AUTOMATIC ASSEMBLY OF FRAMEWORK STRUCTURES.

1. SYNTHESIS, STEREOCHEMISTRY, AND CYCLIZATION OF DERIVATIVES OF α,α'-DIHYDROXY-α,α'-DIMETHYL- AND α-METHYL-α'-ETHYLGLUTARIC ACIDS

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For systems of type A, containing functional groups X and Y capable of paired interaction, the formation of the bicycle B is only possible from the d, ℓ forms, since the trans orientation of X and Y in the monocycle C is produced from the meso form (Scheme 1).

dl-A B (1)

meso-A C

Such stereocontrolled cyclization is clearly a common principle in the construction of framework structures. For instance, ready automatic assembly to the dilactones d, ℓ-A, where X = COOH, Y = OH, and the $(CH_2)_n$ bridge with n = 1, 2 may be expected, since the spontaneous lactonization of γ- and δ-hydroxy carboxylic acids is well known. These examples were studied [1-8], and the above-mentioned principle was formulated as applied to the synthesis of the dilactones from α,α'-dihydroxy-α,α'-dimethylglutaric (DDG) and α,α'-dihydroxy-α,α'-dimethyladipic (DDA) acids [2, 3, 5, 6]. However, the dilactones of DDG and analogs were obtained earlier by the thermolysis* of the monolactones of both the d, ℓ [2] and the meso [1, 2, 4, 8] series, and this cannot be used as evidence for stereocontrolled cyclization.

Therefore, on the basis of the principle under discussion we reproduced the data from the clasical works [1, 2, 4, 8] in order to refine the structure and the stereochemistry of the products and also to achieve the automatic assembly of the bicycles from the derivatives of d,ℓ-DDG and threo-α,α'-dihydroxy-α-methyl-α'-ethylglutaric acid (DMEG) under mild conditions and with high yields.†

By the reaction of acetylacetone (AA) with potassium cyanide and hydrogen chloride according to [1] we obtained a compound which after repeated washing with water and drying under vacuum corresponded, according to elemental analysis, to the compound described in [1, 2, 4, 8] as the nitrile of DDG (the biscyanohydrin of AA) (I). However, on the basis of the chemical transformations (see below) and the spectral data it was shown that it is the product from intramolecular cyclization of Zelinskii's "nitrile" (I) according to Pinner [10], i.e.,

*Only the dilactone of DDA was obtained under mild conditions [4, 6, 7].
†For the preliminary communication, see [9].

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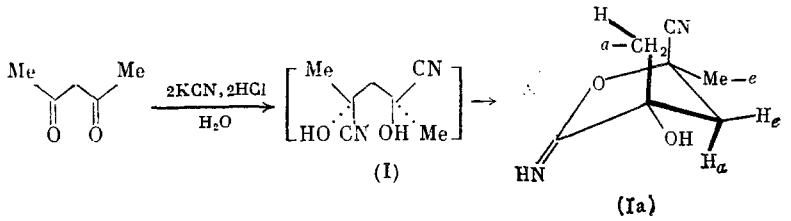
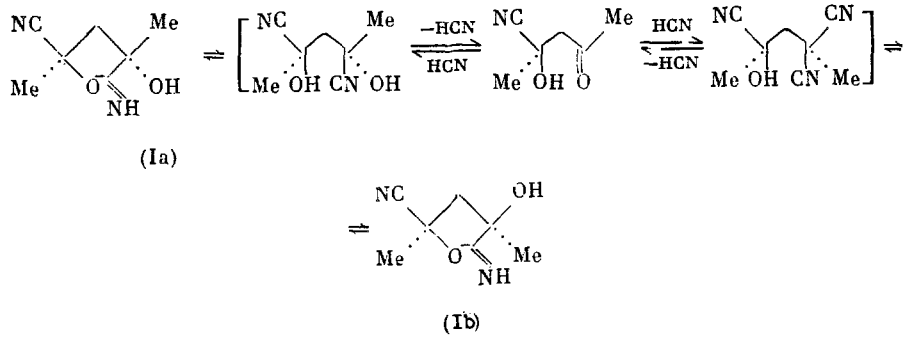
the iminolactone of the dinitrile of meso-DDG (Ia). According to PMR of (Ia), nonequivalence is observed in the Me groups and methylene H atoms (scheme 2); according to ^{13}C NMR, there is nonequivalence in all the C atoms, and there are signals for the C=N and C≡N groups; in the IR spectrum there is a strong band for C=N (the C≡N band does not appear).



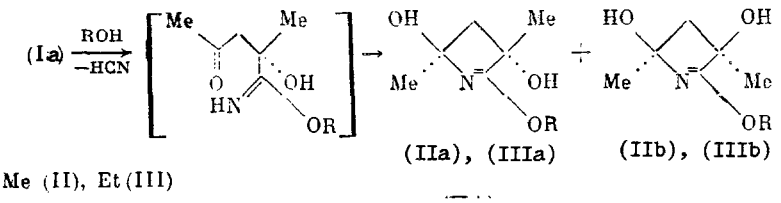
(2)

The appreciable spin–spin coupling constant ^4J = 0.5 Hz for one of the methylene hydrogen atoms with only one of the methyl groups shows that they are in the pseudo-a position, where a w orientation close to planar is possible (cf. [11]). Consequently, the second methyl group is pseudo-e* and (Ia) thus corresponds to meso-DDG. In fact, according to the PMR spectrum in C_5D_5N, only the open form (Ia), i.e., the mesobiscyanohydrin of AA (I), is observed (a singlet for the methyl groups and an AB spectrum for the CH_2 protons). The PMR spectrum of (Ia) in DMSO-d_6 corresponds to a mixture of the diastereomers (Ia)/(Ib) = 1:1, and this can be explained by the equilibrium transformation in the polar solvent. The absence of the spin–spin coupling constant ^4J for (Ia) in DMSO-d_6 is clearly due to the rapid mutual transformations of the forms. (The signals are broadened.)



