Quantitative glpc study of the crude reaction product was conducted at 185° using column D. 3-Chloronortricyclene (45%) had a retention time of about 2 min and the β-chlorocarbamates (39%) had retention times of 16–19 min. The compounds were isolated by preparative glpc at 185° using a column 10 ft × 3/8 in. packed with 20% Carbowax on 60 mesh Anakrom ABS.

Preparation of Ethyl (N-2-Hydroxy-2-phenylethyl)carbamate. —A solution of ethyl (N-2-chloro-2-phenylethyl)carbamate (1.14 g, 0.005 mole) in 50% ethanol (40 ml) in a 100-ml flask was treated with a solution of silver nitrate (1.70 g, 0.010 mole) in 50% ethanol (20 ml), added in one portion. An immediate precipitate of silver chloride formed; the reaction mixture was stirred for 30 min. The silver chloride was separated by filtration (0.70 g, calcd 0.72 g). The filtrate was evaporated to dryness on a rotary evaporator and the residue was extracted with three 30-ml portions of ether. The ether extracts were dried over anhydrous sodium sulfate and the solvent was removed under vacuum. The residue was then taken up in 20% Et_2O–hexane solution (25 ml) and the solution was cooled in an ice bath. Colorless crystals separated which were collected and dried: mp 86–87° (lit.[8] mp 85°); yield 57%; infrared $\nu_{max}^{CHCl_3}$ 3500 (OH), 3450 (NH), 1700 (C=O), 1510 (amide II), 1230, and 700 cm^{-1}.

Stereochemistry of the Most Active Racemate of Norbormide. A Selective Rat Toxicant

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The stereochemistry of the most active of the eight possible racemates of the selective rat toxicant norbormide has been determined by X-ray single-crystal analysis of the *p*-bromobenzyl derivative. The conventional *R* index is 12.6% for the 2547 independent observed reflexions.

Norbormide is the common name for the mixture of stereoisomers of 5-(α-hydroxy-α-2-pyridylbenzyl)-7-(α-2-pyridylbenzylidene)-5-norbornene-2,3-dicarboximide ($C_{33}H_{25}N_3O_3$). It was shown to be a highly selective rat toxicant and a considerable difference in toxicity exists among the different isomers.[1] The eight possible racemates have been isolated and studied chemically by Mohrbacher, *et al.*[2] A three-dimensional, X-ray, single-crystal analysis was undertaken in order to determine in detail the stereochemistry of the most active of the racemates.

Experimental Section

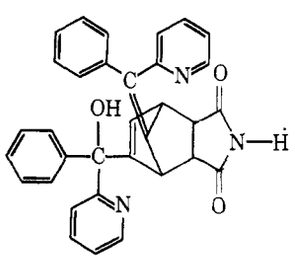
Single crystals of the *p*-bromobenzyl derivative ($C_{40}H_{30}N_3O_3$-Br) suitable for X-ray analysis were kindly provided by McNeil Laboratories Inc. They are triclinic with the following unit cell dimensions (precession photographs, Cu Kα radiation): a = 14.50 ± 0.07 A, b = 11.69 + 0.06 A, c = 10.46 ± 0.06 A, α = 103.07 ± 0.10°, β = 110.91 ± 0.10°, γ = 78.61 ± 0.10°.

Weissenberg photographs were taken for layers 0–8 about the a axis and 0–4 about the b axis. (Crystal size was 0.40 × 0.18 × 0.15 mm.[3]) The intensities were estimated visually and corrected for the Lorentz and polarization factors. No absorption correction was applied.

There are two molecules per unit cell. The racemic nature of the compound indicates that the space group is $P\bar{1}$. A statistical analysis of the distribution of intensities[3] also conforms with this space group.

The position of the bromine atom of the asymmetric unit was easily derived from a three-dimensional Patterson series calculated with coefficients sharpened to correspond to those from point atoms at rest.[4] As there is only one bromine atom in the large molecule, the heavy atom phased electron density series contained much spurious information. The carbon atoms of the *p*-bromobenzyl group could, however, be identified with certainty and were included in the next round of structure factors calculation. The situation in the second electron density series was much clearer and new parts of the molecule could be located. After four rounds of Fourier refinement the whole molecular skeleton had been derived.

