mation with approximately $3m$ (C_{3v}) symmetry (type XVII), and the tribenzyl derivative adopts a 'twist-chair–boat' shape with an approximate twofold symmetry axis, C_2 (type XV). The ring shapes in both these molecules are probably influenced by intra-molecular hydrogen bonding connecting the N—H group (of the cation) and the O—H groups (of the tribenzyl moiety) with the ring N atoms. In both of these, the three alkyl substituent groups are equatorially arranged at N atoms with sp^3 hybridizations; the N atoms are between 0.37 and 0.49 Å displaced from the planes of the three adjacent C atoms. In the title molecule, the N atoms show more nearly sp^2-type arrangements, with displacements of 0.055 (6) and 0.156 (6) Å for the mercaptobenzoyl groups and 0.205 (6) Å for the tosyl group.

Peaks corresponding to likely H atoms of the two thiol groups, at S(1) and S(4), were identified in difference maps, and these H atoms were included in the later cycles of refinement. Both are involved in S—H···O hydrogen bonds, linking the molecules in chains parallel to the b axis (Table 2). This is not the elongated direction of the crystal, which is parallel to the c axis. Other intermolecular contacts, between neighbouring triazacyclononane molecules and involving the disordered hexane molecules, are at normal van der Waals distances.

References

ANDERSON, S. N., RICHARDS, R. L. & HUGHES, D. L. (1986). *J. Chem. Soc. Dalton Trans.* pp. 245–252.

EVANS, D. J., GARCIA, G., LEIGH, G. J., NEWTON, M. S. & SANTANA, M. D. (1992). *J. Chem. Soc. Dalton Trans.* pp. 3229–3234.

EVANS, D. J., LEIGH, G. J. & SANTANA, M. D. (1991). *J. Inorg. Biochem.* **43**, 275.

HENDRICKSON, J. B. (1964). *J. Am. Chem. Soc.* **86**, 4854–4866.

MOORE, D. A., FANWICK, P. E. & WELCH, M. J. (1989). *Inorg. Chem.* **28**, 1504–1506.

SHELDRICK, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.

WIEGHARDT, K., BRODKA, S., PETERS, K., PETERS, E. M. & SIMON, A. (1987). *Z. Naturforsch. Teil B*, **42**, 279–281.

Structure of *trans*-1-{2-[(2-Butoxy)phenylcarbamoyloxy]cycloheptylmethyl}-piperidinium Chloride

By Viktor Kettmann, Eva Frešová and Július Sivý

Department of Analytical Chemistry, Faculty of Pharmacy, Komensky University, Odbojarov 10, CS-83232 Bratislava, Czechoslovakia

and Fridrich Gregáň

Department of Organic Chemistry, Faculty of Pharmacy, Komensky University, Odbojarov 10, CS-83232 Bratislava, Czechoslovakia

Abstract. $C_{24}H_{39}N_2O_3^+.Cl^-$, $M_r = 439.0$, monoclinic, $P2_1/n$, $a = 9.114 (7)$, $b = 18.747 (11)$, $c = 14.185 (9)$ Å, $\beta = 104.57 (6)°$, $V = 2346 (1)$ Å^3, $Z = 4$, $D_m = 1.25 (1)$, $D_x = 1.243$ Mg m^{-3}, $\lambda(Mo\ K\alpha) = 0.71069$ Å, $\mu = 0.187$ mm^{-1}, $F(000) = 952$, $T = 293$ K, final $R = 0.057$ for 1451 unique observed reflections. The title compound, which is a potent local anesthetic of the phenylcarbamate type, was designed to explore the stereostructural requirements of the anesthetic receptor by locking the phenyl-carbamate–amine link into a semirigid system. The mean planes through the piperidine (chair conformation) and the cycloheptane (twist-chair form) rings are approximately normal to each other, with a dihedral angle of 108.7 (5)°. As usually observed in 2-alkoxyphenylcarbamates, the butoxy group is conjugated and the carbamate function deconjugated with the aromatic ring. There is one hydrogen-bond interaction between the protonated amine and the Cl anion, with an N···Cl$^-$ distance of 3.106 (3) Å.

