CROATICA CHEMICA ACTA CCACAA 59 (2) 491—508 (1986)

~~CCA-1663~~ CCA-1662

YU ISSN 0011-1643
UDC 543.852.6
Original Scientific Paper

Bromolactone Structures derived from Cyclohex-3-ene-1,1--dicarboxylic Acids and Syntheses of Multifunctional Cyclohexanecarboxylic Acids

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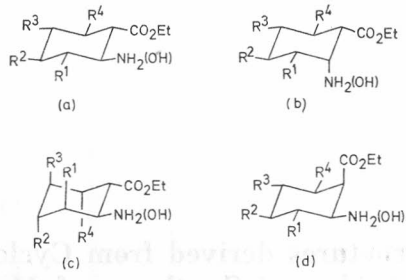
Received September 30, 1985

It was shown that the bromolactonization of 4-cyanocyclohex--3-ene-1,1-dicarboxylic acid (*10*) in water or aqueous $NaHCO_3$ proceeded to t-4-bromo-c-4-cyano-c-3-hydroxycyclohexane-r-le, 1-dicarboxylic acid (*13*) *via* the intermediate c-4-bromo-t-4-cyano--6-oxabicyclo[3.2.1]octan-7-one-r-1-carboxylic acid (*11*). In contrast to this finding, 4-carbamoylcyclohex-3-ene-1,1-dicarboxylic acid (*19*) yielded only c-4-bromo-t-4-carbamoyl-6-oxabicyclo[3.2.1]octan--7-one-r-1-carboxylic acid (*20*) by treatment with bromine in aqueous $NaHCO_3$. The syntheses of 4-cyano-(*25*) and 4-carbamoyl--(*26*)-t-3,4-oxiranecyclohexane-r-le,1-dicarboxylate are also described.

The structures and relative configurations of methyl c-4--bromo-t-4-cyano-6-oxabicyclo[3.2.1]octan-7-one-r-1-carboxylate (*12*), prepared from *11*, and dimethyl c-3-benzoxy-t-4-bromo-c-4--cyanocyclohexane-r-le,1-dicarboxylate (*15*), prepared from *13*, were determined by X-ray analyses, confirmed also by ^{1}H-NMR and ^{13}C-NMR spectroscopies.

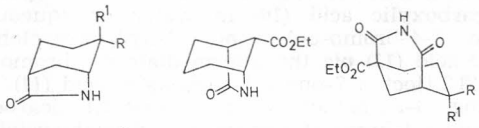
There is continuing interest in amino- and hydroxy-cyclohexane carboxylic acids with specific conformational features and geometries which allow the intramolecular cyclizations of certain steric situations into respective aza- and oxa-bicyclo alkanones. We have already reported on the preparations and separations of the geometrical isomers (a-d) in the diethyl 2-amino-(2-hydroxy-) cyclohexane-1,3[1]-(*1*), 1,4[2]-(*2*), 1,5[3]-(*3*), and 1,6[4]-(*4*) dicarboxylates series (Scheme 1).

In two earlier papers[2,4] we have also described spontaneous intramolecular cyclizations of diethyl c-2-aminocyclohexane-r-1,c-4-(*2d*) and diethyl c-2-aminocyclohexane-r-1-c-6-(*4d*)dicarboxylate at room temperature yielding ethyl 7-oxo-6-azabicyclo[3.2.1]octane-c-4-(*5*) and ethyl 7-oxo-6-azabicyclo[3.2.1]-octane-c-8-(*6*)carboxylate, respectively (Scheme 2). In the meantime we found that the thermodynamically most stable diethyl t-2-aminocyclohexane-r-1,t--4-dicarboxylate (*2a*) having equatorially situated substituents underwent intramolecular cyclization at elevated temperature (250 °C). This transforma-



Scheme 1

tion, however, yielded thermodynamically less favoured ethyl 7-oxo-6-azabicyclo[3.2.1]octane-t-4-carboxylate (7) with axial carboxylate group, and to a lesser extent its epimer 5. Cyclohexene derivatives, as by-products of deamination reactions, were isolated as well.



Scheme 2

To afford a number of bicyclo[3.3.1]nonane derivatives containing special functional groups we have also described intramolecular transformations of diethyl c-2-benzamido- and diethyl t-2-benzamido-r-1-carbamoyl-5,5-dicarboxylate[5] into the corresponding ethyl t-6-benzamido-(*8*; R=NHBz, R¹=H) and ethyl c-6-benzamido-(*8;* R=H, R¹=NHBz)3-azabicyclo[3.3.1]nona-2,4-dione-r-1-carboxylate. We now report on the synthesis, the crystal and molecular structures of the biomedically interesting 6-oxabicyclo[3.2.1]octan-7-ones[6,7] and their ring cleavages into functionalized, hitherto unknown, bromo-hydroxy-cyclohexanecarboxylic acids.

The reported synthesis of multifunctional cyclohexane derivatives was based on the bromolactonization reaction[8,9] of cyclohexene derivatives. For this purpose diethyl 4-cyanocyclohex-3-ene-1,1-dicarboxylate[2] (*9*) was converted into 4-cyanocyclohex-3-ene-1,1-dicarboxylic acid (*10*) by hydrolysis in refluxing 20% methanolic KOH[10] (Scheme 3). In the reaction of cyanocyclohexene *10* with bromine in water the attack of the carboxylate anion on the intermediate C(3),C(4)-bromonium ion appeared to be controlled by electronic and stereochemical factors[11], particularly by a higher degree of carbonium ion character of the latter at the less substituted ethylenic carbon atom. The structure and relative configuration of the thus obtained c-4-bromo-t-4-

-cyano-6-oxabicyclo[3.2.1]octan-7-one-r-1-carboxylic acid (*11*) (58.2%), previously converted into crystalline methyl carboxylate *12*, was unequivocally determined by an X-ray analysis. This determination revealed the axial position for Br in the bromolactone *12* (Figure 1).

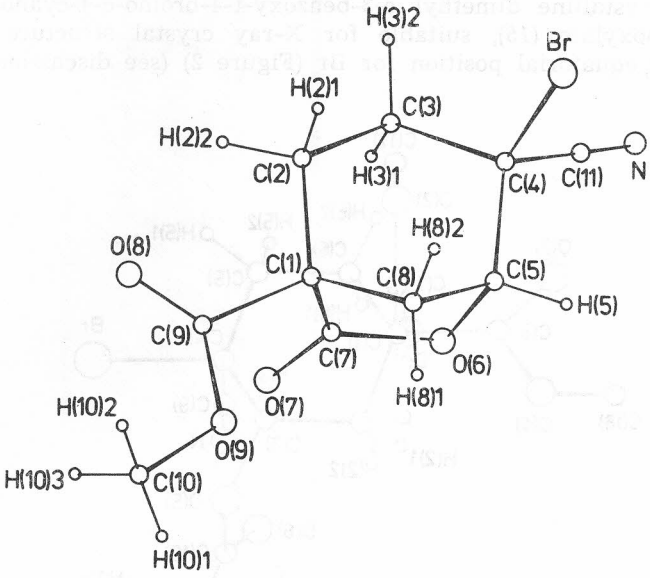
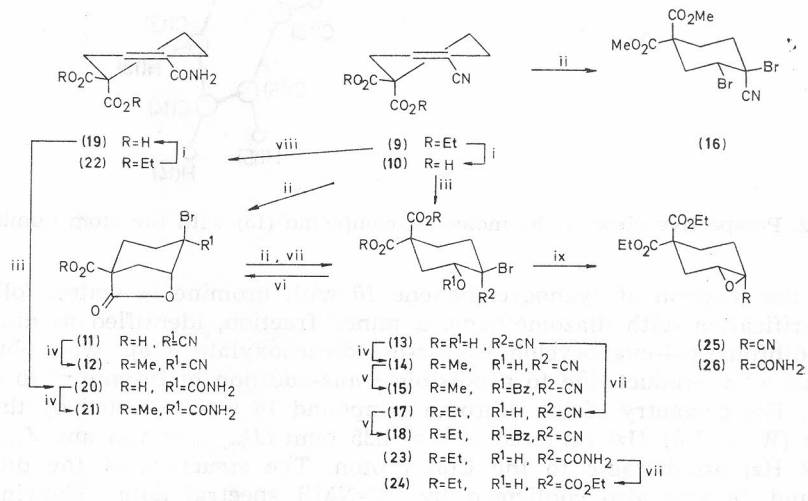


Figure 1. Perspective view of the molecule, compound (12) with the atom numbering.

Scheme 3



Reagents: i, 20% KOH—MeOH; ii, Br_2—H_2O; iii, Br_2-aq.$NaHCO_3$; iv, CH_2N_2—Et_2O; v, BzCl-py; vi, DCCI-dioxane; vii, 3% HCl—EtOH; viii, $(H_3PO_4)_n$; ix, DBU—CH_2Cl_2.

The regio- and stereo-selective bromolactonization of cyanocyclohexene *10*, through a *trans*-diaxial pattern of ionic addition, afforded also t-4-bromo--c-4-cyano-c-3-hydroxycyclohexane-r-le,1-dicarboxylic acid (*13*) in 14.6% yield by the stereocontrolled ring opening of the preformed bromolactone *11* (Scheme 3). It was characterized as dimethyl dicarboxylate *14* and benzoylated into crystalline dimethyl c-3-benzoxy-t-4-bromo-c-4-cyanocyclohexane--r-le,1-dicarboxylate (*15*), suitable for X-ray crystal structure analysis. It revealed the equatorial position for Br (Figure 2) (see discussion bellow).

