

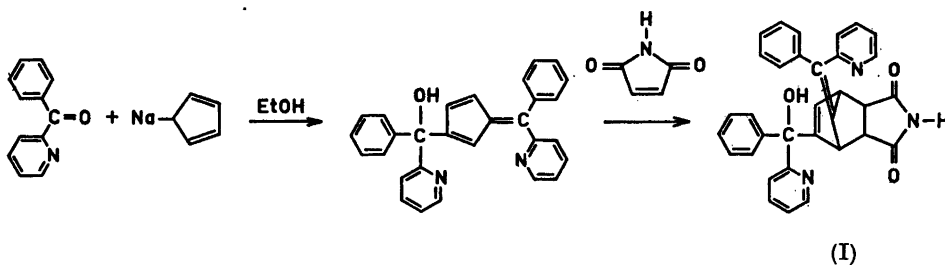
## Stereochemistry of an Inactive Racemate of Norbormide — A Selective Rat Toxicant

BO NILSSON

*Crystallography Group, Medical Research Council Unit for Molecular Structure Analysis,  
University of Göteborg, Göteborg, Sweden*

The stereochemistry of an inactive racemate of the selective rat toxicant norbormide has been determined by X-ray single crystal analysis of the *p*-bromobenzyl derivative of the agent. It was shown to be *cis, exo, erythro*-norbormide. The conventional over all *R* index was 0.121 for 1715 observed independent reflections.

Norbormide is the American Standard Common Name for the active ingredient of the RATicate rat toxicant. It consists of a mixture of stereoisomers of 5-( $\alpha$ -hydroxy- $\alpha$ -2-pyridylbenzyl)-7-( $\alpha$ -2-pyridylbenzylidene)-5-norbornene-2,3-dicarboximide,  $C_{33}H_{25}N_3O_3$ , (I). The synthesis was made by Mohrbacher *et al.*<sup>1,2</sup> using first the reaction of 2-benzoylpyridine with cyclopentadienyl sodium in alcohol to give, under certain conditions,  $\alpha$ -phenyl- $\alpha$ -[6-phenyl-6-(2-pyridyl)-2-fulvenyl]-2-pyridinemethanol which then readily reacts with maleimide to give norbormide:



Norbormide shows a unique selective toxicity to members of the genus *Rattus*.<sup>1,3</sup> The LD<sub>50</sub> dose (that is the dose which causes death to 50 % of the test animals) is about 10 mg per kg body weight for *Rattus norvegicus* and *Rattus hawaiiensis* and approximately 50 mg/kg for *Rattus rattus* when administered orally, whereas the value is roughly 2250 mg/kg for *Mus musculus*. Among non-rat

species the hamster is most susceptible, the LD<sub>50</sub> dose being 140 mg/kg, while all other animals tested, including several species of mammals, fish, and fowl, are still more resistant and as a rule not effected by the highest test dose, 1000 mg/kg orally.

The eight possible racemates of norbormide were isolated by Mohrbacher *et al.*<sup>4</sup> who gave the *cis-trans*, *endo-exo*, and *erythro-threo* definitions for them. As they are considerably different in toxicity<sup>1,5</sup> these authors made a detailed investigation of their stereochemistry, and managed to assign *cis-trans* and *endo-exo* configurations to all of them.<sup>4</sup> To allow complete structural assignments we have undertaken X-ray single crystal analyses of the *p*-bromobenzyl derivatives of the two racemates designated *cis,endo-2-V* and *cis,exo-2-X*, respectively, in the references cited above. The first of these two is a very active racemate (oral LD<sub>50</sub> dose = 2.1 mg/kg for female white rats<sup>5</sup>) and was shown to be *cis, endo, threo*-norbormide.<sup>6</sup> Its determination allowed *erythro-threo* assignments to all *endo* isomers.<sup>4</sup> The second racemate has very low activity (oral LD<sub>50</sub> dose >100 mg/kg for female white rats<sup>5</sup>). It has been subject to a structure analysis described here which will enable *erythro-threo* assignments to the *exo* isomers.

#### EXPERIMENTAL

Single crystals of the *p*-bromobenzyl derivative, C<sub>40</sub>H<sub>30</sub>N<sub>3</sub>O<sub>3</sub>Br, M.W. 680.6, suitable for X-ray analysis, were provided by McNeil Laboratories Inc. They are colourless, prismatic and triclinic, spacegroup *P*1, with the following cell dimensions obtained with CuK $\alpha$  radiation (1.5418 Å) and precession films, uncorrected for shrinkage:

$$\begin{array}{lll} a = 18.97 \pm 4 \text{ \AA}, & b = 9.11 \pm 3 \text{ \AA}, & c = 10.85 \pm 5 \text{ \AA} \\ \alpha = 60.6 \pm 2^\circ & \beta = 86.0 \pm 4^\circ & \gamma = 89.2 \pm 4^\circ \end{array}$$

The cell volume is  $1628 \pm 6 \text{ \AA}^3$  and there are two molecules per unit cell. A crystal of size  $0.25 \times 0.15 \times 0.18 \text{ mm}$ , was used to collect data for layers 0–9 around the *a* axis and layers 0–4 around the *b* axis. Weissenberg multiple film techniques were used throughout and in all 1762 independent reflections were registered. They were estimated visually and corrected for Lorentz and polarization factors but not for absorption.

