Table 2. *Selected bond lengths* (Å), *bond angles* (°) *and torsion angles* (°)

N(1)—C(2)	1·324 (4)	C(2)—O(2)	1·342 (4)
N(1)—C(6)	1·345 (4)	O(2)—C(20)	1·453 (4)
N(3)—C(2)	1·315 (4)	C(4)—O(4)	1·329 (3)
N(3)—C(4)	1·333 (4)	O(4)—C(40)	1·434 (4)
N(5)—C(4)	1·320 (4)	C(6)—N(7)	1·350 (4)
N(5)—C(6)	1·334 (4)	N(7)—C(8)	1·415 (4)

C(2)—N(1)—C(6)	112·8 (3)	N(1)—C(2)—N(3)	128·5 (3)
C(2)—N(3)—C(4)	112·3 (3)	N(3)—C(4)—N(5)	127·1 (3)
C(4)—N(5)—C(6)	114·0 (3)	N(5)—C(6)—N(1)	125·3 (3)
C(2)—O(2)—C(20)	117·7 (3)	C(4)—O(4)—C(40)	117·1 (3)
C(6)—N(7)—C(8)	131·5 (3)		

N(3)—C(2)—O(2)—C(20)	3·9 (4)	N(5)—C(6)—N(7)—C(8)	−3·3 (6)
N(5)—C(4)—O(4)—C(40)	3·3 (4)	C(6)—N(7)—C(8)—C(13)	−5·7 (6)

(Główka & Iwanicka, 1991) while the bonds corresponding to N(7)—C(8) were found to be longer [1·457 (3) and 1·482 (6) Å, respectively] owing to the lack of conjugation with the cyclohexane ring. The methoxy groups of the title compound deviate slightly from the mean plane of the triazine system and the appropriate N—C—O—C torsional angles are 3·9 (4) and 3·3 (4)°. There is a partial stacking of parallel *s*-triazine rings with an interplanar distance of 3·35 Å.

The authors thank Dr Zbigniew J. Kamiński of the Institute of Organic Chemistry, Technical University of Łódź, for the sample of compound and the Ministry of National Education for financial support under the project RP.II.10.

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Structure of *N*-[4-Hydroxy-3,5-bis(1-pyrrolidinylmethyl)phenyl]-*N'*-(4-methoxyphenyl)urea

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(*Received* 27 *July* 1990; *accepted* 11 *September* 1990)

Abstract. $C_{24}H_{32}N_4O_3$, $M_r = 424{\cdot}55$, monoclinic, $P2_1/c$, $a = 15{\cdot}740$ (1), $b = 17{\cdot}279$ (3), $c = 8{\cdot}757$ (2) Å, $\beta = 101{\cdot}67$ (1)°, $V = 2332{\cdot}4$ Å^3, $Z = 4$, $D_x = 1{\cdot}209$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 0{\cdot}0873$ mm^{-1}, $F(000) = 912$, $T = 293$ K, $R = 0{\cdot}057$ for 2095 observed reflections. The title molecule is chemically similar to several active type I antiarrhythmics but it is inactive. Structural results indicate that the lack of activity may be due to modifications of the lipophilic pharmacophore group rather than to conformational differences.

Introduction. In 1983, Stout and co-workers introduced a new family of antiarrhythmic agents originally from changrolin and based on 4-substituted 2,6-bis(1-pyrrolidinylmethyl)phenols (Stout, Mathier, Barcelon-Yang, Reynolds & Brown, 1983, 1984, 1985). Three active compounds [(1), (2) and (3)] have been studied by X-ray diffraction and molecular-mechanics calculations; the study indicated that these molecules adopt a similar shape, both in the crystal and *in vacuo* (Główka, Dargie & Codding, 1991). The limited flexibility of (1), (2) and (3), as compared to classical type I antiarrhythmics like lidocaine, mexiletine, procainamide and disopyramide, helped to establish the required spatial arrangement of binding groups in this class of drugs. In this paper, we present a study of an inactive but chemically similar

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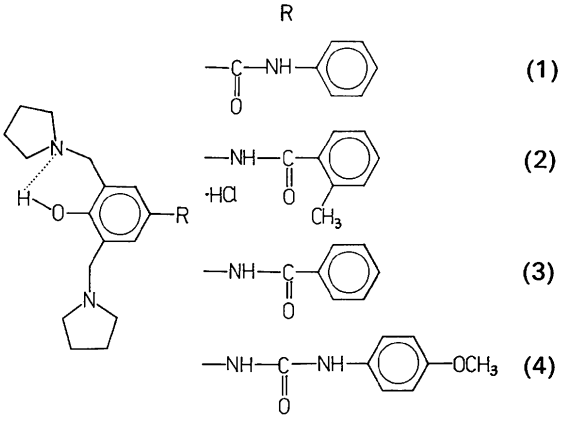
compound, (4), and compare its conformation with those of the active analogs.



