CYCLIZATION REACTIONS OF SOME 2,3-DISUBSTITUTED QUINOXALINES*

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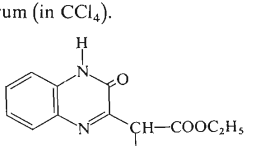
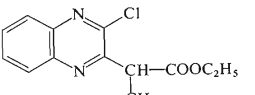
Structure of condensation products of ethyl 2-(3-chloro-2-quinoxalinyl)propionate with aniline, hydrazine, and hydrazobenzene has been determined by spectral methods. Reaction of 2-acetonyl- and 2-phenacyl-3,4-dihydro-3-oxoquinoxalines with phosphorus oxychloride gives 2-(2-chloro--1-propenyl)quinoxaline derivatives the cyclization of which with hydrazine has been studied.

In Part VII (ref.[1]) of this series we described reactions of ethyl 3,4-dihydro-3-oxo--2-quinoxalinylphenyl acetate (*I*). In the present paper we deal with the cyclization reactions of further quinoxaline derivatives and with structure of both the products and the starting materials as potential ketimine-enamine tautomers.

By modification of the known procedure[2] ethyl 2-(3,4-dihydro-3-oxo-2-quinoxalinyl)propionate (*II*) was prepared and transformed into ethyl 2-(3-chloro-2-quinoxalinyl)propionate (*III*) by action of phosphorus oxychloride. Ketimine form of the chloro derivative *III* was proved by the IR band $\nu(C{=}O)$ at 1750 cm^{-1} and by the methyl doublet at 8·33τ (J = 7·1 Hz) and methine quartet (5·66τ) in its ^{1}H-NMR spectrum (in CCl_4).



I, X = C_6H_5
II, X = CH_3



III

Cyclization experiments were carried out with the chloro derivative *III* and aniline, hydrazine, and hydrazobenzene to give pyrrolo[2,3-*b*]- and pyridazo[3,4-*b*]quinoxalines. The reaction with aniline gave a product which was denoted as 1-phenyl-3-methyl-2,3-dihydro-2-oxopyrrolo[2,3-*b*]quinoxaline (*IV*). IR spectrum of this com-

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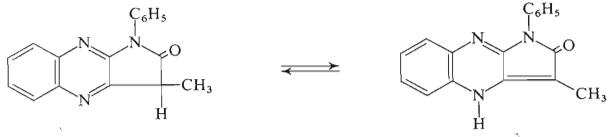
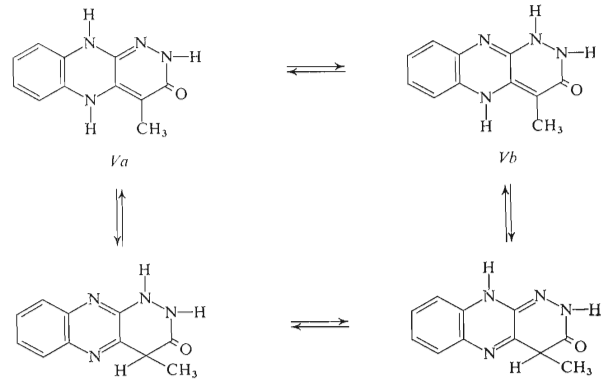
pound contained bands ν(C=O) 1670 cm^{-1}, ν(N—H) 3210 cm^{-1} and a band at 1650 cm^{-1} due probably to valence vibration ν(C=C). It is supposed that the solid compound is present in its enamine form *IVb*, as it is the case with the analogous 3-phenyl derivative[1], which confirms the form *IVb*. A weak doublet of the methyl protons at 8·53τ indicates a small amount of the ketimine form *IVa* in the solution in trifluoroacetic acid.



