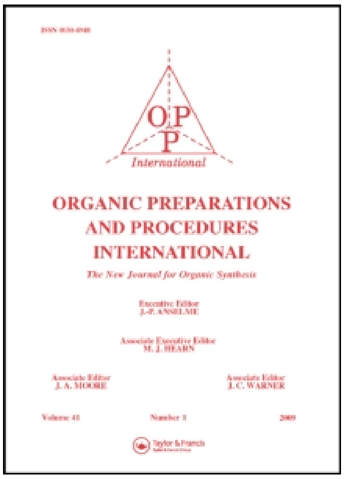

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SYNTHESIS OF *O*-PROTECTED MANDELAMIDE
AND ITS ELABORATION TO 5-HYDROXY-1,5-DIPHENYLHYDANTOIN

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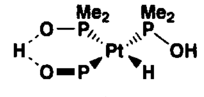
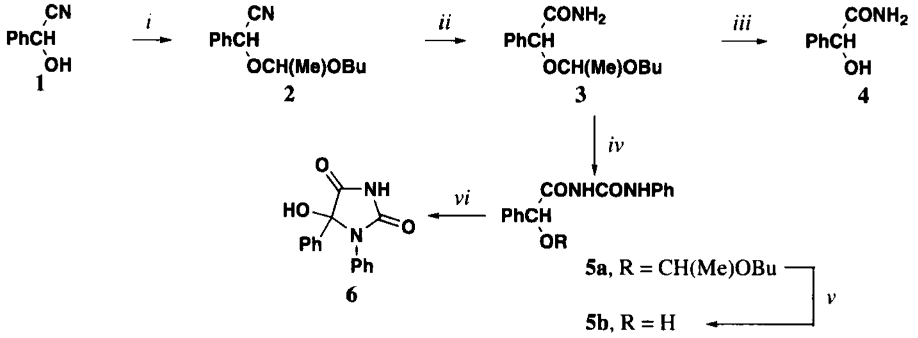
The hydrolysis of the nitrile group of cyanohydrins is usually carried out under acidic conditions and gives the acid rather than the amide. The hydrolysis of O-protected and unprotected cyanohydrins to the amides is not described in a recent review.[1] However, it may be achieved using borate ion catalysis,[2] involving the formation of a borate ester with the hydroxy group; thus it cannot be used with O-protected cyanohydrins. We recently reported[3] an extremely active platinum-containing catalyst **A** for the hydration of nitriles to amides, and its application to the synthesis of atenolol.[4] Since it was found that **A** does not catalyze the direct hydration of mandelonitrile **1** to mandelamide **4**, we decided to investigate whether an O-protected cyanohydrin could be converted to the amide (Scheme).



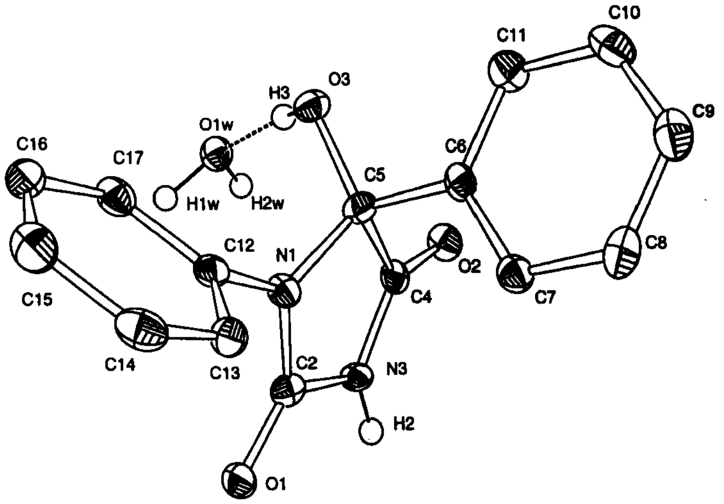
A

Mandelonitrile **1** was converted to the mixed acetal **2**[5] which was hydrated to **3** in 88% yield using **A** as catalyst; removal of the protecting group with dilute acid gave mandelamide **4**. Since some difficulties were encountered when we tried to catalyze the reaction between **3** and phenyl isocyanate, the thermal reaction of **3** with phenyl isocyanate was performed in refluxing toluene and gave the substituted urea **5a**, which was not isolated, and which on deprotection gave N-mandelyl-N'-phenylurea **5b**. The thermal reaction of amides with phenyl isocyanate was originally reported (without solvent) by Kühn[6] in 1884, and subsequently in toluene[7] or xylene[8] as solvent.