The position of the bromine atom was derived from a sharpened<sup>7</sup> three-dimensional Patterson synthesis. A structure factors calculation — Fourier synthesis — peak scanning cycle using bromine phases revealed all heavier atoms except three carbons, which could all the same be included in the list of atoms as they were members of aromatic rings and the positions of their neighbours were revealed. The oxygens were included as such but the nitrogens were treated as carbons. Two cycles of block diagonal least squares refinement of positional and thermal parameters of all atoms lowered the conventional residual factor  $R = \sum ||F_o| - |F_c|| / \sum |F_o|$  from 0.30 to 0.21. The bromine was refined with anisotropic vibrational components, all other atoms were refined with isotropic *B* values. These *B* values turned out to be especially low for the atoms of the norbornene ring and for three more atoms, one of which ( $B = 0.7 \text{ \AA}^2$ ) was the imide nitrogen. The other two atoms belonged to two different aromatic rings and as their *B* values (0.7 and  $0.3 \text{ \AA}^2$ ) were markedly lower than those of the other aromatic ring atoms ( $1.2\text{--}4.2 \text{ \AA}^2$ ) they could be included as nitrogens. The correctness of this assignment was, however, checked: if they were carbon atoms, the necessary attached hydrogens would come inacceptably close to other atoms of the molecule. A new block diagonal least squares refinement cycle gave the nitrogens normal *B* values. All non-hydrogen atoms were now refined anisotropically for some cycles, decreasing the over all *R* value to 0.15. At this stage 47 strong low-order reflections were omitted as they were thought to suffer from extinction. The hydrogens in not easily predictable positions, that is the hydrogen

of the hydroxyl group and the hydrogens bonded to the  $sp^3$ -hybridized carbons of the norbornene nucleus, were then obtained from a difference Fourier synthesis and refined isotropically. The other hydrogens were included in calculated positions, the C—H distance chosen as 1.09 Å, and they were given isotropic  $B$  values approximately evaluated from the vibrations of the carbons to which they are bonded. They were not refined but recalculated at intervals.

Table 1. Fractional coordinates (with standard deviations) for non-hydrogen atoms.

	$x$	$y$	$z$
Br(1)	0.5454 (1)	-0.1899 (2)	-0.2258 (2)
O(1)	0.2624 (5)	0.4467 (11)	-0.4875 (8)
O(2)	0.3301 (4)	0.4077 (9)	-0.0742 (8)
O(3)	-0.0035 (4)	0.2254 (7)	0.0817 (7)
N(1)	0.3106 (4)	0.4288 (8)	-0.2870 (9)
N(2)	0.3026 (5)	-0.0857 (12)	0.0930 (10)
N(3)	0.0843 (4)	0.4437 (9)	0.1044 (8)
C(1)	0.1526 (7)	0.2113 (12)	-0.2278 (10)
C(2)	0.1871 (5)	0.3898 (11)	-0.2731 (9)
C(3)	0.2145 (6)	0.3629 (10)	-0.1259 (9)
C(4)	0.1904 (6)	0.1680 (10)	-0.0194 (10)
C(5)	0.1099 (5)	0.1692 (10)	-0.0042 (10)
C(6)	0.0871 (5)	0.1940 (12)	-0.1286 (10)
C(7)	0.2029 (5)	0.1028 (9)	-0.1187 (9)
C(8)	0.2555 (6)	0.4252 (11)	-0.3674 (11)
C(9)	0.2898 (7)	0.3931 (11)	-0.1516 (10)
C(10)	0.2402 (5)	-0.0232 (11)	-0.1195 (9)
C(11)	0.2872 (5)	-0.1331 (10)	-0.0025 (10)
C(12)	0.3461 (8)	-0.1919 (20)	0.1974 (13)
C(13)	0.3770 (7)	-0.3271 (15)	0.2022 (13)
C(14)	0.3643 (7)	-0.3813 (13)	0.1056 (13)
C(15)	0.3208 (7)	-0.2790 (13)	-0.0017 (12)
C(16)	0.2409 (6)	-0.0661 (10)	-0.2383 (9)
C(17)	0.1774 (7)	-0.1393 (13)	-0.2544 (10)
C(18)	0.1749 (6)	-0.1731 (11)	-0.3637 (11)
C(19)	0.2342 (7)	-0.1476 (13)	-0.4589 (14)
C(20)	0.2940 (8)	-0.0776 (15)	-0.4419 (13)
C(21)	0.2672 (6)	-0.0358 (13)	-0.3286 (11)
C(22)	0.0669 (6)	0.1634 (10)	0.1236 (9)
C(23)	0.0523 (5)	-0.0185 (11)	0.2493 (11)
C(24)	0.0016 (7)	-0.0431 (15)	0.3525 (13)
C(25)	-0.0102 (6)	-0.1995 (13)	0.4712 (10)
C(26)	0.0339 (7)	-0.3295 (11)	0.4975 (11)
C(27)	0.0888 (7)	-0.3043 (12)	0.3967 (11)
C(28)	0.1004 (6)	-0.1487 (12)	0.2725 (12)
C(29)	0.1048 (6)	0.2786 (12)	0.1652 (9)
C(30)	0.1583 (5)	0.2247 (11)	0.2566 (10)
C(31)	0.1930 (7)	0.3374 (12)	0.2825 (11)
C(32)	0.1735 (7)	0.4954 (14)	0.2197 (12)
C(33)	0.1149 (6)	0.5505 (11)	0.1345 (11)
C(34)	0.3841 (6)	0.4615 (14)	-0.3481 (12)
C(35)	0.4238 (6)	0.3017 (12)	-0.3235 (10)
C(36)	0.4285 (6)	0.1730 (13)	-0.1862 (13)
C(37)	0.4633 (7)	0.0246 (13)	-0.1560 (12)
C(38)	0.4963 (7)	0.0153 (13)	-0.2687 (11)
C(39)	0.4932 (6)	0.1381 (13)	-0.4051 (12)
C(40)	0.4546 (6)	0.2822 (12)	-0.4286 (12)