Experimental. The dark-orange crystal used had dimensions 0·21 × 0·14 × 0·11 mm. The unit-cell parameters were calculated by least squares using 25 reflections (θ 8·3 to 13·8°). 4552 (4352 unique) reflections were collected on a CAD-4F diffractometer in $\omega/2\theta$ scan mode to $\theta_{max} = 25°$ from one quadrant (h −18/18, k 0/20, l −10/0). Three standards ($\bar{3}$,12,$\bar{4}$, 4,10,$\bar{1}$ and 690) measured every 100 reflections; 3% intensity variation. Intensities were corrected for Lorentz and polarization effects, but not for absorption.

The structure was solved by direct methods and refined on F using *SHELX*76 (Sheldrick, 1976) and *SHELXS*86 (Sheldrick 1986). H atoms were identified in difference Fourier syntheses. The positions and isotropic displacement parameters of those on N(7), N(8) and N(12) were refined but, owing to the large number of weak reflections, unrestricted refinement of all H atoms was difficult and, therefore, C-bonded H atoms were refined in rigid groups. 372 parameters refined. The final weights were defined as $w = 2{\cdot}621/[\sigma^2(F) + 0{\cdot}00066F^2]$; $R = 0{\cdot}057$ and $wR = 0{\cdot}062$ for 2095 observed $[I > 2{\cdot}5\sigma(I)]$ reflections. $S = 2{\cdot}16$, $(\Delta/\sigma)_{max} = 0{\cdot}16$. The maximum and minimum peaks in the final difference Fourier synthesis were 0·24 and −0·18 e Å^{-3}; the maximum was 1·23 Å from N(16) and 1·28 Å from C(20). Atomic scattering factors were those in *SHELX*76. The calculations were performed on an Amstrad PC 1513 microcomputer.

The atomic coordinates for non-H atoms are given in Table 1* with the atoms labelled as in Fig. 1.

* Lists of H-atom parameters, anisotropic thermal parameters and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53560 (12 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Positional and equivalent isotropic temperature parameters for non-*H *atoms*

$$B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq}(Å^2)
C(1)	−0·1945 (3)	0·7396 (3)	0·0282 (5)	5·34 (13)
C(2)	−0·2610 (3)	0·7014 (3)	−0·0724 (5)	5·75 (15)
C(3)	−0·2763 (3)	0·6252 (3)	−0·0482 (5)	6·25 (15)
O(3)	−0·3390 (2)	0·5815 (2)	−0·1439 (5)	9·43 (14)
C(4)	−0·2291 (3)	0·5866 (3)	0·0785 (6)	6·77 (17)
C(5)	−0·1624 (3)	0·6242 (3)	0·1762 (5)	6·17 (17)
C(6)	−0·1453 (2)	0·7014 (3)	0·1524 (4)	4·76 (13)
N(7)	−0·0756 (2)	0·7389 (3)	0·2564 (4)	6·20 (13)
N(8)	0·0581 (2)	0·7937 (2)	0·3281 (4)	5·37 (12)
O(8)	−0·0079 (2)	0·7861 (2)	0·0719 (3)	5·72 (10)
C(8)	−0·0084 (3)	0·7737 (2)	0·2105 (4)	4·63 (12)
C(9)	0·1399 (2)	0·8212 (2)	0·3098 (4)	4·64 (13)
C(10)	0·2130 (3)	0·7961 (3)	0·4132 (5)	5·38 (14)
C(11)	0·2950 (3)	0·8202 (3)	0·3998 (5)	5·44 (14)
C(12)	0·3033 (3)	0·8713 (3)	0·2804 (5)	5·52 (15)
O(12)	0·3834 (2)	0·8960 (2)	0·2621 (4)	7·82 (13)
C(13)	0·2297 (3)	0·8968 (2)	0·1738 (5)	5·43 (14)
C(14)	0·1494 (3)	0·8715 (3)	0·1911 (5)	5·12 (14)
C(15)	0·2399 (4)	0·9529 (4)	0·0474 (7)	8·15 (21)
N(16)	0·1623 (3)	0·9619 (3)	−0·0737 (5)	7·36 (14)
C(17)	0·1543 (5)	0·9087 (5)	−0·1937 (11)	11·42 (32)
C(18)	0·0888 (5)	0·9427 (4)	−0·3340 (7)	9·47 (26)
C(19)	0·0782 (5)	1·0222 (5)	−0·2871 (9)	10·02 (29)
C(20)	0·1448 (7)	1·0359 (5)	−0·1433 (10)	12·47 (35)
C(21)	0·3757 (3)	0·7875 (3)	0·5051 (7)	6·80 (16)
N(22)	0·4401 (2)	0·8470 (2)	0·5599 (5)	6·72 (14)
C(23)	0·5242 (3)	0·8127 (4)	0·6418 (8)	8·98 (23)
C(24)	0·5693 (5)	0·8785 (6)	0·7377 (10)	11·56 (30)
C(25)	0·4973 (5)	0·9318 (6)	0·7633 (14)	13·09 (37)
C(26)	0·4154 (4)	0·9005 (4)	0·6702 (7)	8·60 (21)
C(30)	−0·3804 (4)	0·6143 (5)	−0·2892 (9)	10·21 (23)

