# REACTION OF 5,6-DIAMINO-1,3-DIMETHYLURACIL WITH CHALCONES

V. D. Orlov, I. Z. Papiashvili,
and P. A. Grigorov

UDC 547.854.2'857.4'859.1'892:
42.953.2.543.422'51

2,4-Diaryl-7,9-dimethyl-6,8-dioxo-2,3-dihydropyrimidino[5,6-b]-1,5-oxazepines are formed instead of the expected dihydrodiazepine derivatives in the reaction of chalcones with 5,6-diamino-1,3-dimethyluracil (I) in the presence of acetic acid. The reaction of 4-dimethylaminochalcone with diamine I leads to 8-(4'-dimethylaminophenyl)theophylline. A uracilyldihydrodiazepine derivative is formed only in the reaction of 2,6-di(4-anisylidene)cyclohexanone with diamine I. The structures of the synthesized compounds were confirmed by the results of elementary analysis and the IR, UV, PMR, and mass spectra.

Continuing our research on the reaction of o-diamines with α,β-unsaturated ketones [1, 2] we studied the chemical behavior of 5,6-diamino-1,3-dimethyluracil (I). Despite the fact that diamine I is widely used in reactions with carbonyl compounds to obtain derivatives of purine, lumazine, and other mononuclear heterocycles [3-5], there has been only one communication [6] regarding its reaction with α,β-unsaturated ketones (mesityl oxide), which leads to the formation of the corresponding pyrimidinodihydrobenzodiazepine derivative (the same product was also obtained by the reaction of diamine I with acetone and diacetone alcohol [6]).

It has been previously shown [1] that o-phenylenediamine reacts readily with chalcones in the presence of tertiary amines to give 2,3-dihydro-1H-1,5-benzodiazepine derivatives. The same starting components form 2-arylbenzimidazoles under acidic catalysis conditions. Experiments carried out with 5,6-diamino-1,3-dimethyluracil (I) showed that the base-catalyzed reactions of this diamine with aromatic α,β-unsaturated ketones lead to complex mixtures of substances, while individual products II-XIV are formed in good yields in the presence of catalytic amounts of acetic or hydrochloric acid. Their identification and the study of their properties are the subject of the present communication. Compounds II-XIV were subjected to elementary analysis, and their UV, IR, and PMR spectra were recorded (Table 1); the mass spectra of the remaining substances were also recorded (Table 2).

In analyzing the experimental data obtained for II-XII one may note the following facts. An intense broad ($\Delta\nu_{1/2}$ ~45-50 $cm^{-1}$) band with $\nu_{max}$ 1690 $cm^{-1}$, which is complex in character, is retained in their IR spectra in the region of carbonyl absorption; a band that is characteristic for the stretching vibrations of the C=N bond appears at 1602-1616 $cm^{-1}$, but a $\nu_{NH}$ band is absent. The signal of the proton of the N–H group is also not observed in the PMR spectra, but two singlets of methyl groups at 2.8-2.9 and 3.35-3.44 ppm and multiplets of a CH–$CH_2$ grouping at 4.12-4.25 and 3.30-3.90 ppm show up distinctly. Compounds II-XII absorb in the near-UV region, but their long-wave bands are shifted significantly to the short-wave region as compared with the absorption bands of the corresponding 2,4-diaryl-1H-2,3-dihydro-1,5-benzodiazepines [1].

In establishing the structures of II-XII we found that it was useful to recall the fact that the 6-amino group of diamine I is capable of undergoing hydrolysis in acidic media [7]. The resulting 5-amino-1,3-dimethylbarbituric acid can react with chalcogens to give 2,4-diaryl-7,9-dimethyl-6,8-dioxo-2,3-dihydropyrimidino[5,6-h]-1,5-oxazepine. (See Scheme 1.)

To verify this assumption we accomplished the stepwise synthesis of II: the hydrolysis of 5,6-diamino-1,3-dimethyluracil (I) in an acidic medium or reduction of 5-nitroso-1,3-dimethylbarbituric acid gave 5-amino-1,3-dimethyl barbituric acid, which was then subjected

A. M. Gor'kii Kharkov State University, Kharkov 310077. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 671-676, May, 1983. Original article submitted August 2, 1982.

