# SYNTHESIS OF CONDENSED PYRAZINES FROM N-SUBSTITUTED AMINO-o-QUINONES AND ETHYLENEDIAMINE

S. A. Chernyak and Yu. S. Tsizin

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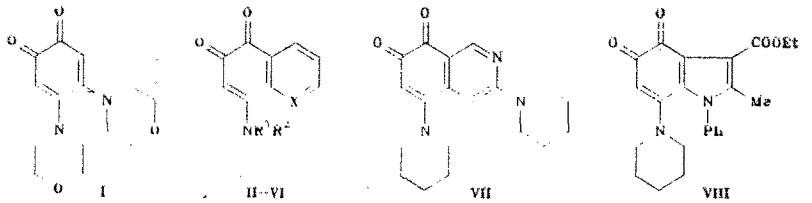
The reaction of N-monosubstituted and N,N-disubstituted amino-o-quinones with ethylenediamine, which leads to condensed pyrazine derivatives, was studied.

A widely known method for the synthesis of quinoxalines and other condensed heterocycles that contain a pyrazine ring is the reaction of the corresponding o-diamines with 1,2-diketones [1]. However, another pathway based on the reaction of o-quinones with ethylenediamines is also possible. The development of this method may be of practical interest, since presently many derivatives of o-quinones, particularly N-substituted amino-o-quinones, are readily accessible [2, 3].

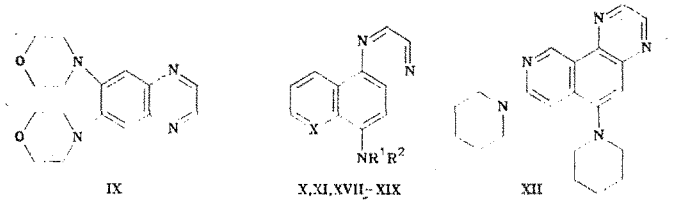



I II–VI VII VIII

II, VI $NR^1R^2$ = morpholyl, III $R^1$ = Ph, IV $R^1 = Et_2NCH_2CH_2$, V $R^1$ = 4-HO—3-$Et_2NCH_2C_6H_2$; III—V $R^2$ = H; II—V X = CH, VI X = N

Only individual references to the condensation of o-quinones with ethylene diamines are available [4, 5], and this reaction has not been studied systematically. The present research is devoted to a study of the reaction of ethylenediamine with a number of carbocyclic (I-V) and heterocyclic (VI-VIII) amino-o-quinones. The condensation of the accessible products of oxidative amination, viz., dialkylamino-o-quinones I, II, and V-VIII [2, 6], was initially studied. It was established that ethylenediamine reacts readily with these compounds at room temperature. In all cases the principal reaction products are aromatic condensed heterocycles. 6,7-Di-morpholino- (IX), 6-morpholinobenzo[f]- (X), 6-morpholino-pyrido[2,3-f]- (XI), 6,8-dipiperidinopyrido[3,4-f]- (XII), and 6-piperidino-7-phenyl-8-methyl-9-ethoxycarbonyl-pyrrolo[2,3-f]quinoxaline (XIII) were obtained in this way. The formation of coproducts was also detected in the reaction of o-quinones with ethylenediamine. Most of them were exceptionally labile, but in the case of quinone I we were able to isolate, in addition to quinoxaline IX, XIV, which was additionally characterized in the form of diacetyl derivative XV.

The formation of XIV makes it possible to propose that this tetrahydroquinoxaline is formed jointly with IX as a result of disproportionation of the primary product of condensation of quinone I with ethylenediamine (XVI). The less stable tetrahydroderivatives are evidently oxidized again by air oxidation or by the starting quinone, as a result of which a single product is formed



IX X,XI,XVII–XIX XII

E. I. Martsinovskii Institute of Parasitology and Tropical Medicine, Ministry of Public Health of the USSR, Moscow 119830. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 959-962, July, 1986. Original article submitted February 9, 1985; revision submitted August 1, 1985.