The refinement continued for some cycles till the shift/standard deviation quotients were small — average 0.2 for positional and 0.3 for vibrational parameters and in no case bigger than 1. A difference synthesis contained no peaks outside the range  $-0.7$  to  $+0.6$  eÅ<sup>-3</sup>. The final  $R$  index was 0.121, unobserved reflections not taken into account.

Table 2. Mean-square amplitude tensors. Allowance was made for anisotropic vibrations with

$$\exp -2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2lhc^*a^*U_{31} + 2hka^*b^*U_{12}).$$

The tensor elements (Å<sup>2</sup>) multiplied by 10<sup>3</sup> are given with standard deviations.

	U <sub>11</sub>	U <sub>22</sub>	U <sub>33</sub>	U <sub>23</sub>	U <sub>31</sub>	U <sub>12</sub>
Br(1)	137 (2)	63 (1)	84 (1)	-22 (1)	0 (1)	-47 (1)
O(1)	75 (8)	80 (6)	25 (5)	-25 (4)	3 (5)	-11 (5)
O(2)	26 (6)	45 (4)	57 (5)	-35 (4)	19 (4)	-23 (4)
O(3)	22 (5)	28 (4)	44 (4)	-24 (3)	-15 (4)	7 (3)
N(1)	8 (6)	11 (4)	51 (6)	-6 (4)	-1 (5)	-12 (4)
N(2)	38 (7)	60 (6)	32 (6)	-20 (5)	6 (5)	-11 (5)
N(3)	14 (6)	27 (4)	15 (5)	2 (3)	2 (4)	-4 (4)
C(1)	58 (10)	28 (5)	11 (5)	-10 (4)	-4 (6)	4 (6)
C(2)	11 (7)	24 (5)	20 (5)	-19 (4)	-9 (5)	5 (5)
C(3)	24 (8)	22 (5)	18 (5)	-20 (4)	7 (5)	-20 (5)
C(4)	15 (7)	7 (4)	33 (6)	-7 (4)	7 (5)	-10 (4)
C(5)	-12 (7)	19 (5)	44 (6)	-21 (4)	8 (5)	-31 (5)
C(6)	-1 (7)	45 (6)	15 (5)	-6 (4)	-11 (5)	-3 (5)
C(7)	11 (7)	8 (4)	15 (5)	-4 (4)	11 (5)	-19 (4)
C(8)	13 (8)	20 (5)	38 (6)	-11 (4)	28 (6)	-20 (5)
C(9)	69 (10)	27 (5)	19 (6)	-23 (5)	35 (6)	-37 (6)
C(10)	6 (7)	32 (5)	16 (5)	-6 (4)	-11 (5)	-18 (5)
C(11)	9 (8)	12 (5)	43 (7)	-13 (4)	4 (6)	-25 (5)
C(12)	51 (11)	131 (12)	29 (7)	-47 (8)	-18 (8)	25 (9)
C(13)	57 (10)	64 (8)	37 (8)	1 (6)	-3 (7)	60 (8)
C(14)	62 (10)	35 (6)	53 (8)	-23 (6)	-17 (7)	17 (6)
C(15)	45 (10)	31 (6)	45 (7)	-19 (5)	5 (7)	10 (6)
C(16)	32 (8)	24 (5)	3 (5)	-12 (4)	10 (5)	11 (5)
C(17)	54 (10)	43 (6)	12 (6)	-14 (5)	13 (6)	4 (6)
C(18)	11 (8)	21 (5)	46 (7)	-16 (5)	-6 (6)	-3 (5)
C(19)	62 (11)	36 (6)	92 (10)	-50 (7)	40 (8)	6 (7)
C(20)	64 (11)	55 (7)	44 (8)	-37 (6)	4 (7)	10 (7)
C(21)	26 (9)	41 (6)	28 (6)	-17 (5)	13 (6)	-41 (6)
C(22)	27 (8)	20 (5)	4 (5)	-7 (4)	11 (5)	-21 (5)
C(23)	2 (7)	29 (5)	39 (6)	-15 (5)	-2 (5)	-20 (5)
C(24)	17 (8)	72 (8)	53 (8)	-47 (7)	-3 (6)	-6 (6)
C(25)	35 (10)	50 (7)	7 (5)	1 (5)	25 (6)	-60 (6)
C(26)	65 (11)	20 (5)	43 (7)	-9 (5)	-44 (7)	-16 (6)
C(27)	71 (11)	27 (6)	22 (6)	-13 (5)	17 (6)	-13 (6)
C(28)	7 (8)	29 (5)	48 (7)	-20 (5)	13 (6)	-20 (5)
C(29)	33 (9)	39 (6)	2 (5)	-13 (4)	49 (5)	-38 (5)
C(30)	3 (7)	31 (5)	37 (6)	-30 (5)	-17 (5)	-4 (5)
C(31)	45 (9)	25 (5)	34 (6)	-15 (5)	-10 (6)	-20 (6)
C(32)	42 (10)	48 (7)	45 (7)	-33 (6)	8 (7)	-50 (6)
C(33)	43 (9)	17 (5)	48 (7)	-25 (5)	-10 (6)	-25 (5)
C(34)	11 (8)	62 (7)	50 (8)	-37 (6)	-6 (6)	-12 (6)
C(35)	25 (8)	33 (5)	19 (6)	-13 (4)	-1 (5)	-14 (5)
C(36)	5 (8)	35 (6)	66 (8)	-27 (6)	-3 (6)	-13 (5)
C(37)	58 (11)	35 (6)	29 (7)	3 (5)	10 (7)	-15 (6)
C(38)	57 (10)	40 (6)	25 (6)	-13 (5)	2 (7)	8 (6)
C(39)	-10 (7)	49 (7)	56 (8)	-25 (6)	15 (6)	-41 (5)
C(40)	37 (9)	29 (5)	47 (7)	-21 (5)	-10 (7)	16 (6)

