neutralized with 5% $Na_2CO_3$, the solvent was removed by distillation, and the residue was fractionated in vacuo. Oxidation with NBK was carried out in the same way as in $CHCL_3$.

2-Aryl-4-methyl-5-piperidinotetrahydropyran-4-ol (VI). A mixture of 0.02 mole of pyran V, 0.08-0.1 mole of piperidine, and 2 ml of water was maintained at 20°C for 7 days. After removal of the excess amine and water by distillation, the residue was recrystallized from a suitable solvent.

The yields, the results of elementary analysis, and the physicochemical characteristics of the products are presented in Table 1.

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# SYNTHESIS OF MACROHETEROCYCLES ON THE BASIS OF 2,2-DIMETHYL-4-OXOTETRAHYDROPYRAN


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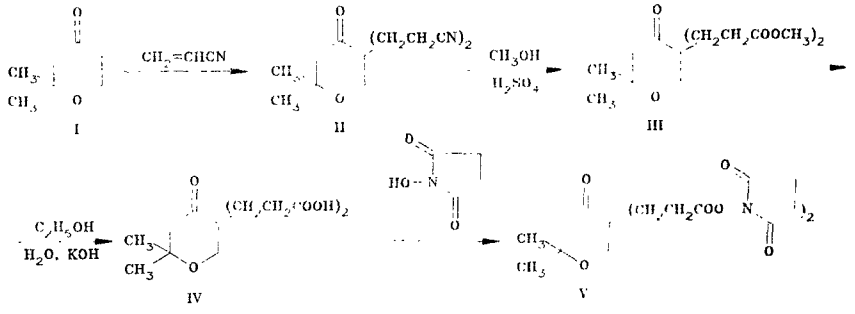
Macrocyclic compounds of a new type were synthesized by the reaction of 2,2-dimethyl-4-oxo-5,5-bis (γ-succiminidooxycarbonylethyl)tetrahydropyran with diamines under conditions that do not require high dilution of the reagents. It was established that 1,9-diazo-12,15-dioxa-2,8-dioxocycloheptadecane-5-spiro-3'-(6,6-dimethyl-4-oxo)tetrahydropyran forms a complex that includes water molecules.


Several natural macrocyclic antibiotics contain a saturated heterocyclic fragment. However, among the macroheterocyclic compounds obtained by synthetic means, representatives of this type are actually lacking [1]. In connection with this, it seemed expedient to synthesize macrocyclic compounds that contain a saturated heterocyclic ring built into the macroring or located in the side chain of the latter and to subsequently study their complexing, solvating, and pharmacological properties.

In the present communication we describe the synthesis of macrocyclic ester amides based on 2,2-dimethyl-4-oxotetrahydropyran.





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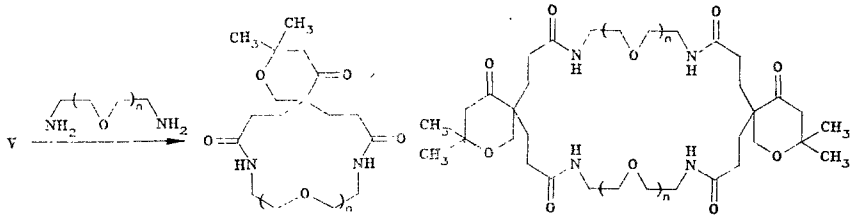
2,2-Dimethyl-5,5-bis(β-cyanoethyl)-4-oxotetrahydropyran (II) was obtained by the reaction of 2,2-dimethyl-4-oxotetrahydropyran (I) [2] with acrylonitrile in a ratio of 1:2 and in the presence of a 40% solution of potassium hydroxide. In the IR spectrum of the latter we observed a band of stretching vibrations of a C≡N group at 2250 $cm^{-1}$. Compound II apparently exists in a distorted chair conformation, since in the PMR spectrum the chemical shift of the protons of the gem-dimethyl groups attached to the $C_{(2)}$ atom (1.3 ppm) coincide. The signals of the protons of the 3-$CH_2$ and 6-$CH_2$ groups, which show up in the spectrum in the form of singlets of 2.4 and 3.7 ppm, respectively, also have identical chemical shifts. It should be noted that singlet character of the signals of the protons of the gem-dimethyl group and the 3-$CH_2$ and 6-$CH_2$ groups is observed in all of the compounds obtained in this research. The presence of a signal of protons of a 3-$CH_2$ group constitutes unambiguous evidence in favor of a gem orientation of the β-cyanoethyl groups.

