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The Synthesis of Tetraiodophthalic-^{131}I Acid Morpholide

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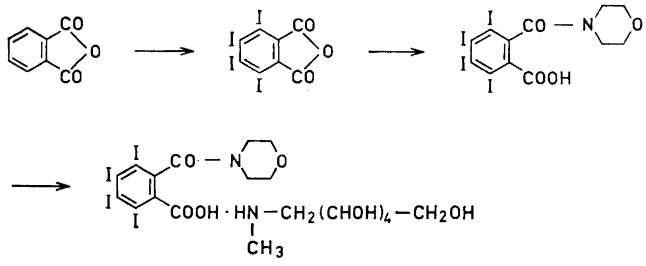
Submitted in honour of the sixtieth birthday of our teacher, Professor *Arne Fredga*

In connection with studies of tetraiodophthalic acid amides as potential X-ray diagnostic agents, the title substance was prepared.

During the last decades the evolution of iodine-containing contrast media has proceeded from compounds with one iodine atom at a benzene ring to compounds, containing three atoms. Since the absorption efficiency of a substance is depending upon its iodine content it seemed logical to investigate substances with even more iodine. However, this increase in iodine content must not destroy the possibilities of obtaining high concentrations of the substance in the tissue to be investigated.

The reaction of the easily accessible tetraiodophthalic anhydride with secondary amines gave a series of tetraiodophthalic acid amides. Many of these were difficult to purify by recrystallization and, in addition, they were easily hydrolyzed especially under acid conditions.

In our preliminary pharmacological tests it was rapidly found, that tetraiodophthalic acid morpholide had a comparatively low acute toxicity and, when given intravenously, gave a very high iodine content of the bile flow [1]. Unfortunately, the substance gave indications of renal damage [2] and could not be introduced as a contrast medium. The high iodine concentration in the bile justified, however, a further study of the elimination of the substance through



the liver. For this purpose tetraiodophthalic-^{131}I acid morpholide was synthesized.

The synthesis was performed according to the scheme given above.

The iodination of phthalic anhydride is described in Organic Syntheses [3]. After a slight modification this method proved suitable for our purpose. The iodinated anhydride was then converted into the morpholinium salt of the morpholide in a solution of dimethyl sulfoxide in toluene. During the reaction the salt was formed as an oil, which solidified and deposited on the walls of the reaction vessel. The mother liquor could then be removed easily. The acid was isolated and converted to a water solution of its N-methylglucamine salt.

The radioactivity, required for the biological investigation, was fairly high. Therefore it was necessary to perform the synthesis with special care. The iodination of phthalic anhydride was carried out in the equipment, shown in Fig. 1. The whole apparatus was built up on the back of a 12 mm thick plexiglas plate. Parts of the apparatus are fixed in movable holders. Thus, the reaction vessel C can be moved to a position F, allowing the transfer of the reaction mixture to the filter funnel E. Similarly, the dropping funnels K can be brought above the funnel E, facilitating the washing of the filtered crystals.

The remaining steps in the synthesis were performed in the equipment, shown in Fig. 2. This apparatus, too, was built up on the back of a 12 mm plexiglas plate. The equipped plate can be turned around the point of attachment (A) to the stand, thus enabling fluids to be decanted through the joint G.

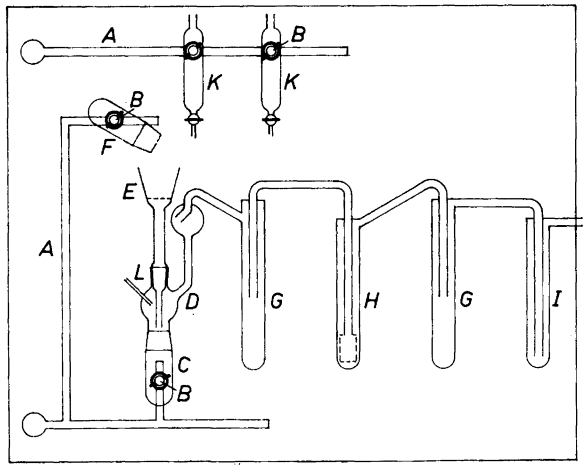


Fig. 1. A. Open cuttings in the plexiglas plate. B. Holders movable in the open cuttings. C. Reaction vessel ($Ø_{inter.}$ 25 mm, length 80 mm). D. Top of the reaction vessel with an air leak tube, an adapter with a splash head and a joint (L). E. Filter funnel. F. Reaction vessel in the upper position. G. Freezing traps. H. Washing bottle with concentrated H_2SO_4. I. Absorption tube with granulated PVC. K. Dropping funnels. L. Joint.