i) n-BuOCH=CH$_2$ *ii*) Catalyst A, H$_2$O, Δ *iii*) H$^+$ *iv*) PhNCO, Δ *v*) H$^+$ *vi*) CrO$_3$, H$^+$

N-Mandelyl-N'-phenylurea (**5b**), previously reported by Aspelund[9] and by Saettone and coworkers,[10] was cyclized by the latter group to 5-hydroxy-1,5-diphenylhydantoin, (**6**), by oxidation using chromium oxide in sulfuric acid. We repeated this oxidation and carried out an X-ray diffraction study of **6**, which has a characteristic carbonyl stretching frequency[10] at ~1775cm^{-1}, very similar to the parent ring system,[11] to provide unequivocal characterization. Several other examples of similar cyclisations involving the attack of an amide nitrogen on a carbonyl group have been reported.[12] The method described here could be extended by using other cyanohydrins to give a range of hydantoins, some of which may be of pharmaceutical value.[13,14] In common with other hydantoins, the heterocyclic ring of **6** is essentially planar.[15] The bond lengths within the ring are similar to those previously reported[16,17] with N1-C2 as the shortest, 1.352(4)Å and C4-C5 as the longest, 1.545(4) Å. The crystal contains one molecule of water for each molecule of **6**, and there is a hydrogen bond between the hydroxyl group and the oxygen of a water molecule O3-H3···O1w. The hydrogen atoms of the water molecule are hydrogen bonded to the carbonyl groups of two adjacent molecules, thus forming a chain through the lattice. Additionally the hydrogen on N3 is hydrogen bonded to the oxygen atom of another water molecule. It is interesting to note that although **6** was prepared using a procedure involving water, the crystallographic sample was recrystallised from toluene. Water is retained in the recrystallisation process, indicating that the water molecule is strongly bound to the hydantoin, as previously reported by Holmberg.[18]



Molecular structure of **6**. Selected bond lengths:
N1-C2, 1.352(4); C2-N3, 1.398(4), N3-C4,1.355(4); C4-C5, 1.545(4); C5-N1, 1.478(4);
C2-O1, 1.226(4); C4-O2, 1.216(4); O3-H3···O1w, 2.730(3) Å.
Hydrogen atoms on the phenyl rings have been omitted for clarity.

EXPERIMENTAL SECTION

Mps were determined using a Electrothermal melting point apparatus. The nitrile hydration catalyst **A** was prepared as previously described.[3] ^{1}H NMR spectra were recorded on a Bruker AM 360 (360.13 MHz) spectrometer and IR spectra were recorded as Nujol mulls using a Perkin Elmer 983G spectrometer. Elemental analyses were performed by the Analytical Laboratory, University College London.

α-(α-Butoxyethoxy)phenylacetonitrile (2) was prepared as described by Makosza, and Goetzen[5] using commercial mandelonitrile as staring material rather than benzaldehyde and sodium cyanide. Thus mandelonitrile (15 mL) was treated at 0° with conc. sulfuric acid (5 drops) and butyl vinyl ether (25 mL), and gave 18 g (62%) of product as a very pale yellow liquid (bp. 147° / 6Torr) somewhat more conveniently than the original method.