Dimethyl ester III was obtained from nitrile II. Saponification of III by means of alcoholic alkali gave dicarboxylic acid IV. The compositions and structures of acid IV and ester III were confirmed by the results of elementary analysis and IR and PMR spectroscopy.

In order to obtain macrocyclic ester amides we used the reaction of succinimide ester V with diamides, which proceeds rapidly under mild conditions to give good yields of the products. An attempt to synthesize macrocyclic compounds by the reaction of acid chloride IV with oligoethylene glycols, as well as with 1,5-diamino-3-oxapentane and 1,8-diamino-3,6-dioxaoctane under conditions of high dilution and by the methods adopted in the chemistry of macrocycles [3, 4], did not lead to the desired results. In all cases we observed, during the course of the reaction, multicomponent mixtures of products, the separation of the desired compounds from which was unsuccessful. Succinimide ester V was obtained from acid IV and N-hydroxy succinimide. Characteristic absorption bands of carbonyl groups of succinimide at 1780 and 1810 $cm^{-1}$ are observed in the IR spectrum of ester V, but bands of stretching vibrations of a hydroxy group are absent.

A study of the reactions of ester V with 1,5-diamino-3-oxapentane demonstrated that the reagent concentrations and the reaction temperature and time have no substantial effect on the yields and ratios of the resulting adducts: 1:1 — "monomer" and 2,2-"dimer."



VI,VIII VII,IX

VI,VII n=1; VIII,IX n=2

Macrocyclic ester amides VI and VII were isolated in 53 and 26% yields, respectively, in the reaction of ester V with 1,5-diamino-3-oxapentane in dry THF. Absorption bands of an amide carbonyl group at 1640-1650 $cm^{-1}$ and bands of deformation vibrations of an N—H group (amide II) at 1550-1560 $cm^{-1}$ are present in the IR spectra of solid samples of VI and VII. The stretching vibrations of the N—H group appear at 3300 $cm^{-1}$. Signals of protons of the $NCH_2CH_2O$ fragment are present in the form of a complex multiplet at 3.5 ± 0.05 ppm in the PMR spectrum.

Macrocyclic ester amides VIII and IX were obtained in 43 and 31% yields, respectively, in the reaction of ester V with 1,8-diamino-3,6-dioxaoctane. Elementary analysis of VIII indicated the probability of the presence in it of water in an equimolar ratio. To confirm this fact, we studied the IR spectra of solid samples and solutions in absolute chloroform with various concentrations of VIII and IX. The IR spectrum of a solid sample of ester amide IX has the spectral peculiarities that are characteristic for VI and VII, whereas in solution ($5 \cdot 10^{-3}$ mole/liter) a broad band with a maximum at 3320 $cm^{-1}$ (associate N—H group) and a band of a nonassociated N—H group at 3400 $cm^{-1}$ are present. The absorption band of a hydroxy group is not observed.

The IR spectrum of ester amide VIII in the solid state contains the following characteristic frequencies: 1550 [N—H (amide II)], 1650 (associated N—C=O), 1680 (free N—C=O), 3330 (associated N—H), 3400 (free N—H), and 3500 $cm^{-1}$ (associated O—H). The IR spectrum of ester amide VIII in solution ($5 \cdot 10^{-3}$ mole/liter) contains the following bands: 3370 (asso-

ciated N—H), 3450 (free N—H), 3610 (associated O—H), and 3670 $cm^{-1}$ (free O—H). The absorption band of a nonassociated hydroxy group appears in the IR spectrum of VIII also at a concentration of 0.1 mole/liter. These data constitute evidence that ester amide VIII forms a complex that includes a water molecule. An examination of a Drieding model confirms the possibility of the formation of this sort of complex.

The mass numbers of the molecular ions found in the mass spectra of ester amides VI, VII, and IX correspond to the calculated molecular masses, whereas the values for VIII correspond to the anhydrous sample.

Thus macrocyclic compounds of a new type (VI-IX) were synthesized by the reaction of 2,2-dimethyl-4-oxa-5-bis (γ-succinimidooxycarbonylethyl)tetrahydropyran with diamines under conditions that do not require high dilution of the reagents.

