CONDENSED AND BONDED QUINOXALINES

V.* SYNTHESIS OF PYRAZOLO[3,4-b]QUINOXALINES

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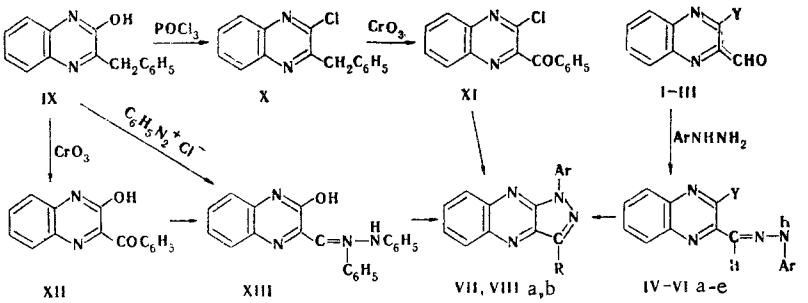
2-Chloro-3-formylquinoxaline was synthesized from 2-chloro-3-methylquinoxaline by the Kröhnke method, and the properties of its phenylhydrazone were studied. It was found that 2-Y-3-formylquinoxalines display an anomalously low reactivity as compared with 2-Y-benzoylquinoxalines (Y = H, OH, Cl) in the synthesis of pyrazolo[3,4-b]quinoxalines.

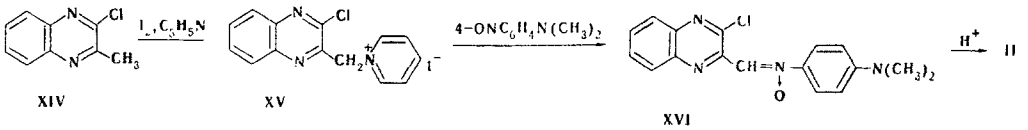
The cyclization of some quinoxaline derivatives by the action of excess phenylhydrazine in the presence of acid catalysts to pyrazolo[3,4-b]quinoxalines ("flavazoles") has been described in [2-4]. It has been assumed [4] that flavazoles are formed by ring closing of the precursor phenylhydrazones.

In the present research we have studied the cyclization of 2-Y-3-formylquinoxalines and 2-Y-benzoylquinoxalines, where Y = OH, Cl, to flavazoles.



a Ar=H; b Ar=C_6H_5; c Ar=4-$NO_2C_6H_4$; d Ar=2,4-$(NO_2)_2C_6H_3$; e Ar=2,4,6-$(NO_2)_3C_6H_2$.
I, IV Y=H; II, V Y=Cl; III, VI Y=OH; VII R=H; VIII R=C_6H_5.

2-Chloro-3-formylquinoxaline was synthesized from 2-chloro-3-methylquinoxaline via the scheme



We were unable to obtain II by oxidation of XIV with selenium dioxide under conditions similar to those used for the synthesis of 2-formylquinoxaline [5] and 2-hydroxy-3-formylquinoxaline [6]. The presence of an aldehyde group in the IR spectrum of II is confirmed by bands at 1735 ($\nu_{C=O}$) and 2885 cm^{-1} (ν_{CO-H}). In accordance with the data in [7], the band of C–Cl stretching vibrations in the spectra of XIV, XV, XVI, and II is displayed as intense absorption at, respectively, 1048, 1050, 1052, and 1060 cm^{-1}. The structure of II is also confirmed by chemical means – oxidation to the known 2-chloroquinoxaline-3-carboxylic acid.

The ν_{N-H} band usually observed in the spectra of phenylhydrazones is absent in the IR spectrum of 2-chloro-3-formylquinoxaline phenylhydrazone (Vb). Nevertheless, the intense absorption at 1052 cm^{-1}, the results of elementary analysis, and the determination of the molecular weight constituted evidence that the C–Cl bond remained unaffected in the molecule, and the composition of the compound corresponds

*See [1] for communication IV.

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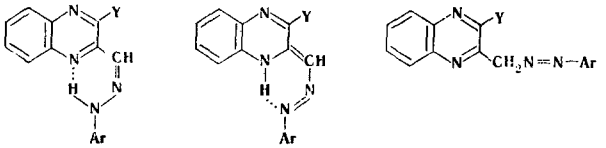
to Vb. Compound Vb proved to be completely inert under the conditions used for the conversion of 2-Y-3-aroylquinoxalines to flavazoles [4]. Prolonged refluxing of Vb in acetic acid or ethanol–pyridine invariably led to the starting compound. Under more severe conditions, when Vb was refluxed in alcohol in the presence of sodium alkoxide or when it was heated at 180°C in hexamethylphosphoric triamide, the degree of conversion to a flavazole was negligibly small.* At the same time, II and Vb are readily converted to 1H-pyrazolo[3,4-b]quinoxaline (VIIa) after brief heating in alcohol with excess hydrazine hydrate. The formation of a pyrazole ring in this case is confirmed by the disappearance of ν_{C-Cl} absorption near 1050 cm^{-1} and by the appearance of broad associated ν_{N-H} bands in the high-frequency region.

