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# AN ASYMMETRIC SIGMATROPIC REARRANGEMENT

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**Abstract**—Catalysis of the isomerization of the symmetrical adduct **1** by (+)-camphor-10-sulfonic acid in chloroform gave (−)-**2**, which was enriched by fractional crystallization techniques and purified by column chromatography. Values for the optical purity of this sample were obtained both by conversion into diastereomers and by the isotopic dilution method, and were in fair agreement with one another. They corresponded to an enantiomeric excess of 1·34% in the original synthesis.

In benzene as solvent the (+)-enantiomer was preferentially formed.

Asymmetric synthesis has been achieved for a wide variety of reaction types and has been the subject of a recent comprehensive text.[1] Prerequisite to it in its broadest, and currently accepted sense, is the formation of two diastereomeric transition states from common starting materials. The transition states lead directly to unequal amounts of either diastereomeric, or more rarely, enantiomeric products. Examples of the latter include the reaction of symmetric reagents with chiral solvents or catalysts which are released from the transition state when the latter goes to the optically active product. We now describe what we believe to be the first example of an asymmetric molecular rearrangement, arising from a symmetric precursor by catalysis with a chiral acid.†

The adduct **1**, which is achiral in its time averaged conformations, readily undergoes on heating a [3,3]-sigmatropic (hetero-Cope) rearrangement to the enantiomeric oxadiazines **2a** and **2b**, by way of enantiomeric transition states of which one, that leading to **2a**, may be reasonably represented by **3**.[4,5]

We have recently found that this isomerization is dramatically catalyzed by strong acids, e.g. hydrogen chloride, trifluoroacetic acid or sulfonic acids.[6] While the mechanism of this catalysis is not known it is certain that in an aprotic solvent the undissociated acid rather than protons must be involved. A reasonable representation of the geometry leading to the transition state is given by **4**, in which co-ordination of the acid hydrogen of HA to the basic amide oxygen initiates attack by the olefinic $\pi$-electrons‡; HA remains complexed in the transition state. If HA is achiral the transition states preceding **2a** and **2b** are enantiomeric, but if HA is chiral they are diastereomeric. Stereoselectivity must then exist in principle between the two pathways.

The optical rotation at 578 m$\mu$ and 22° of a solution in chloroform (3 ml) of **1** (3·3 mmol) and (+)-camphor-10-sulfonic acid (0·26 mmole, corresponding to an initial rotation of +0·185°) attained a final value of −0·52° in 15 min. The experiment was repeated on a larger scale (18·1 mmole), and the product worked up by extraction with $NaHCO_3$ aq which gave a nearly quantitative yield of optically active ([$\alpha$] = −3·41°) almost colourless oxadiazine of m.p. 126–8°, whose IR and NMR spectra were identical with those of racemic **2**, and which had a satisfactory elemental analysis. Crystallization from methanol gave oxadiazine with slight optical activity but a second crystallization gave racemic material (70%). The residues from both mother liquors were again crystallized from methanol, and from the filtrate a 10% yield of slightly discoloured **2** was obtained of [$\alpha$] = −46·2°.

Chromatography of this fraction on alumina-charcoal with benzene–ether (80:20) gave a colourless cut from the eluate of oxadiazine of [$\alpha$] = −96·7° in 4% overall yield§. This sample had

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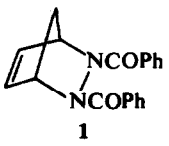
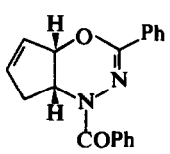
†A referee has drawn our attention to the asymmetric prototropic rearrangement of 1,3-diphenylpropyne to 1,3-diphenylallene by heterogeneous basic catalysis (on alumina mixed with brucine or quinine).[2] Cram *et al.*[3] have examined the rearrangement of 1,3,3-triphenylpropyne-3-d and found 85% intramolecularity in dimethyl sulfoxide-methanol containing triethylenediamine as base. They interpreted the mechanism as a concerted transfer of the proton, attached to the base, across the surface of the $\pi$ cloud. If this mechanism operates for the heterogeneous catalysis the latter can be regarded formally as an asymmetric 1,3-sigmatropic rearrangement involving 4$\pi$ electrons.

‡Whether the oxygen or the nitrogen in this particular system is the more basic, or whether indeed an open protonated structure, rather than **4**, is involved,[4] is conjectural but irrelevant to the main argument.

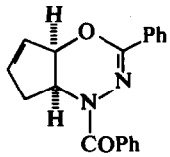
§The coloured fraction was obviously contaminated with by-products which were optically inactive or were more dextrotatory than **2**.



