SYNTHESIS, STRUCTURE, AND TRANSFORMATION OF 1-AMINO-5-PHENYL-2,6,6-TRICYANO-3-CYCLOPROPYL-1,3-CYCLOHEXADIENE INTO 6-PHENYL-2-DICYANOMETHYLENE-3-CYANO-4-CYCLOPROPYL-1,2-DIHYDROPYRIDINE

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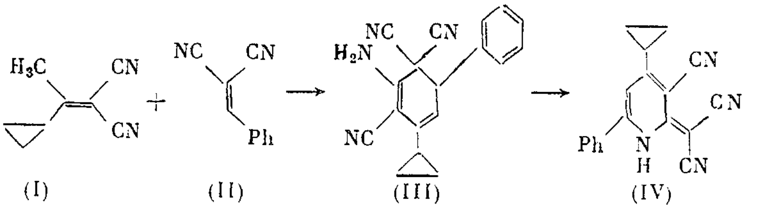
1-Amino-5-phenyl-2,6,6-tricyano-3-cyclopropyl-1,3-cyclohexadiene is prepared by reaction of benzylidenemalononitrile with (1-cyclopropylethylidene)malononitrile. According to x-ray structural data, steric effects of the cyclohexadiene cause the C^1-C^6 and C^5-C^6 bond lengths to increase to 1.541(3) and 1.568(3) Å. The weakest bond of the cyclohexadiene, C^5-C^6, ruptures homolytically on external energy deposition with subsequent formation of a substituted dihydropyridine.

Reaction of arylidene- and alkylidenemalononitriles makes synthesis of carbo- and heterocyclic compounds possible [1, 2]. In order to study these reactions further and to expand their use in the synthesis of difficultly attainable anilines and pyridines containing a cyclopropyl substituent, (1-cyclopropylethylidene)malononitrile (I) was reacted with benzylidenemalononitrile (II) to give cyclohexadiene (III). The cyclohexadiene obtained was thermally transformed into pyridine (IV)



The x-ray crystal structure of 1-amino-5-phenyl-2,6,6-tricyano-3-cyclopropyl-1,3-cyclohexadiene (III) as the 1:1 solvate with methanol was solved. The reasons for its recyclization into 6-phenyl-2-dicyanomethylene-3-cyano-4-cyclopropyl-1,2-dihydropyridine (IV) are found.

DISCUSSION

The aminocyclohexa-1,3-diene ring of (III) adopts a half-chair conformation (Fig. 1). Atoms C^5 and C^6 deviate by 0.369(2) and −0.331(2) Å from the plane through the four remaining ring atoms, which lie within 0.066(2) Å, including both endocyclic double bonds. Also, two approximately planar fragments, $C^6C^1C^2C^3$ [planar within 0.010(2) Å] and $C^2C^3C^4C^5$ [planar within 0.019(2) Å] can be identified in the cyclohexa-1,3-diene ring. The dihedral angle between these (caused mainly by twisting around the C^2-C^3 bond, see below) is 19.4°.

The planar [within 0.005(2) Å] conjugated fragment $N^1-C^1{=}C^2-C^{18}{\equiv}N^2$ is interesting. The coordination plane of the trigonal planar N^1 atom (sum of valence angles is 360°) is approximately coplanar to this fragment. This is favorable for p–π-conjugation of the unshared electron pair of N^1 with the π-system of the $C^1{=}C^2$ double bond. The N^1-C^1 bond of 1.330(2) Å is short in comparison with the standard $N-C_{sp^2}$ length of 1.452(4) Å [3] and coincides in length with the conjugated $N-C_{sp^2}$ bond of 1.336 Å [4] that includes the trigonal planar nitrogen atom. The H_2N-C distance of 1.348(4) Å in the analogous conjugated $H_2N-C{=}C-C{\equiv}N$ fragment of 1-amino-3,5-diphenyl-2,4,4,6,6-pentacyano-1-cyclohexene (V) [1] is only slightly longer than in (III).

