DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN NODAL POSITIONS.

14.* SYNTHESIS OF DIBENZO[1',2'-b,e]-1,4-DIAZABICYCLO[2.2.2]OCTADIENES CONTAINING A TERTIARY AMINO GROUP IN THE AROMATIC RING

G. V. Shishkin and V. N. Sil'nikov

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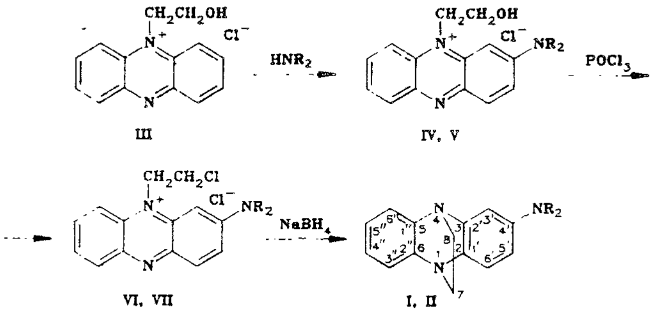
The corresponding 2-amino derivatives of phenazinium salts were obtained by the action of dimethylamine and morpholine on N-(2-hydroxyethyl)phenazinium chloride. The subsequent exchange of the hydroxyl group for chlorine and the reductive cyclization of 2-amino derivatives of N-(2-chloroethyl)phenazinium salts leads to 4'-aminodibenzo[1',2'-b,e]-1,4-diazabicyclo[2.2.2]octadienes, together with unsubstituted dibenzo-[b,e]-1,4-diazabicyclo[2.2.2]octadiene and the corresponding 2-aminophenazines.

It was shown in [2] that in the reductive cyclization of N-2-haloethyl-derivatives of phenazine, dibenzo[b,e]-1,4-diazabicyclo[2.2.2]octadiene is formed. It was of interest to explore the possibility of using this approach for the preparation of its amino derivatives

The synthesis of 4'-dimethylamino- and 4'-morpholinodibenzo[1',2'-b,e]-1,4-diazabicyclo-[2.2.2]octadienes (I and II) is carried out, starting from N-(2-hydroxyethyl)phenazinium chloride (III) [2] according to the scheme



I, IV, VI R=CH_3; II, V, VII $NR_2=N(CH_2CH_2)_2O$

N-(2-Hydroxyethyl)phenazinium chlorides substituted at the 2-position (IV, V) were obtained in a 60-70% yield using the nucleophilic substitution of hydrogen, characteristic of phenazinium salts [3]. The entry of the substituent into the 2-position in the ring was confirmed by the PMR spectra (Table 1). The IR spectra of these compounds contain a characteristic set of bands in the 750-915 cm^{-1} region, in agreement with the data in [4].

It was difficult to purify compounds IV and V by crystallization and, therefore, the well-crystallizable 2-dimethylamino- and 2-morpholino-10-(2-hydroxyethyl)phenazinium perchlorates (IVa and Va) were obtained, whose analytical and spectral characteristics coincided with those expected.

The exchange of the hydroxylic groups for chlorine in compounds IV and V with the formation of derivatives VI and VII was accomplished by the action of phosphorus oxychloride, and the analytical samples (Table 2) were prepared by converting these salts into perchlorates (VIa and VIIa).

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*For Communication 13, see [1].

Novosibirsk Institute of Bioorganic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1658-1661, December, 1986. Original article submitted July 9, 1985.