(3)

The reactions of (Ia) with alcohols are due to similar processes:

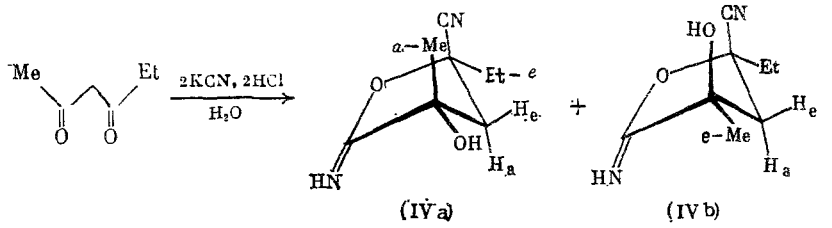


R = Me (II), Et (III)

(4)

Similarly to (Ia), from propionylacetone (PA) we obtained the iminolactone (IV), which was described earlier as a dinitrile (the biscyanohydrin of PA), although a difference in the C≡N groups with respect to concentrated hydrochloric acid was observed [4]. The structure of (IV) was confirmed by chemical and spectral data. In contrast to (Ia), in the PMR of (IV) signals for the diastereomers (IVa) and (IVb) in a ratio of 1:3 are observed.

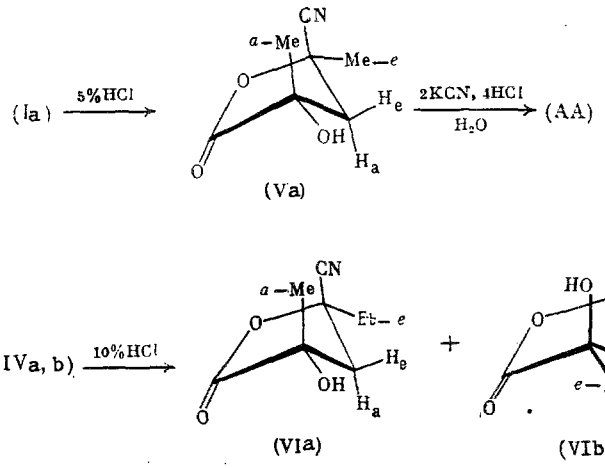
*On account of the limited solubility of (Ia) an unambiguous assignment for the corresponding lactone nitrile was made from the ^{13}C NMR spectrum by selective heteronuclear double resonance: a-Me (geminal to the CO) and e-Me (geminal to C≡N) (see below).



(IVa) (IVb) (5)

For the minor component, like (Ia), there is a ^4J constant and for the predominant component there is no ^4J spin–spin coupling constant for the methylene protons, and this confirms the correspondence to the erythro-series for (IVa) and to the threo-series for (IVb). The regio position of the alkyl groups was proved by means of the ^{13}C NMR of the corresponding lactone nitriles (see below). Thus, Fittig's "dinitrile" also undergoes spontaneous intramolecular cyclization.

The iminolactones (Ia) and (IVa, b) are readily hydrolyzed by dilute hydrochloric acid (0.5 h, 20°C) to the lactone nitriles, and this is typical of cyclic imino ethers [10].



(6)

Compound (Va) was also obtained as a side product from the reaction of AA with potassium cyanide with the rapid addition of or with an excess of hydrochloric acid. From the mixture with (VIa)/(VIb) = 1:3 by fractional crystallization from ether we isolated (VIb), identical in its melting point with the compound described in [4].

In the ^{13}C NMR spectrum of (Va) with suppression of the upfield methyl signal (a-Me) the multiplet of C=O is simplified, but C≡N does not change, and the opposite pattern is observed with suppression of the downfield signal (e-Me). The signals of the quaternary carbon atoms were assigned similarly, and the position of the methyl (geminal with C=O) and ethyl (geminal with C≡N) groups in (VIa, b) was demonstrated.

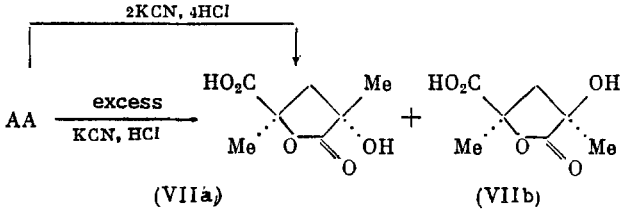
The configurations of (Va) and (VIa, b) were confirmed in the following way. In the ^{13}C NMR spectra of (Va) and (VIa) for one of the alkyl groups (Me) there is a quartet of triplets, i.e., $^3J_{MeH_a} \sim {}^3J_{MeH_e} > 0$, which on the basis of the angular Karplus relationship and analysis of Dreiding models demonstrates that they have the pseudo orientation and, consequently, that (Va) and (VIa) correspond to the meso and erythro series. This is confirmed by the presence in the PMR spectra of both compounds of spin–spin coupling constants between these groups at one of the methylene protons of the ring with respect to the w fragment, similarly to (Ia) and (IVa). On the other hand, the ^4J constant is absent for the predominant diastereomer (VIb), while the ^{13}C NMR spectrum for both alkyl groups only contains the spin–spin coupling constant with one of the protons of the methylene group of the ring. This demonstrates that they have the e orientation and, consequently, that (VIb) corresponds to the threo series (Table 1).