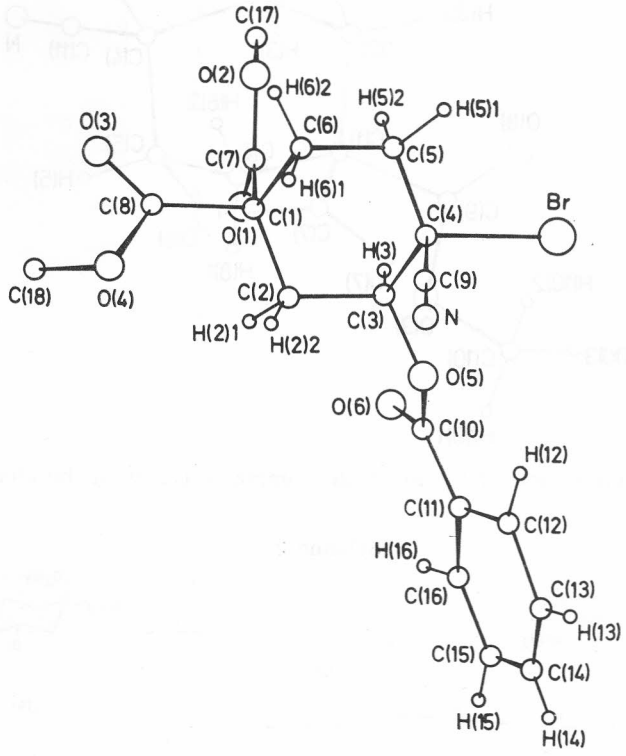


Figure 2. Perspective view of the molecule, compound (15) with the atom numbering.

In the reaction of cyanocyclohexene *10* with bromine in water, followed by esterification with diazomethane, a minor fraction, identified as dimethyl c-3,t-4-dibromo-c-4-cyanocyclohexane-r-le,1-dicarboxylate (*16*), was obtained (11%) as a by-product due to a possible *trans*-addition of bromine[12] to cyclohexene. The geometry of the dibromo compound *16* was reflected by the two doublet (W = 15.87 Hz) centered at δ = 4.35 ppm ($J_{3ax,\,2eq}$ = 4.15 and $J_{3ax,\,2ax}$ = = 11.72 Hz) attributable to the C(3) proton. The structure of the dibromo compound *16* was also confirmed by ^{13}C-NMR spectral data[13] showing the signal for the tertiary C(3)-Br at δ = 51.45 ppm (d). It is worth noting that the IR, ^{1}H-NMR spectra as well as ^{13}C-NMR multiplicities of all compounds (see Experimental) presented in this paper agreed with the proposed structures.

Cyclohexane-dicarboxylic acid *13*, quantitatively obtained in reaction of cyanocyclohexene *10* with bromine in aqueous $NaHCO_3$, was conformationally and structurally approved by an intramolecular cyclization into *11* in the presence of DCCI, and esterification into diethyl t-4-bromo-c-4-cyano-c-3--hydroxycyclohexane-r-le,1-dicarboxylate (*17*) by a treatment with 3% ethanolic HCl. Compound *17* was also characterized as diethyl c-3-benzoxy-t-4--bromo-c-4-cyanocyclohexane-r-le,1-dicarboxylate (*18*) by a reaction with benzoyl chloride in pyridine, giving rise, in the ^{1}H-NMR spectrum, to downfield doublets of the axial C(3) proton at $\delta = 5.48$ ppm ($W = 13.63$ Hz; $J_{3ax,\,2eq} = 3.96$, $J_{3ax,2ax} = 9.67$ Hz).

In order to examine the influence of the substituents of 4-substituted cyclohex-3-ene-1,1-dicarboxylic acid on the bromolactonization and the stabilities of the bromolactones, 4-carbamoylcyclohex-3-ene-1,1-dicarboxylic acid (*19*) was treated with bromine in aqueous $NaHCO_3$. In this study, c-4--bromo-t-4-carbamoyl-6-oxabicyclo[3.2.1.]octan-7-one-r-1-carboxylic acid (*20*) was obtained in nearly quantitative yield. The latter afforded methyl c-4--bromo-t-4-carbamoyl-6-oxabicyclo[3.2.1]octan-7-one-r-1-carboxylate (*21*) in a treatment with ethereal diazomethane. It is noteworthy that the carbamoyl function contributed to the stabilization of bromolactone *20*, most probably by chelate structures formation. Carbamoyl-cyclohexene *19* was prepared in high yield from diethyl 4-cyanocyclohex-3-ene-1,1-dicarboxylate (*9*) in a reaction with polyphosphoric acid,[14] followed by hydrolysis of the resulting diethyl 4-carbamoylcyclohex-3-ene-1,1-dicarboxylate (*22*) in boiling 20% methanolic KOH.[10]

Due to the fact that carbamoyl-lactone *20* persisted under basic conditions as a stabile structure, its ring opening into diethyl t-4-bromo-c-4-carbamoyl-c-3-hydroxycyclohexane-r-le,1-dicarboxylate (*23*) (64%) was successfully achieved in boiling 3% ethanolic HCl. A minor amount of triethyl t-4-bromo-c-3-hydroxycyclohexane-r-le,1,c-4-tricarboxylate (*24*) (21.8%), geometrically related to carbamoyl compound *23*, was isolated too.

The geometrical features of the compounds in the bromo-hydroxycyclohexane series (*13*—*18*), established by X-ray and ^{1}H-NMR analyses, enabled us to exercise a dehydrobromination reaction of diethyl t-4-bromo-c-4-cyano--c-3-hydroxycyclohexane-r-le,1-dicarboxylate (*17*). This attempted elimination by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene[15] (DBU) in CH_2Cl_2, however, led readily to an epoxide which was identified as diethyl 4-cyano--t-3,4-oxiranecyclohexane-r-le,1-dicarboxylate (*25*) (93%).

By analogy with the formation of the epoxide *25*, the dehydrobromination of diethyl t-4-bromo-c-4-carbamoyl-c-3-hydroxycyclohexane-r-le,1-dicarboxylate (*23*) by means of DBU easily afforded diethyl 4-carbamoyl-t--3,4-oxiranecyclohexane-r-le,1-dicarboxylate (*26*) (96.9%). To avoid these C(3)OH—C(4)Br epoxidations, an attempted benzoylation of C(3)-hydroxy group of *23* with an excess of benzoyl chloride in pyridine, however, involved dehydratation of the carbamoyl group[16] yielding cyano compound *18*.

X-Ray Analyses of Compound 12 *and* 15

Crystals of compounds *12* and *15* were obtained from a mixture of CH_2Cl_2, ether, and n-hexane kept in refrigerator at 2—6 °C. In spite of a number of crystallizations, the crystals of *15* were of poor quality. Both

compounds crystallized in the monoclinic space group $P2_1/c$. Crystal and physical data-compound *12*, $C_{10}H_{10}NO_4Br$, $M = 288.10$, $a = 15.380(5)$, $b = 6.402$ (2), $c = 11.335(4)$ Å, $\beta = 95.5(2)^\circ$, $V = 1110.9(3)$ Å^3, $Z = 4$, $D_c = 1.722$ Mgm^{-3}, μ(Mo$K\alpha$) = 36.53 cm^{-1}; compound (*15*), $C_{18}H_{18}NO_6Br$, $M = 424.25$, $a = 12.452$ (1), $b = 26.432(10)$, $c = 11.256(7)$ Å, $\beta = 91.2(8)^\circ$, $V = 3703.9(8)$ Å^3, $Z = 8$, $D_c = 1.521$ Mgm^{-3}, μ(Mo$K\alpha$) = 22.23 cm^{-1}.

Preliminary cell dimensions and space groups were determined from oscillation and Weissenberg photographs recorded with Cu$K\alpha$ radiation. Final cell dimensions were refined from diffractometer measurements of 15 (compound *12*) and 25 (compound *15*) reflections. Intensities were collected on a Phillips PW 1100 computer-controlled four-circle diffractometer in the ω-scan mode [scan width = 1.20° (Θ), scan speed = 0.04 (Θ) s^{-1} for both compounds] with graphite-monocromated Mo$K\alpha$ radiation. The crystals of dimensions 0.20 × 0.14 × 0.22 mm (compound *12*) and 0.11 × 0.15 × 0.27 mm (compound *15*) were used for data collections. 1376 (compound *12*) and 2640 (compound *15*) independently observed reflections [$I \geq 3\sigma(I)$] in the range $2^\circ < \Theta < 30^\circ$ were recorded and used in structure determinations. Three standard reflections were measured every 2 hours. The data were corrected for background, Lorentz and polarization effects but not for absorption.

The structures were solved by a combination of Patterson and direct methods (*MULTAN*80).[17]

Difference Fourier syntheses located hydrogen atoms, but those of C(17) and C(18) methyl groups (compound *15*) were not found. Refinement was done by full-matrix least squares minimizing $\Sigma w \Delta F^2$, $w = 1$. The hydrogen atoms were included in the structure factor calculation only. Their isotropic thermal parameters were those of the bonded atoms plus one. Anisotropic refinement of non-hydrogen atoms ended at conventional $R = 0.050$ (compound *12*) and $R = 0.061$ (compound *15*). The final atomic coordinates for the non-hydrogen atoms are listed in Tables I and II*.

Scattering factors given by Cromer and Mann[18] and (for H) Stewart, Davidson, and Simpson[19] were used. An anomalous dispersion correction for bromine was included.[20]

Calculations were carried out on the Univac 1110 computer at the University Computing Centre in Zagreb with XRAY76.[21]

TABLE I

*Final Atomic Coordinates(*10000) and Isotropic Thermal Parameters(*100) for Non-hydrogen Atoms, Compound (12)*

	x	y	z	U (Å^2)
Br	1046(1)	3292(1)	10169(1)	5.47(4)
C(1)	3019(3)	7318(9)	9931(5)	3.3 (2)
C(2)	3115(4)	5003(11)	9667(6)	4.8 (3)
C(3)	2411(4)	4323(10)	8709(6)	4.7 (3)
C(4)	1480(4)	5072(10)	8955(5)	3.7 (3)
C(5)	1502(4)	7346(9)	9369(5)	3.6 (3)
O(6)	1938(3)	8515(8)	8447(3)	5.0 (2)

Table I to be continued

* Lists of structure factors, anisotropic thermal parameters, and hydrogen atom coordinates are obtainable from the authors Ž. R.-T and B. K.-P on request.