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The synthesis of 4'-amino[1',2'-b,e]-1,4-diazabicyclo[2.2.2]octadienes (I, II) was carried out by the method described in [2], by the action of sodium borohydride in sulfolane on compounds VI and VII. Sulfolane was used instead of diglyme, because of the poorer solubility of compounds VI and VII in the latter solvent. The desired end compounds I and II were isolated by preparative TLC in a 15-25% yield. As in the synthesis of unsubstituted dibenzo[b,e]-1,4-diazabicyclo[2.2.2]octadiene [2], the by-products in this reaction are dealkylation products: 2-dimethyl amino- and 2-morpholinophenazine (VIII and IX). Dibenzo-[b,e]-1,4-diazabicyclo[2.2.2]octadiene, the product of a deamination reaction, in a yield of up to 20%, and inappreciable amounts of phenazine, were isolated from the reaction mixtures. Heating compound V under the reaction conditions caused the appearance of N-(2-hydroxyethyl)phenazinium chloride, 2-morpholinophenazine, and phenazine in the reaction mixture, while 4'-morpholinodibenzo[1',2'-b,e]-1,4-diazabicyclo[2.2.2]octadiene was found to be stable.

In the mass spectra of compounds I and II, besides the molecular ion peak, a fragmentary ion with a mass M-28 is recorded, which indicates splitting of the ethylene bridge, in analogy to [2]. In the PMR spectra (Table 1), a singlet (4H, 3.18 ppm) is observed, which was assigned to the ethylene bridge protons, as well as a doublet in the weak field due to 3-H (1H, $J_{5'-3'}$ = 2.5 Hz), while the proton in the 5'-position gives a signal in the form of two doublets ($J_{3-5'}$ = 2.5 and $J_{3'-2'}$ = 8.5 Hz), which confirms the presence of a substituent at the 4'-position. The remaining aromatic protons give a multiplet with intensity of 5H.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer in KBr tablets, the UV spectra — on a Specord UV-vis spectrophotometer, in ethanol, and the PMR spectra on a Bruker-HA-90 spectrometer, using HMDS as internal standard. The mass spectra were obtained on MS-902 and Finnigan-MAT-8200 spectrometers. Thin layer chromatography (TLC) was carried out on Silufol UV-254 plates in systems: tert-butanol—methyl ethyl ketone—formic acid—water, 8:6:3: (A) and chloroform—acetone, 10:3 (B).

2-Dimethylamino-10-(2-hydroxyethyl)phenazinium Chloride (IV). A 5-ml portion of a 10% methanolic solution of dimethylamine is added at 20°C, with stirring, to 1.4 g (5.4 mmoles) of compound III dissolved in 15 ml of methanol. The precipitate of compound IV that separated is filtered, and an additional amount of the product is precipitated from filtrate by ether. The precipitates are combined and washed with ether. After recrystallization from a 1:1 alcohol—iso-amyl acetate mixture, yield 1 g.

TABLE 1. PMR and UV Spectra of Compounds Synthesized

Compound	PMR spectrum, ppm				UV spectrum (in ethanol, λ_{max}, nm (log ϵ)
	3'-H (1-H)	remaining aromatic H atoms	CH_2CH_2	NR_2	
I†	6,80 d	7,21 m, 6,40 d.d	3,18 s	2,85 s	213 (4,36), 272 (4,15)
II*	6,91 d	7,16 m, 6,57 d.d	3,17 s	3,02 t 3,75 t	215 (4,26), 260 (3,76)
IVa†	(6,85 s)	8,06 m	5,05 t 4,01 t	3,54 s	239 (4,49), 299 (4,52), 385 (3,98), 398 (4,02), 560 (4,20)
Va†	(7,14 s)	8,10 m	5,08 t 3,99 m	3,99 m 3,88 t	238 (4,53), 299 (4,54), 388 (4,02), 405 (4,03), 555 (4,22)
VIa†	(6,85)	8,08 m	5,38 t 4,27 t	3,45 s	238 (4,56), 297 (4,50), 385 (4,00), 398 (4,02), 560 (4,20)
VIIa†	(7,14 s)	8,09 m	5,47 t 4,21 t	4,06 t 3,87 t	239 (4,44), 298 (4,46), 390 (3,99), 405 (4,00), 555 (4,19)

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*PMR spectra were recorded in $CDCl_3$.

†PMR spectra were recorded in DMSO-D_6.