α-(α-Butoxyethoxy)phenylacetamide (3).- α-(α-Butoxyethoxy)phenylacetonitrile **2** (4.0 g, 17.1 mmol) was dissolved in ethanol (25 mL) and treated with water (10 mL) 0.25 mL of aqueous sodium hydroxide solution and the platinum hydrolysis catalyst (20 mg, 0.047 mmol) and heated under reflux for 46 h. The mixture was cooled, poured into brine and extracted with ether. After drying over magnesium sulfate and evaporation, the organic phase gave the amide product 3.8 g (88%). Recrystallisation from 80/100 petroleum ether gave white crystals, mp. 78.5-79.5° IR:1657 cm^{-1}. The ^{1}H NMR ($CDCl_3$) is complex because the product is a ~1:1 mixture of two diastereoisomers. The signal of the benzyl hydrogen appears as two singlets at $\delta = 5.0$ and 5.1, and the two quartets corresponding to the acetal proton appear at $\delta = 4.65$ and 4.8.

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.69; H, 8.27; N, 5.46

Mandelamide (4).- α-(α-Butoxyethoxy)phenylacetonitrile **3** (3.02 g, 12.9 mmol) was mixed with water (6 mL), ethanol (20 mL), the platinum hydrolysis catalyst **A**, (5 mg, 0.012 mmol) and five drops 2M sodium hydroxide and the mixture heated under reflux for 21 hours. After cooling to room temperature the mixture was acidified with 2M hydrochloric acid (1 mL) and the mixture stirred at room temperature for 1 h. Evaporation under reduced pressure gave an oil from which crystals of the product where obtained by addition of light petroleum and cooling. The product was recrystallised from toluene/ethanol to give white flakes of mandelamide (0.83 g, 42%), mp. 126-127°; *lit.*[2] 124°.

N-Mandelyl-N'-phenylurea (5b).- α-(α-Butoxyethoxy)phenylacetamide **3** (1.0 g, 3.98 mmol) was dissolved in dry toluene (20 mL) and treated with phenyl isocyanate (0.44 cm^3, 4.05 mmol) and the mixture heated under reflux for 24 h. The mixture was cooled and the toluene removed by evaporation. The residue was taken up in ethanol (20 mL) and treated with water (6 mL), dilute hydrochloric acid (2 mL) and heated under reflux for 30 min. The mixture was cooled, poured into water and extracted with ether. After drying over magnesium sulfate and evaporation the organic phase gave **5b** as a waxy solid (0.83g, 78%). The analytical sample was recrystallised twice from ethanol yielding white needles, mp 144-145°. *lit.*[9] 144-145°.

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N; 10.36. Found: C, 66.63; H, 5.30; N, 10.21

5-Hydroxy-1,5-diphenylhydantoin (5-hydroxy-1,5-diphenylimidazoline-2,4-dione) (6).- A solution of chromium trioxide was prepared by treating finely ground chromium trioxide (6.7g) with conc. sulfuric acid (6 mL) and adding water to a volume of 25 mL. The solid dissolved slowly on standing overnight. A solution of N-mandelyl-N'-phenylurea, **5b**, (0.20 g, 0.74 mmol) in acetone (8 mL) was mixed with 1.5 mL of the chromium trioxide solution. The mixture was heated to 50° for five minutes and then poured into water. Extraction with ether followed by drying over magnesium sulfate and evaporation gave **6**, (0.172 g, 87%), which was recrystallised from toluene (charcoal) to give white needles, mp. 181-182°. *lit.*[19] 182-183°. IR :1776 and 1712 cm^{-1}; *lit.*[10] 1779 and1709 cm^{-1}.

Crystals of **6** from toluene are a hydrate, $C_{15}H_{14}N_2O_4$, and monoclinic, *a* = 13.0592(14), *b* = 6.0875(5), *c* = 17.3444(17) Å, β = 99.276(6)°, V = 1360.8(2) Å^3. Space group $P2_1/c$, Z = 4. Data was collected at 100K using a Nonius ^{Kappa}CCD diffractometer and Mo Kα radiation, The structure was solved by direct methods using SHELXS-97 and refined using SHELXL-97, to give a final R = 0.0663. Selected bond lengths are given in the caption to the Figure. Data for **6** have been deposited at the Cambridge Crystallographic Data Centre, reference CCDC 163019.

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