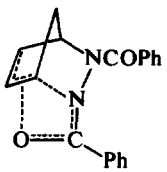

1



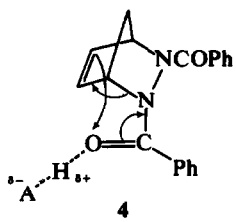

2a



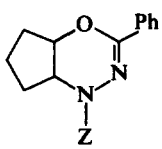

2b




3




4




5: Z = COPh
6: Z = H
7: Z = (R)-PhCH(OMe)CO

Table 1. Effect of temperature, concentration and solvent on asymmetric isomerization of 1

| Run | [catalyst] ($M$) | [1] ($M$) | $\frac{[\text{catalyst}]}{[1]}$ | Temp (°C) | Solvent | $[\alpha]^{22}_{578}$ deg.ml.dm.$^{-1}$.g$^{-1}$ [a] |
|---|---|---|---|---|---|---|
| i | 0·010 | 0·120 | 0·083 | 22 | $CHCl_3$ | −4·11 |
| ii | 0·010 | 0·120 | 0·083 | −25 | $CHCl_3$ | −3·34 |
| iii | 0·010 | 0·120 | 0·083 | 62 | $CHCl_3$ | −3·88 |
| iv | 0·089 | 1·100 | 0·083 | 22 | $CHCl_3$ | −3·90 |
| v | 0·004 | 0·180 | 0·022 | 22 | $CHCl_3$ | −2·70 |
| vi | 0·280 | 0·280 | 1·0 | 22 | $CHCl_3$ | +3·20[b] |
| vii | 0·010 | 0·120 | 0·083 | 22 | $C_6H_6$ | +7·53 |
| viii | 0·010 | 0·120 | 0·083 | 22 | 20% aq. MeOH | 0·00 |

[a] In $CHCl_3$.
[b] Much darkening and decomposition.

the expected spectra and elemental analysis. Its optical purity was determined* both by converting it into diastereomers and by the isotopic dilution technique.[9]

The optically enriched sample of 2 was quantitatively hydrogenated with di-imide to the dihydro derivative 5 which was debenzoylated, without further purification, to the base 6 by brief treatment with concentrated sulfuric acid.[4] Treatment of 6 in chloroform-d with the acid chloride of optically pure (−)-O-methylmandelic acid and pyridine gave the N-(O-methylmandelyl) derivative 7. The diastereomeric composition of 7 was determined[9] from its NMR spectrum by comparing the areas of the benzylic protons which were fully resolved at 100 MHz. The ratio of 2·22: 1 requires an optical purity of 38·0% for the N-methylmandelyl derivative. This gives a value of $[\alpha] = 254°$ for optically pure 2 and an enantiomeric excess of 1·34% in the original asymmetric rearrangement.†

For the isotopic dilution method a $^{14}C$ label was used in the carbonyl groups of 1, which was synthesized from benzoyl chloride-$^{14}C$ by the usual sequence through dibenzoylhydrazine and azodibenzoyl. The cyclopentadiene adduct was isomerized and the oxadiazine crystallized to constant specific activity. It was then mixed with the opti-

*A direct answer might be obtainable on the optically enriched sample by the use of one of the recently described chiral shift reagents.[7]

†We are, like others, assuming a linear relationship between optical activity and concentration, though a contra-indication has been noted.[10]

cally active oxadiazine of $[\alpha] = -96{\cdot}7°$, the mixture was recrystallized and the re-isolated material assayed for $^{14}C$. From the formula of Berson and Ben-Efraim,[11] a value of $[\alpha] = -270°$* was calculated for optically pure **2**.

Table 1 shows that the asymmetric catalysis in chloroform was neither especially sensitive to temperature (runs i–iii) nor to concentration of catalyst and adduct (runs i and iv), but was to the ratio of catalyst to adduct concentration. A low ratio reduced the enantiomeric purity (run v) while an equimolar ratio caused darkening and degradation of the substrate and formation of dextrorotatory products (run vi).

The solvent must play a crucial role in the transition state. The asymmetric catalysis in benzene (run vii) gave enrichment of the (+) enantiomer, in a higher enantiomeric purity, with $[\alpha] = +7{\cdot}53$ (chloroform). Reversal of stereoselectivity by solvent change has been noted by others.[1] In aqueous methanol as solvent (run viii), in which the catalyst would be the hydronium ion, the product was, as expected, racemic.