TABLE 2. Characteristics of Synthesized Compounds

Compound	mp, °C	Rf (system A)	Found					Empirical formula	Calculated					Yield, %
			C, %	H, %	Cl, %	N, %	M		C, %	H, %	Cl, %	N, %	M	
I	114—116	0,48	76,4	7,01	—	16,4	221	$C_{16}H_{17}N_3$	76,4	6,81	—	16,7	221	25
II	139—142	0,62	73,3	6,49	—	14,1	293	$C_{18}H_{19}N_3O$	73,7	6,52	—	14,3	293	15
IVa	255—257	0,36	63,4	6,21	11,6	13,9	—	$C_{16}H_{18}ClN_3O$	63,3	5,93	11,7	13,8	—	61*
Va	208—210	0,30	52,7	4,75	9,47	10,3	—	$C_{18}H_{20}Cl_2N_3O_5$	52,7	4,92	9,20	10,3	—	70*
VIa	217—219	0,42	49,8	4,26	18,3	10,8	—	$C_{16}H_{17}Cl_2N_3O_5$	49,8	4,43	18,4	10,9	—	66*
VIIa	265—267	0,46	50,4	4,34	16,3	9,81	—	$C_{18}H_{19}Cl_2N_3O_5$	50,5	4,47	16,5	9,81	—	76*

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*Indicated for chlorides.

2-Morpholino-10-(2-hydroxyethyl)phenazinium chloride (V) was obtained by the method described above from 1.4 g (5.4 mmoles) of compound III and 0.3 ml of morpholine in a yield of 1.3 g.

2-Dimethylamino-10-(2-chloroethyl)phenazinium Chloride (VI). A solution of 1 g (3.1 mmoles) of compound IV in 20 ml of phosphorus oxychloride is boiled under reflux for 1.5 h. Excess of phosphorus oxychloride is distilled off and the residue is dissolved in 20 ml of alcohol. The solution is boiled for 20 min, then filtered, evaporated, the residue once again dissolved in 20 ml of alcohol, and compound VI is precipitated by ether in the form of a viscous mass. After recrystallization from a 1:1 alcohol—iso-amyl acetate mixture, 0.7 g of compound VI is obtained.

2-Morpholino-10-(2-chloroethyl)phenazinium chloride (VII) was obtained by the method described above for compound VI, from 1 g (2.9 mmoles) of compound V in a yield of 0.8 g.

4'-Dimethylaminodibenzo[1',2'-b,e]-1,4-diazabicyclo[2.2.2]octadiene (I). A 0.45-g portion (1.3 mmole) of compound VI is gradually added with constant stirring to a suspension of 0.2 g sodium borohydride in 30 ml of dry sulfolane. The mixture is held at 20°C until gas evolution ceases. It is then heated to 70°C and held in argon atmosphere for 30 min, while the temperature is raised to 120°C, and held at this temperature for 4 h. The reaction mixture is cooled and 60 ml of a 1:1 dioxane—ether mixture are added. The precipitate is filtered, washed with ether, and from the combined filtrate the mixture of dioxane and ether is distilled off. A 20-ml portion of methanol is added to the residue, and the solution obtained is passed through a column (2 × 40 cm) with KRS-2p in H^+ form. The column is washed with methanol and the material is eluted with 2 N NH_3 in methanol. The eluate is evaporated, the residue is dissolved in 5 ml of methanol and deposited on a plate (35 × 25 cm) with a silica gel L 100/160 layer. The separation is carried out in system B, and the zones are detected in UV light. The colorless zone with Rf 0.2 contains compound I, the orange zone with Rf 0.35 contains compound VIII, and the colorless zone with Rf 0.5 contains unsubstituted dibenzo[b,e]-1,4-diazabicyclo[2.2.2]octadiene (X). The above zones are removed from the column and the corresponding products are desorbed from them by a chloroform—methano mixture. Compound I is crystallized from pentane to yield 0.09 of I after recrystallization. Compounds VIII and X are crystallized from hexane to yield 0.04 g of compound VIII, mp 154-156°C (155-156°C [5]), and 0.05 g of compound X, mp 147-149°C (147-149°C [2]).

