# A STUDY OF THE TRANSANNULAR INTERACTION OF SOME AMINO ACIDS AND OF GLYCYLGLYCINE WITH 3,3,7,7-TETRAMETHYL-1,2 : 5,6-DIBENZOCYCLOOCTANE-4,8-DIONE

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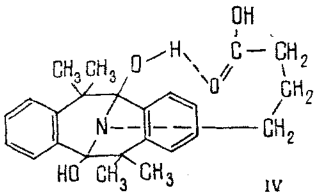
The synthesis of a new class of compounds of the type of 4,4,8,8-tetramethyl-2,3 : 6,7-dibenzo-9-azabicyclo[3,3,1]nonane-1,5-diol by the transannular introduction of the amino groups of sterically unhindered primary amines (including important biogenic amines) into the eight-membered rings of the readily available diketones 3,3,7,7-tetramethyl-1,2 : 5,6-dibenzocyclooctane-4,8-dione (DBC) and dispiro-1',4 : 1",8-dicyclopentane-2,3 : 6,7-dibenzocyclooctane-1,5-dione has been described previously [1-5]. They deserve attention as substituted analogs of argemonine and related alkaloids. Some of them may apparently also be assigned to the group of "base—base" substances that are of interest as models for studying the mechanism of the action of various enzymes bound to nucleosides and nucleotides [6].

We have succeeded in showing [7, 8] that the reaction of DBC in a weakly alkaline medium with glycine, α-D,L-alanine, β-alanine, γ-aminobutyric acid, and glycylglycine forms good yields of aza adducts: 1,5-dihydroxy-4,4,8,8-tetramethyl-2,3 : 6,7-dibenzo-9-azabicyclo[3,3,1]non-9-ylacetic acid (I), α-(1,5-dihydroxy-4,4,8,8-tetramethyl-2,3 : 6,7-dibenzo-9-azabicyclo[3,3,1]non-9-yl)propionic acid (II), β-(1,5-dihydroxy-4,4,8,8-tetramethyl-2,3 : 6,7-dibenzo-9-azabicyclo[3,3,1]non-9-yl)propionic acid (III), γ-(1,5-dihydroxy-4,4,8,8-tetramethyl-2,3 : 6,7-dibenzo-9-azabicyclo[3,3,1]non-9-yl)butyric acid (IV), and 1,5-dihydroxy-4,4,8,8-tetramethyl-2,3 : 6,7-dibenzo-9-azabicyclo[3,3,1]non-9-ylacetylglycine (V). The methyl esters and hydrochlorides of compounds (I-V) have been obtained.



IV

The constants, yields, and analytical figures for the compounds synthesized are given in Table 1.

The structures of these compounds have been confirmed by IR, PMR, and mass spectroscopy.

The IR spectrum of compound (I) shows a characteristic absorption band in the 1720 $cm^{-1}$ region indicating the presence of strong intermolecular interaction of its carboxy group, leading to the existence of the dimeric form. In contrast to compound (I), the presence in the IR spectrum of compound (IV) of a characteristic absorption band in the 1680 $cm^{-1}$ region may serve as a proof of the existence of a strong intramolecular hydrogen bond [9].

The hydroxyl of the carboxy group in (IV) is shown by a broad and comparatively intense band in the 1220 $cm^{-1}$ region. Correspondingly, absorption bands are observed in the 3360, 3415, and 3585 $cm^{-1}$ regions for the alcoholic hydroxy groups. The first two of them are in the region characteristic for OH groups bound by hydrogen bonds, and the third in the range of frequencies of nonassociated OH groups. On the basis of these facts and taking into account the low value of the absorption band of the C = O of the carboxy group, it may be assumed that the intramolecular hydrogen bond is formed through one of the alcoholic hydroxy groups, as a consequence of which a nine-membered ring arises.

