CYCLIZATION OF N-ALKYLAZINIUM CATIONS WITH BIFUNCTIONAL NUCLEOPHILES.

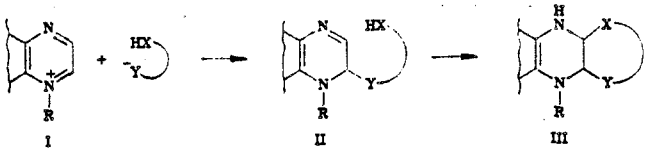
25.* OXIDATION OF TETRAHYDROQUINOXALINES CONDENSED WITH SIX-MEMBERED RING HETEROCYCLES

V. N. Charushin, L. M. Naumova, M. G. Ponizovskii, V. G. Baklykov, and O. N. Chupakhin

UDC 547.863.13'879: 542.943

Reaction of six-membered ring heterocycle-annulated tetrahydroquinoxalines with potassium permanganate in acetone results in the formation of oxidation products containing a common system of conjugated double bonds.

Reactions of 1,4-diazinium salts (I) with bifunctional nucleophiles occur via 1,3- or 1,4-addition to the carbon atoms of the two C=N double bonds in the pyrazine ring and lead to cyclic products III, which contain a tetrahydropyrazine ring condensed with five- and six-membered ring carbo- or heterocycles [2-4].



I II III

In analogy with other nucleophilic addition products of carbo- or hetero-annelated tetrahydropyrazines, the products III are formed as a result of a reversible reaction, which involves two sequential steps. The outstanding feature of the products of monoaddition of dinucleophiles, namely II, is their ability to undergo intramolecular cyclization. The cyclic adducts III may be regarded, on one hand, as limiting examples of ring–chain isomerism between adducts II and their cyclic isomers, or, on the other hand, as double hydride complexes of azoaromatic compounds.

The structural commonality among the bisaddition products III and the azine σ-adducts also determines the similarity in their chemical properties. The bisaddition products III exhibit the characteristic tendency of σ-adducts to undergo aromatization via cleavage of substituents attached to tetragonal carbon atoms. Dissociation of cycloadducts III has been shown to the underlying cause of a whole series of regio- and steroisomerization, as well as other reactions which involve changes in the nature of the annelated ring system [2-4].

Another method of stabilization of hydride σ-complexes involves removal of hydrogen atoms, with their electron pairs, in the presence of oxidizing agents [5-8]. Since dissociation of tetrahydropyrazines III is in many cases an undesirable side reaction, it was of interest to us to study the feasibility of stabilization of the condensed ring system in III by means of oxidative dehydrogenation. In addition, since oxidation of hydride σ-complexes of azines leads to nucleophilic substitution products of hydrogen with retention of the substituent at the reactive site [5-8], it was expected that dehydrogenation of adducts III should lead to retention of the condensed ring system skeleton obtained via bisaddition.

In the present paper we report our results concerning the oxidation of tetrahydroquinoxalines IVa-c, V, and VI, which are condensed with six-membered ring heterocycles. All of the compounds investigated herein are characterized by the presence of a common structural fragment, –NH–CH–CH–NH–, which, as anticipated, undergoes transformation upon interaction with an oxidizing agent.

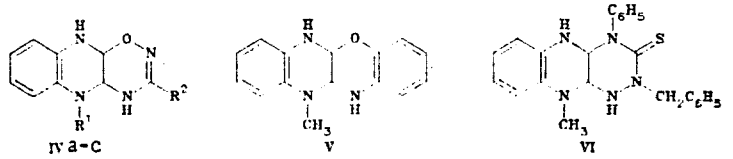
*For Communication 24, see Ref. [1].

S. M. Kirov Ural Polytechnical Institute, Sverdlovsk. Translated from Khimiya Geterotsklicheskikh Soedinenii, No. 9, pp. 1260-1263, September, 1987. Original article submitted April 28, 1986.

