LACTAM AND ACID AMIDE ACETALS.

63.* REACTION OF AMIDE ACETALS WITH ENAMINODICARBONYL COMPOUNDS

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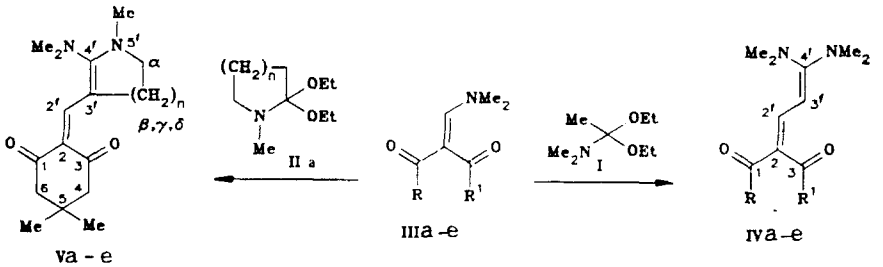
Corresponding dienediaminodicarbonyl compounds were synthesized by the reactions of a series of dimethylaminomethylenedicarbonyl compounds with N,N-dimethylacetamide and N-methylcaprolactam diethylacetals. In the reaction of N-methylvalerolactam diethylacetal, the process is accompanied by a rearrangement with the formation of a 3-methylenepiperidon-2-one derivative. It was found that the introduction of a substituted amino group into the meso-position of the intermediate α-alkoxyenamine (in the preparation of dienediaminodicarbonyl compounds) takes place intermolecularly, and a general scheme of the unusual reaction studied has been proposed.

It has previously [2, 3] been found that N,N-dimethylacetamide (Ia) and N-methylbutyrolactam diethylacetals (IIa) react with 2-dimethylaminomethylenecyclohexane-1,3-dione derivatives (IIIa, b) with the formation of substituted dienediaminodiketones IVa, b and Va, which are promising as starting compounds in heterocyclic synthesis, in particular for the preparation of coumarin and carbostyril derivatives. To extend the range of application of this new and unusual reaction, in the present work we used acetal I and N-methylvalerolactam (IIb) and caprolactam diethylacetals (IIc) as the acetal component and dimethylaminomethylene derivatives of dimedone IIIb, the Meldrum acids IIIc, acetylacetone IIId and dibenzoylmethane IIIe as the enaminodicarbonyl component. The reaction of acetal I with enamines IIIc-e leads smoothly to dienediamines IVc-e. In a similar way, in the reaction of N-methylcaprolactam acetal (IIc) with dimethylaminomethylenedimedone (IIIb), dienediaminodiketone Vc was obtained in good yield, which leads us to conclude that the observed reaction of the amine and lactam acetals with enaminodicarbonyl derivatives [2, 3] is general is character:



Va - e

III, IV a R–R¹=—(CH₂)₃—; b R–R¹=—CH₂—CMe₂—CH₂—; c R–R¹=—O—CMe₂—O—; d R=R¹=Me; e R=R¹=Ph; II, V a $n=1$, b $n=2$, $n=3$

In the PMR spectra of compounds IVa-e (Table 1),† the most characteristic is the presence of singlets of the dimethylamino group protons in the 2.98-3.32 ppm region and doublets of the diene fragment protons at 7.56-8.05 (2'-H) and 5.96-6.88 ppm (3'-H) with $^3J_{2',3'}$ = 13.5-14.7 Hz, which indicates an s-trans-configuration of the olefinic protons. In the PMR spectrum of dienediamine Vc, the olefinic proton 3'-H is represented by a signal at 7.34 ppm,

*For communication 62, see [1].

†The PMR and mass spectra of compound IVa are given in [2].

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TABLE 1. PMR Spectra of Compounds IVb-e, Vc, Xa, b ($CDCl_3$) and VI (DMFA-D_7)

Compound*	Chemical shift, δ, ppm						SSCC, $^3H_{2'};_{3'}$, Hz
	5-C$(CH_3)_2$, s	4,6-H, s	2'-H	3'-H, d	4'-N$(CH_3)_2$, s	other groups	
IVb	1,05	2,35	7,92 d	6,86	3,09	—	14,7
IVc	1,89	—	8,05 d	6,57	3,32	—	14,7
IVd	—	—	7,56 d	6,25	3,03	2,32 (c, $COCH_3$)	13,5
IVe	—	—	7,82 d	5,97	2,98	7,20 7,56 (m, C_6H_5)	14,0
Vc	1,05	2,25	7,34 c	—	2,96	3,12 (c, 5'-NCH_3)	—
VI	1,03	2,13 (6,H); 2,43 (4,H)	6,62 c	—	—	2,86 (c, 3-N$(CH_3)_2$); 2,81 (c, 5'-NCH_3)	
IXa	1,05	2,34	7,95 d	6,88	3,08	4'-NC_5H_9	14,6
IXb	1,05	2,34	7,98 d	6,87	—	1,74 (m, β,β,γ-CH_2) 3,42 (m, α,α-CH_2) 4',4'-NC_5H_9 1,73 (m, β,β,β',β',γ,γ'-$CH)_2$ 3,40 (m, α,α,α',α'-CH_2)	14,6