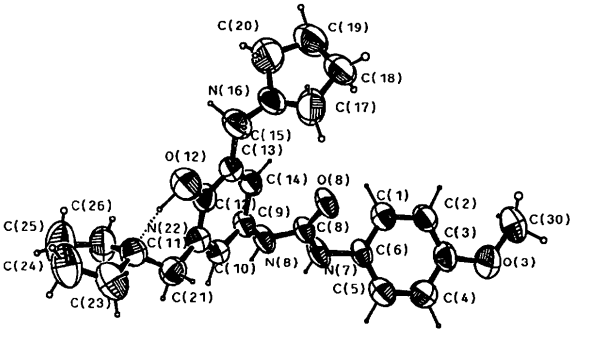


Fig. 1. Overall view and labelling of non-H atoms in the structure (Johnson, 1976).

Table 2 gives selected bond lengths, bond angles and torsion angles.

Discussion. The main difference between (4) and the three active structures (1), (2) and (3) is in the linkage between the two aromatic systems; in (4), urea replaces the amide group of (1), (2) and (3). Despite this difference, (4) displays the same characteristic features in the solid state as the active compounds (Główka, Dargie & Codding, 1991): (i) an intramolecular hydrogen bond between the phenol hydroxy group and the N atom of a pyrrolidinyl ring which constrains the torsion angle C(12)—C(11)—C(21)—N(22) to about 40° [42° in (1), 41 and −48° in (2), 32° in (3) and 46·5 (6)° in (4)]; (ii) an out-of-

Table 2. *Selected bond lengths* (Å), *bond angles* (°) *and torsion angles* (°)

C(3)—O(3)	1·383 (5)	C(12)—O(12)	1·372 (5)
O(3)—C(30)	1·425 (7)	C(11)—C(21)	1·519 (6)
C(6)—N(7)	1·431 (5)	C(13)—C(15)	1·504 (6)
N(7)—C(8)	1·346 (5)	C(15)—N(16)	1·455 (6)
C(8)—O(8)	1·235 (4)	C(21)—N(22)	1·455 (6)
C(8)—N(8)	1·356 (5)	O(12)—H(12)	1·15 (6)
N(8)—C(9)	1·411 (5)	O(12)···N(22)	2·715 (5)
H(12)···N(22)	1·65 (7)		

C(3)—O(3)—C(30)	117·7 (5)	C(11)—C(21)—N(22)	112·2 (4)
C(6)—N(7)—C(8)	124·0 (4)	C(13)—C(15)—N(16)	114·0 (4)
C(8)—N(8)—C(9)	125·6 (4)	C(15)—N(16)—C(17)	114·7 (6)
N(7)—C(8)—O(8)	122·2 (4)	C(15)—N(16)—C(20)	118·1 (5)
N(8)—C(8)—O(8)	123·0 (4)	C(17)—N(16)—C(20)	107·0 (6)
N(7)—C(8)—N(8)	114·8 (3)	C(21)—N(22)—C(23)	111·7 (4)
C(12)—O(12)—H(12)	103 (3)	C(21)—N(22)—C(26)	114·1 (4)
O(12)—H···N(22)	151 (5)	C(23)—N(22)—C(26)	105·3 (4)