## EXPERIMENTAL

The IR spectra of the synthesized compounds were obtained from KBr pellets or, in the case of VIII and IX, solutions in $CHCl_3$, with a UR-20 spectrometer. The PMR spectra of 10% solutions in $CDCl_3$ relative to tetramethylsilane (TMS) were recorded with a JNM-PS-100 spectrometer (100 mHz). The melting points were measured with a Koffler apparatus. The course of the reaction and the purity of the substances were monitored by means of TLC on Wöelm neutral $Al_2O_3$ [chloroform—ethanol (2:0.1) for II, IV and VI-IX and chloroform—hexane (1:1) for III]. Brockmann activity II $Al_2O_3$ was used for column chromatography in all cases, and the substance—adsorbent ratio was 1:60.

2,2-Dimethyl-4-oxo-5,5-bis(β-cyanoethyl)tetrahydropyran (II). An 85-g (1600 mmole) of acrylonitrile was added slowly dropwise with stirring to a mixture of 100 g (800 mmole) of 2,2-dimethyl-4-oxatetrahydropyran (I) and 10 ml of a 40% solution of potassium hydroxide in 300 ml of dioxane in such a way that the temperature in the flask did not rise above 40°C. Stirring was continued at 40°C for 3 h. The alkali was neutralized with hydrochloric acid (1:1), the solvent was evaporated in vacuo, and the reaction product was isolated by column chromatography on $Al_2O_3$ [ether—chloroform (1:1)]. As a result, we obtained 82 g (45%) of a product with mp 103-104°C and $R_f$ 0.50. IR spectrum: 2260 (C≡N), 1710 (C=O), and 1090 $cm^{-1}$ (C—O—C). PMR spectrum: 3.8 (2H, s, $OCH_2$), 2.45 (2H, s, $COCH_2$), 1.4 ppm (6H, s, $CH_3$). Found: C 66.3; H 7.6; N 12.2%. $C_{13}H_{18}N_2O_2$. Calculated: C 66.6; H 7.7; N 12.0%.

2,2-Dimethyl-4-oxyo-5,5-bis(γ-methoxycarbonylmethyl)tetrahydropyran (III). A mixture of 10 g (40 mmole) of nitrile II, 80 ml of methanol, and 10 ml of concentrated $H_2SO_4$ was heated at 115°C in a chemical flask placed in a metal ampul. The solvent was removed by distillation, 10 ml of water was added to the residue, and the reaction product was extracted with ether to give 9.6 g (80%) of an oil with bp 133-135°C (2.6 hPa), $n_D^{20}$ 1.4780, and $R_f$ 0.48. IR spectrum: 1750 (ether C=O) and 1720 $cm^{-1}$ (C=O). PMR spectrum: 3.6 (8H, s, $OCH_2$, $OCH_3$), 2.35 (2H, s, $COCH_2$), and 1.3 ppm (6H, s, $CH_3$). Found: C 59.8; H 8.2%. $C_{15}H_{24}O_6$. Calculated C 60.0; H 8.0%.

2,2-Dimethyl-4-oxo-5,5-bis(β-carboxyethyl)tetrahydropyran (IV). A mixture of 5 g (17 mmole) of ester III and 5 ml of 40% aqueous potassium hydroxide in 25 ml of alcohol was heated at 95°C for 6 h. The alcohol was removed by distillation, the residue was acidified with HCl (1:1), and the product was extracted with ether to give 2.8 g (60%) of a product with mp 116-117°C (from alcohol). IR spectrum: 3450 (OH) and 1720 (acid C=O). PMR spectrum: 3.65 (2H, s, $OCH_2$), 2.4 (2H, s, $OCH_2$), and 1.3 ppm (6H, s, $CH_3$). Found: C 57.3; H 7.3%. $C_{13}H_{20}O_6$. Calculated: C 57.3; H 7.4%.

2,2-Dimethyl-4-oxo-5,5-bis(γ-succinimidooxycarbonylethyl)tetrahydropyran (V). A 1.5-g (7.3 mmole) sample of dicyclohexylcarbodiimide in 10 ml of THF was added dropwise with stirring to a mixture of 1 g (3.6 mmole) of acid IV and 0.84 g (7.3 mmole) of N-hydroxysuccinimide in 40 ml of dry THF. The mixture was stirred at room temperature for 5 h, the dicyclohexylurea was removed by filtration, and the solvent was removed by distillation. The residue was washed with water and crystallized from alcohol to give 0.8 g (47%) of a product with mp 153-155°C. IR spectrum: 1810 and 1780 $cm^{-1}$ (succinimide C=O). Found: C 53.8; H 5.5; N 6.1%. $C_{21}H_{26}N_2O_{10}$. Calculated: C 54.1; H 5.6 N 6.0%.