*For compound Vc, the description of the spectral characteristics of the α,β,γ,δ-CH_2 groups is given in the text; for compound VI: 3.35 (α-CH_2), 1.91 (β-CH_2), 2.55 ppm (γ-CH_2).

and the dimethylamino group by a broadened signal at 2.97 ppm. Increase in the exposure temperature of the sample (to 60°C) leads to a substantial contraction of the latter signal. This change in the form of the NCH_3 group signal is possibly due to a partial retardation of rotation of this group relative to the C—N bond. The signals of the methylene group protons of the tetrahydroazepine ring of compound Vc have a more complex pattern of splitting in the PMR spectrum than in the case of the pyrroline analog Va [3] due to the conformational features of the seven-membered ring. The signals of these fragments could be unequivocally identified by means of the double resonance method. The ring α-methylene protons are represented in the spectrum by two multiplets at 4.05 (α-H_a, $^2J_{a,\alpha}$ = 14.5 Hz, $^3J_{\alpha-a,\beta-a}$ = 11.5 Hz, $^3J_{\alpha-a,\beta-e} \approx 2$ Hz) and 3.25 ppm (α-H_e, $^3J_{\alpha-a,\beta-a}$ = 4.4 Hz, $^3J_{\alpha-e,\beta-e} \approx 1$ Hz). The δ-CH_2 group protons are also represented by two signals at 2.60 (δ-H_e, $^2J_{\delta,\delta}$ = 14.0 Hz, $^3J_{\delta-e,\beta-e}$ = 4.5 Hz, $^3J_{\delta-e,\beta-e} \approx 2$ Hz) and 1.93 ppm (δ-H_a). The last multiplet is partly overlapped by the signal of an axially-oriented proton of the γ-CH_2 group (γ-H_a, 1.90 ppm). The remaining protons of the tetrahydroazepine ring are observed at 1.70 (β-H_e), 1.54 (γ-H_a), and 1.53 ppm (β-H_a).* It should be noted that, in the PMR spectra, the methylene groups at the 4- and 6-positions of the dimedone fragment, both in the dienamine IVb and in compound Vc, are represented by a slightly broadened singlet with an intensity of 4H at 2.35 (IVb) and 2.25 ppm (Vc). A similar pattern is observed in the PMR spectrum of compound Va: 2.33 (s, 4H, 4,6-CH_2).†

The mass spectral decomposition of compound Vc is mainly determined by the elimination of the Me_2N group and the methyl radical (here and below, the values of m/z are given, while the relative intensity with respect to the maximal ion peak, in %, is given in brackets): $M^{+\cdot}$ 304(9) $[M^+-Me_2N]^+$ 280(13), $[M^+-Me_2NH]^+$ 259(22), $[M^+-Me_2N-Me]^+$ 245(17), $[M^+-Me_2NH-Me]^+$ 244(100).

In the reaction of valerolactam acetal (IIb) with enamine IIIb, the dienediamine Vb, structurally analogous to compounds of the five- and seven-membered series (Va, c) was not isolated. Judging from the PMR spectra, the structure of compound VI obtained differs substantially from the structure of compounds Va, c. The characteristic feature of the spectrum of compound VI is the nonequivalence of the methylene groups of the dimedone fragment: 2.43 (2H, 4-H) and 2.12 ppm (2H, 6-H), whereby the two signals are broadened. As has already been mentioned above, in the PMR spectra of dienediamines IVb and Va, b the 4- and 6-methylene group protons are represented by a common signal with the intensity of 4H. At the same time, for the product of the thermal rearrangement of

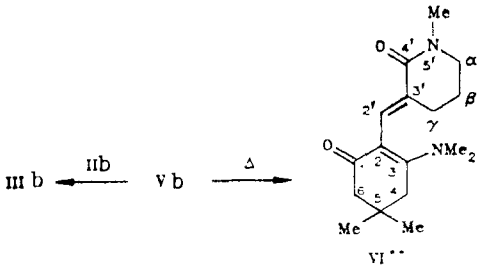
*Because of the overlap of the signals, the values of the vicinal and geminal SSCC for the β- and γ-CH_2 groups and of the vicinal SSCC for δ-H_a were not determined.