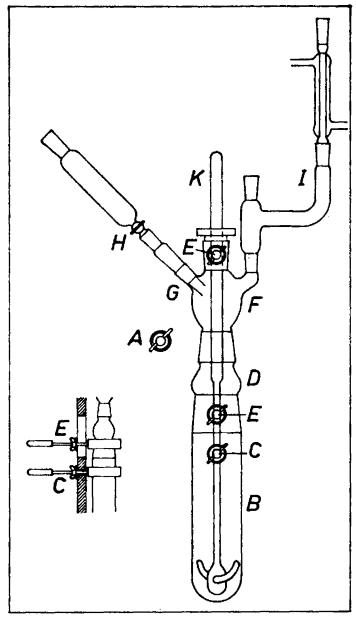


Fig. 2. A. Point of attachment with screw and wing-nut. B. Reaction vessel. C. Holder for reaction vessel. D. Reduction adapter. E. Holder for adapter. F. Three-necked top of reaction vessel. G. Joint. H. Dropping funnel. I. Adapter with reflux condenser.

During operation of the equipment a 5 cm thick lead shelter, fitted with a 14 cm thick lead glass window, was placed in front of the operator.

With the method described, a series of water solutions of the N-methylglucamine salt of tetraiodophthalic-^{131}I acid morpholide was prepared. In a typical experiment 35 ml of a 30 % water solution with a specific activity of 0.1 mC/ml were obtained.

EXPERIMENTAL

Tetraiodophthalic-^{131}I anhydride. 7 mC of iodine-131 (The Radiochemical Centre, Amersham, England) were put in the reaction vessel (C in Fig. 1) in the following way: The sealing of the ampoule was broken, and the ampoule was then inserted into the joint L through a teflon gasket. Most of the iodine fell down into the reaction vessel, which was chilled with dry ice. The upper end of the ampoule was warmed and the iodine on the walls sublimed downwards. The ampoule was then broken about 4 cm from the upper end and 6 ml of oleum (60 % SO_3) were added through the neck of the ampoule. The ice bath was removed and the ampoule replaced by a glass tube of 40 cm length. Through this tube were added 3.0 g (20 mmoles) of phthalic anhydride, 10.2 g (40 mmoles) of iodine and 4 ml of oleum. The tube was replaced by a glass stopper and a very slow stream of air was led through the apparatus by gentle suction. By means of an oil bath the temperature of the reaction vessel was raised to 65°C during an hour and then held there for a further hour. Then the temperature was raised to 170°C within 75 min, and the heating was continued for 30 min. The sublimed iodine was gathered in a gas trap, consisting of two freezing traps, a wash bottle, containing concentrated sulfuric acid, and a tube, filled with granulated polyvinyl chloride.

The heating was stopped and when the temperature was decreased to 125°C the oil bath was removed. When the reaction mixture was cool, the reaction vessel was replaced by an empty one and brought into position F. A filter funnel was fitted into the joint L and the air leak tube was replaced by a stopper. The labelled anhydride was filtered off by suction and washed repeatedly with concentrated sulfuric acid. The vessel, containing the filtrate, was exchanged and stoppered. The anhydride was then washed successively with water, a water solution of sodium pyrosulfite, water and acetone. The yellow needles were air-dried in the funnel over night.

Tetraiodophthalic-^{131}I acid morpholide. The anhydride was placed in the reaction vessel (Fig. 2), 150 ml of dry toluene and 6 ml of freshly distilled dimethyl sulfoxide were added and the mixture was refluxed in an oil bath at 115—120°C. Most of the anhydride dissolved. A solution of 3.0 ml (34 mmoles) of morpholine in 5 ml of toluene was added dropwise. The remaining anhydride rapidly dissolved and at the end of the addition the mixture became turbid. Stirring was continued, and, after about 10 min, the oil bath was removed. The oily salt deposited on the walls of the reaction vessel, and, when room temperature was reached, the mother liquor was removed by decantation. The salt was washed twice with 50 ml of petroleum ether.

140 ml of 95 % ethanol were added and the salt dissolved by heating under reflux on a water bath. The solution was slightly cooled, and 2.2 ml of 8 M methanolic hydrogen chloride were added while stirring vigorously. In a few minutes tetraiodophthalic acid morpholide began to crystallize.

After an hour the acid was filtered off, washed with 300 ml of cold water and air-dried. Yield 10.3 g (69 %). (Found: Equiv. wt. 742. Calc. for $C_{12}H_9I_4NO_4$: 739. An inactive tetraiodophthalic acid morpholide had the following data: Equiv. wt. 744; C 19.8; H 1.3; I 68.7; N 1.9. Calc. for $C_{12}H_9I_4NO_4$: C 19.5; H 1.2; I 68.7; N 1.9.)

N-Methylglucamine salt of tetraiodophthalic-^{131}I acid morpholide. 10.3 g (14 mmoles) of the acid and 2.7 g (14 mmoles) of N-methylglucamine were dissolved in 26 ml of distilled water in a 75 ml reaction vessel of the type, shown in Fig. 2. The solution, which contained 500 mg salt per ml, had a specific activity of 0.15 mC/ml.

REFERENCES

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