Table I continued

C(7)	2851(4)	8471(11)	8733(5)	4.3 (3)
O(7)	3306(3)	9292(8)	8131(4)	5.6 (2)
C(8)	2158(4)	7705(10)	10455(5)	4.0 (3)
O(8)	4515(3)	7358(9)	10774(4)	6.9 (3)
C(9)	3828(4)	8203(12)	10634(5)	4.3 (3)
O(9)	3660(2)	10102(8)	11067(4)	5.6 (2)
C(10)	4384(5)	11139(14)	11750(7)	6.5 (4)
C(11)	869(4)	4826(11)	7870(6)	4.7 (3)
N	411(4)	4681(11)	7037(5)	6.3 (3)

$$U_{eq} = 1/3 \sum_i \sum_j U_{ij}\, a_i^*\, a_j^*\, \vec{a}_i\, \vec{a}_j$$

TABLE II

*Final Atomic Coordinates(*10000) and Isotropic Thermal Parameters(*100) for Non-hydrogen Atoms, Compound (15)*

	x	*y*	*z*	*U* (Å²)
Br(1A)	6147 (1)	9723(1)	—1189 (1)	7.7(1)
Br(1B)	8693 (1)	257(1)	1177 (1)	7.4(1)
C(1A)	6311 (7)	7937(3)	—1551 (8)	4.3(4)
C(2A)	6380 (7)	8167(3)	—304 (8)	4.3(4)
C(3A)	6577 (6)	8735(3)	—317 (8)	4.3(4)
C(4A)	5740 (7)	9009(3)	—1114 (8)	4.6(4)
C(5A)	5677 (7)	8772(4)	—2349 (8)	5.0(5)
C(6A)	5451 (7)	8214(3)	—2308 (8)	4.7(4)
C(7A)	7419 (7)	7945(3)	—2129 (9)	5.4(5)
C(8A)	6011 (9)	7374(4)	—1525 (9)	6.9(6)
C(9A)	4671 (7)	9009(3)	—523 (8)	4.9(4)
C(10A)	7367 (7)	8986(4)	1543 (9)	5.3(5)
C(11A)	7121 (7)	9218(4)	2704 (8)	4.7(4)
C(12A)	6196(10)	9476(5)	2861(11)	8.5(7)
C(13A)	5981(11)	9683(5)	4005(13)	10.5(8)
C(14A)	6735(15)	9618(5)	4913(12)	9.8(8)
C(15A)	7642(12)	9377(6)	4741(12)	9.1(7)
C(16A)	7857 (9)	9182(5)	3639(11)	7.8(6)
C(17A)	8382 (8)	7949(5)	—3912(10)	8.2(7)
C(18A)	5155(11)	6698(4)	—617(11)	9.4(8)
O(1A)	8236 (5)	7883(3)	—1566 (6)	7.6(4)
O(2A)	7360 (5)	7988(3)	—3298 (5)	6.7(4)
O(3A)	6248(16)	7090(4)	—2263(11)	25 (1)
O(4A)	5505 (6)	7226(2)	—638 (6)	7.9(4)
O(5A)	6488 (4)	8931(2)	863 (5)	5.0(3)
O(6A)	8238 (6)	8851(3)	1236 (7)	7.9(5)
N(1A)	3874 (6)	8999(3)	—77 (8)	7.3(7)
C(1B)	8767 (7)	2052(3)	822 (8)	4.3(4)
C(2B)	8740 (7)	1820(3)	2081 (8)	4.7(4)
C(3B)	8445 (7)	1264(3)	2057 (8)	4.3(4)
C(4B)	9188 (7)	965(3)	1274 (9)	4.8(4)
C(5B)	9190 (8)	1191(3)	27 (9)	5.2(5)
C(6B)	9495 (7)	1740(3)	43 (7)	4.3(4)
C(7B)	7617 (7)	2103(3)	304 (8)	5.0(5)
C(8B)	9214 (9)	2598(4)	860 (9)	7.0(6)
C(9B)	10300 (7)	931(3)	1785 (8)	5.0(5)
C(10B)	7758 (7)	1085(3)	3985 (8)	5.2(5)
C(11B)	8034 (7)	859(3)	5156 (8)	4.8(4)
C(12B)	8979 (8)	592(3)	5342 (8)	5.2(5)
C(13B)	9193 (9)	371(4)	6462(11)	6.9(6)
C(14B)	8474(11)	435(4)	7358(10)	6.6(6)
C(15B)	7560(11)	702(5)	7146(10)	7.8(6)
C(16B)	7319 (9)	915(4)	6063(10)	7.4(6)
C(17B)	6540 (9)	2149(5)	—1473(11)	8.7(7)

Table II to be continued

Table II continued

C(18B)	10054(12)	3261(4)	1861(11)	9.8(8)
O(1B)	6852 (5)	2185(3)	902 (6)	7.5(4)
O(2B)	7583 (5)	2055(3)	—859 (5)	6.6(4)
O(3B)	9272(12)	2842(4)	—24 (9)	17.0(9)
O(4B)	9576 (6)	2753(2)	1844 (6)	7.5(4)
O(5B)	8594 (4)	1064(2)	3236 (5)	4.7(3)
O(6B)	6915 (5)	1269(3)	3700 (6)	8.5(4)
N(1B)	11127 (7)	922(3)	2174 (8)	7.2(5)

Intramolecular geometry of both compounds is described by bond lengths and angles (Tables III, and IV) and torsion angles (Tables V and VI). The values of bond lengths and angles of two symmetrically independent molecules (compound *15*) are comparable within 2σ (Table IV).

TABLE III

Interatomic Distances (Å) and Angles (°) for Non-hydrogen Atoms of the Compound (12)

Br(1)—C(4)	1.959(6)
C(1)—C(2)	1.522(10)
C(1)—C(7)	1.546(9)
C(1)—C(8)	1.523(9)
C(1)—C(9)	1.522(8)
C(2)—C(3)	1.521(9)
C(3)—C(4)	1.549(10)
C(4)—C(5)	1.529(9)
C(4)—C(11)	1.489(9)
C(5)—O(6)	1.495(8)
C(5)—C(8)	1.532(8)
O(6)—C(7)	1.411(8)
C(7)—O(7)	1.149(9)
O(8)—C(9)	1.184(8)
O(9)—C(9)	1.345(10)
O(9)—C(10)	1.454(9)
C(11)—N	1.127(9)
C(2)—C(1)—C(7)	107.6(5)
C(2)—C(1)—C(8)	109.8(5)
C(2)—C(1)—C(9)	112.1(5)
C(7)—C(1)—C(8)	100.8(5)
C(7)—C(1)—C(9)	110.0(5)
C(8)—C(1)—C(9)	115.7(5)
C(1)—C(2)—C(3)	110.1(5)
C(2)—C(3)—C(4)	112.6(6)
Br(1)—C(4)—C(3)	109.4(4)
Br(1)—C(4)—C(5)	109.5(4)
Br(1)—C(4)—C(11)	106.3(4)
C(3)—C(4)—C(5)	111.3(5)
C(3)—C(4)—C(11)	110.1(5)
C(5)—C(4)—C(11)	110.1(5)
C(4)—C(5)—O(6)	104.8(5)
C(4)—C(5)—C(8)	112.2(5)
O(6)—C(5)—C(8)	100.4(5)
C(5)—O(6)—C(7)	109.4(4)
C(1)—C(7)—O(6)	106.8(5)
C(1)—C(7)—O(7)	132.8(6)
O(6)—C(7)—O(7)	120.2(6)
C(1)—C(8)—C(5)	101.1(5)

Table III to be continued

Table III continued

C(1)—C(9)—O(8)	125.1(7)
C(1)—C(9)—O(9)	110.6(5)
O(8)—C(9)—O(9)	124.4(6)
C(9)—O(9)—C(10)	116.3(5)
C(4)—C(11)—N	178.3(8)

TABLE IV

Interatomic Distances (Å) and Angles (°) for Non-hydrogen Atoms of the Compound (15)

	Molecule A	Molecule B
Br(1)—C(4)	1.96(1)	1.97(1)
C(1)—C(2)	1.53(1)	1.54(1)
C(1)—C(6)	1.54(1)	1.52(1)
C(1)—C(7)	1.54(1)	1.54(1)
C(1)—C(8)	1.53(1)	1.55(1)
C(2)—C(3)	1.53(1)	1.52(1)
C(3)—C(4)	1.54(1)	1.51(1)
C(3)—O(5)	1.43(1)	1.44(1)
C(4)—C(5)	1.52(1)	1.52(1)
C(4)—C(9)	1.50(1)	1.49(1)
C(5)—C(6)	1.50(1)	1.50(1)
C(7)—O(1)	1.20(1)	1.20(1)
C(7)—O(2)	1.32(1)	1.32(1)
C(8)—O(3)	1.16(2)	1.19(1)
C(8)—O(4)	1.25(1)	1.26(1)
C(9)—N(1)	1.12(1)	1.11(1)
C(10)—C(11)	1.48(1)	1.48(1)
C(10)—O(5)	1.33(1)	1.35(1)
C(10)—O(6)	1.20(1)	1.19(1)
C(17)—O(2)	1.46(1)	1.48(1)
C(18)—O(4)	1.46(1)	1.47(1)
C(2)—C(1)—C(6)	110.0(8)	109.8(8)
C(2)—C(1)—C(7)	110.4(8)	110.2(8)
C(2)—C(1)—C(8)	112.1(8)	111.1(8)
C(6)—C(1)—C(7)	112.3(8)	112.9(8)
C(6)—C(1)—C(8)	107.7(8)	107.7(8)
C(7)—C(1)—C(8)	104.1(8)	105.0(8)
C(1)—C(2)—C(3)	112.9(8)	112.2(8)
C(2)—C(3)—C(4)	111.2(7)	111.4(8)
C(2)—C(3)—O(5)	109.4(7)	108.3(7)
C(4)—C(3)—O(5)	107.8(7)	106.1(7)
Br(1)—C(4)—C(3)	107.8(6)	109.4(7)
Br(1)—C(4)—C(5)	111.4(7)	109.1(7)
Br(1)—C(4)—C(9)	104.6(6)	104.4(7)
C(3)—C(4)—C(5)	111.0(8)	110.2(8)
C(3)—C(4)—C(9)	109.7(8)	112.4(8)
C(5)—C(4)—C(9)	112.0(8)	111.1(8)
C(4)—C(5)—C(6)	112.4(8)	111.9(8)
C(1)—C(6)—C(5)	110.8(8)	112.3(8)
C(1)—C(7)—O(1)	122.2(9)	123.2(8)
C(11)—C(7)—O(2)	113.1(8)	112.3(8)
O(1)—C(7)—O(2)	124.5(9)	124.5(9)