†The PMR spectrum of compound Va was described in [3], and of compound IVb in [2], but in the course of the present investigation compound IVb was isolated again and identified in the reaction of enamine VIII with acetal I.

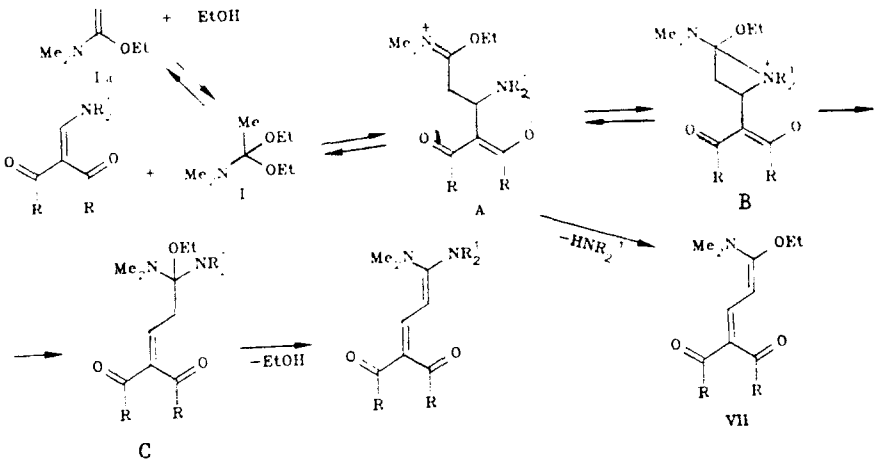
the dienediamine IVb, a nonequivalence of the signals of the 4,6-CH_2 group of the dimedone fragment was noted in the PMR spectrum: 2.43 (2H, 4-H) and 2.23 ppm (2H, 6-H) [2].

In the mass spectrum of compound VI, a peak of the molecular ion 290(90) $M^{+\cdot}$ and the following ion peaks are observed: $[M^+-Me]^+$ 275(48), $[M^+-NMe]^+$ 261(7), $[M^+-Me_2NCH_2]^+$ 247(34), $[M^+-Me-MeNCH_2]^+$ 232(12), $[M^+-MeN-COCH_2]^+$ 219(42), $[M^+-MeN-COCH_2-Me]^+$ 204(28). The maximally intense peak belongs to the ion 213(100), which is probably formed from ion 261 during the elimination of 43 atomic units ($MeNCH_2$ or CO and Me). When the $COCH_2$ group is split off from ion 247, ion 205(60) is formed, while the cleavage of the bond between the rings gives the intense peak of 178(78).

The above data, in combination with the previously obtained results for the thermal rearrangement of dienediamine IVb into the amide of β-(2-N,N-dimethylamino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)acrylic acid [2] indicate that in the reaction of enamine IIIb with acetal IIb, a dienediamine Vb is formed which, under the reaction conditions, rearranges into the derivative of 3-methylenepiperidon-2-one VI:*



For the sake of convenience during the compilation of Table 1, the same numeration of the atoms in the molecules was adopted for compounds IV-VI.

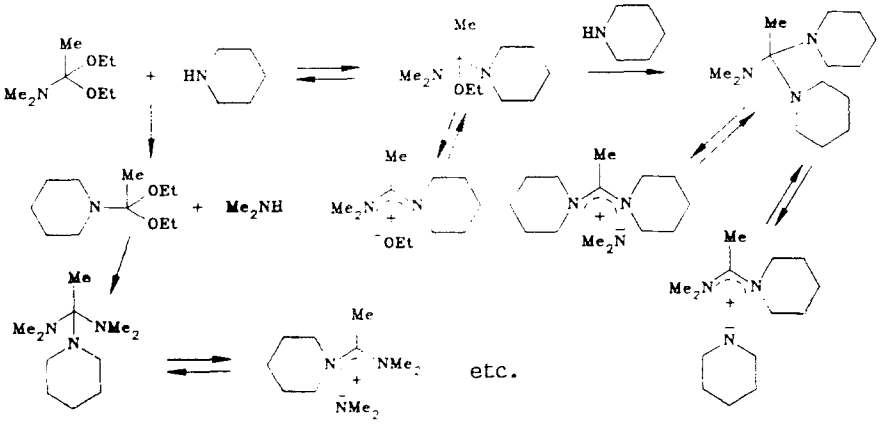


Summarizing the investigations of the reaction of the amide and lactam acetals with enaminodicarbonyl compounds, it can be confidently stated that the first stage in the process is the addition of a ketene acetal (present in equilibrium with the amide and lactam acetals [4]) at the α-position of the starting enamines with the formation of an intermediate zwitterion (A), which is then further stabilized in two ways — due to splitting of the corresponding amine with the formation of ethoxy derivative VII, or by an intramolecular transfer (A → B → C) of the substituted amino group into the meso-position of the iminoether fragment (see Scheme 1).