IVa *IVb*

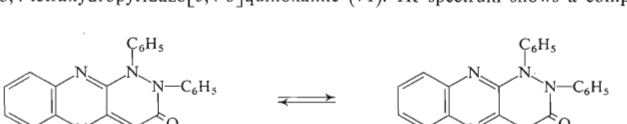
As compared with the phenyl derivative[1] the condensation of the methyl derivative *III* with hydrazine proceeded less smoothly. First at 180°C a uniform product was obtained which was identified as 4-methyl-3-oxo-1,2,3,4-tetrahydropyridazo-[3,4-*b*]-quinoxaline (*V*). IR spectrum shows a band of conjugated carbonyl group at 1650 cm^{-1}, the two bands at 3250 and 3187 cm^{-1} being assigned to N—H groups of the pyrazine nucleus and to lactam group[1]. ^{1}H-NMR signals at −0·55, 1·3, and 1·8τ in dimethyl sulphoxide at 70°C correspond to three N—H groups. From these data it follows that the compound is present probably mainly as the tautomer *Va* or *Vb*. According to electronic spectrum the structure *Va* appears to be more probable.



Va *Vb*

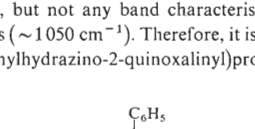
Vc *Vd*

The analogous reaction of the chloro derivative *III* with hydrazobenzene is very difficult, it was possible to obtain only small amount of two individual compounds from the reaction mixture. The yellow product was 1,2-diphenyl-4-methyl-3-oxo--1,2,3,4-tetrahydropyridazo[3,4-*b*]quinoxaline (*VI*). IR spectrum shows a complex

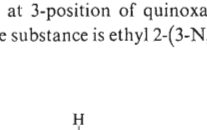


VIa *VIb*

carbonyl band 1650–1670 cm^{-1} and two bands ν(N—H) and 3222 cm^{-1}. From the ^{1}H-NMR spectrum (in trifluoroacetic acid at 50°C) it was found that the compound contained 85% enamine form *VIa* (a singlet at 7·53τ) and 15% ketimine form *VIb* (a doublet at 8·30τ, $J \approx 6$ Hz). The second colourless compound showed the same ν(C=O) value as the starting ester *III*, absorption bands of phenyl and N—H groups, but not any band characteristical for chlorine at 3-position of quinoxaline nucleus (~1050 cm^{-1}). Therefore, it is supposed that the substance is ethyl 2-(3-N,N'--diphenylhydrazino-2-quinoxalinyl)propionate (*VII*).



VII



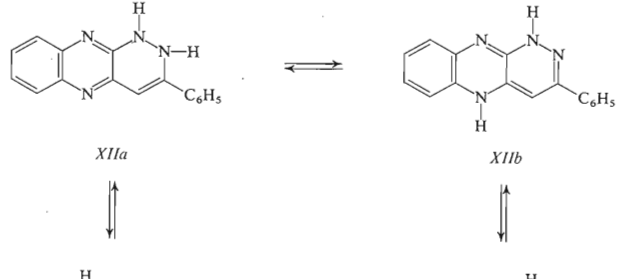
VIII, R = CH_3
IX, R = C_6H_5

X, R = CH_3
XI, R = C_6H_5

We tried to prepare 3-chloro derivatives from 2-acetonyl (*VIII*) and 2-phenacyl--3,4-dihydro-3-oxoquinoxalines (*IX*) which are present in their enamine form[3,4] both as solids and in solution in dimethyl sulphoxide. However, the reaction with