Table IV to be continued

Table IV continued

	Molecule A	Molecule B
O(3)—C(8)—O(4)	120 (1)	122 (1)
C(1)—C(8)—O(3)	123 (1)	121 (1)
C(1)—C(8)—O(4)	116.4(9)	116.7(9)
C(4)—C(9)—N(1)	179 (1)	178 (1)
C(11)—C(10)—O(5)	111.7(8)	111.7(8)
C(11)—C(10)—O(6)	125.7(9)	126.1(9)
O(5)—C(10)—O(6)	122.6(9)	122.2(9)
C(10)—C(11)—C(12)	121.1(9)	121.4(9)
C(10)—C(11)—C(16)	119.7(9)	118.4(9)

Bond distances and angles in phenyl rings of both molecules are omitted. Their mean values are: 1.37(2) Å, 120(1)° (A); 1.38(2) Å, 120(1)° (B).

The crystal packing in both structures is realized by van der Waals interactions only. The conformation of the six-membered ring in the oxabicyclo[3.2.1]octan-7-one moiety (in compound *12*) is in the irregular chair conformation with C(3) [-0.57(3) Å] and C(8) [0.84(3) Å] displaced from the

TABLE V

Torsion Angles (°) of the Compound (12)

C(1)—C(2)—C(3)—C(4)	—48.3(7)
C(2)—C(3)—C(4)—C(5)	43.9(7)
C(3)—C(4)—C(5)—C(8)	—55.3(7)
C(4)—C(5)—C(8)—C(1)	66.6.(6)
C(5)—C(8)—C(1)—C(2)	—71.0(6)
C(8)—C(1)—C(2)—C(3)	64.7(7)
C(4)—C(5)—O(6)—C(7)	—86.9(6)
C(8)—C(5)—O(6)—C(7)	29.7(6)
C(5)—O(6)—C(7)—C(1)	—3.0(7)
O(6)—C(7)—C(1)—C(8)	—25.1(6)
C(7)—C(1)—C(8)—C(5)	42.4(6)
C(1)—C(8)—C(5)—O(6)	—44.3(6)
C(2)—C(3)—C(4)—Br(1)	—77.3(6)
C(2)—C(3)—C(4)—C(11)	166.2(6)
C(5)—O(6)—C(7)—O(7)	—179.8(5)
C(8)—C(1)—C(9)—O(8)	140.8(7)
C(8)—C(1)—C(9)—O(9)	—39.9(8)
C(1)—C(9)—O(9)—C(10)	—179.4(5)

TABLE VI

Torsion Angles (°) of the Compound (15)

	Molecule A	Molecule B
C(1)—C(2)—C(3)—C(4)	53 (1)	55 (1)
C(2)—C(3)—C(4)—C(5)	—52 (1)	—55 (1)
C(3)—C(4)—C(5)—C(6)	55 (1)	56 (1)
C(4)—C(5)—C(6)—C(1)	—57 (1)	—57 (1)
C(5)—C(6)—C(1)—C(2)	56 (1)	54 (1)
C(6)—C(1)—C(2)—C(3)	—55 (1)	—53 (1)
C(5)—C(6)—C(1)—C(7)	—67 (1)	—69 (1)
C(5)—C(6)—C(1)—C(8)	178.5(8)	175.1(3)
C(6)—C(1)—C(7)—O(1)	158 (1)	155 (1)
C(6)—C(1)—C(7)—O(2)	—26 (1)	—26 (1)
C(6)—C(1)—C(8)—O(3)	85 (2)	61 (1)
C(6)—C(1)—C(8)—O(4)	—97 (1)	—114 (1)
C(1)—C(7)—O(2)—C(17)	—174.2(9)	—173.8(9)

Table VI to be continued

Table VI continued

C(1)—C(8)—O(4)—C(18)	176.7(9)	177 (1)
C(1)—C(2)—C(3)—O(5)	172.4(7)	171.6(7)
C(2)—C(3)—O(5)—C(10)	94.9(9)	89.3(9)
C(3)—O(5)—C(10)—O(6)	—4 (1)	—1 (1)
C(3)—O(5)—C(10)—C(11)	177.0(8)	179.3(8)
O(5)—C(10)—C(11)—C(12)	—19 (1)	—9 (1)
C(2)—C(3)—C(4)—Br(1)	—174.6(6)	—175.5(6)
C(2)—C(3)—C(4)—C(9)	72 (1)	69 (1)

four-atom plane. The parameters of the Cremer and Pople ring puckering analysis[22] [for the atom sequence C(8), C(1), C(2), C(3), C(4), C(5)] are $\Theta = 17.1(6)^\circ$, $\varphi = 17(2)^\circ$, $Q = 0.631(7)$ Å. The γ-lactone ring of this bicyclic system appears in the envelope conformation with C(8) sticking out [0.68(2) Å] of the four-atom plane [C(1), C(5), C(6), C(7)]. The values of the ring puckering analysis[22] for the five-membered ring [for the sequence O(6), C(7), C(1), C(8), C(5)] are $\varphi = 69.3(8)^\circ$, $Q = 0.455(7)$ Å. The cyclohexane moieties (molecules A and B) in the crystal structure of compound *15* are in the usual chair conformation.

EXPERIMENTAL

Melting points, uncorrected, were taken with a Kofler hot-stage apparatus. IR spectra were obtained for potassium bromide pellets or liquid films on a Perkin-Elmer 297 spectrophotometer. UV spectra were taken for solutions in ethanol on a Beckman DU-2 spectrophotometer. ^{1}H-NMR spectra, bandwidth (W) in Hz, were measured for solutions in $CDCl_3$ on a JEOL FX 90 Q spectrometer operating at 89.55 MHz with tetramethylsilane as internal standard, unless otherwise stated. ^{13}C-NMR spectra were determined for solutions in $CDCl_3$ on a JEOL FX 90 Q spectrometer operating at 22.5 MHz. Multiplicities s, d, t, and q, refer to off-resonance decoupled spectra. The silica gel (Merck; 0.05—0.2 mm) which was used for column chromatography and silica gel (Merck HF_{254}, type 60) which was used for TLC and for preparative TLC were activated at 110 °C for 60 min. The R_f values of the acidic products were determined by developments in benzene--methanol-glacial acetic acid 9 : 1.6 : 0.8, and rendered visible by bromocresol-green spray, while the R_f values of the neutral products in methylene chloride, unless otherwise stated, and rendered visible by exposure to iodine vapour and by UV illumination.

Cyclization of Diethyl t-2-Aminocyclohexane-r-1,t-4-dicarboxylate (2a)

Diethyl t-2-aminocyclohexane-r-1,t-4-dicarboxylate (*2a*) (110 mg, 0.45 mmol) was heated at 250 °C under nitrogen for 10 min, and then dissolved in CH_2Cl_2. This solution was chromatographed through silica gel (4 g) — Celite (2 g) column. Elution with CH_2Cl_2 afforded a mixture of two unidentified oily by-products (8.0 mg) and then CH_2Cl_2—MeOH 99 : 1 ethyl 6-azabicyclo[3.2.1]octan-7-one-c-4-carboxylate (*5*) (5.9 mg, 6.6%), m. p. 85—86 °C, identical (IR and ^{1}H-NMR spectra) with that described earlier.[2] Further elution with CH_2Cl_2—MeOH 99 : 1 afforded ethyl 6-azabicyclo[3.2.1]octan-7-one-t-4-carboxylate (*7*) (42.6 mg, 47.8%), R_f ca. 0.49 (CH_2Cl_2—MeOH 9 : 1), m. p. 76—77 °C (from ether — *n*-hexane).

Anal. $C_{10}H_{15}NO_3$ (197.23) calc'd.: C 60.89; H 7.67; N 7.10%
found: C 60.84; H 7.87; N 6.87%

IR spectrum: ν_{max} 3194, 3095, 2966, 1723, 1444, 1369, 1311, 1301, 1198, 1160, and 1043 cm^{-1}. ^{1}H-NMR spectrum: δ 6.54br (1H, s, NHCO), 4.19 (2H, q, OCH_2, J_{Et} = 7.08 Hz), 2.75 (1H, m, 4-H), 2.51—1.52 (7H, m, 1-H, 2-, 3-, and 8-H_2), 1.28 (3H, t, Me, J_{Et} = 7.08 Hz).

4-Cyanocyclohex-3-ene-1,1-dicarboxylic Acid (10)

A solution of diethyl 4-cyanocyclohex-3-ene-1,1-dicarboxylate (*9*) (255 mg, 1.01 mmol) in 20% methanolic KOH (3.74 ml) was heated under reflux for 30 min, and then diluted with anhydrous MeOH (3 ml). The heating of this mixture under reflux was continued for additional 3.5 hours, and then evaporated to dryness under reduced pressure. The residue was dissolved in water (5 ml) and then acidified to Congo red with 10% HCl to be partitioned with ether. The organic layer was washed with water, dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give an oily product (200 mg), which on trituration with boiling CH_2Cl_2 afforded the crystalline product *10* (180 mg, 90.9%), R_f ca. 0.37, m. p. 157.5—160 °C (from ether-n-hexane).