At this stage it was obvious that the X-ray analysis fully confirmed the formula (I) of Mohrbacher, *et al.*,[2] for norbormide. The oxygen atoms and the imide nitrogen atom of the molecule were therefore easily identified. These positions were also confirmed from the peak heights in the electron density series. The remaining two nitrogen atoms were identified as follows. The molecular parameters were refined by block diagonal least-



I

squares treatment[5] assigning carbon atom form factor values to all still unidentified heavier atoms. Isotropic factors were refined for all atoms except the bromine atom which was given anisotropic temperature factors. After a few rounds the temperature factors of two atoms had dropped to values about 1.5 A^2 lower than those of the neighboring atoms. This indicates that these atoms represent the two pyridyl nitrogens and they were given nitrogen form factor values in the following structure factors calculations. In the next rounds of refinement the temperature factors of these atoms increased to normal values. The final refinement was performed using anisotropic temperature factors for the heavier atoms. All hydrogens except that of the hydroxyl group were included at their expected positions and with isotropic temperature factors corresponding to those of the parent atoms. These parameters were not varied. The progress of the refinement was checked at various stages by difference series calculations. One of these contained a peak (0.6 e A^{-3}) at a possible position for the hydroxyl hydrogen, which was also included in the structure factors calculation. The refinement was terminated when the *R* value for the 2547 observed independent reflexions was 12.6%. The maximum and mean values of the ratios between the shifts and the standard deviations were then 0.40 and 0.06, respectively, for positional and 0.33 and 0.09, respectively, for vibrational parameters.

The calculations were performed on a Datasaab D21 computer using the integrated program system of Abrahamsson, *et al.*[6]

(1) A. P. Roszkowski, G. I. Poos, and R. J. Mohrbacher, *Science*, **144**, 412 (1964).

(2) R. J. Mohrbacher, H. R. Almond, Jr., E. L. Carson, J. D. Rosenau, and G. I. Poos, *J. Org. Chem.*, **31**, 2141 (1966).

(3) K. Larsson, *Arkiv Kemi*, **25**, 205 (1966).

(4) S. Abrahamsson and E. N. Maslen, *Z. Krist.*, **118**, 1 (1963).

(5) S. Abrahamsson, *Arkiv Kemi*, **25**, 211 (1966).

(6) S. Abrahamsson, S. Aleby, K. Larsson, B. Nilsson, K. Selin, and A. Westerdahl, *Acta Chem. Scand.*, **19**, 758 (1965).

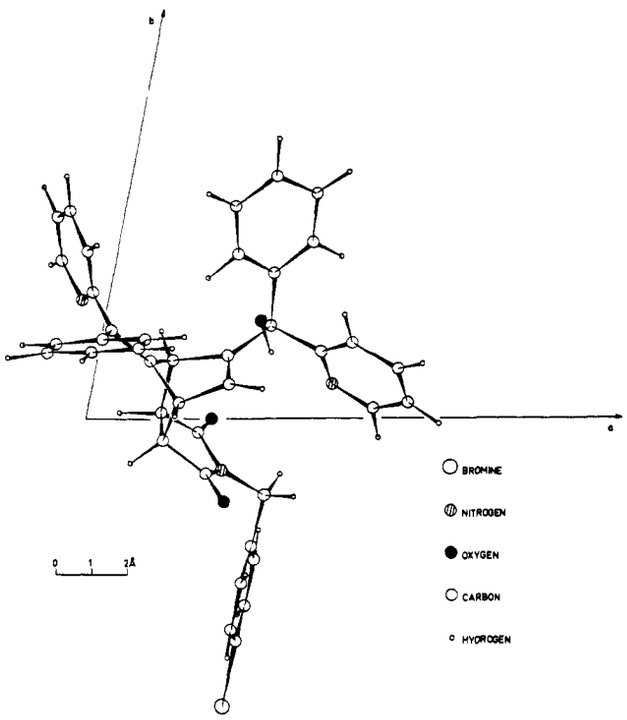


Figure 1.—Spacial drawing of the *p*-bromobenzyl derivative of norbormide.

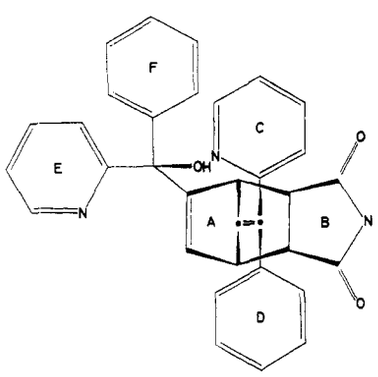


Figure 2.—Schematic illustration of the stereochemistry of the active form of norbormide.

