Synthesis of 4-Bromophthalyl-D,L-glutamic Imide

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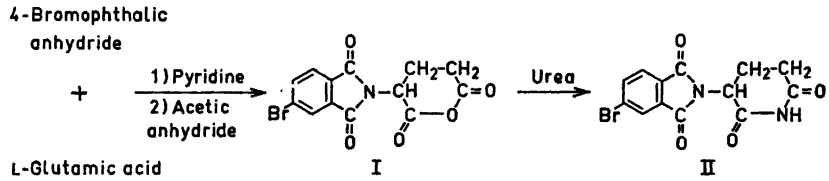
For an X-ray investigation of phthalyl-D,L-glutamic imide, also named "Thalidomide", the presence of a "heavy" atom in the molecule was desirable. From a chrystallographic point of view as well as from synthetic considerations an introduction of a bromine atom into the aromatic part of the molecular skeleton was preferred. The present paper gives the synthesis of 4-bromophthalyl-D,L-glutamic imide ("4-bromo-Thalidomide").

4-Bromophthalic anhydride [1] was condensed with L-glutamic acid to give 4-bromophthalyl-D,L-glutamic anhydride, (I), by analogy with the preparation of phthalyl-D,L-glutamic anhydride by King and Kidd.[2] A well-crystallizing reaction product, equivalent to $C_{13}H_8O_5NBr$, was isolated, m.p. 217.0–217.5°C. By using an excess of glutamic acid, a yield of 92 % was achieved. The essential 4-bromophthalic acid could be prepared in an extremely low yield, 7 % only, by the action of bromine and alkali on phthalic anhydride, following the procedure described by Waldmann.[1]



Conversion of the anhydride (I) to the corresponding imide (II) was effected by heating (I) with urea. Foregoing trials with a synthesized sample of phthalyl-D,L-glutamic anhydride [2] revealed that a temperature of 230°C was required for the reaction to take place, rather than the 170–180°C reported.[3] The final product (II) was produced in equal amounts (45 %) as its bromine-free analogue (when prepared on a millimole scale). Recrystallisation from several solvents under varying conditions failed to give crystals of the quality required. Sublimation of the product under reduced pressure at 180°C over several days afforded fine, transparent crystals, suitable for X-ray examinations; m.p. 303.0–303.5°C.

A marked change of spectral absorption in the ultraviolet and infrared regions followed the conversion of (I) → (II). In the *ultraviolet* (I) exhibited three absorption maxima at *ca.* 229 (ε 29 600), 248 (sh) (ε 11 700) and 302 mμ (ε 1890), respectively. In the imide (II) the lowest wave-length maxima remained unchanged at *ca.* 229 (ε *ca.* 42 000) and 249 mμ (ε *ca.* 16 000) with somewhat increased extinctions, whereas the highest wave-length maximum was displaced by about 14 mμ towards shorter wave-lengths, thus situated at *ca.* 288 mμ (ε *ca.* 2000). The extremely low solubility of (II) in methanol (in which (I) dissolved readily) left the extinction less accurate. Among the dissimilar features of the two compounds in the *infrared* region a band at about 3440 cm^{-1} appeared in (II), which may probably be assigned to the N–H stretching mode. No absorption in this region was observed in the anhydride compound (I). In the 950–1100 cm^{-1} region a change appeared in the imide spectrum, which indicated that an anhydride bonding was no more present. In the anhydride (I), on the other hand, the same bonds were found in this region as are present in glutaric anhydride,[4] although somewhat displaced.

Limited amounts of material left an elementary analysis of the final product undone. However, a micro analysis of the preceding reaction product (I), the spectroscopic features of (II), and preparation parallelly of the bromine-free "Thalidomide" (m.p. 272–273°C) under similar conditions counted for the correctness of the product stated.

X-Ray examinations of the compound have been undertaken by Furberg and Schiander Petersen at this institute.[5] They confirm the presence of 4-bromo-

phthalyl-glutamic imide in its racemic form, the space group being $P\bar{1}$.

Experimental. The *4-bromophthalic anhydride* used in the synthesis was prepared by bromination of phthalic anhydride, after Waldmann.[2] At the conditions given, however, 4-bromophthalic acid was produced in very poor yield (7 %), but a pure reaction product was isolated (m.p. 160–7°C), which on distillation [2] gave 4-bromophthalic anhydride.

4-Bromophthalyl-D,L-glutamic anhydride. A suspension of 4-bromophthalic anhydride (0.50 g; 2.2 mmole) and L-glutamic acid (0.50 g; 3.4 mmole) in dry pyridine [3] was heated under reflux at about 140°C. After 4.5 h all crystalline substance had disappeared, and the clear solution was concentrated under reduced pressure. To the residual red oil was added 3 ml of acetic anhydride and the mixture was heated at 150°C for 4–5 min. During evaporation of the solvent *in vacuo* the reaction product began to solidify, and crystallisation became complete by addition of limited amounts of dry ether to the cooled residue. Filtration, washing on the filter with ether and drying gave an almost colourless, well-crystallising product (0.684 g) of m.p. 209–210.5°C. By carrying out the condensation with glutamic acid in an excess of the latter, the out-put of the reaction was increased by about 20 % to 92 %. (A model reaction with the bromine-free analogue and L-glutamic acid gave 68.3 %; Ling and Kidd [3] reported 74 %). Recrystallisation three times from acetone/petrolether gave fine crystals of constant m.p. 217–217.5°C. (Found: C 46.60; H 2.48; N 4.03; Br 23.20. Calc. for $C_{13}H_8O_5NBr$: C 46.17; H 2.38; N 4.14; Br 23.63 %).

4-Bromophthalyl-D,L-glutamic imide. A mixture of finely divided 4-bromophthalyl-D,L-glutamic anhydride (0.154 g; 0.46 mmole) and urea (0.030 g; 0.50 mmole) was placed in an oil bath of 230°C for 10 min. A spontaneous evolution of gas ceased after a few minutes. The reddish-brown melt was cooled and extracted with portions of warm ethanol, which dissolved solid material very slowly. The last fraction was extracted by additional amounts of acetone, chloroform and ether. Concentration of the successive fractions yielded a crystalline material of increasing purity (total amount 0.069 g).

The product exhibited an extremely low solubility in most organic solvents. Recrystallisation of the fourth fraction (0.038 g) from acetone (50 ml) at −40°C and sublimation at 180°C/0.1 mm Hg during several days gave fine, transparent crystals, suitable for X-ray examinations; m.p. 303.0–303.5°C (without decomp.). Yield 45 %.

By treatment of the anhydride (I) with urea at less high temperatures [3] only minute amounts of reaction product could be isolated.

Under similar conditions 0.204 g of phthalyl-D,L-glutamic anhydride and 0.051 g of urea gave 0.072 g (45 %) of phthalyl-D,L-glutamic imide ("Thalidomide"), m.p. 272–273°C (269–271°C[3]).

The ultraviolet spectra were recorded on a Beckman DK-1 Recording Spectrometer, using methanol as a solvent.

The infrared spectra were recorded on a Beckman IR-5A Infrared Spectrometer and a Perkin-Elmer Infrared Spectrometer Model 21 in KBr pellets.

The melting points (uncorrected) were measured on a Hoover Capillary Melting Point Apparatus.

Acknowledgements. Thanks are due to Mag. sc. Else Augdahl, University of Oslo, for discussion of the infrared spectra.

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Received December 5, 1964.