 0009-3122/87/2309-1010$12.50

TABLE 1. Characteristics of Oxidation Products VIIa-c, VIII, and IX

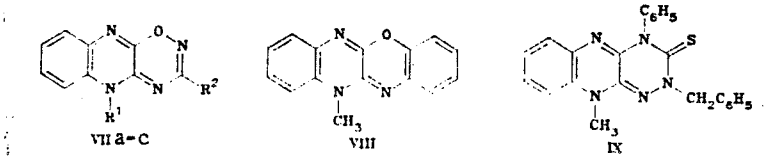
Compound	T_{mp}, °C	UV spectrum, λ_{max}, nm (log ε) (in ethanol)	Found, %			Molecular formula	Calc., %			Yield, %
			C	H	N		C	H	N	
VIIa	181	228 (4,55), 276 (3,47), 380 (3,53), 395 (3,51)	63,1	5,4	24,6	$C_{12}H_{12}N_4O$	63,1	5,3	24,6	20
VIIb	198—199	228 (4,56), 273 (3,61), 381 (3,52), 397 (3,51)	70,4	4,8	19,1	$C_{17}H_{14}N_4O$	70,3	4,9	19,3	78
VIIc	234—236	251 (4,56), 386 (3,54), 403 (3,52),	69,1	4,5	20,5	$C_{16}H_{12}N_4O$	69,5	4,4	20,3	75
VIII	226—227	236 (4,31), 241 (4,51), 394 (4,65), 414 (4,65), 435 (4,41)	72,4	4,5	17,0	$C_{15}H_{11}N_3O$	72,3	4,5	16,9	10
IX	223—225	—	69,6	4,9	17,6	$C_{25}H_{19}N_5S$	69,5	4,8	17,6	70



IVa-c V VI

IV a $R^1=C_2H_5$, $R^2=CH_3$; b $R^1=CH_3$, $R^2=CH_2C_6H_5$; c $R^1=CH_3$, $R^2=C_6H_5$

Oxidation of compounds IVa-c, V, and VI was carried out with potassium permanganate in acetone at 20°C or upon prolonged heating. The choice of this system was not random. Potassium permanganate is recommended for use as one of the most universal oxidizing agents for dihydroazines [6]. Contrasting results were obtained in part, however, in dehydrogenation reactions of amino adducts in the azine series [7, 9]. Potassium permanganate was used in 3-4-fold molar excess (2.2-3 redox equivalents). The extent of the reactions was followed chromatographically on Silufol plates, and the reactions were terminated upon complete consumption of the potassium permanganate. Under these reaction conditions dehydrogenation of the two NH—CH bonds is the main reaction pathway, leading to the formation of oxidation products VIIa-c, VIII, and IX, containing new C=N bonds, in satisfactory yields. This is supported by the electronic absorption spectra of compounds VIIa-c, VIII, and IX (Table 1). The appearance of an absorption band in the visible region, which is not present in the absorption spectra of the starting materials IVa-c, V, and VI, is consistent with excitation of new molecular fragments containing a single conjugation chain.



VIIa-c VIII IX

VII a $R^1=C_2H_5$, $R^2=CH_3$; b $R^1=CH_3$, $R^2=CH_2C_6H_5$; c $R^1=CH_3$, $R^2=C_6H_5$

The structures of the oxidation products VIIa-c, VIII, and IX were confirmed by elemental analysis and by PMR and mass spectroscopy. The PMR spectra of compounds VIIa-c, VIII, and IX do not contain signals in the 4.3-5.3 ppm range, corresponding to the bridgehead protons in the PMR spectra of the hydrogenated precursors IVa-c, V, and VI, and are also missing the two NH group protons; all of this data suggests dehydrogenation of the two NH—CH fragments. In addition, the PMR spectra of compounds VIIa,c VIII, and IX contain a signal due to the N-methyl group protons in the region 3.2-3.7 ppm, i.e., 0.5-1.0 ppm downfield relative to their position in the spectra of the hydrogenated precursors, which is again consistent with aromatization of the pyrazine ring.

Aromatization of the condensed heterocycles makes them extremely stable. Compounds VIIa-c, VIII, and IX have completely lost the tendency towards dissociation, which was inherent to their partially hydrogenated precursors IVa-c, V, and VI. The increased stability of the condensed tricyclic ring system upon aromatization is also indicated by the mass spectral data for compounds VIIb and IX, which contain intense molecular ion peaks (cf. Experimental).