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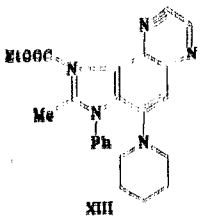
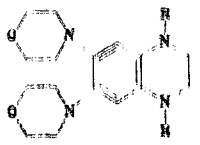


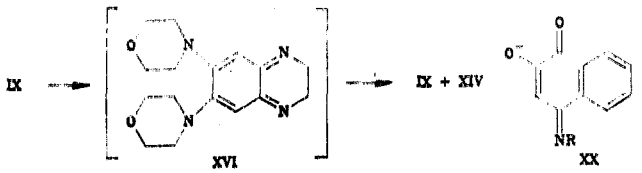
XIII



XIV, XV

X, XI $NR^1R^2$= piperidyl, XVII—XIX $R^1$=H, XVII $R^2$=Ph, XVIII $R^2=Et_2NCH_2CH_2$, XIX $R^2$=4-HO—3-$Et_2NCH_2CH_2$; X, XVII—XIX X=CH, XI X=N; XIV R=H, XV R=Ac

It is noteworthy that substitution of the dialkylamino group is not observed during the reaction, although this reaction proceeds very readily when monofunctional primary amines are used [7]. This fact indicates that the rate of formation of the XVI type significantly exceeds the rate of transamination



XVI XX

It was subsequently established that N-monosubstituted amino-o-quinones (III-V) also undergo condensation with ethylenediamine; the formation of benzo[2,3-f]quinoxalines (XVII-XIX) proceeds under more severe conditions than the formation of IX-XIII. The reaction takes place only at elevated temperatures, and the yields of products are appreciably lower. In our opinion, this difference is explained by the ability of monosubstituted amino-o-quinones to undergo deprotonation in basic media [8]. The formation of the XX anion is also a factor that hinders the course of the condensation. The development of a deep coloration at the start of the reaction, which gradually vanishes during the reaction, also constitutes evidence in favor of this opinion.

Thus we have shown that the condensation of o-quinones with ethylenediamine can be used in the synthesis of condensed heterocycles that contain a pyrazine fragment. It is important that quinoxalines that contain substituents that are characteristic for a number of medicinal preparations (for example, XVIII and XIX) can be obtained by this method.

## EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions in $CDCl_3$ were recorded with a Tesla BS-467 spectrometer (60 MHz) with tetramethylsilane (TMS) as the internal standard. The mass spectra were obtained with a Varian MAT-112 spectrometer (70 eV). The course of the reactions and the individually of the compounds obtained were monitored by thin-layer chromatography (TLC) on Silufol plates in

TABLE 1. Characteristics of the Compounds Obtained

| Compound | mp,* °C | Found, % | | | Empirical formula | Calc., % | | | Yield, % (isolation method) |
|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | | C | H | N | |
| IX | 210—211 | 64,0 | 6,6 | 18,5 | $C_{16}H_{20}N_4O_2$ | 64,0 | 6,7 | 18,7 | 42 |
| X | 171—173 | 72,6 | 6,0 | 15,4 | $C_{16}H_{15}N_3O$ | 72,4 | 5,7 | 15,8 | 97 (A) |
| XI | 150—152 | 67,5 | 5,6 | 20,6 | $C_{15}H_{14}N_4O$ | 67,7 | 5,3 | 21,0 | 68 (A) |
| XII | 184—185 | 72,7 | 7,0 | 20,4 | $C_{21}H_{25}N_5$ | 72,6 | 7,3 | 20,2 | 75 (A) |
| XIII | 150—151 | 72,4 | 6,0 | 13,2 | $C_{25}H_{26}N_4O_2$ | 72,4 | 6,3 | 13,5 | 64 (B) |
| XIV | 223—224 | 63,2 | 8,1 | — | $C_{16}H_{24}N_4O_2$ | 63,1 | 8,0 | — | 35 |
| XV | 194—196 | 61,6 | 7,0 | 14,0 | $C_{20}H_{28}N_4O_4$ | 61,8 | 7,3 | 14,4 | 78 |
| XVII | 163—165 | 80,0 | 5,1 | 15,7 | $C_{18}H_{13}N_3$ † | 79,7 | 4,8 | 15,5 | 37 |
| XVIII | 210—211 | 55,0 | 6,1 | 14,6 | $C_{18}H_{24}N_4O_4S$ | 55,1 | 6,2 | 14,3 | 35 |
| XIX | 181—182 | 59,0 | 5,4 | 12,3 | $C_{23}H_{24}N_4O_5S$ | 58,7 | 5,6 | 12,0 | 30 |