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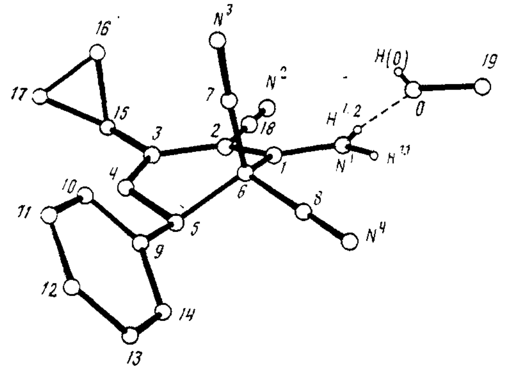

Fig. 1. Asymmetric unit of (III)·MeOH.

TABLE. 1. Short Nonbonded Contacts in Aminocyclohexadiene (III)*

Distance	d, Å	Distance	d, Å
$N^1 \ldots C^7$	3.145(3)	$C^8 \ldots C^9$	2.938(3)
$N^1 \ldots C^8$	2.779(3)	$C^8 \ldots C^{14}$	3.157(3)
$N^1 \ldots C^{18}$	2.829(2)	$C^{15} \ldots C^{18}$	2.866(3)
$C^7 \ldots C^9$	3.007(3)	$C^{16} \ldots C^{18}$	3.377(3)
$C^7 \ldots C^{10}$	3.208(3)		

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*The sum of van der Waals radii of N and C is 3.21 Å. The doubled C radius is 3.42 Å [5, 6].

The $C^1{=}C^2$ bond length in (III) is increased to 1.362(3) Å in comparison to the $C^3{=}C^4$ bond of 1.326(3) Å and to the standard $C_{sp^2}{=}C_{sp^2}$ bond length of 1.332 Å in unsubstituted cyclohexa-1,3-diene [4]. In (V), the length of the corresponding bond is 1.353 Å. The $C^2{-}C^{18}$ and $C^{18}{\equiv}N^2$ bond lengths in (III) of 1.430(2) and 1.149(3) Å are also very similar to the lengths of the corresponding bonds in (V) {1.425(4) and 1.127(4) Å [1]}.

Also as in (V), a short nonbonded contact $N^1 \ldots C^{18}$ of 2.829(3) Å is seen in (III) (Table 1, sum of van der Waals radii is 3.21 Å [5, 6]). This increases the $N^1C^1C^2$ angle to 126.3(3)°, whereas the $C^1C^2C^{18}$ angle [118.1(2)°] does not increase in comparison to the $C^3 \cdot C^2C^{18}$ angle [119.0(2)°] since the CN group on C^2 interacts sterically with the cyclopropyl substituent. The rotation of this ring and the Ph-substituent relative to the planar C^6C^1-C^2C^3 fragment of the cyclohexa-1,3-diene ring by 72.9 and 123.0° is controlled by steric nonbonded contacts of these rings with other substituents in the central ring (see Table 1).

The steric effect of (III) (Table 1) causes a substantial increase in $C^1{-}C^6$ bond length to 1.541(3) Å in comparison to the $C^4{-}C^5$ bond of 1.502(3) Å and standard $C_{sp^3}{-}C_{sp^2}$ length of 1.504 Å in unsubstituted cyclohexa-1,3-diene [4]. The decrease in $C^5{-}C^6$ interatomic distance to 1.568(3) Å is probably related to steric interaction between nitrile groups and Ph-substituents (the typical $C_{sp^3}{-}C_{sp^3}$ bond length is 1.541 Å [4]). The electron-accepting CN groups on C^6, as in the case of (V), apparently affect the $C^1{-}C^6$ and $C^5{-}C^6$ bond lengths along with steric factors.

The cyclohexa-1,3-diene ring of (III) twists around the $C^2{-}C^3$ bond [the $C^1C^2C^3C^4$ torsion angle is −15.7(3)°] and reduces the probability of conjugation of the $C^1{=}C^2$ and $C^3{=}C^4$ bonds. The $C^2{-}C^3$ bond length of 1.473(3) Å, coinciding with the length of the analogous bond in unsubstituted cyclohexa-1,3-diene (1.478 Å) without conjugation [4], is consistent with this.

