Intramolecular Transfer of Chirality from Sulfur to Carbon: Dehydrocyclization of Optically Active *o*-Benzylsulfinylbenzoic Acid with Dicyclohexylcarbodiimide

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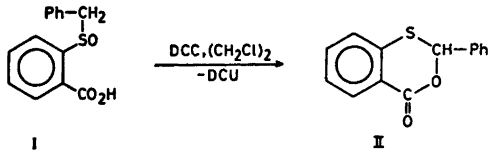
We have found that *o*-benzylsulfinylbenzoic acid (I) is readily converted to 2-phenyl-3,1-benzoxathian-4-one (II) by dicyclohexylcarbodiimide (DCC) in over 90 % yield. The reaction product is obviously the result of a Pummerer-type of rearrangement.[1] It was also found, as expected, that the transformation I→II could be performed using the classical Pummerer reagent acetic anhydride. The latter reaction was reported recently by Numata and Oae [2] after the initiation of our investigation. The lactone II was first described in 1961 as the product from a condensation of thiosalicylic acid with benzaldehyde.[3]



I II

Starting with optically active I we found that product II, after repeated chromatography on silica gel, possesses optical activity. A remarkable difference in the stereochemical course of the reaction, depending upon the nature of the Pummerer reagent and the solvent used, was observed, however. While the DCC-method gave II with an opposite sign of rotation to I, the situation with the use of acetic anhydride (AA) was found to be more complex. While a small excess of AA in benzene similarly gave II with opposite sign of rotation, the reverse was found with AA as both reagent and solvent. The results are given in Table 1.

These data imply that the DCC-reaction in 1,2-dichloroethane proceeds with the highest degree of stereoselectivity, while the reaction in acetic anhydride is associated with much more of racemization. This is not surprising, however, in view of the higher temperature needed in the latter case and the known.[4,5] ability of this medium to cause racemization of sulfoxides due to an acetoxy-interchange at the sulfur atom. Unfortunately, the optical yield of the DCC-reaction remains unestimated because the rotation of optically pure II is not yet known.

To the best of our knowledge, the only stereoselective Pummerer rearrangement so far reported is the reaction of 2,2-dialkyl-1,3-oxathiolan-5-one *S*-oxides with acetic anhydride in dichloromethane to give 4-acetoxy-2,2-dialkyl-1,3-oxathiolan-5-ones, where the 85–90 % stereoselectivity observed was interpreted in terms of an intramolecular migration of the acetoxy-group on one side of the ring.[6]

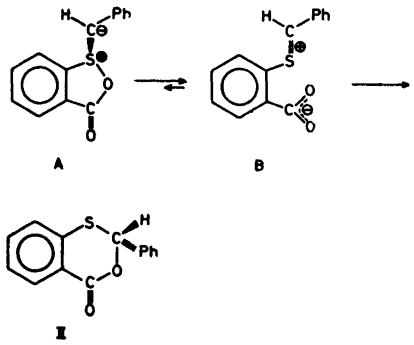
However, the presently described conversion of I to II appears to be the only reported Pummerer type of reaction in which an intramolecular transfer of chirality has occurred with the formation of an optically active product. Although a more detailed investigation of the mechanism is needed, some remarks and conclusions may nevertheless be made.

From Moffatt's investigations on the reactions of DMSO-DCC with carboxylic acids,[7] it was established that the necessary intermediate for the formation of an α-acyloxysulfide in this reaction is an acyloxysulfonium ylide. We feel that the key step responsible for the chirality-transfer is the opening of the cyclic ylide (A) and recombination to the ring-expanded product II, most probably *via* an ion pair (B) with restricted rotation around the partially double C–S-bond.

Stereoselectivity is thus induced with the formation of A as a consequence of the different reactivities of the diastereotopic protons [8] at the prochiral benzylic carbon atom. The ylide A should be a common intermediate in the DCC as well as the AA reaction, although with loss

Table 1.

I, $[\alpha]_D^{25}$	Pummerer reagent	Solvent	Temp. °C	II, $[\alpha]_D^{25}$	Yield %	Reaction time h
+451	DCC	$(CH_2Cl)_2$	25	−46.3	91	15
+451	DCC/H_3PO_4	THF	25	−7.9	89	2
+451	AA	C_6H_6	80	−30.2	91	5
+451	AA	AA	100	+17.3	95	2
+451	AA	AA NaOAc added	100	+8.2	98	2



of stereochemical integrity in more acidic media. The steps preceding A should follow the normal Pummerer mechanism, the difference from the normal route being due to internal nucleophilic participation by the carboxyl group present in the molecule.