*The compounds were recrystallized: IX, XII, and XVIII from ethyl acetate, X, XI, XIV, and XVII from ethanol, XIII from benzene, XV from benzene—hexane, and XIX from ethanol—ether.
†IR spectrum: 3300 $cm^{-1}$ (broad, NH).

a chloroform–methanol system (10:1). Preparative TLC was carried out on plates with a loose layer of L 40/100 silica gel in a chloroform–methanol system (10:1).

Quinones I, II, and VI-VIII were synthesized by oxidative amination [6]. Compounds III and IV were obtained by catalytic transamination of quinone II [9].

The characteristics of the synthesized compounds are presented in Table 1.

4-(4-Hydroxy-3-diethylaminomethylphenyl)amino-1,2-naphthoquinone (V). This compound was synthesized in 72% yield from II and 4-hydroxy-3-diethylaminomethylaniline by the method in [9]. The dark-violet crystals had mp 209-210°C (chloroform–hexane). C 72.3; H 6.1; N 7.9%. $C_{21}H_{22}N_2O_3$. Calculated: C 72.0; H 6.3; N 8.0%.

Compound IX and 6,7-Dimorpholino-1,2,3,4-tetrahydroquinoxaline (XIV). A 0.6-ml (6 mmole) sample of ethylenediamine was added to a stirred suspension of 0.55 g (2 mmole) of quinone I in 6 ml of methanol, after which the mixture was stirred for 2 h. Water was then added, and the resulting precipitate was removed by filtration and crystallized twice from alcohol to give quinoxaline IX. PMR spectrum, δ: 2.82 (m, 8H, α-$CH_2$), 3.42 (m, 8H, β-$CH_2$), 6.88 (s, 2H, 5-H, 8-H), and 8.08 ppm (s, 2-H, 3-H). The mother liquors were combined, the solvent was removed by distillation, and the residue was crystallized three times from ethyl acetate to give XIV. IR spectrum, $cm^{-1}$: 3360, 3330 (NH). Mass spectrum, m/z: $M^+$ 304.

1,4-Diacetyl-6,7-dimorpholino-1,2,3,4-tetrahydro-quinoxaline (XV). A 0.63-ml sample of triethylamine was added to a solution of 0.45 g (1.5 mmole) of XIV in 5 ml of chloroform, 0.32 ml (4.5 mmole) of acetyl chloride was added dropwise, and the mixture was stirred for 1 h. The resulting solution was washed successively with water, 5% hydrochloric acid, and water and dried with $MgSO_4$. The solvents were removed by distillation, and the residue was chromatographed to give XV. IR spectrum, $cm^{-1}$: 1663 (CO). PMR spectrum, δ: 2.23 (s, 6H, $CH_3CO$), 3.12 (m, 8H, α$CH_2$), 3.81 (m, 12H, β-$CH_2$, 2-H, 3-H), and 6.71 ppm (m, 2H, 5-H, 8-H).

Reaction of Dialkylamino-o-quinones II, III, VII, and VIII with Ethylenediamine. The reaction was carried out by the method described above for quinone I. The reaction products were isolated by one of the methods presented below.

A) Water was added to the reaction mixture, and the resulting precipitate was removed by filtration washed with water, dried, and crystallized. PMR spectrum of XII, δ: 1.14 (m, 12H, β,γ-$CH_2$), 2.56 (m, 4H, α-$CH_2$), 3.16 (m, 4H, α-$CH_2$), 6.44[s, III, 7(5)-H], 6.64 [s, 1H, 5(7)-H], 7.96 (m, 2H, 2-H, 3-H), and 9.54 ppm (s, 1H, 10-H).