The form-factor curves used are those given in *International Tables for X-ray Crystallography*, Vol. III, except the hydrogen curve which is the one calculated for bonded hydrogen atoms in the hydrogen molecule.<sup>8</sup> The quantity minimized by the least-squares programmes is  $\sum w (|F_o| - |F_c|)^2$ . The weight  $w$  is<sup>9</sup>

$$w = \frac{1}{1 + \left[ \frac{|F_o| - a}{b} \right]^2}$$

where the constants  $a$  and  $b$  are chosen so as to give an approximately equal value of the minimized quantity for reflections in different intensity regions, in this case 2.5  $|F_{\min}|$  and 1.7  $|F_{\min}|$ , respectively. The computer used is the Datasab D21 at this Institute with an integrated programme system developed here.<sup>10,11</sup>

**Table 3.** Fractional coordinates and isotropic temperature factors for the hydrogen atoms. The first appended number refers to the parent atom. The standard deviations are given for the five refined hydrogens.

	$x$	$y$	$z$	$B(\text{\AA}^2)$
H(34) <sup>a</sup>	-0.013 (3)	0.324 (6)	0.060 (5)	-3.1 (1.0)
H(11)	0.155 (4)	0.221 (8)	-0.351 (7)	0.4 (1.4)
H(21)	0.137 (6)	0.489 (13)	-0.315 (12)	4.6 (2.7)
H(31)	0.193 (4)	0.431 (8)	-0.108 (7)	-1.0 (1.4)
H(41)	0.222 (4)	0.099 (7)	0.088 (7)	-1.2 (1.3)
H(61)	0.032	0.200	-0.154	0.8
H(121)	0.356	-0.163	0.281	4.6
H(131)	0.413	-0.397	0.284	4.1
H(141)	0.387	-0.496	0.113	3.8
H(151)	0.312	-0.308	-0.086	3.1
H(171)	0.131	-0.168	-0.179	2.4
H(181)	0.126	-0.221	-0.378	1.8
H(191)	0.233	-0.182	-0.542	4.6
H(201)	0.340	-0.053	-0.515	4.2
H(211)	0.345	0.020	-0.318	2.4
H(241)	-0.030	0.062	0.342	3.2
H(251)	-0.056	-0.220	0.545	1.8
H(261)	0.026	-0.450	0.595	3.0
H(271)	0.124	-0.408	0.415	2.7
H(281)	0.145	-0.128	0.196	1.7
H(301)	0.173	0.093	0.308	1.2
H(311)	0.236	0.297	0.354	2.7
H(321)	0.203	0.587	0.234	3.6
H(331)	0.096	0.678	0.095	2.6
H(341)	0.384	0.546	-0.462	2.5
H(342)	0.412	0.522	-0.300	2.5
H(361)	0.404	0.188	-0.099	1.8
H(371)	0.464	-0.080	-0.048	3.1
H(391)	0.519	0.126	-0.493	2.4
H(401)	0.450	0.382	-0.538	2.9

<sup>a</sup> Refers to hydroxyl proton.