During the hydrolysis of (Ia) and (Va) the corresponding monolactone acid (VIIa), identical with that described earlier [1, 2, 4, 8], was isolated. Compound (VIIa) was also obtained directly from AA by the addition of concentrated hydrochloric to a mixture of AA with an aqueous solution of potassium cyanide. The isomeric composition of the products here de-

TABLE 1. Observed Spin–Spin Coupling Constants $^3J_{CH}$ and the Corresponding Dihedral Angles (determined on Dreiding molecules)

Interacting groups	(Va)		(VI b)	
	$^3J_{^{13}CH}$, Hz	Angle, deg	$^3J_{^{13}CH}$, Hz	Angle, deg
a-$^{13}CH_3 - H_a$	3,7	~30	–	–
a-$^{13}CH_3 - H_e$	3.7	~150	–	–
e-$^{13}CH_3 - H_a$	0	~90	3,5	~30
e-$^{13}CH_3 - H_e$	3,7	~30	0	~90
e-$^{13}\underline{CH_2}Me - H_a$	–	–	4,9	~30
e-$^{13}\underline{CH_2}Me - H_e$	–	–	0	~90
$^{13}CN - H_a$	6.7	~160	–	–
$^{13}CN - H_e$	4.9	~40	–	–
$^{13}CO - H_a$	0	~90	0	~90
$^{13}CO - H_e$	5.4	~150	4.2	~150

pends on the reaction conditions. Thus, only (VIIa) is formed with the stoichiometric ratio of the reagents; a mixture with (VIIa)/(VIIb) = 2:1 is formed with an excess of potassium cyanide and hydrogen chloride.



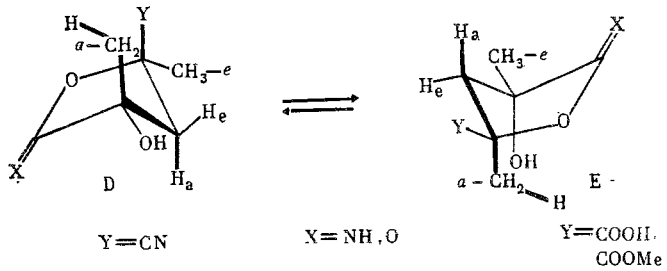
(VIIa) (VIIb) (7)

An analytically pure sample of (VIIb) was obtained in the form of the monohydrate by fractional crystallization of (VIIa, b) from benzene. Compound (VIIb) was obtained earlier by the hydrolysis of the corresponding dilactone [1-4, 8] or from α-bromo-α'-hydroxy-α,α'-dimethylglutaric acid [2].* Both diastereomers have a wide melting range; their methyl esters (VIIIa) and (VIIIb) with distinct melting points were obtained by reaction with diazomethane. The formation of the esters can also be seen by PMR when alcohol solutions of (VIIa) are boiled or held for a long time.

The affiliation of (VIIa) and (VIIIa) to the meso series and of (VIIb) and (VIIIb) to the d,ℓ series was demonstrated earlier on the basis of the retention of the optical activity of (–)-(VIIb) and its loss in the case of (–)-(VIIa) during alkaline hydrolysis to the salt of DDG [8] and was confirmed by ourselves by spectral methods. In the PMR spectra (VIIa) and (VIIIa) are similar to (Ia) and (Va); the ^4J spin–spin coupling constant is not observed for (VIIb) and (VIIIb). In the ^{13}C NMR spectra of (VIIa) and (Va) the multiplicity of the signals for the methyl groups coincides, but in the case of (VIIa) in contrast to (Va) the signal of the COOH group is simplified with suppression of the protons of the upfield a-Me group, but the multiplet of the C=O in the ring is not changed. Consequently, with substitution of the C≡N group by COOH and CO_2Me, the conformational energies of which are significantly larger [12], the conformation of the ring changes from preferred D to E (scheme 8).

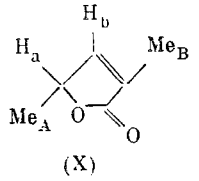
Finally, the PMR spectrum of (VIIa) in D_2O/KOH corresponds to the salt of meso-DDG (a singlet for the methyl groups and an AB spectrum for the CH_2 protons), while the spectra of (VIIa, b) correspond to a mixture of the salts of meso- and d,ℓ-DDG [singlets of the methyl and CH_2 groups for (VIIb)].

*Initially the monohydrate (VIIb) was described erroneously as the "constant form" of DDG on the basis of the data from elemental analysis [1, 2], but (VIIb) was isolated more recently in the dehydrated form by fourfold crystallization from absolute ether [8] or by heating [4].



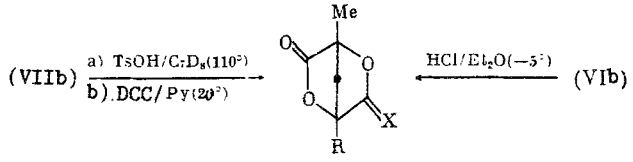
(8)

Thus, we have proved the structures, configurations, and conformations of all the obtained products, which are potential precursors of bicyclic systems of type B (scheme 1). When the synthesis of the dilactone of DDG (IX) by the thermolysis of (VIIa) was reproduced according to [1, 4, 8], only a small amount of the product (2%) sublimed, and the formation of α,γ-dimethyl-γ-crotonolactone (X) was observed.