1,9-Diaza-12-oxa-2,8-dioxocyclotetradecane-5-spiro-3'-(4-oxo-6,6-dimethyl)tetrahydropyran (VI) and 1,9,15,23-Tetraaza-12,26-dioxa-2,8,16,22-tetraoxocyclooctacosane-5,19-dispiro-3'3"-bis(4-oxo-6,6-dimethyl)tetrahydropyran (VII). A solution of 0.3 g (2.8 mmole) of 1.5-diamino-3-oxopentane in 30 ml of THF was added slowly dropwise with stirring to a solution

of 1 g (2.1 mmole) of succinimide ester V in 50 ml of dry THF. The mixture was stirred at room temperature for 6 h, the resulting precipitate was removed by filtration, and the solvent was evaporated. The mixture of products was separated by chromatography on $Al_2O_3$ by elution with ethyl acetate and chloroform.

The first fraction was identified as VI [0.4 g (53%)] with mp 176-178°C [from ethyl acetate–ether (1:0.5)] and $R_f$ 0.66. IR spectrum: 3300 (N–H), 1700 (C=O), 1640 (amide (C=O), and 1560 $cm^{-1}$ [N–H (amide II)]. PMR spectrum: 6.6 (2H, broad s, NH), 3.6 (6H, s, $OCH_2$), 3.45 (4H, m, $NCH_2$), 2.4 (2H, s, $COCH_2$), and 1.2 ppm (6H, s, $CH_3$). Found: C 60.3; H 8.1; N 8.1%; $M^+$ 340. $C_{17}H_{28}N_2O_5$. Calculated: C 60.0; H 8.3; N 8.2%. The second fraction [0.2 g (26%)] was identified as VII with mp 218-219°C [from a mixture of chloroform–hexane (1:0.5)] and $R_f$ 0.56. IR spectrum: 3300 (N–H), 1700 (C=O), 1650 (amide C=O), and 1550 $cm^{-1}$ [N–H (amide II)]. PMR spectrum: 6.7 (4H, broad s, NH), 3.6 (12H, s, $OCH_2$), 3.45 (8H, m, $NCH_2$), 2.5 (4H, s, $COCH_2$), and 1.2 ppm (12H, s, $CH_3$). Found: C 59.9; H 8.2; N 8.0%; $M^+$ 680. $C_{34}H_{56}N_4O_{10}$. Calculated: C 60.0; H 8.3; N 8.2%.

1,9-Diaza-12,15-dioxa-2,8-dioxocyclopentadecane-5-spiro-3'-(4-oxo-6,6-dimethyl)tetrahydropyran (VIII) and 1,9,18,26-Tetraza-12,15,29,32-tetraoxa-2,8,19,25-tetraoxocyclotetracontane-5,22-dispiro-3',3"-bis(4'oxo-6,6-dimethyl)tetrahydropyran (IX). These compounds were similarly isolated from 2 g (4.2 mmole) of activated ester V and 1 g (6.7 mmole) of 1,8-diamino-3,6-dioxaoctane.

The first fraction [0.7 g (43%)] was identified as VIII with mp 136-137°C (from ethyl acetate) and $R_f$ 0.72. IR spectrum: 3500 (O–H); 3330, 3400 (N–H); 1700 (C=O); 1680, 1650 (amide C=O); 1550 $cm^{-1}$ [N–H (amide II)]. PMR spectrum: 6.95 (2H, broad s, NH), 3.6 (10H, s, $OCH_2$), 3.1 (2H, s, $H_2O$), 3.45 (4H, m, $NCH_2$), 2.4 (2H, s, $COCH_2$), and 1.2 ppm (6H, s, $CH_3$). Found: C 56.8; H 8.4; N 7.1%; $M^+$ 384. $C_{19}H_{34}N_2O_7$. Calculated: C 56.7; H 8.7; N 7.0%.

The second fraction [0.5 g (31%)] was identified as IX with mp 174-176°C [from chloroform–hexane (1:0.5)] and $R_f$ 0.63. IR spectrum: 3300 (N–H), 1710 (C=O), 1660 (amide C=O), and 1550 $cm^{-1}$ [N–H (amide (II)]. PMR spectrum: 7.0 (4H, broad s, NH), 3.6 20H, s, $OCH_2$), 3.5 (8H, m, $NCH_2$), 2.4 (4H, s, $COCH_2$), and 1.2 ppm (12H, s, $CH_3$). Found: C 59.5; H 8.2; N 7.2%; $M^+$ 768. $C_{38}H_{64}N_4O_{12}$. Calculated: C 59.3; H 8.4; N 7.3%.

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