Anal. $C_9H_9NO_4$ (195.17) calc'd.: C 55.38; H 4.65; N 7.18%
found: C 55.44; H 4.74; N 7.18%

UV spectrum: λ_{max} 209.5 nm (log ε 4.07). IR spectrum (in dioxane): ν_{max} 3145sh, 3030br, 2217, 1748sh, 1733, 1645, 1227, and 1176 cm^{-1}. ^{1}H-NMR spectrum (DMSO-d_6): δ 13.0br (2H, s, exchanging in D_2O, 2 × CO_2H), 6.75 (1H, m, 3-H), and 2.71—1.67 (6H, m, 2-, 5-, and 6-H_2).

Reaction of 4-Cyanocyclohex-3-ene-1,1-dicarboxylic Acid (10) with Bromine

a) To cooled (0 °C) solution of 4-cyanocyclohex-3-ene-1,1-dicarboxylic acid (*10*) (72 mg, 0.37 mmol) in H_2O (2 ml), bromine (0.047 ml, 0.86 mmol) was added dropwise for 1 hour. The mixture was stirred for 5 hours, treated with an additional amount of bromine (0.016 ml, 0.29 mmol) and then stirred for 16 hours. The crystalline c-4-bromo-t-4-cyano-6-oxabicyclo[3.2.1]octan-7-one-r-1-carboxylic acid (*11*) was separated by suction (41 mg, 58.2%) [all yields were based on transformed 4-cyanocyclohex-3-ene-1,1-dicarboxylic acid (*10*)], R_f ca. 0.41, m. p. 208—212 °C (from acetone-ether-n-hexane).

Anal. $C_9H_8NO_4Br$ (274.08) calc'd.: C 39.44; H 2.94; N 5.11%
found: C 39.68; H 3.24; N 5.10%

IR spectrum: ν_{max} 3552, 2996br, 2883br, 2245, 1785, 1723sh, and 1708 cm^{-1}. ^{1}H-NMR spectrum (DMSO-d_6): δ 5.40 (1H, d, 5-H, J = 4.64 Hz), and 3.05—1.70 (6H, m, 2-, 3-, and 8-H_2). ^{13}C-NMR spectrum (DMSO-d_6): δ 172.57 and 169.02 (2xs, CO_2H and lactone C=O), 118.79 (s, C≡N), 78.78 (d, C-5), 50.74 (s, C-1), 40.86 (s, C-4), 35.84, 33.18, and 23.82 (3xt, C-2, C-3, and C-8).

The aqueous filtrate from the separation of compound *11* was evaporated to dryness under reduced pressure. The residue (50 mg) was treated with ethereal diazomethane [prepared from *N*-nitroso-toluene-4-sulphomethylamide (2.14 g, 10 mmol)]. This mixture was evaporated to an oily residue (52.7 mg), which was dissolved in CH_2Cl_2 and applied to silica gel (10 g) column. Elution with CH_2Cl_2 afforded three oily products with R_f ca. 0.7, 0.38, and 0.16. The product with R_f ca. 0.7 was identified as dimethyl c-3, t-4-dibromo-c-4-cyanocyclohexane-r-1e, 1-dicarboxylate (*16*) (10.8 mg, 10.9%). IR spectrum: ν_{max} 3478, 3006, 2961, 2251, 1761sh, 1739br, 1730br, and 1700sh cm^{-1}. ^{1}H-NMR spectrum: δ 4.35 (1H, dxd, W = 15.87, 3-H, $J_{3ax,2eq}$ = 4.15 and $J_{3ax,2ax}$ = 11.72 Hz), 3.81 and 3.76 (each 3H, 2xs, 2xMe), and 3.22—2.11 (6H, m, 2-, 5-, and 6-H_2). ^{13}C-NMR spectrum: δ 169.34 and 168.90 (2xs, 2xCO_2Me), 116.18 (s, C≡N), 54.71 (s, C-1), 53.20 (2xq, 2xMe), 51.45 (d, C-3), 49.36 (s, C-4), 38.91, 37.79, and 28.84 (3xt, C-2, C-5, and C-6). The product with R_f ca. 0.38 was identified as dimethyl 4-cyanocyclohex-3-ene-1,1-dicarboxylate (25 mg). IR spectrum: ν_{max} 3480, 3008, 2963, 2223, 1753sh, 1735, 1700sh, and 1643 cm^{-1}. ^{1}H-NMR spectrum: δ 6.59 (1H, m, 3-H), 3.75 (6H, s, 2xMe), 2.82—2.66 (2H, m, 2-H_2), and 2.39—2.09 (4H, m, 5-, and 6-H_2). The product with R_f ca. 0.16 was identified as dimethyl t-4-bromo-c-4-cyano-c-3-hydroxycyclohexane-r-1e,1-dicarboxylate (*14*) (12.0 mg, 14.6%), b. p. 140—142 °C at 2.7 Pa.

Anal. $C_{11}H_{14}NO_5Br$ (320.15) calc'd.: C 41.27; H 4.41; N 4.38%
found: C 41.42; H 4.29; N 4.45%

IR spectrum: ν_{max} 3490br, 2996, 2960, 2842, 2245, 1747sh, 1729, and 1717sh cm^{-1}. ^{1}H-NMR spectrum: δ 4.04 (1H, m, W = 18.02 Hz, 3-H), 3.79 and 3.76 (each 3H, 2xs, 2xMe), 3.60 (1H, d, 3-OH, $J_{OH,3ax}$ = 4.39 Hz), 2.85—1.87 (6H, m, 2-, 5-, and 6-H_2). ^{13}C-NMR spectrum: δ 170.15 (s, 2xCO_2Me), 116.87 (s, C≡N), 72.35 (d, C-3), 53.50 (s, C-1), 52.99 (q, 2xMe), 51.47 (s, C-4), and 35.16, 34.99, and 28.39 (3xt, C-2, C-5, and C-6).

b) To a saturated and cooled (0 °C) solution of 4-cyanocyclohex-3-ene-1,1--dicarboxylic acid (*10*) (131 mg, 0.67 mmol) in aqueous $NaHCO_3$ (2.4 ml), bromine (0.053 ml, 0.97 mmol) was added dropwise for 30 min. The mixture was then stirred at room temperature for 2 hours and then acidified with 5% HCl, saturated with NaCl, and partitioned with CH_2Cl_2. The organic layer was removed and the aqueous layer repartitioned with EtOAc. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give crystalline t-4-bromo-c-4-cyano-c-3-hydroxycyclohexane-r-1e,1-dicarboxylic acid (*13*) (175 mg, 89.3%), m. p. 179—183 °C (from acetone-ether-n-hexane), R_f ca. 0.24.

Anal. $C_9H_{10}NO_5Br$ (292.09) calc'd.: C 37.01; H 3.45; N 4.80%
found: C 37.44; H 3.61; N 4.86%

IR spectrum: ν_{max} 3325, 3177br, 2942, 2260, 1737, 1716, and 1221 cm^{-1}. ^{1}H-NMR spectrum (DMSO-d_6): δ 13.17br (2H, s, exchanging in D_2O, 2 × CO_2H), 6.48br, (1H, s, exchanging in D_2O, 3-OH), and 3.88—1.35 (7H, m, 3-H and 2-, 5-, and 6-H_2).

Methyl c-4-bromo-t-4-cyano-6-oxabicyclo[3.2.1]octan-7-one-r-1-carboxylate (12)

a) To a solution of t-4-bromo-c-4-cyano-c-3-hydroxycyclohexane-r-1e,1-dicarboxylic acid (*13*) (115 mg, 0.39 mmol) in anhydrous dioxane (3 ml) DCCI (82 mg, 0.39 mmol) in anhydrous dioxane (7.5 ml) was added. The mixture was stirred for 5 hours and then treated with an additional amount of DCCI (8.2 mg, 0.039 mmol) in anhydrous dioxane (2 ml) and stirred overnight. The precipitate was filtered off, and the filtrate evaporated to dryness. The residue was treated with ethereal diazomethane [prepared from *N*-nitroso-toluene-4-sulphomethylamide (2.14 g, 10 mmol)], and set aside for 2 hours. After evaporation to dryness, the residue (145 mg) was dissolved in CH_2Cl_2 and applied to silica gel (12 g) column. Methylene chloride eluted methyl c-4-bromo-t-4-cyano-6-oxabicyclo[3.2.1]octan-7-one-r-1-carboxylate (*12*) (71.3 mg, 64.4%, based on transformed cyanobromohydrine acid *13*), R_f ca. 0.34, m. p. 124—125 °C (from CH_2Cl_2-ether-n-hexane).

Anal. $C_{10}H_{10}NO_4Br$ (288.10) calc'd.: C 41.69; H 3.50; N 4.86%
found: C 41.74; H 3.40; N 4.86%

IR spectrum: ν_{max} 3567, 3493, 3026, 2972, 2920, 2248d, 1798sh, 1788sh, 1747, 1708, and 1120 cm^{-1}. ^{1}H-NMR spectrum: δ 5.02 (1H, dxd, 5-H, J = 5.27 and 1.1 Hz), 3.82 (3H, s, Me), and 3.17—1.83 (6H, m, 2-, 3-, and 8-H_2). ^{13}C-NMR spectrum: δ 170.99 and 167.89 (2xs, CO_2Me and lactone C=O), 117.66 (s, C≡N), 79.06 (d, C-5), 53.27 (q, Me), 51.13 (s, C-1), 41.25 (s, C-4), and 36.40, 33.80, and 24.44 (3xt, C-2, C-3, and C-8).