In our subsequent studies, we compared the properties of 2-formylquinoxaline phenylhydrazone (IVb), 2-hydroxy-3-formylquinoxaline phenylhydrazone (VIb), and Vb. According to the data in [2], IVb is converted in 70% yield to VIIb after refluxing for 24 h with excess phenylhydrazine in PrOH–HCl. The cyclization of VIb was not investigated, but our experiments showed that its behavior is similar to that of Vb. For comparison, we point out that 2-(p-anisoyl)quinoxaline is converted to the corresponding flavazole [4] in the same yield as in the case of IVb after refluxing for 3 h in C_2H_5OH–HCl with excess phenylhydrazine.

The anomalously low reactivity of 2-formylquinoxalines in the synthesis of flavazoles is manifested when they are compared under comparable conditions with 2-chloro-3-benzoylquinoxaline (XI) and 2-hydroxy-3-benzoylquinoxaline (XII). For XI, the phenylhydrazone cannot be isolated, but refluxing XI for 3 h in ethanol with excess phenylhydrazine gives a high yield of 1,3-diphenylpyrazolo[3,4-b]quinoxaline (VIIIb); XII initially forms a phenylhydrazone (XIII), which is converted to a flavazole after brief refluxing in acetic acid. The structure of intermediate XIII is confirmed by comparison of it with the substance obtained by azo coupling of 2-hydroxy-3-benzylquinoxaline with benzenediazonium salt.

The assumption regarding the existence of 2-formylquinoxaline phenylhydrazones in the stable syn configuration, which hinders closing of the pyrazole ring, should be rejected, since Messmer and Sziman [9] converted 2-methyl-3-acetylquinoxaline phenylhydrazone to 3,4-dimethyl-1-phenyl-1,2,3-triazolo[1,5-a]-quinoxalinium bromide by the action of N-bromosuccinimide. The occurrence of oxidative cyclization of this type for 2-formylquinoxaline phenylhydrazones under the influence of bromine is probably the reason that the latter do not show a positive qualitative reaction for a phenylhydrazone group based on cleavage of the N–NHAr group by bromine and subsequent detection of diazonium coupling with 2-naphthol (on paper) [10]. It is interesting that 2-hydroxy-3-benzoylquinoxaline phenylhydrazone, which is readily cyclized to a flavazole, gives a positive qualitative reaction for the phenylhydrazone grouping.

In view of the difficulties that arise in explaining the properties of 2-formylquinoxaline phenylhydrazones, we considered the following (B and C) as possible isomeric structures:



A B C

For VIb, with an absorption maximum in the visible region at 460 nm, B and C were previously [11] considered as possible structures, since a strong (as compared with the absorption maxima of α-N-acetyl- and α-N-methylphenylhydrazones) bathochromic shift was observed. The PMR spectra of Vb and VIb make it possible to exclude structure C because of the absence of proton signals from a CH_2 group. The chemical shifts from the protons of the C=N and N–H groups in the spectrum of benzal phenylhydrazone are found at, respectively, δ 7.93 and 10.66 ppm. For Vb and VIb we were unable to observe signals of C–H protons, and the chemical shift from the CH=N protons is masked by the signals of aromatic protons.

Analysis of the electronic absorption spectra of IVb, Vb, and VIb confirms the existence of imino–enamine tautomerism (A ⇄ B). The absorption maxima of Vb and VIb in the visible region are close (450 and 460 nm, respectively), while IVb is considerably more weakly colored (λ_{max} 415 nm); in conformity with this, it is necessary to assume that enamine structure B is preferred for Vb and VIb, while imino structure A is preferred for IVb. This is in agreement with the increase in the absorption intensity at ~260 nm in the UV spectrum of IVb, which is assumed to be characteristic for phenylhydrazones [12].

It is interesting to note that, in contrast to the spectrum of Vb, the IR spectrum of IVb contains a ν_{N-H} band as a doublet at 3240 and 3200 cm^{-1}, which is shifted to 3275 cm^{-1} in the spectrum of 2-formyl-

*Data that contradict ours are presented by Sauer and Henseke in [8].

quinoxaline 2,4,6-trinitrophenylhydrazone. An intense band at 3130 cm^{-1}, which is apparently related to the ν_{N-H} vibrations, is present in the spectrum of Ve on the background of the aromatic absorption.