Experimental. o-*Benzylthiobenzoic acid*, prepared by benzylation of thiosalicylic acid, was obtained in 85 % yield. M.p. 183 – 185 °C (lit.[9] m.p. 189 °C).

o-*Benzylsulfinylbenzoic acid (I).* o-Benzylthiobenzoic acid (15 g, 0.0615 mol) was dissolved in 600 ml of acetone-acetic acid (2:1) and oxidized with 5 % excess of a 15 % solution of peracetic acid in acetic acid. The reaction mixture was kept at 5 °C for 5 h and then at 25 °C for 20 h. After evaporation of the solvent, the product was recrystallized from acetone-petroleum ether. The yield was 13.2 g (82 %) of pure I, m.p. 164 – 165 °C (dec.).

Resolution of I. Racemic I (8.5 g, 0.0327 mol) was dissolved, together with brucine (dihydrate; 14.1 g, 0.0327 mol), in 350 ml of boiling acetone-ethyl acetate (6:1). The solution was left at 25 °C for 24 h, and the salt (11.1 g), which had crystallized, was isolated. The acid, liberated from a small amount of this salt, showed $[\alpha]_D^{25} = -373°$ (EtOH). The salt was treated with 300 ml of boiling acetone and, after cooling to room temperature, filtered by suction and dried. An amount of 8.6 g was obtained. A small crop of liberated acid showed an increased negative rotation, $[\alpha]_D^{25} = -444°$ (EtOH). This procedure was repeated, using 100 ml of acetone, which yielded 8.4 g of salt from which the acid, $[\alpha]_D^{25} = -443°$ (EtOH), was liberated. One recrystallization of the acid from acetone-ethanol gave 2.5 g of optically pure (–)-I, $[\alpha]_D^{25} = -449°$ (EtOH, $c = 0.5$). M.p. 165 – 166 °C (dec.).

The other enantiomer was liberated from the mother liquor from the first crystallization, $[\alpha]_D^{25} = +332°$ (EtOH). The optical purity was increased by two recrystallizations of the acid from acetone-ethanol. In this way (+)-I (2.5 g, m.p. 165 – 166 °C (dec.) with maximum rotation, $[\alpha]_D^{25} = +451°$, was obtained.

2-Phenyl-3,1-benzoxathian-4-one (II). A. I + DCC. DCC (0.103 g, 0.5 mmol) was dissolved in 5 ml of dry 1,2-dichloroethane, the solution cooled to 0 °C and finely powdered (racemic) I (0.130 g, 0.5 mmol) was added. The reaction mixture was kept for 1 h at 0 °C and for 14 h at 25 °C. Acetic acid (0.075 g, 1.25 mmol) was added and after stirring for 30 min the precipitated *N,N'*-dicyclohexylurea (DCU) was removed by filtration and the remaining filtrate evaporated to dryness. The product was then chromatographed on silica gel 60 (120 – 230 mesh) with chloroform as the eluent. Pure (racemic) II (0.110 g, 91 %) of m.p. 85.5 – 87.5 °C, (lit.[3] 83 – 84 °C, lit.[2] 90 – 91 °C) was obtained.

Starting with (+)-I this procedure yielded (–)-II, $[\alpha]_D^{25} = -46.3°$ (EtOH, $c = 1$), m.p. 88 – 90 °C, of unknown optical purity. The optical activity remained unchanged when (–)-I was rechromatographed with benzene as the eluent.

DCC (0.309 g, 1.5 mmol) in THF (3 ml) was added at 0 °C to a stirred solution of (+)-I (0.130 g, 0.5 mmol) and anhydrous orthophosphoric acid (0.025 g, 0.25 mmol) in THF (4 ml). Almost immediately crystalline DCU separated. After 30 min at 0 °C the mixture was kept at room temperature for 1.5 h. Oxalic acid (0.19 g, 1.5 mmol) was added and after 30 min the DCU was removed by filtration and the filtrate was evaporated. The residue was dissolved in benzene (10 ml), filtered to remove a small amount of DCU, and evaporated. The product was chromatographed as described above with chloroform as the eluent. 0.108 g (89 %) of II with m.p. 87 – 89 °C and $[\alpha]_D^{25} = -7.9°$ (EtOH, $c = 1$) was obtained.