Further elution with CH_2Cl_2 eluted a mixture of several unidentified by--products (17.7 mg) and then dicarboxylic acid *13* characterized as oily dimethyl t-4-bromo-c-4-cyano-c-3-hydroxycyclohexane-r-1e,1-dicarboxylate (*14*) (3 mg), identical (IR and ^{1}H-NMR spectra) with an authentic sample.

b) c-4-Bromo-t-4-cyano-6-oxabicyclo[3.2.1]octan-7-one-r-1-carboxylic acid (*11*) (56.4 mg, 0.2 mmol) was treated with a solution of diazomethane in ether [prepared from *N*-nitroso-toluene-4-sulphomethylamide (2.14 g, 10 mmol)] and set aside for 4 hours. The solution was then removed under reduced pressure. The residue crystallized in quantitative yield as the product *12*, identical (m. p. and IR and ^{1}H-NMR spectra) with that described under a).

Dimethyl t-4-bromo-c-4-cyano-c-3-hydroxycyclohexane-r-le,1-dicarboxylate (14)

t-4-Bromo-c-4-cyano-c-3-hydroxycyclohexane-r-le,1-dicarboxylic acid (*13*) (114 mg, 0.39 mmol) was added to ethereal diazomethane. The solvent was then removed under reduced pressure. The oily residue (130 mg) was dissolved in CH_2Cl_2 and chromatographed through a silica gel (12 g) column. Elution with CH_2Cl_2—MeOH 99 : 1 gave the product *14* (122.5 mg, 98.0%), R_f ca. 0.81 (CH_2Cl_2—MeOH 9 : 1), which was identical (IR and ^{1}H-NMR spectra) with that obtained in the reaction of 4-cyanocyclohex-3-ene-1,1-dicarboxylic acid (*10*) with bromine.

Dimethyl c-3-benzoxy-t-4-bromo-c-4-cyanocyclohexane-r-le,1-dicarboxylate (15)

To a solution of dimethyl t-4-bromo-c-4-cyano-c-3-hydroxycyclohexane-r-le, 1-dicarboxylate (*14*) (47 mg, 0.15 mmol) in anhydrous pyridine (1.24 ml) and CH_2Cl_2 (0.1 ml), benzoyl chloride (0.02 ml, 0.17 mmol) was added. The mixture was stirred at room temperature for 48 hours and then poured into chilled H_2O. This solution was partitioned with CH_2Cl_2. The organic layer was washed with 5% HCl, 5% $NaHCO_3$ and H_2O. It was dried (Na_2SO_4) and evaporated to dryness. Preparative TLC of crude residue (65 mg) (ether-n-hexane 3 : 7, recovery with the same mixture of solvents) gave the product *15* (53.5 mg, 85.9%), R_f ca. 0.48 (ether-n-hexane 3 : 7), m. p. 114—115 °C (from CH_2Cl_2—Et_2O-n-hexane).

Anal. $C_{18}H_{18}NO_6Br$ (424.25) calc'd.: C 50.96; H 4.28; N 3.30%
found: C 50.78; H 4.34; N 3.55%

UV spectrum: λ_{max} 229 nm (log ε 4.17) λ_{min} 207 nm (log ε 3.48). IR spectrum: ν_{max} 3419, 3061, 3034, 2997, 2953, 2236, 1736sh, 1721, 1683sh, 1599, 1581, and 719 cm^{-1}. ^{1}H-NMR spectrum: δ 8.16—8.0 (2H, m), and 7.47—7.34 (3H, m) (aromatic), 5.47 (1H, dxd, W = 13.19, 3-H, $J_{3ax,2eq}$ = 3.96 and $J_{3ax,2ax}$ = 9.23 Hz), 3.83 and 3.58 (each 3H, 2xs, 2xMe), and 3.03—2.20 (6H, m, 2-, 5-, and 6-H_2). ^{13}C-NMR spectrum: δ 169.98 and 169.81 (2xs, 2xCO_2Me), 164.34 (s, benzoylic C=O), 133.80, 130.03, and 128.61 (aromatic C's), 116.87 (s, C≡N), 73.03 (d, C-3), 53.33 (s, C-1), 53.05 (q, 2xMe), 45.99 (s, C-4), and 35.72, 32.90, and 28.39 (3xt, C-2, C-5, and C-6).

Diethyl t-4-bromo-c-4-cyano-c-3-hydroxycyclohexane-r-le,1-dicarboxylate (17)

A solution of t-4-bromo-c-4-cyano-c-3-hydroxycyclohexane-r-le,1-dicarboxylic acid (*13*) (162 mg, 0.55 mmol) was heated under reflux in ethanolic 3% HCl (16 ml) for 17 hours. The solution was then evaporated to dryness under reduced pressure and the residue partitioned in ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and water, and then evaporated to an oily residue (155 mg). It was dissolved in CH_2Cl_2 and chromatographed through a silica gel (11 g) column. Elution with CH_2Cl_2 gave the oily product *17* (126.5 mg, 65.5%), b. p. 145—150 °C at 2.7 Pa, R_f ca. 0.28.

Anal. $C_{13}H_{18}NO_5Br$ (348.20) calc'd.: C 44.84; H 5.21; N 4.02%
found: C 44.56; H 5.20; N 3.98%

IR spectrum: ν_{max} 3492br, 2989, 2954, 2242, 1737sh, 1728, and 1250 cm^{-1}. ^{1}H-NMR spectrum: δ 4.24 and 4.21 (each 2H, 2xq, 2xOCH_2, J_{Et} = 7.03 Hz), ca. 4.0 (1H, m, overlapped with OCH_2, 3-H), 3.62 (1H, d, exchanging in D_2O, 3-OH, $J_{OH,3ax}$ = 4.62 Hz), 2.84—1.89 (6H, m, 2-, 5-, and 6-H_2), and 1.28 and 1.26 (each 3H, 2xt, 2xMe, J_{Et} = 7.03 Hz). ^{13}C-NMR spectrum: δ 169.98 (s, 2xCO_2Et), 117.10 (s, C≡N), 72.86 (d, C-3), 62.19 (t, 2xOCH_2), 53.95 (s, C-1), 52.15 (s, C-4), 35.55, 35.21, and 28.67 (3xt, C-2, C-5, and C-6), and 13.99 (q, 2xMe).

Diethyl c-3-benzoxy-t-4-bromo-c-4-cyanocyclohexane-r-le,1-dicarboxylate (18)

a) A solution of diethyl t-4-bromo-c-4-cyano-c-3-hydroxycyclohexane-r-le,1--dicarboxylate (*17*) (28 mg, 0.08 mmol) in anhydrous pyridine (0.67 ml) and CH_2Cl_2 (0.1 ml) was treated with benzoyl chloride (0.01 ml, 0.09 mmol) and worked up as already described. Preparative TLC of the oily residue (49 mg) (ether-n-hexane

3 : 7, recovery with CH_2Cl_2) gave the product *18* (26 mg, 96.2%), R_f ca. 0.53 (ether--n-hexane 3 : 7), b. p. 152—155 °C at 1.3 Pa.

Anal. $C_{20}H_{22}NO_6Br$ (452.29) calc'd.: C 53.11; H 4.90; N 3.10%
found: C 53.24; H 4.69; N 3.12%

UV spectrum: λ_{max} 231.5 nm (log ε 4.22), λ_{min} 211 nm (log ε 3.72). IR spectrum: ν_{max} 3474br, 3088, 2996, 2961, 2917, 2254, 1763 sh, 1750sh, 1741, 1706sh, 1612, 1594, and 727 cm^{-1}. ^{1}H-NMR spectrum: δ 8.24—8.0 (2H, m) and 7.78—7.33 (3H, m) (aromatic), 5.48 (1H, dxd, $W = 13.63$, 3-H, $J_{3ax,\,2eq} = 3.96$ and $J_{3ax,\,2ax} = 9.67$ Hz), 4.29 and 4.1 (each 2H, 2xq with the secondary splitting, $2xOCH_2$, $J_{Et} = 7.03$, $J = 1.76$ Hz), 3.03—2.12 (6H, m, 2-, 5-, and 6-H_2), and 1.31 and 1.16 (each 3H, 2xt, 2xMe, $J_{Et} = 7.03$ Hz). ^{13}C-NMR spectrum: δ 169.47 and 169.31 (2xs, $2xCO_2Et$), 164.39 (s, benzoylic C=O), 133.69, 129.97, 128.84, and 128.56 (aromatic C's), 116.82 (s, C≡N), 73.31 (d, C-3), 62.30 and 62.08 (2xt, $2xOCH_2$), 53.39 (s, C-1), 46.22 (s, C-4), 36.06, 33.18, and 28.5 (3xt, C-2, C-5, and C-6) and 13.99 and 13.83 (2xq, 2xMe).

b) To a solution of diethyl t-4-bromo-c-4-carbamoyl-c-3-hydroxycyclohexane--r-le,1-dicarboxylate (*vide infra, 23*) (13 mg, 0.035 mmol) in anhydrous pyridine (1 ml) and CH_2Cl_2 (0.1 ml), benzoyl chloride (0.01 ml, 0.09 mmol) was added. The mixture was stirred at room temperature for 72 hours and then poured into chilled water. This solution was partitioned with CH_2Cl_2. The organic layer was washed with 5% HCl, 5% $NaHCO_3$, and H_2O. It was dried (Na_2SO_4) and evaporated to residue (18 mg). Preparative TLC (ether-n-hexane 3 : 7, recovery with CH_2Cl_2) gave a product (8.5 mg, 52.9%), identical (R_f, IR and ^{1}H-NMR spectra) with that described under a).

4-Carbamoylcyclohex-3-ene-1,1-dicarboxylic Acid (19)

A solution of diethyl 4-carbamoylcyclohex-3-ene-1,1-dicarboxylate (*22*) (204 mg, 0.76 mmol) in 20% methanolic KOH (2.8 ml) was heated under reflux for 1 hour. The mixture was then diluted with anhydrous MeOH (2.4 ml) and heated for additional 3 hours to be evaporated to dryness under reduced pressure. The residue was dissolved in H_2O (2.5 ml), acidified to Congo red with 10% HCl, and then partitioned with EtOAc. The organic layer was dried (Na_2SO_4). The solvent was removed under reduced pressure to give the product *19* (149 mg, 92.3%), R_f ca. 0.15, m. p. 250—253 °C (from ethanol-ether-n-hexane).