(X)

On the other hand, as expected, the bicyclic compounds were obtained from systems of the d,ℓ-A type (scheme 1) under mild conditions and with good yields. Thus, (IX) was obtained from (VIIb): a) with a 50% yield by boiling in toluene-d_8 in the presence of p-toluenesulfonic acid; b) with a 100% yield (PMR) by reaction with dicyclohexylcarbodiimide (DCC) in pyridine; compound (VIIa) does not change under the conditions in a) and b). The previously undescribed hydrochloride of the monoimino dilactone of threo-DMEG (XI) was obtained with a 41% yield by the intramolecular cyclization of the lactone nitrile of threo-DMEG (VIb) under the conditions of the Pinner reaction (−5°C, absolute ether, in a stream of dry hydrogen chloride) [10] (scheme 9).



(9)

X = O, R = Me(IX); X = $\overset{+}{N}H_2Cl^-$, R = Et(XI)

The structure of (XI) was confirmed by the data from the ^{13}C NMR and IR spectra (C=O and C=$\overset{+}{N}H_2$). In the PMR spectra, ΔνAB for the AB spectrum of the methylene group amounts to 36 Hz, whereas for the initial lactone nitrile ΔνAB = 288 Hz. This indicates higher symmetry in (XI) compared with the monocyclic precursor. The structure of (XI) was also confirmed by the mass spectrum.

From the conformational analysis of the monocyclic derivatives of DDG and DMEG examined above it follows that their secondary cyclization is conformationally controlled. In fact, in the monocycles of the d,ℓ and threo series the alkyl groups which have the largest conformational energy occupy the e positions preferentially and thus determine the a,a orientation of the cis-functional groups, and this favors their interaction. On this basis it can be supposed that substituents with even larger conformational energy must facilitate the secondary cyclization; conversely, substituents which are inferior to the functional groups in conformational energy (e.g., H atoms) must hinder it.

EXPERIMENTAL

The PMR spectra were obtained on a Bruker WM-400 spectrometer (^1H 400, ^{13}C 100.62 MHz, from TMS as internal standard). The IR spectra were obtained for tablets of potassium bro-

ide on a UR-20 instrument. The mass spectra were obtained on a Hitachi M-80A mass spectrometer at 70 eV, and the peaks with a relative intensity greater than 10% are given.

Monoiminolactone of the Dinitrile of meso-DDG (Ia). To a soluton of 5.1 g (78 mmoles) of potassium cyanide in 10 ml of distilled water we added 3.9 g (39 mmole) of acetylacetone. (A precipitate separated, and the mixture heated spontaneously.) After cooling with ice water we added a further 10 ml of water and then 6.6 ml (78 mmoles) of concentrated hydrochloric acid to a neutral reaction. The precipitate was washed repeatedly with water. We obtained 3.45 g (57.5%) of (Ia); mp 139-141°C (cf. [1, 4, 8]). Found %: C 54.47; H 6.76; N 17.91%. $C_7H_{10}N_2O_2$. Calculated %: C 54.53; H 6.54; N 18.17. PMR spectrum (deuterochloroform, δ, ppm, J, Hz): 1.69 d (a-Me, $^4J_{MeH_a}$ = 0.5), 1.82 s (e-Me), 2.43 dq (H_a, $^2J_{AB}$ = −13.4), 2.69 d (H_e) (DMSO-d_6). (Ia): 1.44 s (Me) and 1.75 s (Me), 2.35 d and 2.64 d (CH_2, $^2J_{AB}$ = −13.4); (Ib): 1.45 s (Me) and 1.75 s (Me), 2.29 d and 2.71 d (CH_2, $^2J_{AB}$ = −13.7). (C_5D_5N) (I): 1.79 s (Me), 2.58 d and 2.87 d (CH_2, $^2J_{AB}$ = −13.4). ^{13}C NMR spectrum (DMSO-d_6, δ, ppm, J, Hz): 25.88 (Me, ^1J = 129.0), 26.50 (Me, ^1J = 130.4), 48.48 (CH_2, ^1J = 137.3), 72.31 (MeCOH), 73.07 (MeCCN), 120.36 (C≡N), 177.33 (C=NH). IR spectrum (ν, cm^{-1}): 1730 (C=NH).