The $C_{sp^3}{-}C_{sp}$ and $C{\equiv}N$ bond lengths in the nitrile groups on C^6 are 1.484(3), 1.484(3) Å and 1.134(4), 1.138(3) Å, respectively. These lengths are comparable to those found in (V) and with the standard values of 1.470 and 1.136 Å [4].

The C–C bond lengths in the cyclopropyl substituent of (III) are 1.470-1.498(4) Å and approach the lower limit of values 1.497-1.523 Å in unsubstituted cyclopropanes [4].

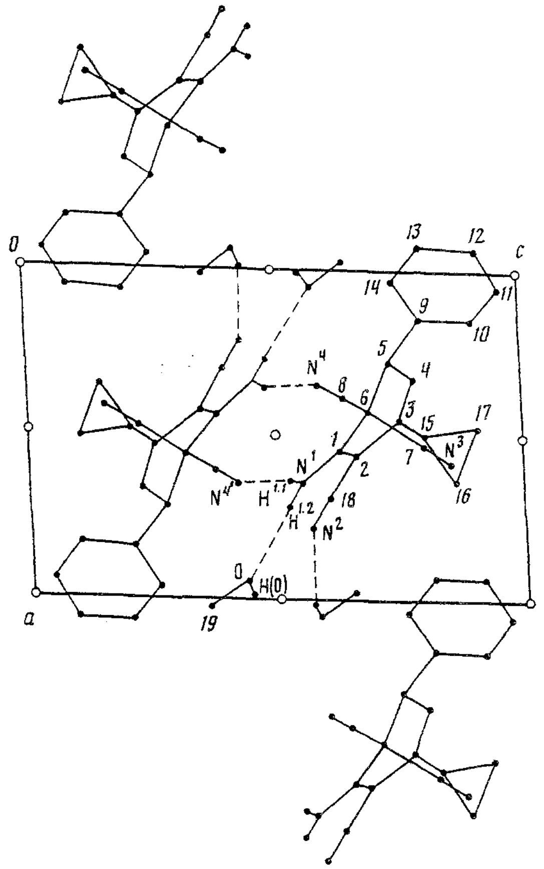

Fig. 2. Projection on *a* of the crystal structure of (III)·MeOH. Dashed lines show hydrogen bonds N—H...O, N—H...N, and O—H...N.

An extensive hydrogen bonding system between molecules of (III) and the methanol solvate is seen. All active hydrogen atoms participate in it: N^1—$H^{1.2}$...O (x, y, z) [N^1...O, 2.880(2): N^1—$H^{1.2}$, 0.81(2); $H^{1.2}$...O, 2.09(2) Å; N^1—$H^{1.2}$...O, 165(2)°], N^1—$H^{1.1}$...$N^{4\prime}$, (1 − x, −y, 1 − z) [N^1...$N^{4\prime}$, 3.070(2); N^1—$H^{1.1}$, 0.82(2); $H^{1.1}$...$N^{4\prime}$, 2.28(2) Å; N^1—$H^{1.1}$...$N^{4\prime}$, 161(1)°], O—H(O)...$N^{2\prime}$ (2 − x, 1 − y, 1 − z) [O...$N^{2\prime}$, 2.957(2); O—H(O), 0.67(2); H(O)...$N^{2\prime}$, 2.32(2) Å; O—H(O)...$N^{2\prime}$, 160(2)°]. These hydrogen bonds join molecules of (III) and methanol into inifinite chains along the *a* axis (Fig. 2).

Thus, steric effects in cyclohexadiene (III) cause homolytic rupture of the weakest bond C^5—C^6 (on deposition of external energy) and subsequent formation of dihydropyridine (IV).

EXPERIMENTAL

IR spectra were taken on a UR-20 spectrometer using KBr pellets. PMR spectra were recorded on a Bruker WH-100 (100 MHz) instrument in DMSO-d_6 relative to TMS. Compounds were identified by TLC on Silufol UV-254 plates using acetone:hexane 3:5.