It was previously [3] noted in the case of 2-hydroxy-3-quinoxalyl 1,2,3-trihydroxypropyl ketone that the presence of a polyhydroxyalkyl chain promotes its cyclization to a flavazole. It must be concluded that this conclusion is more general in character: the presence of a substituent (R) attached to the carbon atom of the carbonyl group has a decisive effect on the ease of formation of a pyrazole ring, while the nature of the substituting group (Y) is of secondary importance and may vary over an unusually wide range (see [4]).

EXPERIMENTAL

The IR spectra of KBr pellets were recorded with a UR-20 spectrometer. The UV spectra of ethanol solutions (10^{-4}-10^{-5} mole/liter) were recorded with an SF-4 spectrometer. The PMR spectra were obtained with a Varian A-60A spectrometer from pyridine solutions with hexamethyldisiloxane as the internal standard. The absorption spectra in the visible region were measured with an SF-10 spectrophotometer.

2-Formylquinoxaline (I) and 2-Hydroxy-3-formylquinoxaline (III). These compounds were synthesized by the methods in [5, 6]. The melting points of the phenylhydrazones obtained from them were in agreement with the literature values [14, 11].

2-Chloro-3-methylquinoxaline (XIV). A mixture of 16.0 g (0.1 mole) of 2-hydroxy-3-methylquinoxaline and 150 ml of phosphorus oxychloride was refluxed gently for 60-80 min until all of the solid had dissolved. The bulk of the phosphorus oxychloride was then removed by distillation in vacuo (with a water aspirator), and the residue was cooled and added in portions to ice. The aqueous mixture was filtered to remove resinous impurities, and the filtrate was treated with ammonia (to neutrality) to precipitate XIV. The resulting light-brown substance was placed in a distilling flask and steam-distilled. The yield of pure substance with mp 85-86° (mp 79-81° [15]) was 17 g (96%). Found: Cl 19.7; N 15.6%. $C_9H_7ClN_2$. Calculated: Cl 19.8; N 15.7%. UV spectrum: λ_{max}, nm (log ε): 238 (4.45), 320 (3.88), and 328 (3.81).

N-(2-Chloro-3-quinoxalymethyl)pyridinium Iodide (XV). A 17.9-g (0.1 mole) sample of XIV was dissolved in 40 ml of dry pyridine, and 25.4 g (0.1 mole) of iodine was dissolved in 30 ml of pyridine. The solutions were mixed and held at 80° for 3 h. The mixture was cooled, and the resulting crystalline substance was removed by filtration and washed on the filter with a small amount of pyridine to give 28.7 g (75%) of light-brown needles with mp 213-214° (from pyridine). Found: C 42.7; H 2.7; N 10.4%. $C_{14}H_{11}ClN_3$. Calculated: C 43.8; H 2.9; N 10.9%.

2-Chloro-3-formylquinoxaline p-Dimethylaminophenylnitrone (XVI). A 38.4-g (0.1 mole) sample of XV was added to 250 ml of methanol to which a solution of 14 g (0.1 mole) of potassium acetate in 200 ml of water had been previously added. The mixture was stirred vigorously, and 15 g (0.1 mole) of p-nitrosodimethylaniline in 150 ml of methanol was added to it. The mixture was then stirred for another 10-15 min, after which the reaction mass was allowed to stand at room temperature for 5-6 h. It was then cooled, and the resulting dark-red needles were removed by filtration and washed thoroughly on the filter with a large amount of water to give 20.5 g (63%) of a product with mp 124-125° (from aqueous alcohol). Found: C 62.7; H 5.2; Cl 10.7%. $C_{17}H_{15}ClN_4O$. Calculated: C 62.5; H 4.6; Cl 10.9%. UV spectrum: λ_{max}, nm (log ε): 242 (4.49), 315 (4.16).

2-Chloro-3-formylquinoxaline (II). A 3.27-g (0.01 mole) sample of XVI was added to 50 ml of 1 N hydrochloric acid, and the mixture was stirred vigorously for 5-10 min. The aldehyde crystallized as shiny plates. Workup gave 1.43 g of a product with mp 153-154° (from aqueous alcohol). The product can also be purified by sublimation at 120-130° (10 mm). Found: Cl 18.5; N 14.5%. $C_9H_5ClN_2O$. Calculated: Cl 18.5; N 14.5%. UV spectrum: λ_{max}, nm (log ε): 242 (4.52), 322 (3.95), 330 (3.88). IR spectrum, cm^{-1}: 1060 (C–Cl), 1735 (C=O), 2885 (CO–H).