Introduction. The title compound belongs to the phenylcarbamate class of local anesthetics which are esters of 2-alkoxyphenylcarbamoic acid with primary or secondary amines. Common structural features of these compounds are a (protonated) amine N atom, a phenylcarbamate moiety, a two- or three-C-atom spacer separating this pair of anesthesiophoric groups, and a hydrophobic moiety, typically in the *ortho* position on the phenyl ring. Previous studies,

aimed at exploring the stereostructural requirements for interaction at the anesthetic receptor, were performed on flexible derivatives so that the problem of the receptor-bound conformation remained unclear. Therefore, we have synthesized *cis* and *trans* isomers of a semirigid derivative having two atoms of the three-C-atom spacer and the amino N atom embedded in a seven-membered ring and a six-membered (piperidine) ring, respectively. We now report on the crystal structure of the *trans* isomer.

Experimental. Single crystals were obtained from ethanol solution. A colourless needle-shaped crystal of dimensions $0.15 \times 0.20 \times 0.55$ mm was used for data collection. D_m was measured by flotation in bromoform/cyclohexane. Systematic absences $0k0$ for k odd and $h0l$ for $h + l$ odd were observed from Weissenberg photographs. Data were collected on a Syntex $P2_1$ diffractometer. Accurate unit-cell parameters were determined by least-squares refinement of 15 reflections, $10 < 2\theta < 24°$. Intensity data ($h = 0$ to 9, $k = 0$ to 20, $l = -15$ to 14) were collected with graphite-monochromated Mo $K\alpha$ radiation, θ–2θ scan mode, variable scan speed, and scan width $2°$ (in 2θ) plus $\alpha_1 - \alpha_2$ dispersion. Two standard reflections measured every 100 reflections varied by less than 5%. Intensities were corrected for Lorentz–polarization effects but not for absorption. 3068 unique reflections were obtained by merging 3294 measured ($2\theta_{max} = 45°$) reflections ($R_{int} = 0.047$); 1451 reflections with $I > 2\sigma(I)$ were considered observed and included in the refinement. The structure was solved by direct methods using *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) and refined on F by block-diagonal least-squares methods using anisotropic thermal parameters for non-H atoms. Although most H atoms could be located from a $\Delta\rho$ map, all H atoms were included in their calculated positions with B_{iso} set to 0.5 higher than the value of B_{eq} for the associated C or N atoms. 271 parameters were refined. In the final cycle $R = 0.057$, $wR = 0.067$, $S = 1.56$ for the observed reflections only; maximum shift/e.s.d. $= 0.11$. The function minimized was $\sum w(\Delta F)^2$, where $w^{-1} = \sigma^2(F_o) + (0.03|F_o|)^2$ with $\sigma(F_o)$ based on counting statistics. Maximum and minimum heights in the final $\Delta\rho$ synthesis were 0.22 and -0.21 e Å^{-3}. Scattering factors for neutral atoms were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). All calculations except those by *MULTAN* were performed with a local version of the *NRC* program system (Ahmed, Hall, Pippy & Huber, 1973).

Discussion. Final atomic coordinates for the non-H atoms and equivalent isotropic B values are listed in

Table 1.* Bond distances and angles are given in Table 2. A view of the molecule with atom numbering is shown in Fig. 1, which also displays the overall conformation.

The cycloheptane ring has a twist-chair conformation (Flapper & Romers, 1975) with a pseudo-twofold axis passing through C(8) and the midpoint of the C(11)—C(12) bond (Fig. 1). Such a conformation has been found in most other cycloheptane derivatives (Ponnuswamy & Trotter, 1985), thus supporting the prediction of Hendrickson (1967) rather than that made by Bocian, Pickett, Rounds & Strauss (1975) that the boat is the most stable conformation.

The C—C bond lengths within the cycloheptane ring are consistently shorter [average 1.498 (6) Å] than 1.533 Å (Bartell, 1959) and the endocyclic C—C—C angles larger [average 115.7 (3)°] than the theoretical values of 114.1 and 114.7° given for the twist-chair conformation (Bixon & Lifson, 1967; Hendrickson, 1967). Obviously, these deviations from the normal geometry arise from the high thermal motion; the C(9)—C(10) and C(7)—C(13) distances especially [1.454 (6) and 1.477 (5) Å, respectively] seem unrealistically shortened. During the final stages of refinement, no peaks in the difference Fourier synthesis appeared close to any ring atom, and so the geometrical anomalies do not appear to result from the disorder which is frequently found in cycloheptane derivatives (de Kok & Romers, 1980); nevertheless, they may result from unresolved disorder (separation of the disordered sites less than the resolution of the data).