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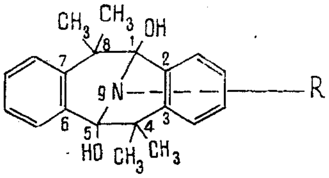
TABLE 1



| Compound | R | Yield, % | mp, °C | Found, % |  |  |  | Empirical formula | Calculated, % |  |  |  |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  | C | H | N | Cl |  | C | H | N | Cl |
| I | $-CH_2COOH$ | 44 | 204–205 | 71,5 | 6,9 | 3,7 | — | $C_{22}H_{25}O_4N$ | 71,9 | 6,8 | 3,8 | — |
| Ia | $-CH_2COOH \cdot HCl$ | 85 | 180–181 | — | — | — | 8,6 | $C_{22}H_{25}O_4N \cdot HCl$ | — | — | — | 8,8 |
| Ib | $-CH_2COOCH_3$ | 98 | 188–189 | 76,6 | 7,2 | 3,3 | — | $C_{23}H_{27}O_4N$ | 72,4 | 7,1 | 3,7 | — |
| Ic | $-CH_2COOCH_3 \cdot HCl$ | 96 | 192 | — | — | — | 8,4 | $C_{23}H_{27}O_4N \cdot HCl$ | — | — | — | 8,5 |
| II | $CH_3-CH-COOH$ | 70 | 215–216 | 72,8 | 7,0 | 3,8 | — | $C_{23}H_{27}O_4N$ | 72,4 | 7,1 | 3,7 | — |
| IIa | $CH_3-CH-COOH \cdot HCl$ | 86 | 230–232 | — | — | — | 8,0 | $C_{23}H_{27}O_4N \cdot HCl$ | — | — | — | 8,5 |
| IIb | $CH_3-CH-COOCH_3$ | 70 | 168–169 | 73,4 | 7,5 | 3,5 | — | $C_{24}H_{29}O_4N$ | 72,9 | 7,3 | 3,5 | — |
| III | $-CH_2CH_2COOH$ | 72 | 220–221 | 72,1 | 7,0 | 3,9 | — | $C_{23}H_{27}O_4N$ | 72,4 | 7,1 | 3,7 | — |
| IIIa | $-CH_2CH_2COOH \cdot HCl$ | 92 | 202–205 | — | — | — | 8,2 | $C_{23}H_{27}O_4N \cdot HCl$ | — | — | — | 8,5 |
| IIIb | $-CH_2CH_2COOCH_3$ | 67 | 139–140 | 73,4 | 7,2 | 3,6 | — | $C_{24}H_{29}O_4N$ | 72,9 | 7,3 | 3,5 | — |
| IV | $-CH_2CH_2CH_2COOH$ | 45 | 146–147 | 73,1 | 7,6 | 3,5 | — | $C_{24}H_{29}O_4N$ | 72,9 | 7,3 | 3,5 | — |
| IVa | $-CH_2CH_2CH_2COOH \cdot HCl$ | 96 | 195–196 | — | — | — | 8,1 | $C_{24}H_{29}O_4N \cdot HCl$ | — | — | — | 8,2 |
| IVb | $-CH_2CH_2CH_2COOCH_3$ | 85 | 160–161 | 73,4 | 7,6 | 3,3 | — | $C_{25}H_{31}O_4N$ | 73,3 | 7,6 | 3,4 | — |
| IVc | $-CH_2CH_2CH_2COOCH_3 \cdot HCl$ | 95 | 186–187 | — | — | — | 7,9 | $C_{25}H_{31}O_4N \cdot HCl$ | — | — | — | 8,0 |
| V | $-CH_2CONHCH_2COOH$ | 42 | 164–165 | 67,6 | 6,4 | 6,3 | — | $C_{24}H_{28}O_5N_2$ | 67,3 | 6,6 | 6,6 | — |
| Va | $-CH_2CONHCH_2COOCH_3$ | 93 | 186–187 | 68,6 | 6,6 | 6,3 | — | $C_{25}H_{30}O_5N_2$ | 68,5 | 6,8 | 6,4 | — |
| Vb | $-CH_2CONHCH_2COOCH_3 \cdot HCl$ | 85 | 177–178 | — | — | — | 7,7 | $C_{25}H_{30}O_5N_2 \cdot HCl$ | — | — | — | 7,6 |