 0009-3122/83/1905-0544$07.50 

TABLE 1. 2-R-4-R'-7,9-Dimethyl-6,8-dioxo-2,3-dihydropyrimidino[5,6-b]-1,5-oxazepines (II-XII)

| Compound | R | R' | mp, °C | IR spectrum (in KBr), ν, cm⁻¹ | | UV spectrum (in methanol), $\lambda_{max}$, nm ($\varepsilon \cdot 10^{-3}$) | N found, % | Empirical formula | N calc., % | Reflux time, h | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | νC=N | νC=O | | | | | | |
| II | $C_6H_5$ | $C_6H_5$ | 227—228 | 1613 | 1698 | 308 (1,4), 245 (17,2) | 11,8 | $C_{21}H_{19}N_3O_3$ | 11,6 | 3 | 82 |
| III | $C_6H_5$ | 4-$CH_3$—$C_6H_4$ | 204—205 | 1608 | 1688 | 311 (10,7), 246 (25,2), 229 (30,8) | 11,3 | $C_{22}H_{21}N_3O_3$ | 11,2 | 1,5 | 74 |
| IV | $C_6H_5$ | 4-$CH_3O$—$C_6H_4$ | 190—191 | 1612 | 1690 | 317 (5,5), 277 (21,5) | 10,7 | $C_{22}H_{21}N_3O_4$ | 10,7 | 1,5 | 67 |
| V | $C_6H_5$ | 4-$NH_2$—$C_6H_4$ | 213—214 | 1610 | 1690 | 318 (15,5), 226 (19,2) | 14,8 | $C_{21}H_{20}N_4O_3$ | 14,9 | 1,5 | 70 |
| VI | $C_6H_5$ | 4-$C_6H_5$—$C_6H_4$ | 193—194 | 1612 | 1688 | 370 (2,0), 286 (26,1), 230 sh. | 9,6 | $C_{27}H_{23}N_3O_3$ | 9,6 | 1,5 | 75 |
| VII | $C_6H_5$ | 4-Cl—$C_6H_4$ | 197—198 | 1615 | 1690 | 317 (3,6), 255 (24,8) | 10,6 | $C_{21}H_{18}ClN_3O_3$ | 10,6 | 1 | 80 |
| VIII | $C_6H_5$ | 4-Br—$C_6H_4$ | 220—221 | 1616 | 1688 | 318 (3,6), 262 (26,0) | 9,4 | $C_{21}H_{18}BrN_3O_3$ | 9,5 | 2 | 83 |
| IX | $C_6H_5$ | 2-$C_4H_3S$* | 195—196 | 1602 | 1686 | 350 (2,5), 289 (10,8), 259 (11,5), 230 (13,8) | 11,7 | $C_{19}H_{17}N_3O_3S$ | 11,4 | 2 | 79 |
| X | 4-$CH_3O$—$C_6H_4$ | $C_6H_5$ | 224—225 | 1610 | 1688 | 310 sh., 285 sh., 246 (20,0), 231 (22,0) | 10,8 | $C_{22}H_{21}N_3O_4$ | 10,7 | 1,5 | 64 |
| XI | 4-Cl—$C_6H_4$ | $C_6H_5$ | 220—221 | 1615 | 1690 | 307 (1,2), 285 sh., 243 (19,2), 235 (17,3) | 10,6 | $C_{21}H_{18}ClN_3O_3$ | 10,6 | 1 | 80 |
| XII | 4-Br—$C_6H_4$ | $C_6H_5$ | 241—242 | 1613 | 1685 | 306 (2,3), 285 sh, 242 (20,8), 234 (20,8) | 9,5 | $C_{21}H_{18}BrN_3O_3$ | 9,5 | 1,5 | 82 |

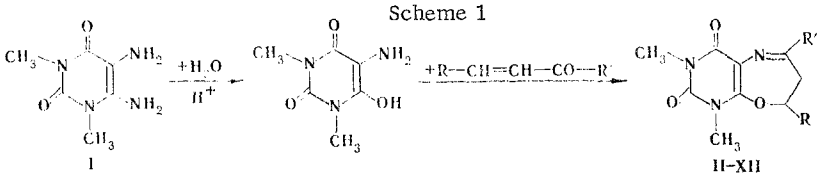
*2-Thienyl.