In other words, the problem consists in ascertaining whether the final reaction products — the dienediamines of type IV — are formed as a result of an intra- or intermolecular process. To clarify this problem, in the reaction with acetal I we used an enaminodiketone having as the amino fragment not the dimethylamino group (as in acetal I), but the piperidino group — 2-piperidinomethylenedimedone (VIII), which was obtained by transamination of compound IIIb with piperidine [4]. It is clear that under the conditions of an intramolecular process (A → C) only one dienediaminodiketone should be formed, which contains dimethylamino and piperidino groups. To find the

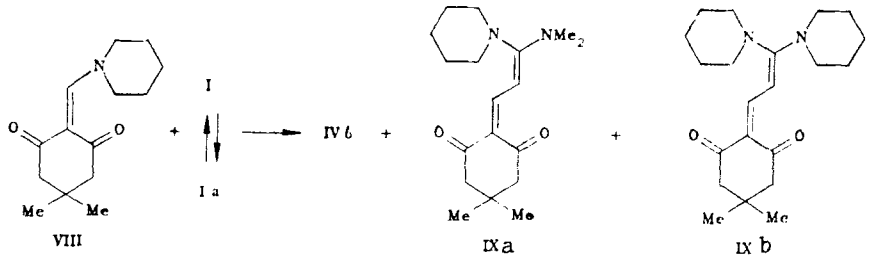
*A detailed investigation of this new rearrangement of dienediamines and examination of the scheme of its occurrence will be published in one of forthcoming articles.

possible composition of the products of the intermolecular introduction of the substituted amino group, let us consider the problem of the reaction of secondary amines with excess acetal present in the reaction mixture. It follows from the numerous investigations concerning this problem and summarized in [5] that this reaction proceeds according to the following scheme (using the compounds of the present investigation as an example):

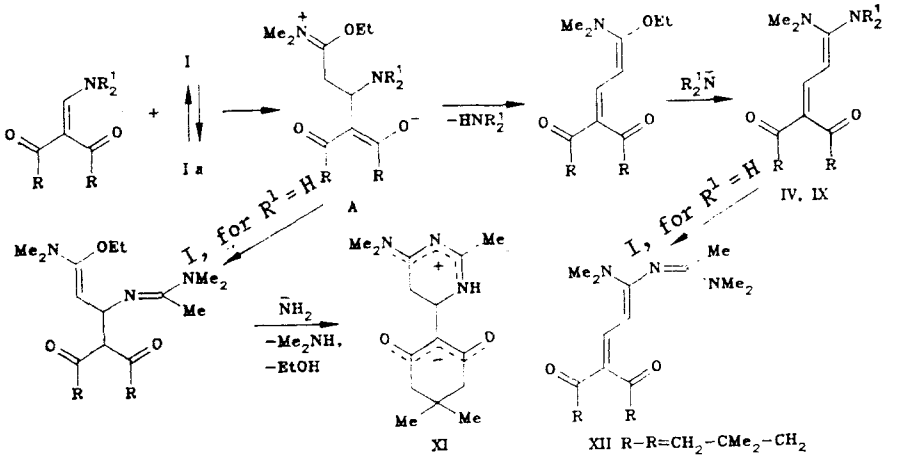


Thus, in the equilibrium mixture there are both dimethylamide and piperidine anions which are free to react with the intermediate alkoxyenamine VII with the formation of three dienediamines containing bisdimethylamino- and bispiperidinomethylene fragment, and also a compound having both dimethylamino and piperidino groups in its structure.

In the experimental investigation of the reaction of piperidinomethylenedimedone VIII with acetal I, all three possible dienediamines IVb and IXa,b were isolated and characterized, which indicates the intermolecular character of the transfer of the amino fragment during the formation of dienediaminodicarbonyl compounds.



Thus, taking into account the results of the present and earlier investigations [2, 3], the general scheme of the unusual reaction of amide acetals (for lactam acetals the scheme is similar) with enaminodicarbonyl compounds can be represented as follows (the bipolar compound X and enamidine XI have been described in [2]):



EXPERIMENTAL

The PMR spectra were recorded on a Varian XL-200 spectrometer using TMS as internal standard. The mass spectra were obtained on a Varian MAT-112 (Finnigan) spectrometer with direct introduction of the sample into

the ionic source. The temperature of the ionization chamber was 180°C, and the energy of the ionizing electrons 70 eV. The melting points were determined on a Boetius-type heating stage.