## RESULTS AND DISCUSSION

The list of observed and calculated structure factors is voluminous and therefore omitted here, but it may be obtained from this Institute. Positional and anisotropic vibrational parameters for non-hydrogen atoms are given in

Tables 1 and 2 and the hydrogen parameters are given in Table 3. Of the five refined hydrogens four have obtained negative  $B$  values during the refinement despite the fact that the scattering curve used is the one for molecularly bonded hydrogen. Our data are evidently not good enough for a reliable hydrogen refinement.

A spatial drawing of the molecule is shown in Fig. 1 and a schematic illustration of the stereochemistry is given in Fig. 2. The results conform with the structural analysis of the racemate<sup>4</sup> as regards the *cis, exo* assignment: the pyridyl ring C is on the same side of the C(7)=C(10) double bond as the carbinol group and the imide ring B is *exo* fused to the norbornene ring. In agreement with the *erythro-threo* definition by Mohrbacher *et al.* we have made the arbitrary

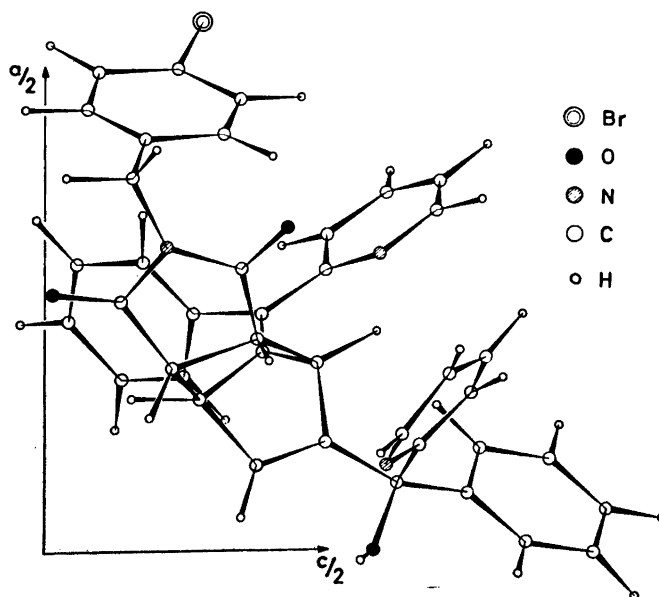


Fig. 1. Spatial drawing of the molecule.

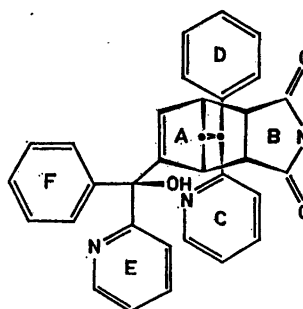


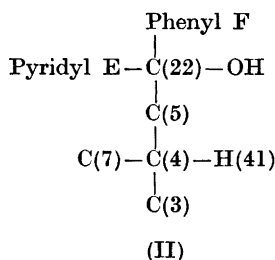
Fig. 2. Schematic illustration of the stereochemistry.



Table 4(b) cont.