TABLE 2. PMR Spectra of Compounds VIIa-c, VII, IX

Compound	Solvent	Chemical shifts, δ, ppm		
		N—R¹	aromatic protons	R² and other substituents
VIIa	$CDCl_3$	1.31 (3H, m, CH_3); 4.17 (2H, q, N—CH_2)	6.9—7.6 (4H, m)	2.00 (3H, s., CH_3)
VIIb	$CDCl_3$	3.46 (3H, s, N—CH_3)	6.9—7.6 (9H, m)	3.52 (2H, s, CH_2)
VIIc	DMSO-D_6	3.64 (3H, s, N—CH_3)	6.9—7.6 (7H, m); 7.8—8.1 (2H, m)	
VIII	$CDCl_3$+DMSO-D_6	3.52 (3H, s, N—CH_3)	6.8—7.3 (8H, m)	
IX	DMSO-D_6	3.21 (3H, s, N—CH_3)	6.7—7.7 (14H, m)	5.41 (2H, s, N—CH_2)

The oxidative dehydrogenation of cyclic adducts IVa-c, V, and VI which has been demonstrated herein constitutes not only a method for the preparation of novel heterocyclic derivatives, but also represents the concluding step in a series of chemical reactions, the goal of which is the synthesis of condensed systems via annelation of 1,4-diazine fragments with 1,4-bifunctional nucleophilic reagents. The possibility of preparing partially hydrogenated cyclic adducts of very different structures starting with 1,4-diazinium salts holds excellent promise for the wide application of this method in the synthesis of condensed heterocycles.

EXPERIMENTAL

PMR spectra were obtained on a Perkin Elmer R12B (60MHz) spectrometer. Mass spectra were recorded on a Varian MAT 311 A spectrometer using direct sample introduction into the ion source. Conditions: accelerating voltage, 3kV; cathode emission current, 300 μA; electron ionizing energy, 70 eV. Sample vaporization temperature, 70-150°C.

Chromatographic separations were carried out using LS 5/40 grade silica gel with benzene as eluent. The characteristics of compounds VII-IX are summarized in Tables 1 and 2.

3-Methyl-5-ethyl-1,2,4-oxadiazino[5,6-b]quinoxaline (VIIa). A suspension of 1 g (4.3 mmole) 3-methyl-5-ethyl-4a,5,10,10a-tetrahydro-1,2,4-oxadiazino[5,6-b]-quinoxaline (IVa) [1] in 75 ml acetone was treated with 1.8 g (11 mmole) potassium permanganate and the mixture was heated in a water bath for 30 min; the mixture was then stirred an additional 4 h at 20°C. The precipitate of manganese dioxide was removed by filtration and washed copiously with acetone. The combined filtrates were evaporated to dryness under vacuum and the residue was recrystallized from ethanol. Yield 0.2 g (20%), mp 181°C.

In an analogous manner, oxidation of compounds VIb and c gave oxadiazinoquinoxalines VIIb,c. Mass spectrum of compound VIIb, m/e (I ≥ 10%): 51 (10), 65 (15), 90 (18), 92 (11), 116 (10), 117 (26), 290 (M^+, 38).

N-Methylbenzoxazino[1,4][2,3-b]quinoxaline (VIII). A solution of 3.6 g (14.2 mmole) N-methyl-5,5a,6,11,11a,12-hexahydrobenzoxazino[1,4][2,3-b]quinoxaline (V) [10] in 30 ml acetone at 20°C was treated with stirring with a solution of 6.5 g (41.1 mmole) potassium permanganate in 270 ml acetone, in several portions. After addition of the oxidizing agent was complete the mixture was stirred an additional 1 h at 20°C. The resulting precipitate of manganese dioxide was removed by filtration and washed with several portions of acetone on the filter. The solvent was removed in vacuo and the product was isolated from the oily residue by preparative TLC on silica gel (benzene eluent). The yellow green layer with R_f 0.8 was collected. The sample of compound VIII obtained in this manner was recrystallized from ethanol. Yield 0.35 g (10%), mp 226-227°C.

2-Benzyl-10-methyl-4-phenyl-2,3,4,10-tetrahydro-1,2,4-triazino[5,6-b]-quinoxaline-3-thione (IX). A solution of 1 g (2.5 mmole) octahydro-1,2,4-triazino[5,6-b]quinoxaline (VI) [11] in 10 ml acetone was treated in several small portions (0.1-0.2 g) of 1.6 g (10 mmole) potassium permanganate while stirring at 20°C. After addition of the oxidant was complete the mixture was stirred an additional 2 h at 20°C. The manganese dioxide precipitate was filtered and washed repeatedly with acetone on the filter. The filtrate was evaporated and the residue recrystallized from ethanol. Yield 0.7 g (70%), mp 223-225°C. Mass spectrum, m/e (I ≥ 15%): 51 (15), 65 (17), 77 (42), 82 (15), 91 (85), 135 (25), 207 (28), 306 (16), 364 (45), 397 (M^+, 100).