## EXPERIMENTAL

IR spectra were obtained on a Beckman IR-10 spectrometer and NMR spectra on a Varian T-60 or HA-100 spectrometer. A Zeiss photoelectric precision polarimeter was used for the measurement of optical rotations; all values are in chloroform at 578 mμ and 22°.

(+)-Camphor-10-sulfonic acid was purchased from Matheson, Coleman and Bell, (−)-mandelic acid from Eastman, and benzoic acid (carbonyl-$^{14}C$) from Amersham-Searle Corporation.

McKenzie's method[12] using silver oxide and MeI was used to prepare the (−)-O-methyl derivative of (−)-mandelic acid; $[\alpha]_{578}^{25} = -141°$ (EtOH) (lit.[12]. $[\alpha]_D^{13} = -150°$ (EtOH)).

*Acid chloride of* (−)-O-*methylmandelic acid.* The acid (3·0 g) was refluxed with freshly distilled $SOCl_2$ (5 ml) for ½ hr, and the excess then immediately fractionated off. The last traces were removed from the product by a stream of dry $N_2$.

Longer exposure of the product to the $SOCl_2$ or attempted distillation, caused decomposition, the odour of benzaldehyde being evident. Its optical purity was essentially complete, since its ester with (−)-menthol showed but a single methine resonance in its 60 MHz NMR spectrum.[9]

*Asymmetric isomerization of* 2,3-*dibenzoyl*-2,3-*diazabicyclo*[2.2.1]*hept*-5-*ene* (**1**) *to* cis-4-*benzoyl*-4,4a,5,7a-*tetrahydro*-2-*phenylcyclopenta*-1,3,4-*oxadiazine* (**2**)

(a) *Polarimetry experiment.* A soln of **1** (1·00 g, 3·3 mmole) in chloroform (1·5 ml) was added to a soln of (+)-camphor-10-sulfonic acid (0·061 g, 0·26 mmole) in chloroform (1·5 ml) and the whole shaken and transferred to a 1 dm polarimeter. The rotation was monitored at 578 mμ and 22°. It rapidly fell from a theoretical initial value of +0·185° to a minimum of −0·60° after 5 min and then slowly rose to a value of −0·52° after 15 min.

(b) *Preparative scale.* Solns of **1** (5·5 g, 18·1 mmole) in chloroform (92 ml) and the sulfonic acid (0·33 g, 1·42 mmole) in chloroform (52 ml) were mixed and allowed to stand for 15 min. The soln was then extracted with 2% $NaHCO_3$ aq (2 × 16 ml), washed with water (10 ml) and dried ($MgSO_4$). Evaporation gave the almost colourless optically active oxadiazine **2** (5·3 g), m.p. 126–8°; $[\alpha] = -3{\cdot}41°$; IR and NMR spectra identical with those of racemic **2**.[4] (Calcd. for $C_{19}H_{16}N_2O_2$: C, 75·0; H, 5·3; N, 9·2; O, 10·5. Found: C, 75·0; H, 5·2; N, 9·5; O, 10·8%).

(c) *Effect of temperature and concentration.* Chloroform solns of the adduct **1** and the sulfonic acid at the temps and in the concentrations shown in Table 1 were allowed to react to completion (checked polarimetrically). The solns were then worked up as described in (b) and the specific rotations determined.

(d) *Effect of solvent.* The isomerization was carried out both in benzene and in 20% aqueous MeOH on the scale shown in Table 1. When reaction was complete the solns were evaporated, taken up in chloroform and worked up as before. The benzene run gave oxadiazine of $[\alpha] = +7{\cdot}53$ and the aqueous MeOH run gave racemic oxadiazine.

*Optical enrichment of* **2**. A soln in hot MeOH (75 ml) of the sample of **2** (5·3 g) prepared in (b) deposited slightly optically active crystals on cooling. These were again crystallized from MeOH (30 ml) to give (±)-**2** (3·8 g), and the filtrates from both crystallizations were combined and evaporated. The residue was again crystallized from MeOH (15 ml) to give slightly active crystals of **2** (1·0 g) and from the mother liquor a discoloured solid residue (0·53 g) of $[\alpha] = -46{\cdot}2°$.

This residue was dissolved in chloroform (10 ml) and fed on to a 1½″ diameter column of superimposed layers of alumina/alumina–charcoal/alumina (2″ each) prepared in benzene–ether (4:1), which was also used for elution. After a small inactive yellow forerun, colourless strongly laevorotatory fractions were collected (222 mg in all, 4% overall yield) before coloured contaminants again appeared. This fraction had $[\alpha] = -96{\cdot}7°$ and the required IR and NMR spectra. (Found: C, 74·7; H, 5·8).