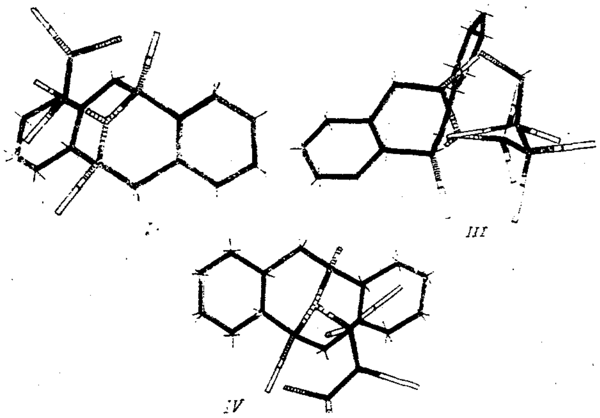
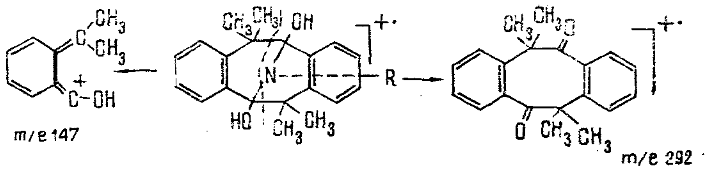


Fig. 1

The band at 1120 $\text{cm}^{-1}$, the intensity of which is relatively high because of an intramolecular hydrogen bond, may be assigned to a tertiary hydroxy group, while for the other >C−OH group the band characteristic for ordinary alcoholic hydroxyls in the 1030 $\text{cm}^{-1}$ region is observed. In the IR spectrum of compound (III), the absorption band in the 1710 $\text{cm}^{-1}$ region is apparently due to the appearance of a comparatively weak intramolecular hydrogen bond between the carboxy group and the hydroxyl in position 1. These facts are in harmony with spatial models of these compounds (Fig. 1), from which it can be seen that the distance between the carbonyl group of the carboxyl and the hydrogen of a hydroxy group decreases considerably in the sequence (I) → (III) → (IV). A more complex pattern of intermolecular interaction is observed in the IR spectra of compounds (IVb) and (V) and their hydrochlorides, the study of which from the point of view of conformational analysis will be the subject of a separate future investigation.

The PMR spectra of the methyl esters (Ib-IVb, Va) contain nonequivalent singlets of methyl protons in an eight-membered ring in the δ 1.3-1.6 ppm region, and signals at δ 7.0, 3.5, and 2.5 ppm, which are assigned to the chemical shifts of the protons of an aromatic ring, the methyl protons of the esters, and the methylene protons of $>N-CH_2$ groups. The signal of the proton of a hydroxy group is located in the weak-field region at δ 7.4 ppm. In compound (IIb) a doublet and a quartet at δ 1.1 and 2.9 ppm correspond to the protons of the $CH_3$ and CH groups in the $CH_3-CH-COOCH_3$ fragment.

The mass spectra of these compounds show basically the same fragmentation of the molecular ions as takes place for the analogous compounds described previously [3]. The most characteristic fragments are ions with m/e 147 $(M-147)^+$, which formed as the result of the breakdown of the eight-membered ring, as shown by the dashed line, and an ion with m/e 292 $(M-H_2NR)^+$ formed by the elimination of the corresponding primary amines from the molecular ion.



## EXPERIMENTAL

The mass spectra were obtained on a LKB 900 instrument (LKB, Sweden) at an accelerating voltage of 70 eV, the IR spectra on a UR-20 instrument (GDR), and the PMR spectra on a Varian DA-60 instrument (USA) in $CHCl_3$. The molecular weights of all the compounds synthesized were determined mass-spectrometrically.

1,5-Dihydroxy-4,4,8,8-tetramethyl-2,3:6,7-dibenzo-9-azabicyclo[3,3,1]acetic Acid (I). A solution of DBC in 50 ml of ethanol was added to an alkalinized solution of 0.35 g of glycine in 3 ml of distilled water (pH ~ 9), and the mixture was boiled on the water bath for 12 h. Then it was diluted with water. The DBC that had not reacted was separated off by filtration, and the filtrate was treated with ether several times to eliminate the residual DBC completely. Then the solution was acidified with dilute $H_2SO_4$ to a weakly acid reaction and was extracted with ether (5 × 25 ml) and with benzene (3 × 25 ml). The combined extracts were dried over $Na_2SO_4$ and the solvent was distilled off in vacuum. The solid residue was recrystallized from benzene–ethanol (20 : 1). Yield 0.55 g of (I).

Compounds (II), (III), (IV), and (V) were obtained similarly.