The protonated piperidine ring adopts an almost perfect chair conformation, with the torsion angles ranging from 55.4 (4) to 57.0 (4)°.

In the area of the substituted phenyl ring, the C(16)—O(3) bond length of 1.345 (4) Å is considerably shorter than a value of 1.406 (4) Å reported for a C(sp^2)—O single bond (Ammon, Mazzocchi, Regan & Colicelli, 1979), the bond angle at O(3) [118.6 (3)°] shows a widening from the normal sp^3 value, and the oxymethylene O(3)—C(21) moiety is approximately coplanar with the adjacent aromatic ring [torsion angle C(17)—C(16)—O(3)—C(21) = 27.2 (3)°]. On the other hand, the C(15)—N(2) bond length of 1.411 (4) Å is not far from a value of 1.425 Å found for a pure C(sp^2)—N single bond (Adler, Goode, King, Mellor & Miller, 1976) and the carbamate function [atoms N(2), C(14), O(1) and

$$C_{24}H_{39}N_2O_3^+.Cl^-$$

Table 1. Final atomic coordinates ($\times 10^4$) and equivalent isotropic thermal parameters (Å^2)

$$B_{eq} = (4/3)\Sigma_i\Sigma_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq}
C(1)	6088 (4)	1120 (2)	3762 (3)	5.36 (13)
C(2)	6095 (4)	675 (2)	2894 (3)	6.30 (14)
C(3)	7560 (4)	686 (2)	2648 (2)	5.36 (12)
C(4)	8816 (5)	444 (2)	3521 (3)	6.12 (14)
C(5)	8798 (4)	903 (2)	4397 (3)	5.05 (13)
C(6)	7342 (4)	1363 (2)	5473 (2)	4.67 (12)
C(7)	8136 (4)	1051 (2)	6454 (2)	4.06 (11)
C(8)	9267 (4)	1586 (2)	7040 (3)	5.13 (13)
C(9)	9713 (4)	1497 (2)	8134 (3)	5.96 (16)
C(10)	10050 (4)	771 (2)	8486 (3)	6.81 (16)
C(11)	8699 (5)	359 (2)	8610 (3)	7.03 (15)
C(12)	7593 (5)	166 (2)	7675 (3)	6.63 (16)
C(13)	7021 (4)	766 (2)	6954 (2)	5.11 (13)
C(14)	11554 (4)	2073 (2)	6811 (2)	4.16 (11)
C(15)	13969 (4)	2376 (2)	6595 (2)	4.29 (11)
C(16)	14827 (4)	2583 (2)	7495 (2)	5.10 (13)
C(17)	16039 (4)	3025 (2)	7569 (3)	5.78 (14)
C(18)	16421 (5)	3236 (2)	6755 (3)	6.94 (16)
C(19)	15607 (4)	3020 (2)	5851 (3)	6.43 (15)
C(20)	14404 (4)	2594 (2)	5782 (3)	5.01 (13)
C(21)	15495 (4)	2249 (3)	9154 (3)	7.67 (15)
C(22)	14883 (6)	1792 (3)	9816 (4)	11.63 (24)
C(23)	14440 (7)	1092 (3)	9417 (4)	13.54 (27)
C(24)	13803 (6)	721 (3)	10193 (4)	12.17 (26)
N(1)	7335 (3)	886 (1)	4629 (2)	4.01 (9)
N(2)	12726 (3)	1906 (1)	6487 (2)	4.54 (10)
O(1)	10540 (2)	1524 (1)	6650 (2)	4.70 (8)
O(2)	11310 (3)	2622 (1)	7199 (2)	5.53 (9)
O(3)	14395 (3)	2328 (2)	8269 (2)	6.84 (9)
Cl(1)	12931 (1)	718 (1)	4892 (1)	5.17 (3)

Table 2. Bond lengths (Å) and angles ($°$)