2-Chloroquinoxaline-3-carboxylic Acid. An aqueous solution of potassium permanganate was added dropwise to 0.96 g (0.005 mole) of II in 20 ml of acetone until decolorization ceased. The mixture was then diluted with water and extracted with ether to give 0.83 g (80%) of a substance with mp 145-147°; crystallization from water gave a product with mp 151-152° (mp 146-147° [5]). Found: Cl 16.9; N 13.5%. $C_9H_5ClN_2O_2$. Calculated: Cl 17.00; N 13.4%. IR spectrum, cm^{-1}: 1045 (C–Cl), 1710 (C=O).

1H-Pyrazolo[3,4-b]quinoxaline (VII). A mixture of 0.86 g (0.005 mole) of II and 20 ml of ethanol was refluxed with a fivefold excess of hydrazine hydrate in 20 ml of water for 30 min. It was then cooled to give 0.6 g (71%) of a crystalline substance, which was purified by crystallization from aqueous dioxane to

give a product with mp 283.5-284.5° (mp 281-282°). Found: C 63.4; H 3.8%. $C_9H_6N_4$. Calculated: C 63.5; H 3.6%.

2-Chloro-3-formylquinoxaline Phenylhydrazone (Vb). Aqueous alcohol solutions of 0.86 g (0.005 mole) of II and 0.5 ml of phenylhydrazine were mixed, and the mixture was heated for 2-3 min on a water bath. The mixture was then filtered to give orange needles of Vb with mp 163-164° (from aqueous alcohol). The yield was almost quantitative. Found: Cl 12.6; N 20.1%. $C_{15}H_{11}ClN_4$. Calculated: Cl 12.5; N 19.8%. Electronic spectrum: λ_{max}, nm (log ε): 240 (4.43), 318 (3.98), 450 (4.33).

2-Chloro-3-formylquinoxaline 4-Nitrophenylhydrazone (Vc). This compound was obtained by mixing solutions of equivalent amounts of II and 4-nitrophenylhydrazine in acetic acid. The yield of orange crystals with mp 289-290° (from $CH_3COOH-DMF$) was almost quantitative. Found: Cl 10.5; N 20.8%. $C_{15}H_{10}N_5O_2$. Calculated: Cl 10.8; N 21.4%.

2-Chloro-3-formylquinoxaline 2,4-Dinitrophenylhydrazone (Vd). This compound was similarly obtained from II and 2,4-dinitrophenylhydrazine. The yield of yellow crystals with mp 275-277° (from $CH_3COOH-DMF$) was almost quantitative. Found: Cl 9.3; N 22.1%. $C_{15}H_9ClN_6O_4$. Calculated: Cl 9.5; N 22.5%.

2-Chloro-3-formylquinoxaline 2,4,6-Trinitrophenylhydrazone (Ve). This compound was similarly obtained from II and 2,4,6-trinitrophenylhydrazine. The yield of yellow crystals with mp 267-270° was almost quantitative. Found: Cl 8.7; N 23.0%. $C_{15}H_8ClN_7O_6$. Calculated: Cl 8.5; N 23.5%.

2-Chloro-3-formylquinoxaline N-Acetylphenylhydrazone. A 0.28-g (0.001 mole) sample of Vb was refluxed for 1 h in 10 ml of acetic anhydride. Cooling of the mixture gave 0.27 g (85%) of yellow crystals of the acetyl derivative with mp 216-218° (from alcohol). Found: Cl 10.8; N 17.1%. $C_{17}H_{13}ClN_4O$. Calculated: Cl 10.9; N 17.3%. IR spectrum, cm^{-1}: 1060 (C–Cl), 1690 (C=O).

2-Hydroxy-3-benzylquinoxaline (IX). A mixture of 14.8 g (0.1 mole) of phenylpyruvic acid and 11.9 g (0.11 mole) of o-phenylenediamine in 200 ml of propyl alcohol was heated on a boiling-water bath for 30 min, after which it was cooled, and the precipitate was removed by filtration and washed thoroughly on the filter with a large amount of water to give 18.4 g (78%) of a product with mp 194-197° (mp 196° [13]). Found: N 11.7%. $C_{15}H_{12}N_2O$. Calculated: N 11.9%.