N(1) — C(9) — H(31)	119.0	(2.3)	C(23) — C(22) — C(29)	113.4	(0.8)
C(3) — C(9) — H(31)	23.1	(2.4)	C(22) — C(23) — C(24)	118.7	(1.0)
C(7) — C(10) — C(11)	122.7	(1.0)	C(22) — C(23) — C(28)	120.6	(0.9)
C(7) — C(10) — C(16)	123.5	(0.8)	C(24) — C(23) — C(28)	119.3	(0.8)
C(11) — C(10) — C(16)	113.8	(0.9)	C(23) — C(24) — C(25)	121.1	(1.2)
N(2) — C(11) — C(10)	119.0	(0.9)	C(24) — C(25) — C(26)	121.3	(1.1)
N(2) — C(11) — C(15)	120.6	(0.9)	C(25) — C(26) — C(27)	118.3	(0.8)
N(2) — C(11) — C(15)	120.1	(1.1)	C(26) — C(27) — C(28)	121.6	(1.1)
N(2) — C(12) — C(13)	124.5	(1.6)	C(23) — C(28) — C(27)	117.8	(1.0)
C(12) — C(13) — C(14)	122.1	(1.2)	N(3) — C(29) — C(22)	116.9	(0.9)
C(13) — C(14) — C(15)	115.7	(1.2)	N(3) — C(29) — C(30)	119.9	(1.1)
C(11) — C(15) — C(14)	120.6	(1.3)	C(22) — C(29) — C(30)	123.1	(0.9)
C(10) — C(16) — C(17)	118.3	(0.9)	C(29) — C(30) — C(31)	120.0	(0.9)
C(10) — C(16) — C(21)	122.2	(1.0)	C(30) — C(31) — C(32)	118.7	(1.1)
C(17) — C(16) — C(21)	119.5	(1.1)	C(31) — C(32) — C(33)	122.1	(1.3)
C(16) — C(17) — C(18)	120.0	(1.0)	N(3) — C(33) — C(32)	118.5	(0.9)
C(17) — C(18) — C(19)	122.1	(1.2)	N(1) — C(34) — C(35)	114.0	(0.9)
C(18) — C(19) — C(20)	116.9	(1.5)	C(34) — C(35) — C(36)	118.6	(1.1)
C(19) — C(20) — C(21)	121.9	(1.2)	C(34) — C(35) — C(40)	123.2	(0.8)
C(16) — C(21) — C(20)	119.5	(1.1)	C(36) — C(35) — C(40)	118.2	(1.0)
O(3) — C(22) — C(5)	108.7	(0.8)	C(35) — C(36) — C(37)	121.8	(1.3)
O(3) — C(22) — C(23)	103.5	(0.7)	C(36) — C(37) — C(38)	117.1	(0.9)
O(3) — C(22) — C(29)	109.9	(0.8)	Br(1) — C(38) — C(37)	116.8	(0.7)
C(5) — C(22) — C(23)	113.5	(0.9)	C(37) — C(38) — C(39)	123.2	(1.1)
C(5) — C(22) — C(29)	107.7	(0.8)	C(38) — C(39) — C(40)	116.7	(1.2)
			C(35) — C(40) — C(39)	122.9	(0.9)

assignment that if the bond to the phenyl group F is in the plane of the C(5)=C(6) double bond then the *erythro-threo* configuration is determined by the relation of the hydrogen H(41) at C(4) to the hydroxyl group. The Fischer projection (II)



of this part of the molecule shows that these elements are *erythro* to each other, and the racemate is accordingly *cis, exo, erythro*-norbormide.

Bond distances and angles, atomic numbering and ring labelling are given in Fig. 3, and in Table 4 bond distances and angles are given with individual standard deviations calculated according to Ahmed and Cruickshank<sup>12</sup> and Darlow.<sup>13</sup> They agree within experimental error with those of the previously examined racemate 2-V in spite of the latter being of a different configuration. To facilitate a comparison of the norbornene-2,3-dicarboximide nuclei of the two racemates, the geometry of this part of the 2-V molecule is also shown



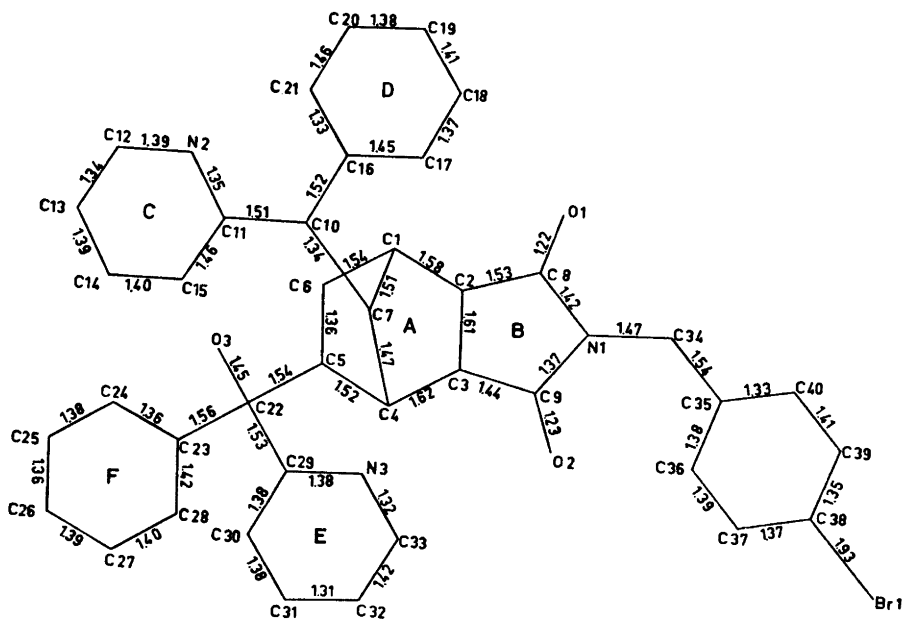


Fig. 3(a). Bond distances (Å), atomic numbering and ring labelling.

