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NN-DI-CHLOROETHYLAMINOBUTYRATES AND PREPARATION THEREOF

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1 Claim. (Cl. 260—518)

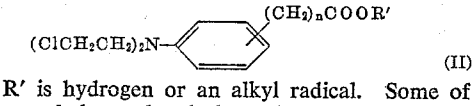
This invention relates to chemotherapeutic agents and has as an object to provide improved compounds having tumour growth inhibitory action.

Bis-chloroethylamines of the general formula

$$RN(CH_2CH_2Cl)_2 \qquad (I)$$

(in which R is an aliphatic residue) are well known as cytotoxic agents which are capable of arresting the growth of transplanted animal tumours (see Haddow, Brit. Med. Bull. (1947), 4, 422. One disadvantage of the compounds so far examined which limits their use as chemotherapeutic agents is the non-specificity of their action. They are toxic to all types of rapidly proliferating tissue, e.g. bone marrow, gonadal tissue and gastric mucosa, as well as towards neoplastic tissue.

With a view to obtaining substances which would exert a more selective chemical action we have investigated compounds of the general formula:

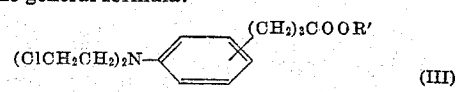


(II)

in which R' is hydrogen or an alkyl radical. Some of these compounds have already been described (see Ross, J.C.S. (1949), 183 and British Empire Cancer Campaign 29th Annual Report for the year 1951, page 8).

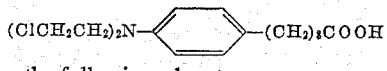
It has now been found according to this invention that compounds of the aforesaid general Formula II where $n=3$ and particularly the para compound in which R' is hydrogen, have outstanding tumour growth inhibitory action.

Accordingly, the present invention comprises compounds of the general formula:



(III)

in which R' is hydrogen or an alkyl group, preferably one containing not more than eight carbon atoms. The preferred compound is p-NN-di-(2-chloroethyl)-aminophenylbutyric acid of the formula:



and this has the following advantages:

(1) This compound exerts a more powerful inhibitory effect upon the growth of various experimental tumours in the rat and mouse than do higher and lower homologues of this series;

(2) At the dosage levels employed, the growth-inhibitory effect is not accompanied by serious depression of the bone-marrow such as may be induced by alkyl bis-2-chloroethylamines and many other aryl bis-2-chloroethylamines, so far tested;

(3) From the results available, the compound appears outstanding not only in the series to which it belongs, but in comparison with many other growth-inhibitory agents studied in the Royal Cancer Hospital over the past 15 years, in that it can induce complete suppression of the growth of the Walker rat carcinoma, and substantial retardation of the growth of certain mouse neoplasms, which hitherto had been regarded as markedly resistant to chemical treatment. Thus preliminary clinical investigations (over a period of nine months) indicate that p-NN-di-(2-chloroethyl)-aminophenylbutyric acid is as effective as triethylenemelamine and methyl-di-2-chloroethylamine in the treatment of certain lymphomas and chronic lymphatic leukaemias and that its use is more easily controlled and further that in therapeutic doses side effects have been negligible. Triethylenemelamine and 2-chloroethylamine are in current use for the treatment of lymphomas and chronic lymphatic leukaemias.

The present invention also includes a process for the manufacture of compounds of the general Formula III above wherein an alkyl NN-di-(2-hydroxyethyl)-aminophenylbutyrate is treated with phosphorus oxychloride to form an alkyl NN-di-(2-chloroethyl)-aminophenylbutyrate which is, if desired, converted by hydrolysis in an acid medium into a NN-di-(2-chloroethyl-aminophenylbutyric acid.

The following examples in which the parts are by weight, illustrate how the process of the invention may be carried into effect:

(1) 10 parts of methyl p-aminophenylbutyrate (prepared as by L. D. Freedman and G. O. Doak, J. Amer. Chem. Soc. (1949), 71, 779) was treated with ethylene oxide (6 parts) and benzene (10 parts) at 150° C. for 18 hours. The resulting methyl p-NN-di-(2-hydroxyethyl)-aminophenylbutyrate (5 parts) was treated with $POCl_3$ (15 parts) and benzene (100 parts) under reflux for one hour. The methyl p-NN-di-(2-chloroethyl)-aminophenylbutyrate (8 parts) thus obtained was treated with hydrochloric acid (25 parts) by refluxing for 30 minutes. The mixture was cooled, neutralised with ammonia, and acidified with a few drops of acetic acid. The resulting p-NN-di-(2-chloroethyl)-aminophenylbutyric acid was recrystallised from petrol-ether (60–80° C.) M.P. 63° C. Yields, 5 parts. (Found: C, 55.5; H, 6.1. $C_{14}H_{19}O_2NCl_2$ requires C, 55.3; H, 6.2%.)

The process of the example may be modified by treating the methyl-p-aminophenylbutyrate with ethylene oxide (25 parts) in N acetic acid (50 parts) at room temperature for 4 hours.

(2) 21 parts of p-nitrophenylbutyric acid dissolved in 60 parts of ethyl alcohol were treated with 4 parts of acetyl chloride and the mixture heated under reflux for one hour. 4 parts of acetyl chloride were then added and heating continued for a further four hours. After removing the excess of alcohol by distillation the product was poured into 10 parts of water and extracted with ether. The ether solution was washed with 2N sodium hydroxide, dried with anhydrous sodium sulphate, and

distilled to remove solvent. The resulting ethyl p-nitrophenylbutyrate (21.8 parts) was reduced by shaking an alcoholic solution with Raney-nickel in an atmosphere of hydrogen. The ethyl p-aminophenylbutyrate (21.2 parts) thus obtained was heated at 150° C. in a sealed tube with 20 parts of dry benzene and 12 parts of ethylene oxide for 12 hours. The resulting ethyl p-NN-di-(2-hydroxyethyl)-aminophenylbutyrate (15 parts) was treated with phosphorus oxychloride (15 parts) in benzene (100 parts) by heating under reflux for one hour. In this way ethyl p-NN-di-(2-chloroethyl)-aminophenylbutyrate was obtained as a colourless oil (8 parts): it was characterised by hydrolysis to the acid, M.P. 63° C.

We claim:

p-NN-di-(2-chloroethyl)-aminophenylbutyric acid.

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