TABLE 2. Mass Spectra of II, VII, X, and XII

| Compound | m/z values (peak intensities, %)* |
|---|---|
| II | 362 (10), **361 (60)**, 344 (9), 258 (11), 257 (58), 246 (6), 206 (10), 201 (7), 200 (47), 199 (29), 191 (7), 172 (11), 115 (15), 106 (9), 105 (100), 104 (9), 103 (9), 78 (7), 77 (27), 68 (7), 60 (7), 58 (7), 57 (10), 55 (9) |
| VII | 398 (6), **397 (27)**, 396 (20), **395 (75)**, 378 (12), 293 (23), 292 (14), 291 (62), 240 (18), 236 (18), 235 (8), 234 (44), 206 (15), 191 (7), 189 (8), 149 (9), 141 (36), 140 (13), 139 (100), 115 (11), 114 (10), 111 (16), 104 (16), 103 (8), 102 (7), 78 (10), 77 (8), 69 (12), 58 (10), 55 (12) |
| X | **391 (58)**, 390 (27), 389 (6), 376 (7), 375 (21), 374 (6), 287 (8), 286 (11), 283 (26), 276 (7), 256 (8), 236 (18), 200 (38), 199 (29), 172 (10), 144 (7), 138 (8), 136 (8), 135 (100), 121 (8), 119 (17), 106 (7), 105 (56), 104 (38), 103 (9), 91 (13), 77 (16), 68 (11) |
| XII | **441 (14)**, **439 (14)**, 424 (6), 422 (6), 285 (10), 283 (9), 258 (7), 257 (48), 256 (19), 201 (8), 200 (52), 199 (8), 172 (14), 130 (6), 115 (9), 106 (10), 105 (100), 104 (19), 103 (12), 77 (24) |

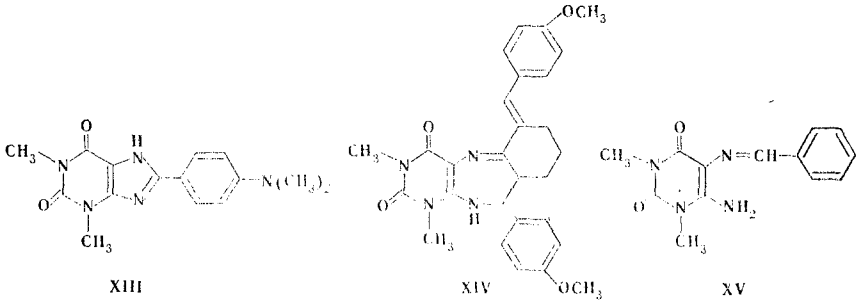
*The peaks of ions with m/z > 50 and intensities >5% are presented; the molecular-ion peaks are printed in boldface.

Scheme 1



See Table 1 for the R and R' values

to reaction with chalcone by the general method. The product was identical to II. The proposed structure is in good agreement with the results of elementary analysis and the spectral characteristics (Tables 1 and 2).



The reaction of diamine I with 4-dimethylaminochalcone proceeded via a new pathway. According to the results of elementary analysis and the spectral characteristics, 8-(4'-dimethylaminophenyl)theophylline (XIII) was obtained in this case. It was previously demonstrated [8] in the case of the base-catalyzed reaction of α,β-unsaturated ketones with o-phenylenediamine that the inclusion of a dimethylamino group in the aromatic ring of ketones hinders the formation of a dihydrodiazepine structure. This is probably due to the reduced polarity of the chalcone multiple bond due to strong mesomeric interaction of the electron-donor dimethylamino group and the electron-acceptor O=C group. It is also known [9] that in acidic media benzodihydrodiazepines readily undergo rearrangement to benzimidazole derivatives with retention of the group in the 2 position of the seven-membered heteroring. The formation of XIII is probably due to the combined manifestation of both factors.

The desired pyrimidinodihydrodiazepine product (XIV) was obtained in good yield (75%) only in the reaction of diamine I with 2,6-di(4-anisylidene)cyclohexanone. This is confirmed by the presence in the IR spectrum of a $\nu_{NH}$ band (3440 $cm^{-1}$), by the presence in the PMR spectrum of a signal of the proton of the N–H group ($\delta$ = 2.93 ppm), and by the results of elementary analysis. The electronic absorption spectra of XIV and II-XII also differ substantially in character. The change in the direction of the process is possibly associated with the fixed s-cis conformation of the ketone, although 2,6-dibenzyldienecyclohexanone

under similar conditions gave a complex mixture of substances. It should be noted that, according to the data in [4, 6], the synthesis of a number of compounds on the basis of 6-aminouracils was realized in acidic media, in which hydrolysis was not observed. We also obtained the same azomethine (XV) in the reaction of benzaldehyde with diamine I both in the presence and absence of acetic acid; the azomethine bond is formed in the 5 position of the uracil ring [4], and the amino group in the 6 position is retained, which is confirmed by the presence of a doublet of intense $\nu_{NH}$ bands in the IR spectra at 3407 and 3287 $cm^{-1}$. It may therefore be assumed that the nature of the carbonyl compound has a substantial effect on the rate of hydrolysis of diamine I, but this problem requires special study.