B) The reaction mixture was dissolved in chloroform, and the solution was washed with 5% HCl and water and dried with $MgSO_4$. The solvent was removed by distillation, and the residue was chromatographed on plates with silica gel to isolate the product. IR spectrum of XIII: 1725 $cm^{-1}$ (CO). Mass spectrum, m/z: $M^+$ 414.

Reaction of Quinones III-V with Ethylenediamine. A mixture of 2 mmole of quinone III (or IV or V) and 6 mmole of ethylenediamine was refluxed in 6 ml of methanol for 3 h. For the isolation of IX, 15 ml of water was added to the reaction mixture, and the resulting precipitate was removed by filtration, washed with water, and dried. In the case of XVIII and XIX the mixture was dissolved in chloroform, and the chloroform solution was washed with water and dried. The solvent was removed by distillation, and XVIII and XIX were isolated from the residue in the form of the sulfates.

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# CHEMICAL PROPERTIES OF YLIDENE DERIVATIVES OF AZINES. 3*. SYNTHESIS AND REACTIONS OF YLIDENE DERIVATIVES OF HALOPYRIMIDINES

O. A. Zagulyaeva, I. V. Semushkina, and V. P. Mamaev

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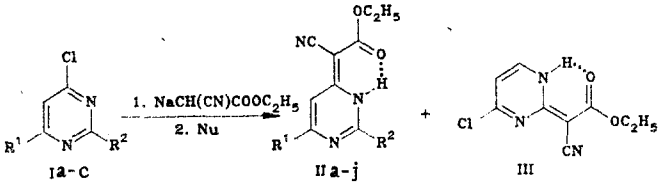
Some dihydropyrimidines have been obtained which contain a cyanoacetic ester or malononitrile residue and chlorine in positions, 2, 4, and 6. The reactions of these compounds with nucleophiles has been examined.

Continuing an investigation of methods of synthesis and chemical reactions of substituted ylidene derivatives of pyrimidine, we have examined the reaction of the dichloropyrimidines (Ia-c) with the sodium salts of cyanoacetic ester and malononitrile in aprotic bipolar solvents, and some further reactions of the products. Replacement of one chlorine atom by a cyanoacetic ester residue occurs with (Ia-c) to give the sodium salts of esters (IIa-c). The solvents used for the stable 4-chloro-derivative (IIa) may be DMSO or other aprotic bipolar solvents, but in the case of unstable pyrimidines such as (IIb), dimethoxy ethanes with the addition of DMF was employed. We have described the synthesis of the 4-chloro-compound (IIa) previously [2], but the spectral properties and some further reactions of this compound are described here.




I, II a $R^1$=Cl, b $R^1$=H, c $R^1$=$C_6H_5$; a $R^2$=H, b, c $R^2$=Cl; II d $R^1$=$N(CH_3)_2$, e $R^1$=$NC_5H_{10}$, f $R^1$=$NHNH_2$, g $R^1$=H, h–j $R^1$=$C_6H_6$; d–f $R^2$=H, g, i $R^2$=$NC_5H_{10}$, h $R^2$=$N(CH_3)_2$, j $R^2$=$NHNH_2$; Nu=$NH(CH_3)_2$, $NHC_5H_{10}$, $NH_2NH_2$

We have failed to observe replacement of a second chlorine atom by the cyanoacetic ester residue in pyrimidines (Ia-c), even in the presence of a large excess of sodiocyanoacetic ester, apparently as a result of the considerable deactivation of the chlorine in the sodium salts of (IIa-c). For example, we were unable to replace the chlorine atom in (IIa-c) by an alkoxy group on treatment with sodium alkoxides, this treatment also resulting, according to the UV spectra, in ionization. If, however, no ionization takes place, such as in the N-methylation product of (IIa) (IV), obtained as described in [1], the pyrimidine (IV) reacts with sodium ethoxide under mild conditions to give the ethoxy-compound (Va).

*For communication 2, see [1].

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