The form factor values are those given in the International Tables for Crystallography (Vol. III, p 202). The least-squares program minimizes $\Sigma w(|F_a| - |F_c|)^2$ where the weight was[7]

$$w = \frac{1}{1 + \left\{\frac{|F_o| - 11\ |F_{min}|}{8\ |F_{min}|}\right\}^2}$$

Results and Discussion

The final parameters are given in Tables I and II. Lists of calculated and observed structure factors and anisotropic vibration parameters of the heavier atoms can be obtained from this laboratory.

A spacial drawing of the bromo derivative is given in Figure 1 and a schematic diagram of the stereochemistry is given in Figure 2. Bond distances and angles are given in Figure 3, tables of these data with standard deviations calculated according to Ahmed and Cruickshank[8] and Darlow[9] can be obtained from the authors.

(7) O. S. Mills and J. S. Rollett, "Computing Methods and the Phase Problem in X-Ray Crystal Analysis," Pergamon Press, Ltd., London, 1960, p 107.

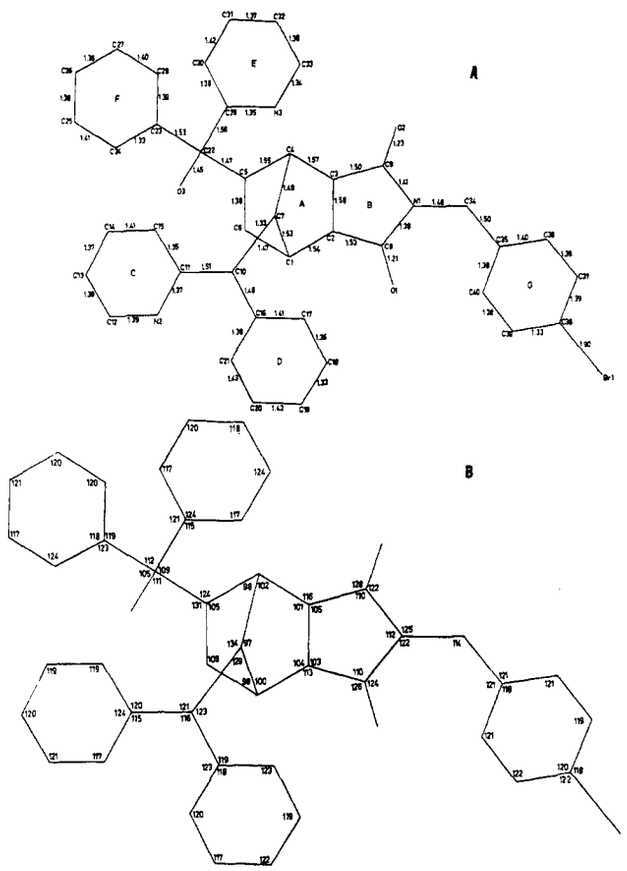


Figure 3.—Atomic numbering and bond distances (A); bond angles (B).

The results of the X-ray analysis are, as mentioned above, in complete agreement with the structural formula (I) of Mohrbacher, *et al.*[2] Their description of the most active isomer as *cis,endo*-norbormide is also confirmed by this analysis. The pyridyl ring C is thus on the same side of the C-7–C-10 double bond as the carbinol group and the imide ring B is *endo* fused to the norbornene ring.

The remaining stereochemical question concerning the configuration of the carbinol carbon atom C-22 in relation to the nearest asymmetric carbon atom C-4 is illustrated by a Fisher projection (II). If the bond

```
        Ph
        |
Py—C-22—OH
        |
        C-5
        |
H-41—C-4—C-7
        |
      —C-3—
        |
        II
```

to the phenyl group F is in the plane of the C-5–C-6 double bond the hydroxyl group is *threo* to the hydrogen atom (H-41) of C-4. This arbitrary assignment agrees with the *erythro,threo* definition of Mohrbacher, *et al.*[2] The active form should accordingly be described as *cis,endo,threo*-norbormide.

(8) F. R. Ahmed and D. W. J. Cruickshank, *Acta Cryst.*, **6**, 385 (1953).
(9) S. F. Darlow, *ibid.*, **13**, 683 (1960).