The formation of two isomeric pyrimidinodihydrodiazepine two-ring systems is possible in the reaction of diamine I with α,β-unsaturated ketones. The selection of structure XIV as the preferred structure was based on the following considerations. The amino group in the 5 position of diamine I has aromatic character and is more inclined to undergo condensation reactions with carbonyl compounds [3, 7]. The $\nu_{NH}$ and $\delta_{NH}$ bands of XIV are typical for unperturbed H association of the imino group; in the alternative isomer, however, the spatial closeness of the proton of the N—H group and the oxygen atom of the carbonyl group in the 4 position could promote the establishment of an intramolecular hydrogen bond. It is also noteworthy that a structure similar to that of XIV has also been proposed for the product of condensation of diamine I with mesityl oxide [6].

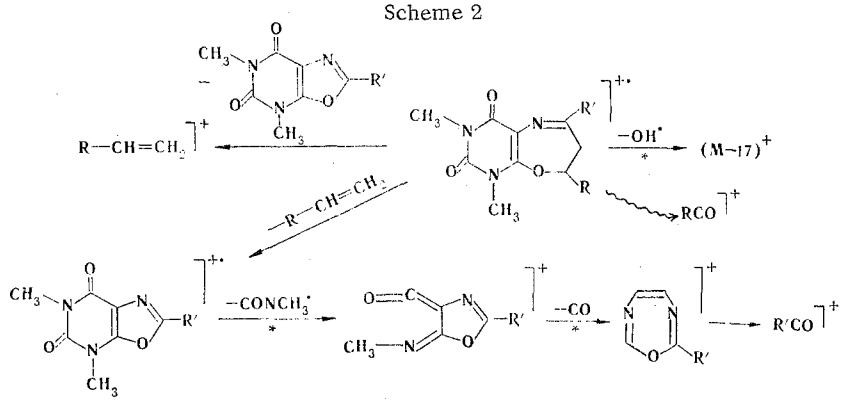
Compounds II-XII are derivatives of the previously undescribed pyrimidinodihydrooxazepine two-ring system, and a more detailed analysis of their spectral characteristics therefore seemed of interest. These compounds have rather specific electronic absorption spectra: an intense band at 245-290 nm is observed in them (Table 1). The presence of inflections and weakly expressed maxima on its long-wave branch indicate that the absorption of several electron transitions with close energies appear in this region. The lowest-frequency transition of these appears in some cases (for example, in the spectra of III, VI, IX, and XII) in the form of an autonomous band of low intensity. This transition has $\pi—\pi^*$ character, as evidenced by the solvent effect; replacement of alcohol by isooctane promotes a hypsochromic shift of the band under discussion (for example, $\Delta\lambda_{max}$ is 5 nm for II). The electronic absorption spectra of compounds that contain a dihydrodiazepine ring are completely different in character and in the near UV consist of a series of well-resolved and intense bands [1, 2]; this is also the case for the spectrum of XIV [$\lambda_{max}(\varepsilon\cdot10^{-3})$ in ethanol: 363 (9.5), 267 sh, and 261 nm (33.0)].

In the PMR spectra of II-XII one's attention is drawn to the fact that replacement of substituents R and R' has virtually no effect on the chemical shifts of the protons of the methyl groups and the seven-membered ring. Moreover, in comparing the δ values of the protons of the $N—CH_3$ groups of II-XII (discussed above) and compounds in which the nitrogen atom in the 6 position is retained [for example, starting diamine I (3.39, 3.52 ppm), azomethine XV (3.41, 3.54 ppm), lumazine XVI (3.63, 3.86 ppm; obtained for comparison from diamine I and benzil), 4-phenyltheophylline (3.63 and 3.88 ppm, in $CF_3COOH$ [5]), and a number of other groups of compounds [5]] one may note the high sensitivity of these values ($\delta N—CH_3$) to the size of the ring fused with uracil and particularly to the character of the heteroatom in the 6 position of the uracil ring. This primarily applies to the protons of the $N^1$-methyl group. It may therefore be assumed that the anisotropic effect of the heteroatom under discussion affects their chemical shift. The difference in the δ values of the methyl groups for the uracilyldihydrooxazepines ranges from 0.52 to 0.62 ppm (whereas it does not exceed 0.25 ppm for the nitrogen analogs) and may serve as an analytical characteristic of these compounds.