1-Amino-5-phenyl-2,6,6-tricyano-3-cyclopropyl-1,3-cyclohexadiene (III). Morpholine (3 drops) was added to a mixture of 1.32 g (10 mmoles) (1-cyclopropylethylidene)malononitrile (I) and 1.56 g (10 mmoles) benzylidenemalononitrile (II) in 15 ml methanol with stirring. The mixture was stirred for 0.5 h at 25°C. The precipitate was filtered, washed with ethanol and hexane, and recrystallized from methanol. Yield 2.86 g (90%) of the methanol solvate of 1-amino-5- phenyl-2,6,6-tricyano-3-cyclopropyl-1,3-cyclohexadiene, dec. 84-85°C, mp 105-106°C. The solvate obtained was dried to constant weight to give (III) with mp 106-107°C. IR spectrum (KBr, ν, cm^{-1}): 2212 and 2272 CN, 3156 NH, 3389 NH_2. PMR spectrum (DMSO-d_6, δ, ppm): 7.72 s (2H, NH_2), 7.37 m (5H, C_6H_5), 5.18 d (1H, H^4), 4.46 d (1H, H^5), 1.70 m (1H, CH-cyclopropyl), 0.50 and 0.81 m (4H, CH_2—CH_2-cyclopropyl). Found: C, 71.59; H, 5.60; N, 17.62%. $C_{18}H_{14}N_4 \cdot CH_4O$. Calculated: C, 71.68; H, 5.70; N, 17.60%.

TABLE 2. Atomic Coordinates ($\cdot 10^4$ for O, N, C; $\cdot 10^3$ for H)

Atom	X	Y	Z
O *	9447(2)	2711(2)	4276(1)
N^1	6520(2)	2406(2)	5464(1)
N^2	7857(2)	5886(2)	5607(1)
N^3	5874(2)	853(2)	8469(1)
N^4	3482(2)	518(2)	5794(1)
C^1	5539(2)	3311(2)	6221(1)
C^2	5619(2)	4753(2)	6549(1)
C^3	4563(2)	5615(2)	7455(1)
C^4	3244(2)	5202(2)	7817(2)
C^5	2738(2)	3954(2)	7281(1)
C^6	4312(2)	2579(2)	6880(1)
C^7	5174(2)	1615(2)	7792(2)
C^8	3838(2)	1422(2)	6259(2)
C^9	1541(2)	3254(2)	7945(2)
C^{10}	1617(3)	2946(3)	9029(2)
C^{11}	528(3)	2261(3)	9619(2)
C^{12}	−643(3)	1887(3)	9110(2)
C^{13}	−730(2)	2189(3)	8040(2)
C^{14}	341(2)	2876(3)	7450(2)
C^{15}	5041(3)	6942(2)	7905(2)
C^{16}	6447(3)	6522(3)	8596(2)
C^{17}	4769(3)	7251(3)	9064(2)
C^{18}	6858(2)	5391(2)	6035(1)
C^{19} *	10159(4)	1513(4)	3554(3)
$H^{1.1}$	638(2)	158(2)	525(1)
$H^{1.2}$	728(2)	267(2)	516(1)
H(O) *	992(2)	314(2)	440(2)
H^4	254(2)	572(2)	840(1)
H^5	227(2)	445(2)	663(1)
H^{10}	235(2)	320(2)	935(1)
H^{11}	59(2)	204(2)	1037(2)
H^{12}	−134(2)	143(2)	951(2)
H^{13}	−152(3)	196(3)	765(2)
H^{14}	31(2)	309(2)	670(2)
H^{15}	491(2)	786(2)	743(1)
$H^{16.1}$	697(2)	531(2)	881(2)
$H^{16.2}$	718(3)	727(3)	842(2)
$H^{17.1}$	441(2)	831(2)	925(2)
$H^{17.2}$	429(2)	654(2)	953(2)
$H^{19.1}$ *	1137(3)	110(3)	345(2)
$H^{19.2}$ *	997(3)	173(3)	296(2)
$H^{19.3}$ *	983(4)	77(4)	364(3)

*Atoms of the methanol solvate molecules.