LITERATURE CITED

1. L. M. Naumova, V. N. Charushin, and O. I. Chupakhin, Khim. Geterotsikl. Soedin., No. 8, 1118 (1987).
2. V. N. Charushin and O. N. Chupakhin, Usp. Khim., 53, 1648 (1984).
3. V. N. Charushin, M. G. Ponizovskii, and O. N. Chupakhin, Khim. Geterotsikl. Soedin., No. 8, 1011 (1985).
4. V. N. Charushin and O. N. Chupakhin, Izv. Sev.-Kav. Nauchn. Tsentra Vyshch. Shk., No. 3 (1987).
5. O. N. Chupakhin, Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk, No. 2, 46 (1980).
6. A. K. Sheinkman, Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk, No. 9, 111 (1983).
7. H. Hara and H. C. van der Plas, J. Heterocycl. Chem., 19, 1527 (1982).
8. I. Ya. Postovskii, O. N. Chupakhin, and A. I. Matern, Khim. Geterotsikl. Soedin., No. 10, 1299 (1984).
9. H. C. van der Plas, V. N. Charushin, and A. Veldhuizen, J. Org. Chem., 48, 1354 (1983).
10. V. N. Charushin, M. G. Ponizovskii, O. N. Chupakhin, A. I. Chernyshev, N. A. Klyuev, T. I. Malinovskii, V. Kh. Kravtsov, and V. N. Biyushkin, Khim. Geterotsikl. Soedin., No. 8, 1116 (1985).
11. V. G. Baklykov, V. N. Charushin, O. N. Chupakhin, and N. N. Sorokin, Khim. Geterotsikl. Soedin., No. 7, 960 (1985).

SYNTHESIS OF PYRIDO[1,2-b][2,4]BENZODIAZEPIN-6(11H)-IMINES

V. A. Kovtunenko, O. T. Fal'kovskaya, A. K. Tyltin, A. V. Turov, and F. S. Babichev

UDC 547.821.3'822.7'828'892.07:543.422

Condensation of o-bromomethylbenzonitrile and α-bromo-o-cyanophenylmethane with 2-aminopyridines gives 6-amino-6,11-dihydropyrido[1,2-b][2,4]benzodiazepines. Quaternary 2-aminopyridinium salts are intermediates in these reactions.

We have previously demonstrated that reaction of o-chloromethylbenzonitrile with 1-amino-3H-isoindole leads to the formation of a condensed derivative of a little-studied heterocyclic system, 2,4-benzodiazepine [1]. It was of interest to us to carry out the analogous conversion on 2-aminopyridine. This reaction is interesting from the point of view of synthesizing potentially neurotropic substances, such as those obtained via reaction of o-chloromethylbenzonitrile with anthranilic acid, for example [2].

Depending on the duration of reflux, two different compounds A and B can be obtained from an eqimolar mixture of o-bromomethylbenzonitrile (Ia) (experiments revealed that it was more convenient to work with this material rather than with o-chloromethylbenzonitrile Ib) with 2-aminopyridine IIa in acetonitrile.

Since IIa contains two sites which are receptive to electrophilic addition, namely, the ring nitrogen atom and the exocyclic amino group, the site of initial electrophilic attack will determine the structure of all of the possible subsequent products; it was therefore necessary to establish its structure by an independent pathway. It is not possible to determine this structure based on literature data, since it is known that the direction of alkylation of α-aminopyridine depends on the reaction conditions [3]. We have synthesized the quaternary salts IIIa,b starting from 2-bromopyridine; these were then treated with an excess of a saturated solution of ammonia in alcohol.

Treatment of quaternary salt IIIb results in the formation of 1-benzyl-2-aminopyridinium bromide IVb, while salt IIIa gives the quaternary salt IVa. Amination of salt IIIa does not result in loss of the nitrile group. A mixed melting point analysis of A and quaternary

T. G. Shevchenko Kiev State University, Kiev. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1264-1269, September, 1987. Original article submitted April 29, 1986.

0009-3122/87/2309-1013$12.50