We also measured the mass spectra of II, VII, X, and XII (Table 2). This choice of compounds makes it possible, in our opinion, to ascertain the general tendencies of the fragmentation of the molecules. We found that splitting out of a hydroxy radical is an indispensable primary process. The process is confirmed by the presence of metastable ions in the mass spectra. However, considering the low intensity of the peak of the $(M-17)^+$ ion, it may be assumed that this process is not the principal process. As in the case of aromatic derivatives of 2,3-dihydro-1H-1,5-benzodiazepines [10], the principal primary pathway of the fragmentation of the molecular ion is rearrangement to an oxazolouracil system (with the loss of $R—CH—CH_2$). The fragmentation of such oxazolouracils has not been described in the literature, but, judging from the most intense peaks, it is basically identical to the processes described for theophylline [11]. However, the presence of an endocyclic oxygen atom in the molecules of the investigated compounds nevertheless is reflected in the high

probability of the formation of $R'CO^+$ ions (and the $RCO^+$ ion in the case of X). Thus the overall pathway of the fragmentation of the molecules of the investigated compounds can be represented by the following scheme:

Scheme 2



*Metastable ions.

The fact that the principal fragment ions have m/z values that are one unit lower than in the case of the corresponding 8-R'-theophyllines confirms the presence of an oxygen atom in the seven-membered ring of the compounds.

## EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Specord IR-75 spectrometer. The electronic absorption spectra of solutions of the compounds in methanol [$(2-3)\cdot10^{-5}$ mole/liter] were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in $CDCl_3$ were recorded with a Tesla-80 spectrometer with tetramethylsilane as the internal standard. The mass spectra were obtained with a Varian MAT CH-6 spectrometer with direct introduction of the samples into the ion source (the ionization-chamber temperature was 180°C, the ionizing voltage was 70 eV, and the emission current was 100 μA; the temperature at which the samples were heated ranged from 50 to 70°C, depending on their volatilities).

2,4-Diphenyl-7,9-dimethyl-6,8-dioxo-2,3-dihydropyrimidino[5,6-b]-1,5-oxazepine (II). Glacial acetic acid (0.5-1 ml) was added to a solution of 0.5 g (2.9 mmole) of 5,6-diamino-1,3-dimethyluracil (I) and 0.6 g (2.9 mmole) of chalcone in 25 ml of methanol, and the mixture was refluxed for 3 h. It was then cooled, and the resulting yellowish precipitate was crystallized from acetic anhydride to give 0.87 g (82%) of white crystals with mp 227-228°C. Compounds III-XII (see Table 1), as well as XIII [mp 255-256°C, reflux time 2 h, 72% yield; $\lambda_{max}(\varepsilon\cdot10^{-3})$ in methanol: 357 (29.0), 267 (20.0), and 228 nm (24.5)] and XIV [mp 164-165°C, reflux time 1.5 h, 75% yield; $\lambda_{max}(\varepsilon\cdot10^{-3})$ in methanol: 363 (9.5), 267 sh, and 261 nm (33.0)], were similarly synthesized with variation of only the reflux time.

6-Amino-5-benzylideneamino-1,3-dimethyluracil (XV). A solution of 0.5 g (2.9 mmole) of diamine I and 0.3 ml (2.9 mmole) of benzaldehyde in 20 ml of methanol was refluxed for 1 h, after which it was cooled, and the precipitated crystals were removed by filtration and crystallized from methanol to give 0.66 g (87%) of a product with mp 224-225°C (mp 225°C [4]).

1,3-Dimethyl-6,7-diphenyllumazine (XVI). The formation of light-yellow crystals was observed when a solution of 0.5 g (2.9 mmole) of diamine I and 0.61 g (2.9 mmole) of benzil in 40 ml of methanol was heated to the boiling point. The solution was refluxed for 1 h and cooled, and the precipitate was removed by filtration and crystallized from methanol to give 0.84 g (83%) of XVI with mp 220°C; $\lambda_{max}(\varepsilon\cdot10^{-3})$ in methanol: 336 (8.3), 280 (12.0), and 227 nm (21.5).

## LITERATURE CITED


1. V. D. Orlov, N. N. Kolos, F. G. Yaremenko, and V. F. Lavrushin, Khim. Geterotsikl. Soedin., No. 5, 697 (1980).
2. V. D. Orlov, I. Z. Papiashvili, M. V. Povstyanoi, V. A. Idzikovskii, and O. M. Tsyguleva, Khim. Geterotsikl. Soedin., No. 1, 93 (1983).