6-Phenyl-2-dicyanomethylene-3-cyano-4-cyclopropyl-1,2-dihydropyridine (IV). A mixture of 1 g (3.5 mmoles) aminocyclohexadiene (III) in 10 ml o-xylene was refluxed for 0.5 h in the presence of 1 ml triethylamine. The oil that separated after cooling was triturated with 5-10 ml conc. HCl. The precipitate was filtered and washed with water, ethanol, and hexane. Yield 0.3 g (30%), mp 224-226°C (from AcOH). IR spectrum (KBr, ν, cm^{-1}): 1623 NH, 2190 CN. PMR spectrum (DMSO-d_6, δ, ppm): 7.58 and 7.87 m (5H, C_6H_5), 6.59 s (1H, C^5), 5.70 br.s (1H, NH), 2.02 and 2.38 m (1H, CH-cyclopropyl), 0.92 and 1.45 m (4H, CH_2—CH_2-cyclopropyl). Found: C, 75.87; H, 4.31; N, 19.59%. $C_{18}H_{12}N_4$. Calculated: C, 76.04; H, 4.25; N, 19.71%.

Crystals of (III)·CH_3OH are triclinic, at 20°C a = 8.6327(11), b = 8.6315(8), c = 12.5408(13) Å, α = 85.950(8), β = 84.406(10), γ = 71.918(8)°, V = 883.3(2) Å^3, d_{calc} = 1.202 g/cm^3, Z = 2, space group P$\bar{1}$. Cell constants and intensities of 2204 independent reflections were measured on a Hilger—Watts 4-circle automatic diffractometer (λ MoKα, graphite monochromator, θ/2θ scanning up to θ_{max} = 26°). The structure was solved by direct methods using MULTAN and was refined by anisotropic full-matrix least squares for nonhydrogen atoms using 2126 reflections with I ≥ 2σ. All hydrogen atoms were located in different syntheses and were refined isotropically. The final agreement factors were R = 0.039 and R_w = 0.036. All calculations were carried out on an Eclipse S/200 computer using INEXTL programs [7]. Atomic coordinates are given in Table 2 [isotropic equivalent thermal parameters for nonhydrogen atoms (isotropic for H atoms) can be obtained from the authors].

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SYNTHESIS OF DIASTEREOISOMERS OF DIMETHYL 4-ARYLAMINO-N-PHTHALOYL-L-GLUTAMATES

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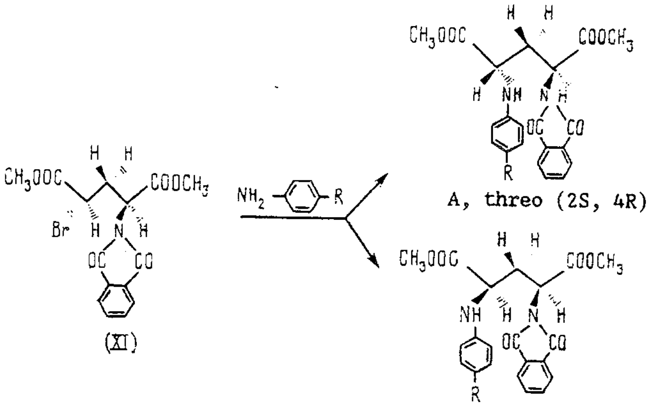
Reaction of p-substituted arylamines with dimethyl (2S,4RS)-4-bromo-N-phthaloylglutamate followed by separation of the stereoisomers has given the pure dimethyl (2S)-4-arylamino-N-phthaloylglutamates. Nucleophilic replacement of the halogen in dimethyl (2S,4RS)-4-bromo-N-phthaloylglutmate is diastereoselective, giving the threo-isomer preferentially.

Some glutamic acid derivatives have been found to posses antitumor [1] and radioprotectant properties [2]. The spatial structure of these compounds plays an important part in their activity.

The object of the present study was to obtain the dimethyl (2S)-4-arylamino-N-phthaloylglutamates (I)-(X) with a variety of substituents in the para position of the benzene ring.

These compounds were obtained by heating dimethyl (2S,4RS)-4-bromo- N-phthaloylglutamate (XI) [3] with an excess of the arylamine in acetonitrile or alcohol (Table 1).



(XI)

A, threo (2S, 4R)

B, erythro (2S, 4S)

2S, 4S (threo): R = CH_3O (I), OH (III), CH_3 (IV), H (VI), $NHCOCH_3$ (VII), I (VIII), Cl (IX), Br (X); 2S, 4R (erythro): R = CH_3O (II), CH_3 (V).

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