TABLE I

FRACTIONAL ATOMIC COORDINATES WITH STANDARD DEVIATIONS ($\times 10^4$) WITHIN BRACKETS FOR THE HEAVIER ATOMS OF THE STRUCTURE

	x	y	z
Br-1	0.3658 (1)	0.2950 (1)	0.2019 (2)
O-1	0.2999 (6)	0.7957 (5)	0.7267 (6)
O-2	0.2435 (5)	0.9982 (5)	0.3768 (6)
O-3	0.3040 (5)	1.2346 (5)	0.5546 (5)
N-1	0.2834 (6)	0.8725 (5)	0.5364 (7)
N-2	−0.0522 (7)	1.2938 (7)	0.5500 (8)
N-3	0.4626 (6)	1.0825 (6)	0.6592 (7)
C-1	0.1736 (7)	1.0390 (6)	0.7784 (8)
C-2	0.1593 (8)	0.9452 (6)	0.6456 (8)
C-3	0.1423 (8)	1.0185 (6)	0.5278 (7)
C-4	0.1472 (7)	1.1475 (6)	0.6128 (8)
C-5	0.2556 (7)	1.1549 (6)	0.7111 (8)
C-6	0.2672 (7)	1.0872 (6)	0.8091 (7)
C-7	0.1018 (8)	1.1433 (6)	0.7188 (8)
C-8	0.2546 (8)	0.8616 (6)	0.6450 (8)
C-9	0.2253 (7)	0.9679 (7)	0.4699 (8)
C-10	0.0291 (7)	1.2107 (7)	0.7617 (8)
C-11	−0.0324 (8)	1.3123 (7)	0.6905 (9)
C-12	−0.1019 (10)	1.3894 (10)	0.4827 (14)
C-13	−0.1268 (12)	1.4989 (11)	0.5568 (18)
C-14	−0.1053 (11)	1.5132 (9)	0.6973 (15)
C-15	−0.0576 (9)	1.4162 (8)	0.7656 (11)
C-16	0.0085 (8)	1.1972 (7)	0.8855 (9)
C-17	0.0879 (8)	1.1921 (8)	1.0121 (10)
C-18	0.0762 (12)	1.1751 (9)	1.1298 (13)
C-19	−0.0136 (16)	1.1609 (10)	1.1267 (16)
C-20	−0.0990 (12)	1.1660 (10)	1.0044 (16)
C-21	−0.0845 (10)	1.1836 (9)	0.8820 (12)
C-22	0.3233 (7)	1.2270 (6)	0.6986 (7)
C-23	0.3114 (7)	1.3555 (6)	0.7709 (7)
C-24	0.2353 (8)	1.4018 (7)	0.8167 (9)
C-25	0.2177 (9)	1.5223 (8)	0.8733 (10)
C-26	0.2852 (9)	1.5945 (7)	0.8812 (9)
C-27	0.3651 (9)	1.5502 (7)	0.8379 (10)
C-28	0.3771 (8)	1.4304 (7)	0.7779 (9)
C-29	0.4325 (7)	1.1657 (6)	0.7533 (8)
C-30	0.4883 (8)	1.1886 (7)	0.8923 (8)
C-31	0.5832 (8)	1.1209 (7)	0.9356 (9)
C-32	0.6155 (8)	1.0373 (7)	0.8409 (9)
C-33	0.5528 (8)	1.0215 (7)	0.7048 (10)
C-34	0.3765 (8)	0.8107 (7)	0.5167 (9)
C-35	0.3685 (8)	0.6864 (6)	0.4379 (8)
C-36	0.3708 (9)	0.6570 (7)	0.3012 (9)
C-37	0.3673 (9)	0.5415 (8)	0.2303 (9)
C-38	0.3660 (8)	0.4532 (8)	0.2991 (9)
C-39	0.3659 (9)	0.4807 (7)	0.4300 (11)
C-40	0.3671 (9)	0.5953 (7)	0.5010 (10)

The average values for the benzene–carbon bond distance and angle are 1.383 A and 120.2°, respectively. The aromatic C–N distance is 1.360 A and the angle at the pyridyl nitrogen is 116.8°. The bonds of the dicarboximide group agree very well with those for the same group of atoms in 1,3,7,9-tetramethyluric acid.[10] The angles, however, are appreciably different. As seen from Figure 3B the two oxygen atoms have been forced away from C-1 and C-4 by the close approaches of these atoms (Figure 4). The atoms of the imide ring are approximately planar the maximum deviation being 0.1 A for N-1. C-34 of the attached bromobenzyl group is also in the same plane while the bromobenzyl group lies at an angle of 123° to the imide ring.

(10) D. J. Sutor, *Acta. Cryst.*, **16**, 97 (1963).