Anal. $C_9H_{11}NO_5$ (213.19) calc'd.: C 50.70; H 5.20; N 6.57%
found: C 50.86; H 5.05; N 6.61%

UV spectrum: λ_{max} 209.5 nm (log ε 4.05). IR spectrum: ν_{max} 3440, 3336, 3197, 2959, 2916, 2563br, 2455sh, 2328sh, 1746, 1731, 1710sh, 1696, 1661, and 1639 cm^{-1}. ^{1}H-NMR spectrum (DMSO-d_6): δ 11.82br, (2H, $2xCO_2H$, exchanging in D_2O), 7.22 and 6.87 (each 1H, 2xs, $CONH_2$, exchanging in D_2O), 6.52 (1H, m, 3-H), 2.40—1.74 (6H, m, 2-, 5-, and 6-H_2), ^{13}C-NMR spectrum (DMSO-d_6): δ 172.40 (s, $2xCO_2H$), 168.57 (s, $CONH_2$), 132.0 (s, C-4), 130.08 (d, C-3), 51.69 (s, C-1), 30.53, 27.15, and 21.56 (3xt, C-2, C-5, and C-6).

c-4-Bromo-t-4-carbamoyl-6-oxabicyclo[3.2.1]octan-7-one-r-1-carboxylic Acid (20)

To a solution of 4-carbamoylcyclohex-3-ene-1,1-dicarboxylic acid (*19*) (48 mg, 0.23 mmol), cooled at 0 °C, in saturated aqueous $NaHCO_3$ (0.95 ml), bromine (0.039 ml, 0.71 mmol) was added dropwise. This mixture was stirred at room temperature for 2 hours, and then acidified with 5% HCl. The crystalline product *20* separated (54 mg). The mother liquor was partitioned with CH_2Cl_2 and then with EtOAc. The EtOAc extract afforded an additional amount of the product *20* (11 mg) (98.8% as total yield), R_f ca. 0.21, m. p. 245—250 °C (from acetone-ether-n-hexane).

Anal. $C_9H_{10}NO_5Br$ (292.09) calc'd.: C 37.01; H 3.45; N 4.80%
found: C 36.71; H 3.54; N 4.89%

IR spectrum: ν_{max} 3461, 3311, 3184, 2846br, 1781, 1693, 1653sh, and 1645 cm^{-1}. ^{1}H-NMR spectrum (DMSO-d_6): δ 7.70 and 7.54 (each 1H, 2xs, $CONH_2$, exchanging in D_2O),

5.35 (1H, d, 5-H, $J = 4.64$ Hz), and 3.05—1.63 (6H, m, 2-, 3-, and 8-H_2). ^{13}C-NMR spectrum (DMSO-d_6): δ 173.19, 169.79, and 169.61 (CO_2H, $CONH_2$, and lactone C=O), 78.44 (C-5), 57.30 (C-4), 51.49 (C-1), 36.81, 30.35, and 24.25 (C-2, C-3, and C-8).

Methyl c-4-bromo-t-4-carbamoyl-6-oxabicyclo[3.2.1]octan-7-one-r-1-carboxylate (21)

c-4-Bromo-t-4-carbamoyl-6-oxabicyclo[3.2.1]octan-7-one-r-1-carboxylic acid (*20*) (52 mg, 0.18 mmol) was treated with a solution of ethereal diazomethane [prepared from *N*-nitroso-toluene-4-sulphomethylamide (2.14 g, 10 mmol)] The solvent was removed under reduced pressure to give the product *21* (51.7 mg, 94.9%), R_f 0.49 (CH_2Cl_2—MeOH 9 : 1), m. p. 209—210 °C (from acetone-ether).

Anal. $C_{10}H_{12}NO_5Br$ (306.12) calc'd.: C 39.23; H 3.95; N 4.58%
found: C 39.21; H 3.84; N 4.83%

IR spectrum: ν_{max} 3418, 3304, 3158, 2943, 1785sh, 1769, 1732, 1697, and 1624 cm^{-1}. ^{1}H-NMR spectrum (DMSO-d_6): δ7.72 and 7.56 (each 1H, 2xs, $CONH_2$, exchanging in D_2O), 5.38 (1H, d, 5-H, $J = 4.64$ Hz), 3.72 (3H, s, Me), 2.90—2.57 (2H, m, 8-H_2), 2.27—1.86 (4H, m, 2-, and 3-H_2). ^{13}C-NMR spectrum (DMSO-d_6): δ 172.69 and 169.69 (2xs, CO_2Me and lactone C=O), 168.51 (s, $CONH_2$), 78.56 (d, C-5), 57.23 (s, C-4), 52.65 (q, Me), 51.75 (s, C-1), 36.68, 30.31, and 24.27 (3xt, C-2, C-3, and C-8).

Diethyl 4-carbamoylcyclohex-3-ene-1,1-dicarboxylate (22)

A mixture of diethyl 4-cyanocyclohex-3-ene-1,1-dicarboxylate (*9*) (340 mg, 1.35 mmol) and polyphosphoric acid (1.6 g) was heated at 120—130 °C for 2.5 hours. The solution was diluted with ice-H_2O (ca. 100 ml), neutralized with $NaHCO_3$ and then partitioned with EtOAc. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to give the product *22* (316 mg, 86.7%), R_f ca. 0.64 (ether--methanol 9 : 1), m. p. 126—127.5 °C (from ether).

Anal. $C_{13}H_{19}NO_5$ (269.29) calc'd.: C 57.98; H 7.11; N 5.20%
found: C 58.17; H 6.87; N 5.37%

IR spectrum: ν_{max} 3443, 3170, 2989, 2971sh, 2936, 1728, 1684, 1670, 1642, and 1605 cm^{-1}. ^{1}H-NMR spectrum: δ 6.62 (1H, m, 3-H), 5.82br (2H, s, $CONH_2$, exchanging in D_2O), 4.19 (4H, q, 2xOCH_2, $J_{Et} = 7.08$ Hz), 2.95—2.59 (2H, m, 2-H_2), 2.59—2.07 (4H, m, 5-, and 6-H_2) and 1.25 (6H, t, 2xMe, $J_{Et} = 7.08$ Hz). ^{13}C-NMR spectrum: δ 170.94 (s, 2xCO_2Et), 169.58 (s, $CONH_2$), 131.83 (s, C-4), 131.15 (d, C-3), 61.57 (t, 2xOCH_2), 52.43 (s, C-1), 30.81, 27.20, and 21.61 (3xt, C-2, C-5, and C-6), and 13.99 (q, 2xMe).

Reactions of c-4-Bromo-t-4-carbamoyl-6-oxabicyclo[3.2.1]octan-7-one-r-1-carboxylic Acid (20) with Ethanolic 3% Hydrochloric Acid

The title compound *20* (144 mg, 0.49 mmol) was heated under reflux in ethanolic 3% HCl (18 ml) for 17 hours. The mixture was then evaporated to dryness under reduced pressure, and the residue partitioned between H_2O (6.4 ml) and ether. The organic layer was washed with a saturated solution of $NaHCO_3$ and H_2O. It was dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue (165 mg) was dissolved in CH_2Cl_2 and chromatographed through silica gel (36 g) column. Methylene chloride-methanol 99 : 1 eluted a product identified as triethyl t-4-bromo-c-3-hydroxycyclohexane-r-1e,1,c-4-tricarboxylate (*24*) (42.5 mg, 21.8%), R_f ca. 0.83 (CH_2Cl_2—MeOH 9.5 : 0.5), m. p. 69—70 °C (from ether-n-hexane).

Anal. $C_{15}H_{23}O_7Br$ (395.25) calc'd.: C 45.58; H 5.87%
found: C 45.43; H 5.61%

IR spectrum: ν_{max} 3541, 2989, 1752, 1740, 1719, 1271, and 1245 cm^{-1}. ^{1}H-NMR spectrum: δ 4.28 (2H, q, OCH_2, $J_{Et} = 7.08$ Hz), 4.19 (4H, q, 2xOCH_2, $J_{Et} = 7.08$ Hz), 3-H obscured by OCH_2 envelope, 3.67 (1H, d, OH), 2.89—1.87 (6H, m, 2-, 5-, and 6-H_2), 1.32 (3H, t, Me, $J_{Et} = 7.08$ Hz) and 1.25 (6H, t, 2xMe, $J_{Et} = 7.08$ Hz). ^{13}C-NMR spectrum: δ 171.79, 170.94, and 170.54 (3xCO_2Et), 70.88 (C-3), 62.25 (OCH_2 of 4-CO_2Et), 61.97 (C-4), 61.68 (2xOCH_2 of 1,1-CO_2Et), 52.15 (C-1), 32.85, 28.78, and 27.37 (C-2, C-5, and C-6), 13.99 (2xMe of 1,1-CO_2Et), and 13.88 (Me of 4-CO_2Et).

Methylene chloride-methanol 99 : 1 then eluted a fraction (115.5 mg, 64%), identified as diethyl t-4-bromo-c-4-carbamoyl-c-3-hydroxycyclohexane-r-le,1-dicarboxylate (*23*), R_f ca. 0.32 (CH_2Cl_2—MeOH 9.5 : 0.5), m. p. 124—126 °C (from CH_2Cl_2-ether-n--hexane).