N(1)—C(1)	1.514 (5)	O(1)—C(14)	1.364 (4)
C(1)—C(2)	1.490 (5)	C(14)—N(2)	1.302 (4)
C(2)—C(3)	1.462 (6)	C(14)—O(2)	1.213 (4)
C(3)—C(4)	1.529 (5)	N(2)—C(15)	1.411 (4)
C(4)—C(5)	1.515 (5)	C(15)—C(16)	1.374 (5)
C(5)—N(1)	1.452 (5)	C(16)—C(17)	1.363 (5)
N(1)—C(6)	1.493 (4)	C(17)—C(18)	1.346 (6)
C(6)—C(7)	1.515 (5)	C(18)—C(19)	1.372 (6)
C(7)—C(8)	1.526 (5)	C(19)—C(20)	1.340 (5)
C(8)—C(9)	1.512 (5)	C(20)—C(15)	1.373 (5)
C(9)—C(10)	1.454 (6)	C(16)—O(3)	1.345 (4)
C(10)—C(11)	1.501 (6)	O(3)—C(21)	1.403 (5)
C(11)—C(12)	1.494 (6)	C(21)—C(22)	1.480 (7)
C(12)—C(13)	1.522 (6)	C(22)—C(23)	1.446 (8)
C(13)—C(7)	1.477 (5)	C(23)—C(24)	1.534 (8)
C(8)—O(1)	1.411 (4)		

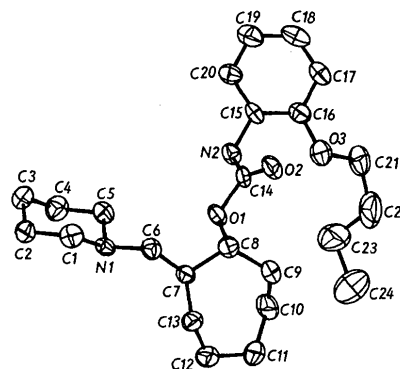|			
C(1)—N(1)—C(5)	110.8 (3)	C(8)—O(1)—C(14)	117.5 (3)
C(1)—N(1)—C(6)	109.2 (3)	O(1)—C(14)—N(2)	109.9 (3)
C(5)—N(1)—C(6)	110.5 (3)	O(1)—C(14)—O(2)	121.5 (3)
N(1)—C(1)—C(2)	110.5 (3)	O(2)—C(14)—N(2)	128.6 (3)
C(1)—C(2)—C(3)	112.5 (3)	C(14)—N(2)—C(15)	121.2 (3)
C(2)—C(3)—C(4)	110.2 (3)	N(2)—C(15)—C(16)	122.1 (3)
C(3)—C(4)—C(5)	109.6 (3)	N(2)—C(15)—C(20)	119.2 (3)
C(4)—C(5)—N(1)	111.9 (3)	C(16)—C(15)—C(20)	118.5 (3)
N(1)—C(6)—C(7)	114.2 (3)	C(15)—C(16)—C(17)	120.3 (3)
C(6)—C(7)—C(8)	110.4 (3)	C(15)—C(16)—O(3)	116.2 (3)
C(6)—C(7)—C(13)	110.7 (3)	C(17)—C(16)—O(3)	123.4 (3)
C(8)—C(7)—C(13)	115.3 (3)	C(16)—C(17)—C(18)	119.4 (4)
C(7)—C(8)—C(9)	117.2 (3)	C(17)—C(18)—C(19)	121.3 (4)
C(7)—C(8)—O(1)	104.0 (3)	C(18)—C(19)—C(20)	118.9 (4)
C(9)—C(8)—O(1)	111.0 (3)	C(19)—C(20)—C(15)	121.4 (4)
C(8)—C(9)—C(10)	115.7 (3)	C(16)—O(3)—C(21)	118.6 (3)
C(9)—C(10)—C(11)	114.4 (4)	O(3)—C(21)—C(22)	109.6 (4)
C(10)—C(11)—C(12)	114.2 (4)	C(21)—C(22)—C(23)	112.9 (5)
C(11)—C(12)—C(13)	117.3 (3)	C(22)—C(23)—C(24)	104.5 (5)
C(12)—C(13)—C(7)	115.4 (3)		

Fig. 1. A perspective view of the title compound showing the numbering of the atoms. The thermal ellipsoids are drawn at the 50% probability level.

through the phenyl ring, the carbamate group is not involved to any appreciable extent in conjugation with the aromatic system.