*Determination of optical purity*

(a) *Formation of diastereomers.* The chromatographically purified sample was reduced by di-imide (from hydrazine and hydrogen peroxide in ethanol) to the dihydro derivative **5**, which was then debenzoylated to the oily base **6** by brief treatment with conc $H_2SO_4$.[4] Both steps were quantitative. A portion of the base (75 mg, 0·37 mmole) and pyridine (35 mg, 0·44 mmole) in chloroform-d (10 ml) was warmed with (−)-O-methylmandelyl chloride (75 mg, 0·41 mmole) for 30 min. The soln was then extracted with 2% $NaHCO_3$ aq, water (10 ml), dried, and the volume reduced to 0·5 ml in a stream of $N_2$. The mixture of derivatives **7** was analyzed by NMR spectroscopy at 100 MHz which cleanly resolved the benzylic proton absorptions, occurring at 4·15τ in the major and 4·08τ in the minor diastereomer. These were recorded at slow sweep in both directions and the relative areas determined by photocopying, cutting out and weighing. The mean value of the ratio, 2·22 ± 0·05 : 1, corresponded to an optical purity of 38·0 ± 0·9% of the optically enriched (−) **2** and a specific rotation of $[\alpha] = -254 \pm 6°$ for optically pure oxadiazine.

The work up technique used in the purification of **7**

*At a 95% confidence level. Inspection of the formula shows that of the variables, count rate, rotation and weighing, errors in the first of these are by far the most critical at the count rate levels and the optical enrichment used here.

caused no fractionation of diastereomers. In a separate experiment the chloroform-d solution was concentrated without washing; NMR analysis gave the same ratio for the benzylic protons.

(b) *Isotopic dilution method.* Benzoyl chloride (25 ml) was heated for 2 hr at 100° with a sample of radioactive benzoic acid (carbonyl-$^{14}$C) (100 $\mu$C) and fractionated, its specific activity then being $7{\cdot}2 \times 10^8$ counts min$^{-1}$ mole$^{-1}$. Established procedures were used to convert it into dibenzoylhydrazine[13] and to oxidize the latter (N-bromosuccinimide) to azodibenzoyl (carbonyl-$^{14}$C).[5]

The labelled azo compound (1·2 g, 5·0 mmole) was shaken with cyclopentadiene (15 ml) for 10 min and the colourless suspension evaporated in a stream of $N_2$. The residual adduct **1** was washed with pentane, which induced crystallization, and was isomerized by refluxing it for 5 min in MeOH (25 ml) containing one drop of conc HCl. The labelled oxadiazine **2** was obtained on cooling and was crystallized three times to a m.p. of 129·5–130° and a constant specific activity of $7{\cdot}162 \times 10^8$ counts min$^{-1}$ mole$^{-1}$.

Portions of the radioactive and optically active oxadiazine were combined, recrystallized from MeOH and the crystals re-isolated. Their radioactivity and optical activity were measured. The specific rotation of optically pure (−)-**2** was calculated as $-270 \pm 9°$ by the formula of Berson and Bem-Efraim:[11]

$$A = \left\{ \frac{S_i n^2 \alpha^2 - S_o mn[\alpha][\alpha_i]}{S_i(m+n)^2 - S_o m(m+n)} \right\}^{1/2}$$

where $S_o$ and $S_i$ are the specific activities of the original and re-isolated label, m and n are the weights of labelled and optically active oxadiazine, and A, $[\alpha]$ and $[\alpha_i]$ are the specific rotations of pure enantiomer, added optically active oxadiazine and re-isolated oxadiazine.

The values for these were: $S_o = 7{\cdot}162 \times 10^8$, $S_i = 3{\cdot}926 \times 10^8$ count min$^{-1}$ mole$^{-1}$; $[\alpha] = -96{\cdot}7°$, $[\alpha_i] = -11{\cdot}9°$; m = 77·4, n = 66·7 mg.

The activities of the oxadiazine samples were obtained by dissolving constant total weights (75 mg) in 20 ml of scintillation fluid and measuring the counts on a Tri-Carb Scintillation Spectrometer. At least 50 determinations were made in each case and averaged, background count being subtracted. The scintillation fluid consisted of 2,5-diphenyloxazole (PPO, 2·8 g), *p*-bis-[2-(4-methyl-5-phenyloxazolyl)]benzene (dimethylPOPOP, 0·7 g) and Cab-O-Sil (30 g) dissolved in toluene (700 ml) and abs EtOH (300 ml).

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