Synthesis of Some Dialkyl Esters of *m*-Nitrobenzenephosphonic Acid

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The dimethyl, di-*n*-propyl, diisopropyl, di-*n*-butyl, and diisobutyl esters of *m*-nitrobenzenephosphonic acid were synthesized for pharmacological screening. Two of the derivatives displayed some anticancer activity.

IT HAS BEEN shown that *m*-nitrobenzenephosphonic acid has *in vitro* antibacterial activity (1) and possesses the ability to immobilize *T. pallidum* (2). These cytotoxic properties, accompanied by low toxicity, prompted the synthesis of dialkyl esters of the acid for investigation as chemotherapeutic agents.

The only simple dialkyl ester of *m*-nitrobenzenephosphonic acid which has been reported is the diethyl derivative (3). The compounds reported in this paper were synthesized by the same procedure, except that a higher temperature was maintained during esterification.

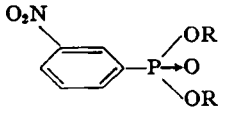
Preliminary pharmacological testing[1] of these compounds indicated that compounds II and III were toxic when tested against carcinoma 585 at a concentration of 200 mg./Kg.

EXPERIMENTAL

m-Nitrobenzenephosphonic acid was prepared according to the method of Kosolapoff (4) and converted to the dichloride by the procedure described by Freedman and Jaffe (3). These latter investigators esterified *m*-nitrobenzenephosphonic acid under conditions similar to those prescribed by Toy (5), whereby a pressure of less that 30 mm. and a temperature of not substantially over 30° were maintained during the alcohol addition. We found the use of an increased temperature during esterification more satisfactory for the synthesis of the higher homolog esters.

Preparation of Dialkyl m-Nitrobenzenephosphonates.—*m*-Nitrobenzenephosphonic acid (0.089 mole) and phosphorus pentachloride (0.187 mole) were intimately mixed in a 250-ml. three-necked flask with a glass stirring rod. The powders partially liquified with evolution of heat, and the flask was gently heated until no solid particles remained. The flask was immediately equipped with a thermometer, an outlet to a water aspirator, and an air leak. Both the air leak and outlet were protected with drying tubes. Vacuum from the water aspirator was applied (approx. 10 mm.), and the flask was gradually heated to 90° until the excess phosphorus pentachloride and most of the phosphorus oxychloride formed in the reaction were removed. Carbon tetrachloride (20 ml.) was added to the reaction mixture and the flask equipped with a dropping funnel, thermometer, and reflux condenser with an outlet to a water aspirator. Vacuum was applied (approx. 10 mm.), and the appropriate alcohol was added dropwise. Heat was applied as needed to maintain a reflux temperature for 15 minutes. Following the alcohol addition, the condenser was replaced with a water aspirator outlet and the flask heated to 90° *in vacuo* to remove the carbon tetrachloride and excess alcohol. The residual liquid was cooled and washed with 50 ml. of water, 50 ml. of 10% sodium carbonate solution, and 50 ml. of water. Vacuum distillation of the organic layers gave the pale yellow products.

TABLE I.—DIALKYL *m*-NITROBENZENEPHOSPHONATES



No.	R	B.p., °C.[a]	Yield, %[b]	Anal. % C Calcd.	C Found	H Calcd.	H Found
I	Methyl	148–152/1 mm.	49	41.6	41.6	4.4	4.7
II	*n*-Propyl	161–164/1 mm.	39	50.2	49.9	6.3	6.5
III	Isopropyl	156–160/1 mm.	58	50.2	50.1	6.3	6.6
IV	*n*-Butyl	162–167/0.6 mm.	44	53.3	52.7	7.0	7.2
V	Isobutyl	161–163/0.6 mm.	62	53.3	52.8	7.0	7.2

[a] All boiling points are uncorrected. [b] Based on analytically pure compounds achieved by triple distillation.

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