2-Methoxy-3,5-dimethyl-3,5-dihydroxy-1-pyrroline, Mixture of Diastereomers (IIa, b). To 1.758 g (11.4 mmoles) of (Ia) we added 60 ml of absolute methanol. The mixture was kept at 20°C for 4 h, the solvent was removed under vacuum, and the residue was crystallized from a mixture of acetone and pentane. We obtained 0.74 g (41%) of a product melting at 120-121°C. Found %: C 52.81; H 8.15; N 8.75. $C_7H_{13}NO_3$. Calculated %: C 52.83; H 8.18; N 8.81. PMR spectrum (C_5D_5N, δ, ppm, J, Hz). (IIa): 1.74 s (Me) and 1.86 s (Me), 2.64 d and 2.70 d (CH_2, $^2J_{AB}$ = −13.4), 3.86 s (MeO). (IIb): 1.60 s and 1.72 s (Me), 2.52 d and 2.89 d (CH_2, $^2J_{AB}$ = −13.4), 3.81 s (MeO). ^{13}C NMR spectrum (CD_3OD, δ, ppm, J, Hz). (IIa): 25.61 and 29.88 (Me, ^1J = 127.0), 55.03 (CH_2, ^1J = 130.6), 56.55 (MeO, ^1J = 146.5), 79.11 (CCOH), 92.67 (NCOH), 175.69 (C=N); (IIb): 25.92 and 30.66 (Me, ^1J = 127.0), 54.48 (CH_2, ^1J = 130.6), 56.57 (MeO, ^1J = 146.5), 79.74 (CCOH), 93.67 (NCOH), 176.16 (C=N). IR spectrum (ν, cm^{-1}): 1660 (C=N). Mass spectrum, m/z (relative intensity, %): 160 (8.1) $[M + H]^+$, 144 (11.6), 101 (11.6), 102 (11.6), 86 (15.6), 60 (16.2), 43 (100).

2-Ethoxy-3,5-dimethyl-3,5-dihydroxy-1-pyrroline, Mixture of Diastereomers (IIIa, b). A 3-g sample (19.5 mmoles) of (Ia) was dissolved in boiling ethanol. The solvent was removed under vacuum, and the oily residue was washed with cold ether and dried under vacuum. We obtained 1 g (29.7%) of the product; mp 103-106°C. Found %: C 55.63; H 8.90; N 8.15. $C_8H_{15}NO_3$. Calculated %: C 55.47; H 8.72; N 8.08. PMR spectrum (C_5D_5N, δ, ppm, J, Hz) (IIIa): 1.66 s (Me) and 1.75 s (Me), 2.66 and 2.71 d (CH_2, $^2J_{AB}$ = −13.4), 4.19 dq and 4.40 dq (CH_2O, $^2J_{AB}$ = −10.5, ^3J = 7.1), 1.18 t (Me). (IIIb): 1.79 s (Me) and 1.88 s (Me), 2.55 d and 2.92 d (CH_2, $^2J_{AB}$ = −13.4), 4.24 dq and 4.46 dq (CH_2O, $^2J_{AB}$ = −10.5, ^3J = 7.1), 1.31 t (Me). Mass spectrum, m/z (relative intensity, %): 174 (43.1) $[M + H]^+$, 102 (16.9), 101 (16.8), 86 (16.2), 85 (10.8), 84 (10.8), 49 (10.8), 60 (25.6), 43 (100).

Iminolactone of DMEG, Mixture of Stereoisomers (IVa, b). To a solution of 1.5 g of potassium cyanide (23 mmoles) in 3 ml of water, while stirring and cooling (−5°C), we added 1.2 g (10.5 mmoles) of propionylacetone (obtained according to [13]) and then over 30 min 2 ml (23 mmoles) of concentrated hydrochloric acid (d = 1.17). The precipitate was filtered off, washed with water, and dried under vacuum. We obtained 1.3 g (73.4%) of (IVa, b); mp 121-134°C. Found %: C 57.13; H 7.06; N 16.33. $C_8H_{12}N_2O_2$. Calculated %: C 57.13; H 7.19; N 16.55. PMR spectrum (deuterochloroform, δ, ppm, J, Hz). (IVa): 1.17 t ($MeCH_2$, ^3J = 7.3), 2.01 m and 2.09 m (CH_2Me, $^2J_{AB}$ = −14.2), 2.43 dq (H_a, $^2J_{AB}$ = −13.7, $^2J_{H(a\text{-}Me)}$ = 0.5), 2.66 d (H_B), 1.72 d (a-Me); (IVb): 1.18 t ($MeCH_2$, ^3J = 7.3), 1.91 m and 2.01 m (CH_2Me, $^2J_{AB}$ = −14.2), 2.07 d and 2.77 d (CH_2, $^2J_{AB}$ = −13.7), 1.58 s (e-Me).

Lactone Nitrile of meso-DDG (Va). To 0.5 g (3.2 mmole) of (Ia) we added 3 ml of 5% hydrochloric acid. The mixture was kept at 20°C for 24 h, the solution was evaporated to dryness under vacuum, and the residue was extracted with chloroform. After removal of the solvent the oily residue was crystallized from a mixture of ether and pentane. We obtained 0.35 g (70%) of (Va) in the form of needle crystals; mp 62°C. Found %: C 54.20; H 5.67; N 9.09. $C_7H_9NO_3$. Calculated %: C 54.19; H 5.84; N 9.02. PMR spectrum (deuterochloroform): 1.65 d (a-Me, $^4J_{MeH_a}$ = 0.5), 1.86 s (e-Me), 2.48 dq (H_a, $^2J_{AB}$ = −13.9), 2.75 d (H_e). ^{13}C NMR spectrum (deuterochloroform, δ, ppm, J, Hz): 24.27 (a-Me, ^1J = 129.4, $^3J_{CH_a}$ = $^3J_{CH_e}$ = 3.7), 26.58 (e-Me, ^1J = 131.8, $^3J_{CH_a}$ = 3.7, $^3J_{CH_e}$ = 0), 47.23 (CH_2, ^1J = 138.7), 71.92 (MeCCN, $^2J_{CH_e}$ = 1.8, $^2J_{CH_a}$ = 4.2), 72.89 (MeCOH), $^2J_{CH_e}$ = 2.4, $^2J_{CH_a}$ = 6.1), 118.51 (C≡N, $^3J_{CH_a}$ = 6.7,

$^3J_{CH_e}$ = 4.9), 176.66 (CO, $^3J_{CH_e}$ = 5.4, $^3J_{CH_a}$ = 0, $^3J_{C(a\text{-}Me)}$ = 3.7). IR spectrum (ν, cm^{-1}); 1800 (CO).

