45,6	5,1	3,5	–	$C_{16}H_{22}INO_4$	45,8	5,3	3,3	–	176 (decomp.)	58

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

Compound	PMR spectrum, δ, ppm							IR spectrum, ν, cm^{-1}
	(R^2)$_2$-C$_3$	s, 2H, CH$_2$—C$_4$	N—CH$_3$(CH$_2$), s	2CH$_3$O, 2s	Ar	s HC=N	s, NH$^+$ salt	
IIc	1,28...2,03m, 4CH$_2$	2,83	—	—	7,18...7,93 m	8,03	15,10	1630 (C=N)
IId	1,40...2,25m, 4CH$_2$	2,95	—	3,80; 3,82	6,40 s, H–C5; 6,62 s, H–C$_8$	7,93	14,60	1625 (C=N)
IIe	1,25...2,05m, 5CH$_2$	2,86	—	—	7,20...7,90 m	8,01	15,05	1630 (C=N)
IIf	1,38...2,30m, 5CH$_2$	2,96	—	3,81; 3,83	6,38 s, H–C$_5$; 6,57 s, H–C$_8$	7,92	14,80	1630 (C=N)
IVa	1,25 s, 2CH$_3$	3,00	—	—	7,45...7,83 m	8,02	—*	1625 (C=N)
IVb	1,52...1,75m, 4CH$_2$	2,97	—	—	7,42...7,72 m	7,80	15,20	1625 (C=N)
Va	1,35 s, 2CH$_3$	3,05	3,63	—	7,18...8,10 m	8,90	—	—
Vb	1,31 s, 2CH$_3$	3,03	3,56	3,71; 3,93	7,00 c, H–C$_5$; 7,45 c, H–C$_8$	8,83	—	—
Vc	1,37...2,15m, 4CH$_2$	3,07	3,57	—	7,25...8,10 m	8,97	—	—
Vd	1,35...2,20m, 5CH$_2$	3,04	3,60	—	7,30...8,05 m	9,02	—	—
VI	1,37s, 2CH$_3$	3,05	5,06	—†	6,60 s, H–C$_5$; 7,53, H–C$_8$	9,66	—	1740 (C=O)

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*In exchange of the solvent with water.

†The three OCH$_3$ groups appear in the form of the corresponding singlets at 3.80, 3.89, and 3.97 ppm.

In order to characterize the obtained imines, we synthesized their quaternary salts. The reaction leading to the production of the methiodides of the imines (IIa, b, e) was similar to that described earlier in [13]. The products of this reaction are the corresponding N-methylisoquinolinium iodides (Va-d) (Table 1). The reaction of the isoquinoline (IIb) with methyl iodoacetate gives the stable salt (VI). Structures of type (VI) are of interest as starting compounds for the production of isoquinolinium ylides [14].

Except for the colorless crystalline naphthalene derivatives (IVa, b), the bases of the obtained imines are liquids. The characteristics of the azomethines in Table 1 are given for their stable salts. The iodides (Va-d, VI) form yellow crystals.

The PMR spectra of the compounds described for the first time (Table 2) were recorded in deuterochloroform both for the bases of the azomethines (IIa-f) and for their salts except for compound (IVa), the sulfate of which is only soluble in DMSO-d_6. The spectra of the azomethines (IIc-f, IVa, b) given in the table apply to the bases of these compounds except for the signal of NH^+, the position of which is given for the respective protic salts. The azomethine structure of the bases is proved by the presence of a singlet in the region of 7.80-8.03 ppm (HC=N) [1]. The IR spectra of the bases contain a band in the region of 1625-1630 cm^{-1} (C=N). The PMR spectra of the salts of the imines, recorded in deuterochloroform, contain a singlet in the region of 14.60-15.20 ppm (NH^+).

Quaternization of the imines [the salts (Va-d), in DMSO-d_6] shifts the singlet of the proton of the azomethine group by an average of 1 ppm (8.83-9.02 ppm). In the spectrum of compound (VI), recorded in deuterochloroform, the signal of $HC=N^+$ is observed in the region of 9.66 ppm. In this case, the downfield shift compared with the initial imine [1] amounts to 1.70 ppm, due to the inductive effect of the ester group.

EXPERIMENTAL

The PMR spectra were recorded on a Tesla BS-587A instrument (80 MHz) with HMDS as internal standard. The IR spectra were recorded in Vaseline oil on a UR-20 instrument. The reactions were monitored by TLC on Silufol UV-254 plates in the 1:3:6 acetone—ethanol—chloroform system with bromine vapor as developer.

The compounds were recrystallized from dioxane (IId), ethyl acetate (IIf), and isopropyl alcohol (all the others).

3,3-(R^2)$_2$-6,7-(R^1)$_2$-3,4-Dihydroisoquinolines (IIc-f) and 3,3-(R^2)$_2$-Benzo[*f*]isoquinolines (IVa, b). To a mixture of 0.85 g (13 mmole) of potassium cyanide and 10 mmole of the respective carbinol (Ic-f) or (IIIa, b) in 50 ml of benzene at a temperature not above 5°C, we added dropwise 4 ml of concentrated sulfuric acid [compounds (IIc, e, IVa, b)] or a mixture of 2 ml of glacial acetic acid and 4 ml of concentrated sulfuric acid [the azomethines (IId, f)]. The mixture was heated with vigorous stirring for 40 min at 60-70°C [(IId, f) and (IVa, b)] or 1.5 h at 80°C [compounds (IIc, e)]. It was then cooled and poured onto 50 g of ice, and the benzene layer was separated. The precipitate of the water-insoluble sulfate (IVa) that separated was immediately filtered off, dried, and recrystallized. In the case of all the other substances, the aqueous phase was neutralized with ammonia. The obtained bases were extracted with ether, and the extract was dried with potassium carbonate. Approximately a third of the ether was distilled in order to remove the traces of ammonia, after which the corresponding hydrochlorides were obtained by passing dry hydrogen chloride. The hydrochlorides were filtered off, dried, and recrystallized.

3,3-(R^2)$_2$-6,7-(R^1)$_2$-N-Methyl-3,4-dihydroisoquinolinium Iodides (Va-d) and 3,3-Dimethyl-6,7-dimethoxy-N-(methoxycarbonylmethyl)-3,4-dihydroisoquinolinium Iodide (VI). A mixture of 10 mmole of the respective base and 0.8 ml (13 mmole) of methyl iodide or 2.40 g (12 mmole) of methyl iodoacetate in 5 ml of acetone was tightly covered with a stopper and left at 20°C for 4 h. The precipitate was filtered off, dried, and recrystallized.

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