phosphorus oxychloride gave different compounds not containing carbonyl groups. IR spectra (CCl_4) show absorption bands characteristical for a chlorine atom bound to heterocyclic ring (1048 resp. 1058 cm^{-1}) and bands of a —CH=C< group: ν(C—H) 3100 cm^{-1}, γ(C—H) 857 resp. 823 cm^{-1} for the chlorination products of 2-acetonyl (*VIII*) resp. 2-phenacyl (*IX*) derivatives. In ^{1}H-NMR spectrum (CCl_4, 25°C) of the chlorination product of the compound *VIII* two doublets of methyl protons were found at 7·29τ and 7·56τ with a small coupling constant J = 1·2 Hz, which indicates the presence of two *cis-trans* isomers at the double bond of the side chain. The doublets are due to coupling with the proton of —CH group (2·89 and 3·12τ). The chlorination product of the phenacyl derivative *IX* gives one complex multiplet at 2–3τ. On the basis of these spectral data, elemental analyses and the preparation method the chlorinated derivatives were denoted as mixtures of *cis-trans* isomers of 2-(2-chlorophenyl)- (*X*) and 2-(β-chlorostyryl)-3-chloroquinoxaline (*XI*).

The both chlorinated derivatives *X* and *XI* were submitted to reaction with hydrazine, because we wanted to prepare more easily the pyridazo[3,4-*b*]quinoxalines which had before been obtained by hydrazinolysis of the ketones *VIII* and *IX* (refs[5,6]). The methyl derivative *X* did not react, whereas the hydrazinolysis of the phenyl derivative *XI* gave 3-phenyl-9,10-dihydropyridazo[3,4-*b*]quinoxaline (*XII*).



XIIa *XIIb*

XIId *XIIc*

According to spectral analysis the derivative *XII* contains N—H groups (ν(N—H) 3350 cm^{-1}, two signals of N—H groups about 1·4τ). With respect to the presence of the group =C—H (3·80τ, dimethyl sulphoxide) two (*XIIa* and *XIIb*) out of the

four tautomeric structures are possible. For comparison we tried to prepare the derivative *XII* by hydrazinolysis of the ketone *IX* according to ref.[6]. However, another not identified compound was obtained as it was the case with the attempt of hydrazinolysis of ketone *XIII*.

EXPERIMENTAL

The melting points were determined with a Kofler apparatus. IR spectra were measured with a UR 20 spectrophotometer (Zeiss, Jena), the wave numbers being calibrated with polystyrene. If not otherwise stated, the IR spectra were measured in KBr discs. ^{1}H-NMR spectra were measured with a Tesla BS 487 B apparatus at 80 MHz. Saturated solutions in dimethyl sulphoxide (compounds *V*, *IX*, *XII*), trifluoroacetic acid (compounds *IV* and *VI*) or CCl_4 (compounds *III*, *X*, and *XI*) were used for the measurements, dimethyl sulphoxide or tetramethylsilane being used as internal standard.

Ethyl 2(3-chloro-2-quinoxalinyl)propionate (*III*)

18·4 g (0·065 mol) ester *II*, 30 ml phosphorus oxychloride, and 5 ml pyridine were heated to boiling with exclusion of moisture for 1/2 hour. The mixture was poured onto ice and neutralized with 20% sodium carbonate solution (cooled with ice). The chloroderivative was extracted with chloroform, dried with calcium chloride, and obtained as a brown oil after distilling off the solvent. The oil was dissolved in light petroleum, filtered through a layer of alumina, and concentrated to give crystals. Recrystallization from 50% ethanol gave 7 g (42%) crystals melting at 43—44°C and turning dark and decomposing after a time. For $C_{13}H_{13}ClN_2O_2$ (264·7) calculated: 58·99% C, 4·99% H, 14·03% Cl; found: 59·12% C, 4·88% H, 13·96% Cl.

1-Phenyl-3-methyl-2,3-dihydro-2-oxopyrrolo[2,3-*b*]quinoxaline (*IV*)

2·66 g (0·01 mol) chloroderivative *III* and 10 ml aniline were heated to boiling for 4 hours. After cooling 25 ml methanol was added, and the precipitated product was collected by suction and twice crystallized from butylcellosolve. Yield 2·3 g (84%) yellow needles melting at 293—294°C (decomp.). For $C_{17}H_{13}N_3O$ (275·3) calculated: 74·16% C, 4·76% H, 15·26% N; found; 74·37% C, 5·17% H, 15·28% N.