3. D. J. Brown, R. F. Evans, and F. J. Batterham, The Pyrimidines, Suppl. 1, Wiley-Interscience (1970), pp. 106, 254.
4. F. Yoneda and M. Hiquchi, J. Chem. Soc. Perkin Trans. I, No. 6, 1336 (1977).
5. S. Wawzonek, J. Org. Chem., 41, 310 (1976).
6. D. Q. Quan, R. Caujolle, and T. B. T. Dang, Compt. Rend., Ser. C, 274, 885 (1972).
7. D. J. Brown and S. F. Mason, The Pyrimidines, Interscience, New York (1962), pp. 229, 321.
8. V. D. Orlov, N. N. Kolos, and V. F. Lavrushin, Khim. Geterotsikl. Soedin., No. 6, 827 (1981).
9. V. D. Orlov, N. N. Kolos, S. M. Desenko, and V. F. Lavrushin, Khim. Geterotsikl. Soedin., No. 6, 830 (1982).
10. V. D. Orlov, N. N. Kolos, and B. M. Zolotarev, Khim. Geterotsikl. Soedin., No. 3, 390 (1983).
11. G. Spiteller and M. Spiteller-Friedmann, Monatsh. Chem., 93, 632 (1962).

# DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE NODAL POSITIONS. 9.* INTRAMOLECULAR CYCLIZATION OF N-(γ-BROMOPROPYL)-TETRAHYDROQUINOXALINES AND BEHAVIOR OF BENZO[f]-1,5-DIAZABICYCLO[3.2.2]NONENE IN HYDROBROMIC ACID

A. A. Gall' and G. V. Shishkin

UDC 547.863.13'859.5.7'896'897.07:543.422'51

The introduction of an N,N'-trimethylene bridge in the tetrahydroquinoxaline molecule is complicated by cyclization of γ-bromopropyl derivatives of tetrahydroquinoxaline at the carbon atom of the aromatic ring. The reaction of N-R-tetrahydroquinoxalines (R = H, $COCH_3$) with 1,3-dibromopropane leads to products of cyclization at the aromatic ring (1,2,3,5,6,8,9,10-octahydropyrazino[1,2,3,4-*l*,m,n][1,10]phenanthroline and N-acetyl-1,2,6,7-tetrahydro-3H,5H-pyrido[1,2,3-d,e]quinoxaline) and to an N-alkylation product [N-acetyl-N'-(γ-bromopropyl)-1,2,3,4-tetrahydroquinoxaline]. Benzo[f]-1,5-diazabicyclo[3.2.2]nonene is formed in only trace amounts in the cyclization of N-(γ-bromopropyl)tetrahydroquinoxaline and upon heating in HBr can be isomerized with migration of the trimethylene bridge to the aromatic ring.

Continuing our search for methods for the preparation of diazabicycloalkanes with nitrogen atoms in the nodal positions we investigated the possibility of the synthesis of the previously described benzo[f]-1,5-diazabicyclo[3.2.2]nonene (I) system [2] by the introduction of a trimethylene bridge in the 1,2,3,4-tetrahydroquinoxaline (II) molecule. The introduction of a trimethylene bridge in an aromatic diamine molecule has been described in the literature. Thus naphtho[1,8-f,g]-1,5-diazabicyclo[3.3.3]undecene was obtained by the reaction of 1,8-diaminonaphthalene with 1,3-dibromopropane [3], while benzo[j]-1,5-diazabicyclo[3.3.2]-decene was obtained from o-phenylenediamine under similar conditions [4]. However, the yields of these compounds were only 5 and 3.7%, respectively. The data on the synthesis of 4'-methylbenzo[1',2'-f]-1,5-diazabicyclo[3.2.2]nonene by the action of dibromopropane on 6-methyl-1,2,3,4-tetrahydroquinoxaline [5] were not confirmed when they were checked [2]. The formation of I also was not observed in the action of excess 1,3-dibromopropane on II in the presence of calcium oxide. According to the results of elementary analysis and the mass spectrum, the principal reaction product contained two trimethylene fragments per molecule of tetrahydroquinoxaline. The PMR spectrum of this compound contains a singlet of two aromat-

*See [1] for Communication 8.

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 677-681, May, 1983. Original article submitted August 16, 1982.