From the pharmacological point of view, the most important structural feature of the phenylcarbamate-type local anesthetics is the three-dimensional disposition of the common functional groups, i.e. the protonated amino N atom, the N^+—H vector, and the phenylcarbamate function (namely, the carbonyl O atoms and the π-excessive phenyl ring), which are assumed to define the interaction with the anesthetic receptor (Remko & Scheiner, 1988). The spatial relationship between these primary anesthesiophoric groups is defined by torsion angles along the N(1)—C(6)—C(7)—C(8) linking chain: $\tau_1[C(1)$—N(1)—C(6)—C(7)], $\tau_2[N(1)$—C(6)—C(7)—C(8)] and $\tau_3[C(6)$—C(7)—C(8)—O(1)]. In the present semirigid derivative, $\tau_1 = 160.2$ (3), $\tau_2 = 130.3$ (3) and τ_3 is fixed at -79.7 (3)$°$ by the trans position of C(6) and O(1) and by the twist-chair conformation of the cycloheptane ring. As a result, the mean planes through the piperidine and cycloheptane rings are approximately perpendicular to each other [dihedral angle 108.7 (5)$°$].

The principal interaction between the cations and the Cl anions is via an $N(1)\cdots Cl^-$ ($2 - x$, $-y$, $1 - z$) hydrogen bond [$N\cdots Cl^- = 3.106$ (3) Å]. Other packing forces are of Coulombic and van der Waals types acting at distances > 3.4 Å.

References

ADLER, R. W., GOODE, N. C., KING, T. S., MELLOR, J. M. & MILLER, B. W. (1976). J. Chem. Soc. Chem. Commun. pp. 173–174.

AHMED, F. R., HALL, S. R., PIPPY, M. E. & HUBER, C. P. (1973). NRC Crystallographic Programs for the IBM 360 System. Accession Nos. 133–147. J. Appl. Cryst. 6, 309–346.

AMMON, H. L., MAZZOCCHI, P. H., REGAN, M. C. & COLICELLI, E. (1979). Acta Cryst. B35, 1722–1724.

O(2)] is rotated by 60.4 (4)$°$ out of the plane of the phenyl ring. These results confirm previous observations that while the lone-pair electrons on the ether O atom in 2-alkoxyphenylcarbamates are delocalized

MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

PONNUSWAMY, M. N. & TROTTER, J. (1985). *Acta Cryst.* C41, 915–917, and references therein.

REMKO, M. & SCHEINER, S. (1988). *J. Pharm. Sci.* 77, 304–308.

BARTELL, L. S. (1959). *J. Am. Chem. Soc.* 81, 3497–3498.

BIXON, M. & LIFSON, S. (1967). *Tetrahedron*, 23, 769–784.

BOCIAN, D. F., PICKETT, H. M., ROUNDS, T. C. & STRAUSS, H. L. (1975). *J. Am. Chem. Soc.* 97, 687–695.

FLAPPER, W. M. J. & ROMERS, C. (1975). *Tetrahedron*, 31, 1705–1713.

HENDRICKSON, J. B. (1967). *J. Am. Chem. Soc.* 89, 7036–7046.

KOK, A. J. DE & ROMERS, C. (1980). *Acta Cryst.* B36, 1887–1893.

Structures of Diels–Alder Reaction Bis-Adducts of 4-Phenyl- or 4-Methyl-1,2,4-triazoline-3,5-dione with 1,6-Methano[10]annulene

BY I. AGMON, P. ASHKENAZI AND M. KAFTORY*

Department of Chemistry, Technion-Israel Institute of Technology, Haifa 32000, Israel