Lactone Nitrile of erythro-DMEG (VIa) and threo-DMEG (VIb). A 1.3 g sample (7.7 mmoles) of (IVa, b) was kept at 20°C for 30 min with an excess of 10% hydrochloric acid, evaporated to dryness, and extracted with acetone. The solvent was removed under vacuum, and 1 g (76.9%) of a mixture of the diastereomers (IVa, b) was obtained. After crystallization from a mixture of ether and pentane, mp 101-110°C. Found %: C 56.36; H 6.70; N 8.36. $C_8H_{11}NO_3$. Calculated %: C 56.79; H 6.55; N 8.28. PMR spectrum (deuterochloroform, δ, ppm, J, Hz), (VIa): 1.20 t ($\underline{Me}CH_2$, ^3J = 7.6), 1.71 d (a-Me, $^4J_{MeH_e}$ = 0.5), 2.02 m and 2.14 m ($\underline{CH_2}Me$, $^2J_{AB}$ = −14.2), 2.49 dq (H_a) and 2.74 d (H_e, $^2J_{AB}$ = −13.9); (VIb): 1.21 t ($\underline{Me}CH_2$, ^3J = 7.6), 1.56 s (Me), 1.95 m and 2.04 m ($\underline{CH_2}Me$, $^2J_{AB}$ = −14.2), 2.13 d and 2.85 d ($\underline{CH_2}$, J_{AB} = −13.9). ^{13}C NMR (deuterochloroform, δ, ppm, J, Hz). (VIa): 7.74 ($\underline{Me}CH_2$, ^1J = 127.6, ^2J = 4.2), 24.27 (Me, ^1J = 129.7, ^3J = 4.2), 32.75 ($\underline{CH_2}Me$, ^1J = 131.8), 46.10 (CH_2, ^1J = 133.7), 72.31 (Et$\underline{C}$CN), 76.67 (Me$\underline{C}$OH), 117.62 (CN, ^3J = 4.9), 176.57 (CO, ^3J = 4.9); (VIb): 7.74 ($\underline{Me}CH_2$, ^1J = 127.6, ^2J = 4.2), 22.76 (Me, ^1J = 128.3, ^3J = 3.5), 32.52 ($\underline{CH_2}Me$, ^1J = 131.8, ^3J = 4.9), 45.64 (CH_2, ^1J = 136.4), 72.64 (Et$\underline{C}$CN), 75.99 (Me$\underline{C}$OH), 117.74 (CN), 175.34 (CO).

Compound (VIa) was isolated from the mixture (VIa, b) by extraction with pentane and was characterized by the PMR spectrum. Compound (VIb) was obtained by fractional crystallization of the mixture (VIa, b) from absolute ether. The yield was 46.6%; mp 112-114°C. Found %: C 56.76; H 6.48; N 8.58. $C_8H_{11}NO_3$. Calculated %: C 56.79; H 6.55; N 8.28%. ^{13}C NMR spectrum (CD_3OD, δ, ppm, J, Hz): 8.54 ($\underline{Me}CH_2$, ^1J = 127.6, ^2J = 4.2), 23.03 (Me, ^1J = 128.2, $^3J_{CH_a}$ = 3.5, $^3J_{CH_e}$ = 0), 33.71 ($\underline{CH_2}Me$, ^1J = 131.8, $^3J_{CH_a}$ = 4.9, $^3J_{CH_e}$ = 0), 47.61 (CH_2, ^1J = 136.4), 73.59 (Et$\underline{C}$CN), 78.06 (Me$\underline{C}$OH), 119.5 (CN), 176.72 (CO, $^3J_{COMe}$ = 4.3, $^3J_{CH_a}$ = 4.2, $^3J_{CH_e}$ = 0). IR spectrum (ν, cm^{-1}): 1780 (CO), 2248 (C≡N). Mass spectrum, m/z (relative intensity, %): 170 (21.6), $[M + H]^+$, 82 (100), 43 (20.6).

Monolactone of meso-DDG (VIIa). To a solution of 5 g (77 mmole) of potassium cyanide in 10 ml of water, while stirring and cooling with iced water, we added 3.5 g (35 mmoles) of acetylacetone. A precipitate separated. Over 40 min under the same conditions (0°C, with stirring) we added dropwise 13 ml (76 mmoles) of concentrated hydrochloric acid. The mixture was stirred at 20°C for 5 h and heated at 100°C for 40 min. After evaporation of the water the residue was extracted with boiling ethanol, the solvent was removed under vacuum, and the residue was extracted with acetone. After removal of the acetone it was washed repeatedly with chloroform to remove the (Va). We obtained 0.9 g (14.8%) (VIIa) after recrystallization from a mixture of acetone and hexane, mp 180-192°C.