In the case of compounds (III) and (IV), after the extraction of the unchanged DBC the solution was first evaporated to 1/2 of its original volume and was then acidified with sulfuric acid and treated under the conditions described in the preceding experiment. To obtain compound (IV), the γ-aminobutyric acid was first dissolved in a small amount of water. After acidification of the sodium salt of the product with sulfuric acid, the solution was concentrated by evaporation. On cooling, (IV) deposited. The reaction for the preparation of compound (V) was performed in 50% ethanol.

Preparation of the Hydrochloride (Ia). A mixture of 0.2 g of compound (I) and 3 ml of a saturated solution of hydrogen chloride in absolute ether was allowed to stand for 30 min and was then evaporated. After recrystallization from ethanol–benzene (5 : 1), 0.18 g of the hydrochloride (Ia) with mp 180–181°C was obtained.

Preparation of the Methyl Ester (Ib). A solution of diazomethane in ether was added to a solution of 0.25 g of compound (I) in 50 ml of absolute ether until the evolution of bubbles ceased. Then the ether was evaporated off and the residue was recrystallized from benzene. This gave 0.22 g of the methyl ester (Ib).

The hydrochlorides (Ic), (IIa), (IIIa), (IVa), (IVc) and (Vb) and the methyl esters (IIb), (IIIb), and (IVb), and (Va) were obtained similarly.

## SUMMARY

It has been shown that the transannular interaction in a weakly alkaline medium of 3,3,7,7-tetramethyl-1,2:5,6-dibenzocyclooctane-4,8-dione with glycine, α-D,L-alanine, β-alanine, γ-butyric acid, and glycylglycine forms the corresponding aza adducts of the type of derivatives 4,4,8,8-tetramethyl-2,3:6,7-dibenzo-9-azabicyclo[3,3,1]nonane-1,5-diol derivatives with good yields.

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# SYNTHESIS OF A FRAGMENT OF HISTONE H4 WITH THE SEQUENCE 14-21

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In recent years, intensive investigations have been carried out on the structural and functional features of histones [1-3]. In spite of the considerable advances in this field, there still remain urgent problems of the elucidation of the molecular organization of the higher levels of the structure of histones, and also their role in the organization of nuclear structures. A knowledge of the structural features of histones will permit a further deepening of investigations of their biological role and, in particular, will reveal the role of histones in the regulation of the activity of the genetic apparatus of the cell.

With the aim of structural and functional investigations, we have synthesized the N-terminal section of histone H4 with the sequence 14-21. The selected section of the histone is interesting by virtue of the fact that it is saturated with basic amino acids – lysine and arginine – which are arranged symmetrically in relation to a histidine residue. It is not excluded that this section may play an important role in the blocking of a DNA template [4].

The synthesis of the octapeptide was carried out by means of the scheme shown below. The choice of this scheme predicated the exclusion of the possibility of the occcurrence of side reactions. With this aim, at all stages of the synthesis CDI was used as the condensing agent and methylmorpholine as the base. The Cbo and $NO_2$ protective groups were used for blocking the side functions of lysine and arginine, respectively, and t-BOC protection for blocking $\alpha$-amino groups. (See scheme on following page.)

A number of difficulties arose in the introduction of histidine into the peptide chain. An attempt to synthesize a peptide with the sequence 18-21 using the $N^{\alpha}$-BOC-$N^{im}$-FDN derivative of histidine was unsuccessful. Satisfactory results were obtained when the methyl ester of histidine was introduced from the N-end of the peptide chain. The formation of byproducts was observed at the stages of the synthesis of the pentapeptide (14-18) and of the octapeptide (14-21). (The results of the elementary and amino acid analyses of these products showed the impossibility of the formation of acylureas [5]). The yields of peptides in these stages fell to 60%. In all the other stages the peptides were isolated with fairly good yields and were chromatographically pure. The peptides were purified by repeated crystallization from a mixture of ethanol and ethyl acetate and also by chromatography on Sephadex LH-20. The Cbo and $NO_2$ groups were removed from the octapeptide with anhydrous hydrogen fluoride. The absence of absorption bands in the UV spectrum in the 257 and 271 nm regions showed the completeness of the elimination of the protective groups. The free octapeptide was purified on a column of Sephadex G-15. The peptides synthesized and their constants are given in Table 1.

## EXPERIMENTAL

Amino acids of the L series were used in experiments. All the products obtained were analyzed for C, H, and N. In all cases the results of the elementary analysis corresponded to the calculated figures. The course

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