Abstract. 2,9-Dimethyl-1,2,3,5,5a,6,8,9,10,12,12a,-13-dodecahydro-5,13;6,12-bisetheno-5a,12a-methano[1,2,4]triazolo[1′,2′:1,2]pyridazino[4,5-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-1,3,8,10-tetraone (1), $C_{17}H_{16}N_6O_4$, $M_r = 368.35$, triclinic, $P\bar{1}$, $a = 8.756$ (4), $b = 12.373$ (6), $c = 8.426$ (5) Å, $\alpha = 102.99$ (3), $\beta = 115.79$ (3), $\gamma = 98.06$ (3)°, $V = 770.86$ Å^3, $Z = 2$, $D_x = 1.588$ g cm^{-3}, $\lambda(\text{Mo } K\alpha) = 0.71069$ Å, $\mu = 0.110$ cm^{-1}, $F(000) = 384$, $T = 298$ K, $R = 0.047$, for 2670 reflections. 2,9-Diphenyl-1,2,3,5,5a,6,8,9,10,12,-12a,13-dodecahydro-5,13;6,12-bisetheno-5a,12a-methano[1,2,4]triazolo[1′,2′:1,2]pyridazino[4,5-*d*]-[1,2,4]triazolo[1,2-*a*]pyridazine-1,3,8,10-tetraone (2), $C_{27}H_{20}N_6O_4$, $M_r = 492.50$, monoclinic, $P2_1/c$, $a = 14.440$ (7), $b = 9.416$ (5), $c = 16.227$ (9) Å, $\beta = 98.42$ (3)°, $V = 2182.55$ Å^3, $Z = 4$, $D_x = 1.499$ g cm^{-3}, $\lambda(\text{Mo } K\alpha) = 0.71069$ Å, $\mu = 0.098$ cm^{-1}, $F(000) = 1024$, $T = 298$ K, $R = 0.072$ for 2344 reflections. 2,9-Diphenyl-1,2,3,5,5a,6,8,9,10,12,-12a,13-dodecahydro-5,13;6,12-bisetheno-5a,12a-methano[1,2,4]triazolo[1′,2′:1,2]pyridazino[4,5-*d*]-[1,2,4]triazolo[1,2-*a*]pyridazine-1,3,8,10-tetraone 0.5-ethanol solvate (3), $C_{27}H_{20}N_6O_4 \cdot \frac{1}{2}C_2H_6O$, $M_r = 515.53$, triclinic, $P\bar{1}$, $a = 12.673$ (6), $b = 11.431$ (6), $c = 9.439$ (5) Å, $\alpha = 68.49$ (3), $\beta = 111.39$ (3), $\gamma = 97.72$ (3)°, $V = 1184.52$ Å^3, $Z = 2$, $D_x = 1.446$ g cm^{-3}, $\lambda(\text{Mo } K\alpha) = 0.71069$ Å, $\mu = 0.097$ cm^{-1}, $F(000) = 538$, $T = 298$ K, $R = 0.065$ for 2834 reflections. Crystal structures of two Diels–Alder bis-adducts of 4-phenyl- and 4-methyl-1,2,4-triazaoline-3,5-dione with 1,6-methano[10]annulene show that the molecules adopt the *exo–endo* configuration. The phenyl derivative crystallizes with or without a solvent molecule.

Introduction. Many Diels–Alder reactions between propellanes containing one or two cyclohexadiene rings and bridged [10]annulenes with triazolinediones show a preference for the *endo* mono-adducts (Kalo, Vogel & Ginsburg, 1977; Kalo, Bloomfield & Ginsburg, 1978; Kalo & Ginsburg, 1978; Ashkenazi, Kalo, Ruttimann & Ginsburg, 1978; Ashkenazi, Vogel & Ginsburg, 1977, 1978; Ashkenazi, Peled, Vogel & Ginsburg, 1979; Gleiter & Ginsburg, 1979). Only one mono-adduct of both the *exo* and the *endo* were detected in 11-cyano-1,6-methano[10]annulene, while its bis-adduct afforded the *endo–endo* derivative (Ashkenazi, Kaftory, Arad, Apeloig & Ginsburg, 1981) whose crystal structure has been published (Kaftory, 1983; Kaftory & Agmon, 1984).

1,6-Methano[10]annulene itself affords the *endo–exo* bis-adduct (1). We describe here the crystal structure of three compounds: (1) the *endo–exo* bis-adduct of 1,6-methano[10]annulene with the methyl derivative of the triazolinedione; (2) the solvent free *endo–exo* bis-adduct with the phenyl derivative of triazolinedione and (3) the same as (2) with a molecule of ethanol.
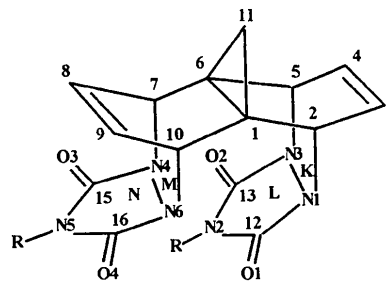
(1) *R* = Me
(2), (3) *R* = Ph

---

* To whom correspondence should be addressed.