Compound (VIIa) was also obtained by hydrolysis with concentrated hydrochloric acid (48 h at 20°C) from (Ia) (yield 75%) and from (Va) (yield 60%). Found %: C 48.20; H 6.00. $C_7H_{10}O_5$. Calculated %: C 48.27; H 5.78. PMR spectrum (CD_3OD, δ, ppm, J, Hz): 1.40 d (a-Me, $^4J_{MeH_a}$ = 0.5), 1.66 s (e-Me), 2.29 dq (H_a, $^2J_{AB}$ = −13.7), 2.67 d (H_e). ^{13}C NMR (CD_3OD): 24.98 (a-Me, ^1J = 128.2, $^3J_{CH_a}$ = $^3J_{CH_e}$ = 3.7), 25.45 (e-Me, ^1J = 129.4, $^3J_{CH_a}$ = 3.7, $^3J_{CH_e}$ = 0), 48.31 (CH_2, ^1J = 135.5), 74.30 (Me$\underline{C}$OH), 81.76 (Me$\underline{C}$COOH), 175.12 (CO), 179.66 (COOH).

Monolactone of d,ℓ-DDG (VIIb). To a solution of 6 g (92 mmoles) of potassium cyanide in 12 ml of water, while stirring and cooling (−10°C), we added dropwise 2.4 g (24 mmoles) of acetylacetone and then over 1 h 16 ml (92 mmoles) of concentrated hydrochloric acid. The mixture was stirred at 20°C for 3 h and at 100°C for 1 h. The residue after removal of the water was extracted with acetone, the solvent was removed under vacuum, and the residue was washed with chloroform. We obtained 2.25 g (53.8%) of a mixture of the monolactones of d,ℓ- and meso-DDG (1:2) (VIIa, b); mp 110-176°C. The products were separated in the following way: 0.37 g of the mixture was boiled in 30 ml of benzene, the insoluble residue of (VIIa) (0.25 g) was filtered off, and the filtrate was left to crystallize at ~20°C. We obtained 90 mg (73%) of the almost pure (VIIb) in the form of the crystal hydrate with one molecule of water; mp 70-97°C. Found %: C 44.18, H 6.32. $C_7H_{12}O_6$. Calculated %: C 43.75, H 6.25. PMR spectrum (CD_3OD, δ, ppm, J, Hz): 1.42 s (Me) and 1.60 s (Me), 2.16 d and 2.75 d (CH_2, $^2J_{AB}$ = −13.7). Mass spectrum, 12 eV, m/z (relative intensity, %): 175 (6.19) $[M + H]^+$, 147 (16.8), 129 (10.6), 113 (69.9), 101 (100), 87 (69.0), 69 (33.6), 59 (16.8), 43 (34.5).

Methyl Ester of the Monolactone of meso-DDG (VIIIa). To a solution of 0.25 g of (VIIa) in absolute methanol at −70°C we added dropwise an ether solution of diazomethane to a stable yellow color. The mixture was immediately evaporated under vacuum, and the residue was crystallized from a mixture of absolute ether and petroleum ether. The first portion of crystals with the initial monolactone as impurity (20 mg, 20%) was separated. The solution was evap-

orated to dryness, and the residue was crystallized from a mixture of absolute ether and hexane. The colorless shiny plates were separated, rubbed thoroughly, and dried under vacuum. We obtained 60 mg (22.2%) of (VIIIa), mp 56.5-58.5°C. Found %: C 51.33, H 6.48. $C_8H_{12}O_5$. Calculated %: C 51.06, H 6.43. PMR spectrum (CD_3OD, δ, ppm, J, Hz): 1.37 d (a-Me, $^4J_{MeH_a}$ = 0.5), 1.66 s (e-Me), 2.29 dq (H_a, $^2J_{AB}$ = −13.9), 2.65 d (H_e), 3.78 s (MeO).

Methyl Ester of the Monolactone of d,ℓ-DDG (VIIIb). To a solution of 90 mg of the crystal hydrate (VIIb) in the smallest amount of absolute methanol at −70°C we added dropwise an ether solution of diazomethane to a stable yellow color. The mixture was evacuated, and the residue was crystallized from a mixture of absolute ether and petroleum ether. We obtained 27 mg (30.6%) of (VIIIb); mp 65-67°C. Found: C 50.96; H 6.34. $C_8H_{12}O_5$. Calculated %: C 51.06; H 6.43. PMR spectrum (CD_3OD, δ, ppm, J, Hz): 1.41 s (Me) and 1.59 s (Me), 2.15 d and 2.73 d (CH_2, $^2J_{AB}$ = −13.7), 3.75 s (MeO).

Dilactone of DDG (IX). To a solution of 0.28 g (1.46 mmoles) of the crystal hydrate (VIIb) in 5 ml of dry pyridine we added 0.62 g (3 mmoles) of DCC in 6 ml of dry pyridine. The mixture was stirred at 20°C for 6.5 days. The signals for the initial (VIIb) in the PMR spectrum disappeared. The precipitate was filtered off, and the filtrate was evaporated to dryness and washed with hexane. The crystalline residue (0.23 g) was sublimed under vacuum (100°C at 1 mm Hg). We obtained 50 mg (22%) of (IX); mp 102-104°C. Found %: C 53.99, H 5.12. $C_7H_8O_4$. Calculated %: C 53.85, H 5.16. PMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 1.69 s (Me), 2.44 s (CH_2).