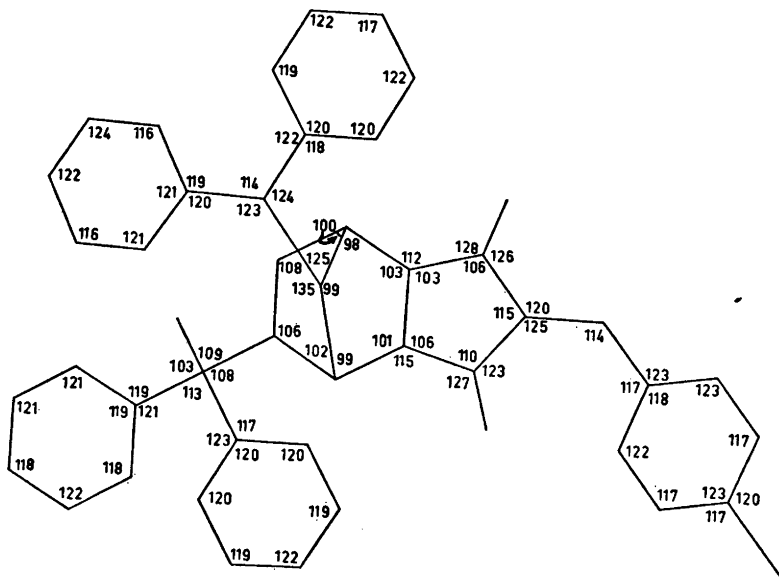


Fig. 3(b). Bond angles (degrees).



D which are attached to the bridge *via* the C(7)=C(10) double bond. Such steric interaction caused a twist around this double bond in racemate 2-V whereas the angles  $\angle A1 A3$  and  $\angle A2 A3$  were both  $123^\circ$ .

The imide ring B including the two keto oxygens is planar within  $0.06 \text{ \AA}$ . The nitrogen deviates by only  $0.01 \text{ \AA}$  from this plane whereas its deviation was  $0.1 \text{ \AA}$  in the racemate 2-V. The angle between plane B and plane A2 of the norbornene nucleus is  $119^\circ$ , somewhat smaller than in *endo* racemate 2-V where it is  $125^\circ$ , and between B and the *p*-bromobenzyl group plane  $91^\circ$ .

In the aromatic rings the average C—C distance is  $1.385 \text{ \AA}$  with a standard deviation of  $0.029 \text{ \AA}$ . The standard deviation was calculated as  $\sigma = \sqrt{\sum \Delta^2 / N}$  where  $\Delta$  is the deviation of each bond length from the arithmetic mean value and  $N$  is the number of bonds. The average C—N distance is  $1.359 \text{ \AA}$  with a maximum deviation of  $0.040 \text{ \AA}$ . The standard deviation from the aromatic ring planes for the nonhydrogen atoms in or directly bonded to these rings is  $0.025 \text{ \AA}$ , the maximum deviation being  $0.081 \text{ \AA}$  for C(23). The angles between the aromatic ring planes are:  $\angle CD = 72^\circ$ ,  $\angle CE = 31^\circ$ ,  $\angle CF = 67^\circ$ ,  $\angle DE = 82^\circ$ ,  $\angle DF = 84^\circ$ , and  $\angle EF = 85^\circ$ .

The molecular packing viewed down the *b* axis is shown in Fig. 5 where short intermolecular distances are also given. The shortest intermolecular

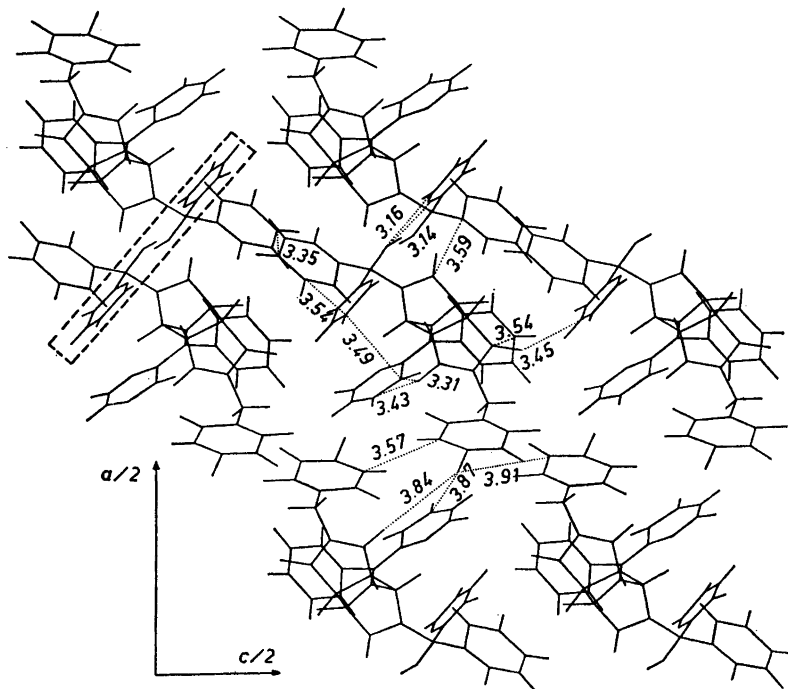


Fig. 5. The molecular packing viewed down the *b* axis. Intermolecular non-hydrogen atom distances up to  $3.6 \text{ \AA}$  are indicated together with the shortest contact distances to the bromine atom. The area enclosed by the hatched rectangle is shown in detail in Fig. 6.