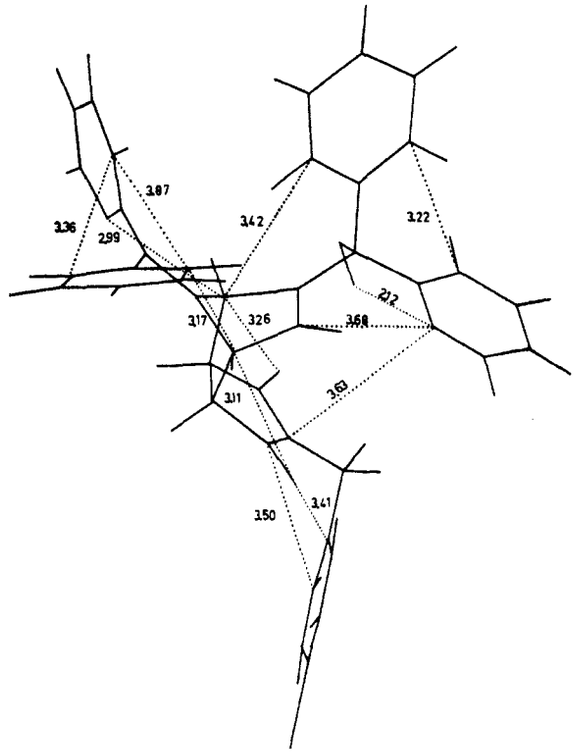


Figure 4.—Some intramolecular distances relevant for the molecular conformation.

TABLE II

FRACTIONAL COORDINATES AND ISOTROPIC TEMPERATURE FACTORS FOR THE HYDROGEN ATOMS. THE FIRST APPENDED NUMBER REFERS TO THE PARENT ATOM

	x	y	z	B (A²)
H-34[a]	0.3385	1.1607	0.5106	3.0
H-11	0.1699	1.0062	0.8660	2.1
H-21	0.1026	0.8925	0.6370	2.4
H-31	0.0764	1.0162	0.4355	2.2
H-41	0.1164	1.2155	0.5475	2.0
H-61	0.3342	1.0711	0.8962	1.9
H-121	−0.1212	1.3792	0.3712	5.8
H-131	−0.1621	1.5739	0.5028	7.2
H-141	−0.1240	1.5983	0.7572	5.9
H-151	−0.0418	1.4238	0.8767	4.3
H-171	0.1611	1.2026	1.0147	4.1
H-181	0.1407	1.1733	1.2253	6.3
H-191	−0.0187	1.1449	1.2216	7.7
H-201	−0.1717	1.1565	1.0064	7.6
H-211	−0.1470	1.1861	0.7868	4.8
H-241	0.1828	1.3437	0.8097	3.2
H-251	0.1534	1.5571	0.9091	3.8
H-261	0.2761	1.6885	0.9238	3.5
H-271	0.4202	1.6066	0.8477	3.7
H-281	0.4384	1.3953	0.7370	2.9
H-301	0.4616	1.2566	0.9655	3.1
H-311	0.6293	1.1346	1.0443	3.1
H-321	0.6886	0.9855	0.8718	3.3
H-331	0.5781	0.9540	0.6292	3.0
H-341	0.3996	0.8605	0.4596	3.2
H-342	0.4326	0.8069	0.6185	3.2
H-361	0.3762	0.7250	0.2500	3.4
H-371	0.3653	0.5207	0.1232	3.8
H-391	0.3627	0.4110	0.4818	3.6
H-401	0.3698	0.6141	0.6096	3.9

[a] Refers to hydroxyl proton.

The strain in the norbornene ring is most clearly illustrated by the large angles at the bridge atom (C-7) and the small ring angles at the C-5–C-6 double

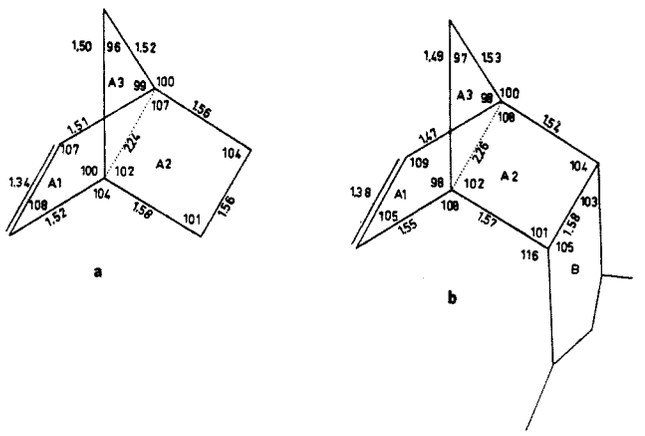


Figure 5.—Geometry of the norbornene nucleus in (a) *anti*-7-norbornenyl-*p*-bromobenzoate[11] and (b) norbormide: (a) ∠A1A2, 111°; ∠A1A3, 126°; (b) ∠A1A2, 114°; ∠A1A3, 123°; ∠A2B, 125°.

between C and D is 101°, whereas the angle between E and F is 108°.