Anal. $C_{13}H_{20}NO_6Br$ (366.21) calc'd.: C 42.63; H 5.50; N 3.83%
found: C 42.76; H 5.22; N 4.06%

IR spectrum: ν_{max} 3418, 3282br, 3005, 2978, 2952, 2926, 1741, 1722sh, 1714, 1688sh, 1682, and 1596 cm^{-1}. ^{1}H-NMR spectrum: δ 6.99br and 5.83br (each 1H, 2xs, $CONH_2$), 3-H obscured by OCH_2 envelope, 4.23 and 4.18 (each 2H, 2xq, 2xOCH_2, J_{Et} = 7.08 Hz), ca. 4.0 (1H, obscured by those of OCH_2, OH), 2.98—1.70 (6H, m, 2-, 5-, and 6-H_2), and 1.27 and 1.24 (each 3H, 2xt, 2xMe, J_{Et} = 7.08 Hz). ^{13}C-NMR spectrum: δ 172.12 (s, $CONH_2$), 170.77 (s, 2xCO_2Et), 72.46 (d, C-3), 64.67 (s, C-4), 61.80 (t, 2xOCH_2), 53.39 (s, C-1), 34.65, 32.73, and 28.56 (3xt, C-2, C-5, and C-6), and 13.99 (q, 2xMe).

Diethyl 4-cyano-t-3,4-oxiranecyclohexane-r-le,1-dicarboxylate (25)

a) To a solution of diethyl t-4-bromo-c-4-cyano-c-3-hydroxycyclohexane-r-le,1--dicarboxylate (*17*) (158 mg, 0.45 mmol) in anhydrous CH_2Cl_2 (24 ml), DBU (0.072 ml, 0.5 mmol) was added. The mixture was stirred at room temperature for 2 hours and then concentrated to a small volume (ca. 1.5 ml), which was applied to silica gel (11 g) column. Elution with CH_2Cl_2 gave the product *25* (112.8 mg, 93.0%), R_f ca. 0.36, b. p. 100—110 °C at 2.7 Pa.

Anal. $C_{13}H_{17}NO_5$ (267.27) calc'd.: C 58.42; H 6.41; N 5.24%
found: C 58.31; H 6.35; N 5.52%

IR spectrum: ν_{max} 3464br, 2986, 2933, 2907, 2244, 1749sh, 1734sh, 1725, and 1719sh. ^{1}H-NMR spectrum: δ 4.23 and 4.18 (each 2H, 2xq, 2xOCH_2, J_{Et} = 7.03 Hz), 3.67 (1H, d, 3-H, J 4.39 Hz), 2.89—1.76 (6H, m, 2-, 5-, and 6-H_2), and 1.27 and 1.24 (each 3H, 2xt, 2xMe, J_{Et} = 7.03 Hz). ^{13}C-NMR spectrum: δ 170.21 and 169.81 (2xs, 2xCO_2Et), 118.17 (s, C≡N), 62.08 and 61.74 (2xt, 2xOCH_2), 56.83 (d, C-3), 50.73 (s, C-1), 46.84 (s, C-4), 29.01, 23.98, and 23.53 (3xt, C-2, C-5, and C-6) and 13.99 (q, 2xMe).

b) To a solution of diethyl c-3-benzoxy-t-4-bromo-c-4-cyanocyclohexane-r-le,1--dicarboxylate (*18*) (40 mg, 0.09 mmol) in anhydrous CH_2Cl_2 (75 ml), 0.19% ethanolic KOH (7.9 ml) was added. The mixture was stirred at room temperature for 15 minutes, acidified with 0.3% HCl, and then extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The oily residue (26 mg) was dissolved in CH_2Cl_2 and chromatographed through silica gel (8 g) column. Methylene chloride eluted the starting compound *18* (2.5 mg). Further elution with CH_2Cl_2 gave a product *25* [19.0 mg, 85.7% based on transformed diethyl c-3-benzoxy-t-4-bromo-c-4-cyanocyclohexane-r-le,1-dicarboxylate (*18*)], which was identical (R_f, IR and ^{1}H-NMR spectra) with that obtained under a).

Diethyl 4-carbamoyl-t-3,4-oxiranecyclohexane-r-le,1-dicarboxylate (26)

To a solution of diethyl t-4-bromo-c-4-carbamoyl-c-3-hydroxycyclohexane-r-le, -1-dicarboxylate (*23*) (57 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (11 ml), DBU (0.025 ml, 0.17 mmol) was added. The mixture was stirred at room temperature for 1 hour and then evaporated to a small volume (ca. 1 ml), which was applied to a silica gel (11 g) column. Methylene chloride-methanol 99 : 1 eluted the product *26* (43 mg, 96.8%), R_f ca. 0.35 (CH_2Cl_2—MeOH 19 : 1), m. p. 93—94 °C (from CH_2Cl_2-ether-n--hexane).

Anal. $C_{13}H_{19}NO_6$ (285.29) calc'd.: C 54.73; H 6.71; N 4.91%
found: C 54.71; H 6.59; N 5.08%

IR spectrum: ν_{max} 3441, 3282, 2996, 2952, 1738, 1722sh, and 1688 cm^{-1}. ^{1}H-NMR spectrum: δ 6.25 and 5.72 (each 1H, 2xs, $CONH_2$), 4.21 and 4.19 (each 2H, 2xq, 2xOCH_2, J_{Et} = = 7.08 Hz), 3.36 (1H, dxd, 3-H, J 3.42 and 1.22 Hz), 2.80—1.74 (6H, m, 2-, 5-, and 6-H_2), and 1.26 (6H, t, 2xMe, J_{Et} = 7.08 Hz). ^{13}C-NMR spectrum: δ 172.75 (s, $CONH_2$), 170.71 and 170.43 (2xs, 2xCO_2Et), 61.97 and 61.51 (2xt, 2xOCH_2), 58.18 (s, C-4), 57.96 (d, C-3), 51.3 (s, C-1), 29.8, 24.38, and 19.75 (3xt, C-2, C-5, and C-6), and 14.05 (q, 2xMe).

REFERENCES

1. V. Škarić and V. Turjak-Zebić, *Croat. Chem. Acta* **55** (1982) 457.
2. V. Škarić, V. Turjak-Zebić, and D. Škarić, *J. Chem. Soc. Perkin I* (1974) 1406.
3. V. Škarić, B. Djuras, and V. Turjak-Zebić, *J. Chem. Soc. Perkin I* (1975) 1959.
4. V. Škarić, B. Djuras, and V. Turjak-Zebić, *Croat. Chem. Acta* **48** (1976) 341.
5. V. Škarić, M. Sedjak, V. Turjak-Zebić, and D. Škarić, *Can. J. Chem.* **58** (1980) 1860.
6. Hisamitsu Pharmaceutical Co. Inc. Japan Kokai Tokkyo Koho JP 57, 131, 780; cf. *C. A.* **98** (1983) No 3, 16578d.
7. *Ibid.* JP 57, 131, 778; cf. *C. A.* **98** (1983) No 1, 4472b.
8. S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *Tetrahedron* **33** (1977) 807.
9. M. D. Dowle and D. I. Davies, *Chem. Soc. Rev.* **8** (1979) 171.
10. D. Škarić, V. Škarić, V. Turjak-Zebić, and Z. Veksli, *Croat. Chem. Acta* **34** (1962) 75.
11. W. E. Barnett and L. L. Needham, *J. Org. Chem.* **40** (1975) 2843.
12. H. O. House, *Modern Synthetic Reactions*, W. A. Benjamin, Inc., New York, Amsterdam, 1965, p. 134—136.
13. E. Breitmaier and G. Bauer, *^{13}C-NMR-Spektroskopie*, G. Thieme Verlag, Stuttgart, 1977, p. 54.
14. H. R. Snyder and C. T. Elston, *J. Amer. Chem. Soc.* **76** (1954) 3039.
15. H. Oediger, F. Möller, and K. Eiter, *Synthesis* (1972) 591.
16. K. Friedrich and K. Wallenfels, *The Chemistry of the Cyano Group*, Intersci. Pub. Editor Z. Rappoport, New York 1970, p. 96—103.
17. P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*, Univ. of York, England, and Louivain, Belgium, 1980.
18. D. T. Cromer and J. B. Mann, *Acta Crystallogr.* **A24** (1968) 321.
19. R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.* **42** (1965) 3175.
20. D. T. Cromer and D. Liberman, *J. Chem. Phys.* **53** (1970) 1891.
21. J. M. Stewart, P. A. Machin, C. W. Dickinson, H. L. Ammon, H. Heck, and H. Flack, *The XRAY76 system. Tech. Rep. TR-446*, Computer Science Center, Univ. of Maryland, College Park, Maryland, 1976.
22. D. Cremer and J. A. Pople, *J. Amer. Chem. Soc.* **97** (1975) 1354.

SAŽETAK

Strukture bromolaktona dobivene iz cikloheks-3-en-1,1-dikarboksilnih kiselina i sinteze polifunkcionalnih cikloheksankarboksilnih kiselina

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Pokazano je da bromolaktonizacija 4-cijanocikloheks-3-en-1,1-dikarboksilne kiseline (*10*) u vodi ili vodenoj otopini $NaHCO_3$ daje t-4-bromo-c-4-cijano-c-3-hidroksicikloheksan-r-le,1-dikarboksilnu kiselinu (*13*) preko intermedijarne c-4-bromo-t-4-cijano-6-oksabiciklo[3.2.1]oktan-7-on-r-1-karboksilne kiseline (*11*). Suprotno tom nalazu, 4-karbamoilcikloheks-3-en-1,1-dikarboksilna kiselina (*19*) u reakciji s bromom u vodenoj otopini $NaHCO_3$ daje isključivo c-4-bromo-t-4-karbamoil-6-oksabiciklo[3.2.1]oktan-7-on-r-1-karboksilnu kiselinu (*20*). Također je opisana priprava 4-cijano-(*25*) i 4-karbamoil-(*26*)-t-3,4-oksirancikloheksan-r-le,1-dikarboksilata.

Strukture i relativne konfiguracije metil c-4-bromo-t-4-cijano-6-oksabiciklo-[3.2.1]oktan-7-on-r-1-karboksilata (*12*), priređenog iz *11*, i dimetil c-3-benzoksi-t-4-bromo-c-4-cijanocikloheksan-r-le,1-dikarboksilata (*15*), priređenog iz *13*, određene su rendgenskom strukturnom analizom, ^{1}H- i ^{13}C-NMR spektroskopijom.