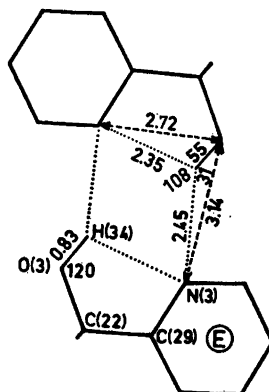


Fig. 6. The geometry within the plane of the probably bifurcated hydrogen bond, stretching from the hydroxyl oxygen to the ring E nitrogen of both the same molecule and the antipode. Distances in Å, angles in degrees.

Br—O distance is 3.84 Å ( $3\sigma = 0.02$  Å) and the shortest Br—C distance is 3.87 Å ( $3\sigma = 0.04$  Å). The molecules are held together by van der Waals' forces and, pairwise across centres of symmetry, by hydrogen bonds stretching from the hydroxyl oxygen of one molecule to the ring E nitrogen of the other. These hydrogen bonds are probably bifurcated, however, so that they branch even to the ring E nitrogen of the same molecule. The four atoms involved in such a bifurcated bond, namely O(3), H(34), N(3), and N(3') are approximately planar, the maximum deviation from the plane being 0.12 Å for H(34). A detailed study of the geometry within this plane is shown in Fig. 6. Hydrogen bonds supposed to be bifurcated are reported in a number of cases but have sometimes had to be revised after neutron diffraction determination of the proton position.<sup>15</sup> In the present case the correctness of the hydroxyl proton position is somewhat strengthened by the low isotropic  $B$  value of this atom. The intermolecular forces caused by these hydrogen bonds are rather weak as the donor-acceptor distance is as large as 3.14 Å ( $3\sigma = 0.03$  Å), not far from the value 3.3 Å which may be assumed to be the limiting H bond distance for the O—H...N bond.<sup>16</sup> In racemate 2-V only an intramolecular hydrogen bond was possible between the hydroxyl oxygen and the ring E nitrogen.

The molecular packing is strongly determined by the aromatic rings. There are no short intermolecular distances between atoms belonging to the norbornene-2,3-dicarboximide nuclei, and just a few between these and aromatic ring atoms. The aromatic rings mainly pack with perpendicular and, across centres of symmetry, parallel planes.

*Acknowledgements.* I am much indebted to professor S. Abrahamsson for his advice throughout the analysis, and to McNeil Laboratories Inc., Fort Washington, Pa., for good crystal samples. I also wish to thank Mr. G. Spuller for good technical assistance. Financial support has been granted from the *Swedish Natural Science and Medical Research Councils* and from the *U.S. Public Health Service* (GM 11653).

## REFERENCES

1. Roszkowski, A. P., Poos, G. I. and Mohrbacher, R. J. *Science* **144** (1964) 412.
2. Mohrbacher, R. J., Paragamian, V., Carson, E. L., Puma, B. M., Rasmussen, C. R., Meschino, J. A. and Poos, G. I. *J. Org. Chem.* **31** (1966) 2149.
3. Roszkowski, A. P. *J. Pharmacol. Exptl. Therap.* **149** (1965) 288.
4. Mohrbacher, R. J., Almond, H. R., Jr., Carson, E. L., Rosenau, J. D. and Poos, G. I. *J. Org. Chem.* **31** (1966) 2141.
5. Poos, G. I., Mohrbacher, R. J., Carson, E. L., Paragamian, V., Puma, B. M., Rasmussen, C. R. and Roszkowski, A. P. *J. Med. Chem.* **9** (1966) 537.
6. Abrahamsson, S. and Nilsson, B. *J. Org. Chem.* **31** (1966) 3631.
7. Abrahamsson, S. and Maslen, E. N. *Z. Krist.* **118** (1963) 1.
8. Stewart, R. F., Davidson, E. R. and Simpson, W. T. *J. Chem. Phys.* **42** (1965) 3175.
9. Mills, O. S. and Rollett, J. S. *Computing Methods and the Phase Problem in X-ray Crystal Analysis*, Pergamon, London 1960, p. 107.
10. Abrahamsson, S., Aleby, S., Larsson, K., Nilsson, B., Selin, K. and Westerdahl, A. *Acta Chem. Scand.* **19** (1965) 758.
11. Abrahamsson, S. *Arkiv Kemi* **25** (1966) 211.
12. Ahmed, F. R. and Cruickshank, D. W. J. *Acta Cryst.* **6** (1953) 385.
13. Darlow, S. F. *Acta Cryst.* **13** (1960) 683.
14. Sim, G. A. *J. Chem. Soc.* **1965** 5974.
15. Sikka, S. K. and Chidambaram, R. *Acta Cryst.* **23** (1967) 107.
16. Pimentel, G. C. and McClellan, A. L. *The Hydrogen Bond*, Freeman, San Francisco and London 1960, p. 293.

Received September 30, 1967.