4-Methyl-3-oxo-1,2,3,4-tetrahydropyridazo[3,4-*b*]quinoxaline (*V*)

Mixture of 2·65 g (0·01 mol) compound *III* and 10 ml 80% hydrazine hydrate was heated at 180°C in an ampoule for 1 hour. The product precipitated on cooling was collected by suction washed with methanol and twice recrystallized from pyridine. Yield 1·92 g (79%) yellow prisms melting at 295°C (decomp.). For $C_{11}H_{10}N_4O$ (214·2) calculated: 61·67% C, 4·71% H, 26·16% N; found: 61·90% C, 5·06% H, 25·85% N.

1,2-Diphenyl-4-methyl-3-oxo-1,2,3,4-tetrahydropyridazo[3,4-*b*]-quinoxaline (*VI*) and Ethyl 2-(N,N'-Diphenylhydrazino-2-quinoxalinyl)propionate (*VII*)

Mixture of 2·65 g (0·01 mol) chloro derivative *III* and 1·84 g hydrazobenzene (0·01 mol) was melted under nitrogen and slowly heated to 220°C. Vigorous reaction gave a black greasy product; its tarry portion was extracted with cold methanol. The obtained yellow-green substance

was purified by two crystallizations from propanol. Yield 44·5 mg yellow crystals, m.p. 272 to 273°C. For VI, $C_{23}H_{13}N_4O$ (366·4) calculated: 15·29% N; found: 15·02% N. The mother liquor was filtered with charcoal and concentrated to give colourless crystals. After two crystallizations from ethyl acetate–hexane mixture the compound *VII* was obtained as 6 mg needles melting at 241—243°C.

2-(2-Chloro-1-propenyl)-3-chloroquinoxaline (*X*)

20 g compound[6] *VIII* in 30 ml phosphorus oxychloride and 10 ml pyridine was heated to boiling for 10 minutes. After cooling the mixture was poured onto ice and neutralized with solution of sodium carbonate. The product was extracted with chloroform, the extract was dried with calcium chloride and filtered through alumina. After distilling off the solvent and crystallization from 70% acetic acid 14·2 g (62%) needles was obtained, m.p. 75—76°C. For $C_{11}H_8Cl_2N_2$ (239·1) calculated: 55·39% C, 3·37% H, 29·70% Cl; found: 56·16% C, 3·76% H, 29·62% Cl.

2-(β-Chlorostyryl)-3-chloroquinoxaline (*XI*)

20 g compound *IX* (see ref.[6]) was heated to boiling with 30 ml phosphous oxychloride and 10 ml pyridine for 1/2 hour. After pouring onto ice and neutralization with sodium carbonate solution the product was extracted with chloroform, the extract was dried with calcium chloride and the solvent was distilled off. The remaining oil was poured in 100 ml light petroleum to give yellowish precipitate which was recrystallized from light petroleum–ethyl acetate (1 : 1) mixture. Yield 11 g (47%) yellow needles, m.p. 94—95°C. For $C_{16}H_{10}Cl_2N_2$ (301·1) calculated: 63·80% C, 3·35% H, 9·30% N; found: 63·57% C, 3·53% H, 9·64% N.

3-Phenyl-9,10-dihydropyridazo[3,4-*b*]quinoxaline (*XII*)

2·93 g chloro derivative *XI* and 10 ml 80% hydrazine hydrate was heated under nitrogen to boiling for 1 hour. After dilution with water the precipitated product was collected by suction and washed with methanol. Yield 2·35 g yellow-orange substance which after crystallization from methanol gave yellow portion (1·9 g, 76%) melting at 269—270°C. For $C_{16}H_{16}N_4$ (262·3) calculated: 73·26% C, 5·38% H, 21·36% N; found: 73·36% C, 5·35% H, 21·21% N.

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