B. I + AA. Treatment of I (0.130 g, 0.5 mmol) with an excess of acetic anhydride[2] (5 ml), evaporation and chromatographic purification of the product as described above, gave II in more than 90 % yields. By this method, however, (+)-I was converted to a product with $[\alpha]_D^{25} = +17.3°$ (EtOH, $c = 1$), m.p. 89 – 90 °C. The optical rotation was retained when the product was rechromatographed with benzene or ether as the eluents.

Addition of sodium acetate (0.1 g, 1.22 mmol) gave II with $[\alpha]_D^{25} = +8.2°$ (EtOH, $c = 1$), m.p. 89 – 90 °C.

When the reaction was performed in benzene (10 ml) with a 3:1 molar ratio of acetic anhydride (0.153 g, 1.5 mmol), the rotatory power of the chromatographed product was $[\alpha]_D^{25} = -30.2°$ (EtOH, $c = 1$) and m.p. 88 – 89.5 °C.

The optical rotations were determined at 589 nm with a Perkin-Elmer model 141 photoelectric polarimeter with the use of 1 ml microcells of 10 cm length.

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Electrolytic Generation of Nucleophiles. III.[1] Reductive Acetylation of Nitro and Nitroso Compunds

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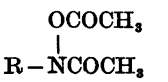
During the current investigations [2] of the reaction between electrophiles and electrolytically generated nucleophiles reductive acetylation of *N*-heterocyclic compounds was found useful.[3] Below is reported the analogous electrolysis of nitro and nitroso compounds in the presence of acetic anhydride to *N*,*O*-diacetyl-*N*-substituted hydroxylamines (I).



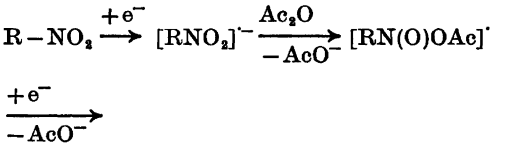
I

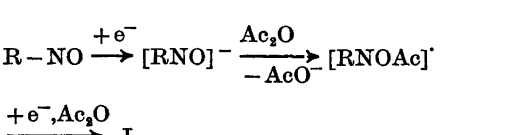
N,*O*-Diacetylhydroxylamines, which are of interest in chemical carcinogenesis,[4,5] mutagenesis,[6] and nucleic acid transformations,[7] have been obtained by acetylation of the corresponding hydroxylamines [8] or monoacetylated derivatives;[9] direct catalytic reduction of nitroarenes in the presence of acetic anhydride to I has only very limited success.[10]

Electrolytic reduction at a suitable potential of nitro or nitroso compounds in an aprotic medium, such as acetonitrile, containing an excess of acetic anhydride gives the desired compounds in one step in fair to good yield (47 – 87 % isolated yield). In Table 1 are given the yields from some electrolytic reductions and some of the properties of the isolated products.

The mechanism of the reaction has not been established; besides the scheme given below, where anion radicals or anions act as nucleophiles towards the electrophile acetic anhydride, there might be the possibility that the anion radicals acts as an electron donor towards acetic anhydride. Acetic anhydride could then cleave into an acetate ion and an acetyl radical, which then could couple with a substrate anion radical. The nucleophilic reaction mechanism is at present thought more likely than the radical coupling, mainly for the following two reasons: (a) *n*-values for the nitro and nitroso compounds are found close to 4 and 2, respectively, which is less likely for a radical process where acetyl radicals may react with other substrates than the nitro anion radicals, and (b) no "catalytic" increase [11] in the polarographic waveheight of *t*-nitrosobutane was obtained in the presence of acetic anhydride.

Nitroso compounds seem to be intermediates during the reductive acetylation of nitro compounds as judged from the fact that a slight blue colour, presumably due to the monomer *t*-nitrosobutane,[12] is observed during the electrolysis of *t*-nitrobutane. The same products have been isolated from the reductive acetylation of either nitro or nitroso compounds, and the following reaction scheme is thus suggested:





The same experimental procedure, which here has been applied to nitro and nitroso compounds and previously to heteroaromatic compounds,[3] has also been applied to the reductive acetyla-