2,2-Dimethyl-4,6-dioxo-4-(γ,γ-bis-N,N-dimethylaminopropylidene)-1,3-dioxane (IVc, $C_{13}H_{20}N_2O_4$). A solution of 1.44 g (0.01 mole) of compound IIIc and 3.28 g (0.02 mole) of acetal I in 8 ml of absolute toluene was boiled for 2 h and then evaporated. The residue was ground with 2 ml of toluene, and 1.9 g (71%) of compound IVc was filtered off, mp 219-220°C (from toluene). $M^{+\cdot}$ 268.

3-(γ,γ-Bis-N,N-dimethylaminopropylidene)-2,4-pentane-2,4-dione (IVd, $C_{12}H_{20}N_2O_2$). A solution of 1.55 g (0.01 mole) of compound IIId and 4.02 g (0.025 mole) of acetal I in 20 ml of absolute toluene was allowed to stand for 2 weeks at 20-25°C, and then evaporated. The residue was partitioned on a column (cellulose PH 101, benzene). The first fraction contained 1.41 g of compound IVd (63%), mp 95-96°C (from toluene). $M^{+\cdot}$ 224.

2-(γ,γ-Bis-N,N-dimethylaminopropylidene)-1,3-diphenylpropane-1,3-dione (IVe, $C_{22}H_{24}N_2O_2$) was obtained in a similar way as compound IVd from enamine IIIe and acetal I, mp 161-163°C. $M^{+\cdot}$ 348. Yield 1.4 g (40%).

2-(N-Methyl-2-dimethylamino-4,5,6,7-tetrahydroazepin-3-yl)methylene-5,5-dimethylcyclohexane-1,3-dione (Vc, $C_{18}H_{28}N_2O_2$). A mixture of 1.95 g (0.01 mole) of compound IIIb and 2.2 g (0.012 mole) of caprolactam diethylacetal IIa was boiled for 2 h in 10 ml of absolute toluene, and then was evaporated. The residue was ground with 5 ml of toluene, and 2 g (66%) of compound Vc was filtered off, mp 159-162°C (from toluene). $M^{+\cdot}$ 304.

1-Methyl-3-[(2-N,N-dimethylamino)-4,4-dimethyl-6-oxocyclohex-1-en-3-yl])methylenepiperid-2-one (VI, $C_{17}H_{26}N_2O_2$). A mixture of 1.95 g (0.01 mole) of compound IIIb and 2.06 g (0.11 mole) of valerolactam diethylacetal IIb in 15 ml of absolute toluene was boiled for 2 h, and then evaporated. The residue was ground with 2 ml of toluene, and 2.15 g (74%) of compound VI was filtered off, mp 176-178°C (from toluene). $M^{+\cdot}$ 290.

2-(1-Piperidinomethylene)-5,5-dimethylcyclohexane-1,3-dione (VIII, $C_{14}H_{21}NO_2$). A solution of 1.95 g (0.01 mole) of compound IIIb and 1.28 g (0.015 mole) of piperidine in 10 ml of absolute ethanol was boiled for 2 h, and then evaporated to 1/4 of its volume. The precipitate was filtered, washed with 2 ml of ethanol. Yield 1.55 g (66%) of compound VIII, mp 114-115°C.

2-(γ,γ-Bisdimethylaminopropylidene)-5,5-dimethylcyclohexane-1,3-dione (IVb), 2-(γ-N,N-dimethylamino-γ-(1-piperidino)propylidene)-5,5-dimethylcyclohexane-1,3-dione (IXa, $C_{18}H_{28}N_2O_2$), and 2-(γ,γ-Bis(1-piperidino)propylidene)-5,5-dimethylcyclohexane-1,3-dione (IXb, $C_{21}H_{32}N_2O_2$). A solution of 4.7 g (0.02 mole) of enamine VIII and 6.44 g (0.04 mole) of acetal I in 30 ml of absolute toluene was boiled for 1 h, and then was evaporated. A mixture of compounds IVb and IXa, b was obtained, which was partitioned on a column (silica gel 40/100, methanol). The second fraction — 0.95 g (14%) of IXb, mp 198-201°C (from toluene). $M^{+\cdot}$ 344; third — 2.94 g (48%) of IXa, mp 188-190°C (from toluene). $M^{+\cdot}$ 304; fourth — 1.43 g (27%) of IVb, mp 162-163°C (from toluene). $M^{+\cdot}$ 264.

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