A short intramolecular contact of 2.67 A exists between N-3 and O-3 which is indicative of a hydrogen bond. The hydroxyl hydrogen found from the difference series is also in a suitable position for such a bond (Figure 4). There are no other close nitrogen neighbors to the hydroxyl oxygen.

The molecular packing is shown in Figure 6 with some of the H–H contacts given. Layers containing only aromatic rings run parallel to the *ab* plane. Within these the rings pack as usual both with perpendicular planes and (around centers of symmetry) with parallel planes. These layers alternate with regions in which the central ring system of the molecule packs with the aromatic groups, but also here van der Waals interaction exists between aromatic rings at centers of symmetry.

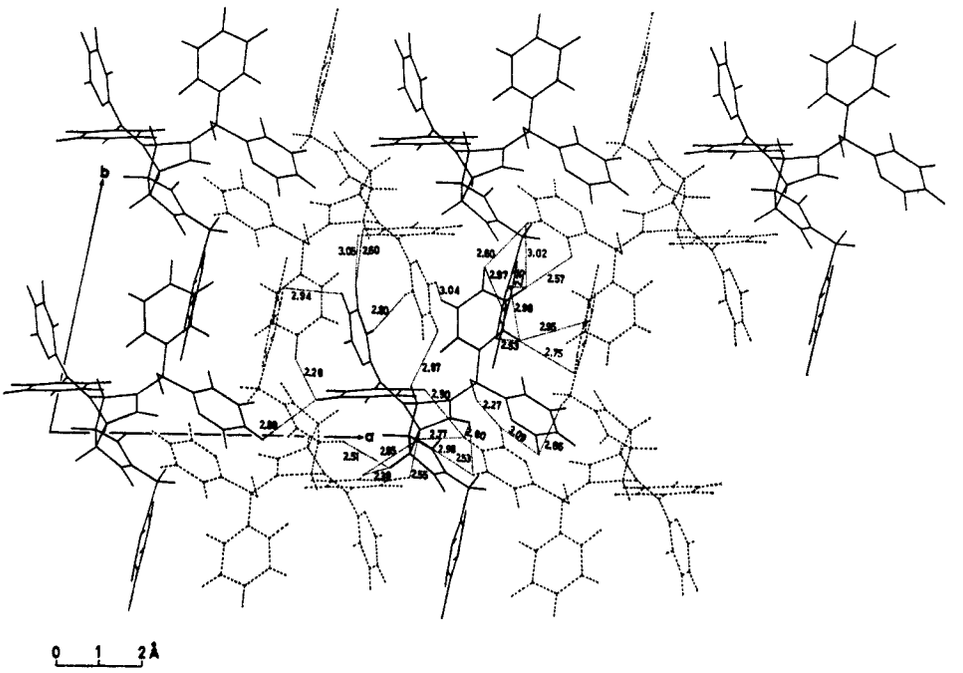


Figure 6.—Molecular packing. Dashed lines represent symmetry equivalent molecules. Some short intermolecular H–H contacts are indicated by dotted lines.

bond. The geometry of the norbormide nucleus is very similar to that found in *anti*-7-norbornenyl *p*-bromobenzoate[11] (Figure 5). The present analysis gives a larger value (1.38 A) for the double bond which is reasonable considering the distortion of the sp^2 hybridization.

As shown by Figure 4 there are strong steric interactions between rings C and D and the norbornene nucleus. There is a slight twist about the double bond, the angles between the planes defined by C-1, C-4, C-7, and C-10, C-11, C-16 being 8°. The angle

(11) A. C. MacDonald and J. Trotter, *Acta Cryst.*, **19**, 456 (1965).

A calculation of interatomic distances with hydrogen atoms attached to the two pyridyl nitrogens provided indirect evidence that our identification of these nitrogen atoms is correct since such hydrogen atoms come inacceptably close to other atoms.

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