A 50% yield of (IX) was recorded by means of the PMR spectra after boiling (VIIb) in $C_6D_5CD_3$ in the presence of p-toluenesulfonic acid. Compound (IX) was also obtained with a yield of 2% during distillation of (VIIa) by heating in a flame. The formation of α,γ-dimethyl-γ-crotonolactone was recorded. PMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 1.39 d (A-Me, ^3J = 6.8), 1.90 dd (B-Me, $^4J_{M_eH_b}$ = $^5J_{M_eH_a}$ = 1.7), 4.97 qqd (H_a), 7.00 dq (H_b, $^3J_{HH_a}$ = 1.7).

Hydrochloride of the Monoiminodilactone of threo-DMEG (XI). A stream of dry hydrogen chloride was passed into a solution of 0.22 g (1.3 mmoles) of (IVb) in the smallest amount of absolute ether (30 min, −5 to −10°C), and the mixture was left overnight at 20°C. The crystals which separated were filtered off, and the solution was evaporated to two thirds of the volume and left in the refrigerator. We obtained 0.11 g (41%) of (XI); mp 130-132°C. Found %: C 46.67, H 6.02, N 6.88. $C_8H_{12}NO_3Cl$. Calculated %: C 46.72, H 5.88, N 6.81. PMR spectrum (deuterochloroform, δ, ppm, J, Hz): 1.03 t ($\underline{Me}CH_2$, ^3J = 7.3), 1.81 s (Me), 2.14 m ($\underline{CH_2}Me$, $^2J_{AB}$ = −2.7), 2.79 d and 2.88 d (CH_2, $^2J_{AB}$ = −15.1). ^{13}C NMR ($CDCl_3$): 7.98 ($MeCH_2$, ^1J = 127.6, ^2J = 4.2), 27.64 (Me, ^1J = 131.8, ^3J = 1.2), 31.01 ($\underline{CH_2}Me$, ^1J = 126.2), 47.21 (CH_2, ^1J = 135.9), 61.66 () and 85.73 (), 173.36 ($C=\overset{+}{N}H_2$), 173.77 (CO). IR spectrum (ν, cm^{-1}): 1696 ($C=\overset{+}{N}H_2$), 1788 (CO). Mass spectrum, m/z (relative intensity, %): 208 (7.0), 206 (21.0) $[M + H]^+$, 163 (15.2), 161 (48.6), 57 (100).

CONCLUSIONS

1. The principle of the stereocontrolled assembly of framework structures was confirmed for the case of the synthesis of bicyclic compounds with high yields under mild conditions from derivatives of d,ℓ-α,α'-dihydroxy-α,α'-dimethyl- and threo-α,α'-dihydroxy-α-methyl-α'-ethylglutaric acids.

2. The conformation of the five-membered heterocycles in the derivatives of d,ℓ- and meso-α,α'-dihydroxy-α,α'-dimethylglutaric acid and threo- and erythro-α,α'-dihydroxy-α-methyl-α'-ethylglutaric acids was studied. For the former it was shown that the functional groups have the a,a orientation, which favors secondary cyclization. On this basis the general principle of conformational control during the assembly of bicyclic systems from the monocyclic precursors was formulated. In the derivatives of the meso and erythro series the conformation of the ring changes with increase in the size of the substituent from a-CN to e-COOH and e-COOR.

3. It was shown that the products previously described as biscyanohydrins of acetylacetone and propionylacetone have the iminolactone structure.

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REACTION OF 3-INDOLETHIOLS WITH ACETYLENES

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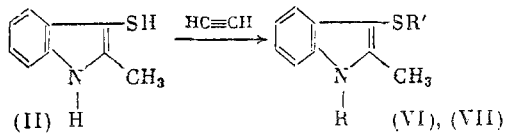
Indole derivatives, in particular those of 3-indolethiol, have various forms of biological activity [1-3]. In order to expand the number of potentially useful biologically active compounds and also to investigate the nucleophilic addition reaction of 3-indolethiols to acetylenes, we have studied the reaction of 3-indolethiol (I) and 2-methyl-3-indolethiol (II) with acetylene, phenylacetylene (III), 1-phenyl-2-cyanoacetylene (IV), and 3-hydroxy-3-methyl-1-cyano-1-butyne (V).

It was previously shown that mono- and divinyl monomers [4] are formed depending on the conditions of the reaction between (I) and acetylene. Introduction of a methyl group into the 2-position of the indole ring slightly reduces the reactivity of (II) in this reaction. The formation of both 2-methyl-3-vinylthioindole (VI) and 1-vinyl-2-methyl-3-vinylthioindole (VII) needs greater heating (180 and 200°C, respectively) than for the preparation of the corresponding vinyl derivatives of indole (I), which is apparently due to the electron-donating effect of the Me group, resulting in an increase in binding of the protons with the N and S heteroatoms



R = H, R′=CH=CH$_2$(VI); R = R′=CH=CH$_2$(VII).

Introduction of an electron-withdrawing substituent into the acetylene molecule activates the triple bond in the reaction with indoles (I) and (II). Thus, with phenylacetylene (III) in the presence of alkali the reaction takes place at 90-95°C. It should be noted that the addition reaction is complicated by a competing oxidation reaction which results in the formation of bisindolyl sulfides, which considerably reduces the yield of 3-[(2-phenylvinyl)thio]indoles (VIII) and (IX) (Table 1).

The addition of indoles (I) and (II) to acetylenes (IV) and (V), which are activated by a nitrile group, occurs at ~20°C in triethylamine with a high yield of the corresponding 2-R-3-](1-R′-2-cyanovinyl)thio]indoles (X)-(XII)

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