C(2)—C(3)—O(3)—C(30)	10·5 (7)	O(8)—C(8)—N(8)—C(9)	−8·8 (6)
C(1)—C(6)—N(7)—C(8)	−56·1 (6)	N(7)—C(8)—N(8)—C(9)	171·1 (4)
C(6)—N(7)—C(8)—O(8)	11·0 (7)	C(8)—N(8)—C(9)—C(14)	38·6 (6)
C(6)—N(7)—C(8)—N(8)	−168·9 (4)	C(11)—C(12)—O(12)—H(12)	−18 (3)

plane orientation of the other 1-pyrrolidinylmethyl group which is characterized by a C(12)—C(13)—C(15)—N(16) torsion angle of 167·6 (5)° and which is thought to be more stable for compounds with an unprotonated N atom (Główka, Dargie & Codding, 1991); and (iii) an antiparallel orientation of the carbonyl group and the phenol O—H bond which places the carbonyl group on the same side of the molecule as the free (non-hydrogen-bonded) 1-pyrrolidinylmethyl moiety.

In addition, the relative orientation of the two phenyl rings in (4) is similar to that observed in the benzanilide fragments of (1), (2) and (3) rather than to the orientation found in the crystal structures of known *N,N'*-diphenylurea compounds. The angles between the least-squares planes calculated for the two phenyl rings are 38, 23, 57, 69 and 45° in (1), (2*a*), (2*b*), (3) and (4), respectively, while this angle is only 21° in the two independent molecules of *N,N'*-bis(3,4-dichlorophenyl)urea (Stanković & Andreetti, 1978) and 27° in *N,N'*-diphenylurea (Dannecker, Kopf & Rust, 1979). The two other *N,N'*-diarylurea structures described in the literature (Lapore, Lapore, Ganis & Goodman, 1975) cannot be compared with (4) because, in these structures, the two H atoms in the urea linkage are replaced by substituents which influence the urea conformation.

Since the orientations of the pyrrolidinyl rings and of the phenyl–linkage–phenyl fragment are similar the overall shape of (4) is analogous to those of the active agents (1), (2) and (3); also, the spatial arrangement of the three key recognition groups is similar. The recognition groups are defined by three points: (i) the N atom of the free (non-hydrogen-bonded) amine group; (ii) the center of the 4-substituted phenyl ring (Ph); and (iii) the O atom of the carbonyl group in the linkage region. The average Ph···N, Ph···O and N···O intramolecular distances in the active compounds are 8·3, 3·8 and 5·1 Å, respectively, while the analogous distances in the urea structure, (4), are 8·065 (5), 3·818 (3) and 4·405 (6) Å. Although these distances differ by as much as 0·7 Å for N···O separation, they are within the range found for active semirigid antiarrhythmic agents (Główka & Codding, 1987).

Since (4) has a similar shape and can be presumed to fit in the recognition site for type I antiarrhythmics, an alternative explanation of the inactivity of this compound must be sought. Comparison of the structures (1)–(4) suggests that the inactivity of compound (4) is due to the presence of the *p*-methoxy substituent in the lipophilic fragment of the molecule. This substituent may reduce the interaction of the phenyl ring with the hydrophobic pocket of the binding site in the Na channel of the protein.

The molecules of the title compound are linked into chains by intermolecular bifurcated hydrogen bonds between urea residues. The two N atoms of the urea each donate a proton to the same carbonyl O atom of a symmetry-related molecule. A similar molecular arrangement was found by Stanković & Andreetti (1978) in *N,N'*-bis(3,4-dichlorophenyl)urea and by Dannecker, Kopf & Rust (1979) in *N,N'*-diphenylurea, and was postulated by Deshapande, Meredith & Pasternak (1968) for all disubstituted symmetric ureas.

The authors thank Dr D. M. Stout for the sample of compound (4), and the Polish Ministry of National Education (project RP.II.10 to MLG), the Alberta Heritage Foundation for Medical Research (fellowship for MLG, scholarship to PWC) and the Medical Research Council of Canada (grant MA8087 to PWC) for financial support.

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