4'-Morpholinodibenzo[1',2'-b,e]-1,4-diazabicyclo[2.2.2]octadiene (II) is obtained by the method described above for compound I, from 0.45 g of compound VII. From the plate, zones are removed with Rf 0.45 (contains compound IX), Rf 0.5 (contains X), and Rf 0.3 (contains II). Compound II is crystallized from pentane in a yield of 0.06 g, and compound IX is crystallized from hexane in a yield of 0.08 g, mp 174-176°C (172-173°C [6]).

Analytical samples of compounds I and II are isolated by additional crystallization from pentane. Compounds IV-VII were identified as perchlorates obtained by the action of a calculated amount of a 10% solution of lithium perchlorate in water on concentrated aqueous solution of these compounds (yield 90-95%).

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α-DIMETHYLAMINOMETHYLENE DERIVATIVES OF SUCCINIMIDE AND GLUTARIMIDE IN THE FISCHER REACTION

G. P. Tokmakov, T. G. Zemlyanova,
and I. I. Grandberg

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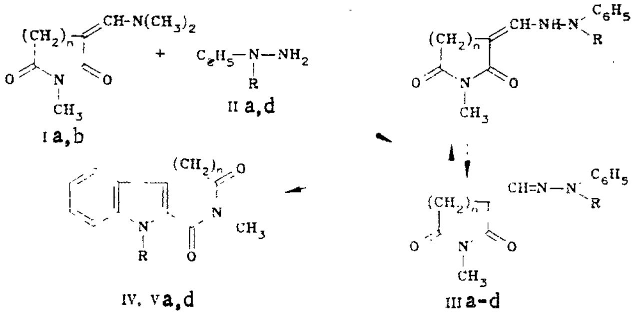
A study has been made of the behavior of α-dimethylaminomethylene derivatives of succinic and glutaric acid N-methylimides when reacted with different arylhydrazines under the conditions of the Fischer reaction.

It has been shown previously [1, 2] that the interaction of α-formylbutyrolactams with arylhydrazines in the Fischer reaction is accompanied by an intramolecular rearrangement and this leads to the formation of 1-oxo-1,2,3,4-tetrahydro-β-carbolines.

It was of interest to study the possibility of this rearrangement occurring for other heterocyclic aldehydes or their enamines.

In the present work a study was made of the reaction of α-dimethylaminomethylene derivatives of succinic and glutaric acid N-methylimides I with arylhydrazines II.



Ia, IV n=1; Ib, V n=2; II—V a $R=CH_2C_6H_5$, b $R=C_6H_5$, c $R=CH_3$, d R=H

It is known that in the Vilsmeier reaction N-substituted succinimides, unlike γ-lactams [3], do not give dimethylaminomethylene derivatives but undergo aromatization and are converted to α,α'-dichloro-β,β'-diformylpyrroles [4]. Consequently, we obtained the necessary enamines Ia, b by the action of bis(dimethylamino)methoxymethane on the N-methylimides of succinic [5] and glutaric acid.

When enamines Ia, b are reacted with arylhydrazines in aqueous 2-propanol in the presenc of hydrochloric acid (the conditions for obtaining 1-oxo-1,2,3,4-tetrahydro-β-carbolines), the reaction stops at the stage where hydrazones III are formed. For example, the α,α-diphen hydrazone of α-formyl-N-methylsuccinimide IIIb was separated and it consisted of a mixture of at least two isomers with a markedly different chromatographic mobility on Silufol. Howev separation of them chromatographically turned out to be impossible as in solution in the presence of adsorbents or acids both isomers are quite rapidly interconverted with the formation of an equilibrium mixture. On standing, crystals of a pure isomer with the lower Rf value precipitate out from a concentrated benzene or chloroform solution of the mixture of isomers. Separation of the second isomer in a pure form was not achieved.

K. A. Timiryazev Moscow Agricultural Academy, Moscow 127550. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1662-1667, December, 1986. Original article submitted July 25, 1985.

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