2-Hydroxy-3-benzoylquinoxaline (XII). This compound was obtained in 70% yield by oxidation of IX with chromic anhydride by the method described in [4]. The colorless crystals had mp 255-258°. Found: N 9.9%. $C_{15}H_{10}N_2O_2$. Calculated: N 11.2%. IR spectrum, cm^{-1}: 1685 (lactam CO), 1710 (C=O), 2850-3050 (NH, OH).

2-Hydroxy-3-benzoylquinoxaline Phenylhydrazone (XIII). A. From 2-Hydroxy-3-benzoylquinoxaline (XII). A 1.00-g (0.004 mole) sample of XII was refluxed for 2 h with a fivefold excess of phenylhydrazine in 40 ml of methanol containing 0.1 ml of concentrated hydrochloric acid. The mixture was cooled to precipitate 1.30 g (96%) of red crystals of XIII with mp 248-250° (from alcohol). Found: N 16.4%. $C_{21}H_{16}N_4O$. Calculated: N 16.5%. IR spectrum, cm^{-1}: 1690 (C=O), 2800-3200 (NH, OH).

B. From 2-Hydroxy-3-benzylquinoxaline (IX). A 4.73-g (0.02 mole) sample of IX was dissolved in 250 ml of acetic acid, and an equivalent amount of a solution of benzenediazonium sulfate in 20 ml of concentrated hydrochloric acid was added with vigorous stirring at 5-7°. Stirring was continued for another 3 h, after which the mixture was allowed to stand in a refrigerator overnight. The red-violet precipitate was removed by filtration and purified by crystallization from alcohol to give 3.4 g (50%) of a product with mp 248-250°. The substance was identical to that obtained from XII and phenylhydrazine.

2-Chloro-3-benzylquinoxaline (X). This compound was obtained in 88% yield from IX by the method described above. The colorless crystals had mp 86-88° (from alcohol). Found: Cl 13.8; N 11.2%. $C_{15}H_{11}ClN_2$. Calculated: Cl 13.9; N 11.0%.

2-Chloro-3-benzoylquinoxaline (XI). This compound, with mp 138-141° (from methanol), was obtained in 55% yield by the method in [4]. Found: Cl 13.2; N 10.4%. $C_{15}H_9ClN_2O$. Calculated: Cl 13.2; N 10.4%. IR spectrum, cm^{-1}: 1060 (C–Cl), 1680 (C=O).

1,3-Diphenylpyrazolo[3,4-b]quinoxaline (VIIIb). A. From 2-Chloro-3-benzoylquinoxaline. A 2.69-g (0.01 mole) sample of XI was refluxed in 20 ml of ethanol with a threefold excess of phenylhydrazine for 3 h. The mixture was cooled, and the precipitate was removed by filtration and purified by crystallization from acetic acid to give 2.2 g (68%) of product. The melting point and IR spectrum of the product were identical to those reported in [3].

B. From 2-Hydroxy-3-benzoylquinoxaline Phenylhydrazone. A 0.34-g (0.001 mole) sample of XIII was refluxed in 20 ml of acetic acid for 1 h, after which the mixture was cooled to give 0.19 g (60%) of VIIIb.

LITERATURE CITED

1. V. D. Romanenko, N. E. Kul'chitskaya, and S. I. Burmistrov, Khim. Geterotsikl. Soedin., 264 (1973).
2. G. Henseke, Z. Chem., 6, 329 (1966).
3. G. Henseke, W. Dose, and K. Dittrich, Angew. Chem., 69, 479 (1957).
4. H. Dahn and J. Nussbaum, Helv. Chim. Acta, 52, 1661 (1969).
5. A. S. Elina and O. Yu. Magidson, Zh. Obshch. Khim., 25, 161 (1955).
6. S. N. Baranov and N. E. Plevachuk-Tarnavskaya, Ukr. Khim. Zh., 29, 82 (1963).
7. J. Klicnar, M. Hajek, and J. Hoffmann, Coll. Czech. Chem. Commun., 36, 262 (1969).
8. W. Sauer and G. Henseke, Z. Chem., 10, 381 (1970).
9. A. Messmer and O. Sziman, Angew. Chem. Internat. Ed., 4, 1074 (1965).
10. S. I. Burmistrov, Soobshch. VKhO im. Mendeleeva, No. 7, 7 (1946).
11. H. Ohle and G. Hoetzel, Ber., 76B, 624 (1943).
12. R. O'Connor, J. Org. Chem., 26, 4375 (1961).
13. S. N. Baranov and N. E. Tarnavskaya, Ukr. Khim. Zh., 25, 620 (1959).
14. W. Borsche and W. Doeller, Ann., 537, 39 (1938).
15. J. L'Italien and C. K. Banks, J. Am. Chem. Soc., 73, 3246 (1951).