ROLE OF NITRO GROUPS IN THE MECHANISM OF THE ANTIEDEMA ACTIVY OF BUTYRIC ACID DERIVATIVES AND ESTERS

M. Yu. Ladinskaya

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Introduction of nitro groups in the γ-position and also in the ester group of butyric acid and its derivatives is accompanied by an increase in the antiedema activity and also in the toxicity of these compounds in experiments on rats. A maximal increase in the antiedema activity of the compounds is found after introduction of three nitro groups.

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According to data described in the literature [3, 6, 7], compounds containing nitro groups (nitrophenols, nitrobenzenes, nitrofurans) possess high physiological activity. It has been shown [5] that introduction of a nitro group into benzoylmorphine in the para position increases its analgesic activity and reduces its side effects associated with depression of the respiratory center.

Only the 5-nitrofurans possess marked antibacterial activity [1]. Displacement of the nitro group from position 5 into position 3 or introduction of a second nitro group into the furan molecule weakens the antibacterial action of these compounds.

In the present investigation the role of nitro groups in the mechanism of the anti-inflammatory activity of butyric acid derivatives and esters was studied. In all more than 40 compounds were tested. The compounds were tested. The compounds were synthesized at the Institute of Organic Chemistry, Academy of Sciences of the USSR, by S. S. Novikov, I. S. Ivanova, and T. A. Alekseeva.

EXPERIMENTAL METHOD

Experiments were carried out on intact rats weighing 110-150 g. The compounds for testing were injected intraperitoneally in a dose of 50 mg/kg, the solids as a suspension with 10% sterile gelatin solution and the liquids as an aqueous emulsion with gum arabic. Edema of the animal's hind limb was produced by subcutaneous injection of 0.1 ml of 6% polyglucin (dextran, mol. wt. 60,000-80, 000) solution.

The compounds were injected 30 min before production of edema. Their activity was judged by the degree of inhibition of the edema reaction. The degree of edema in the control animals was taken as 100%. A more detailed account of the method is given in [4]. The toxicity of the compounds was also determined by calculating LD_{50} by Karber's method. The antiedema activity and toxicity of the nitro-derivatives of butyric acid and its esters were compared with those of the corresponding analogs.

EXPERIMENTAL RESULTS

As the investigations showed, introduction of nitro groups into butyric acid and its derivatives in the γ-position significantly affects the antiedema activity and toxicity of these compounds. The ability of the compounds to inhibit edema development was found to depend on the number of nitro groups introduced. If one nitro group was introduced into butyric acid in the γ-position the antiedema activity was slightly reduced. It is interesting to note that introduction of an amino group in the same position (γ-aminobutyric acid) also very slightly reduces its antiedema action. Meanwhile, introduction of three nitro groups in the γ-position is accompanied by a marked increase in antiedema activity. However, this increased antiedema activity is accompanied by increased toxicity (Fig. 1).

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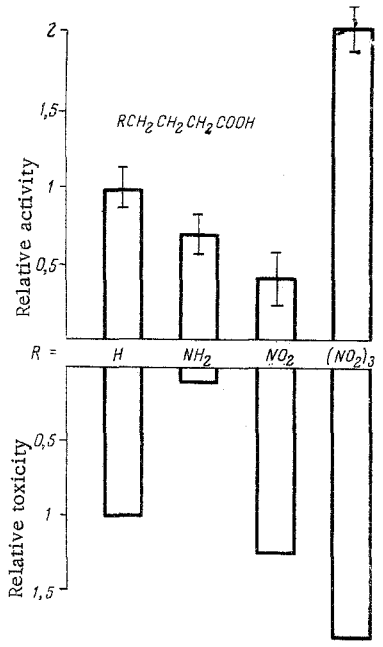

Fig. 1. Comparative activity and toxicity of butyric and γ-amino-, γ-nitro, and γ,γ,γ-trinitrobutyric acids.

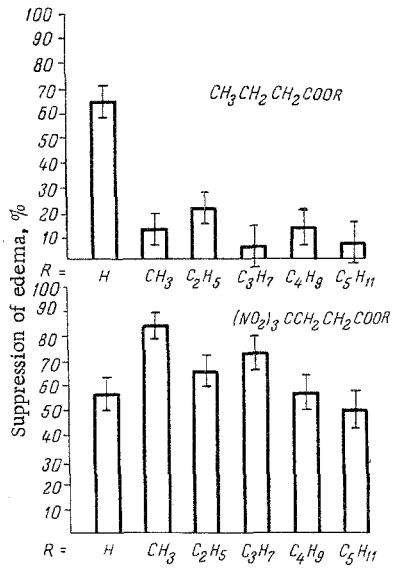

Fig. 2. Relationship between chemical structure and antiedema activity in a series of derivatives of butyric acid and its esters.

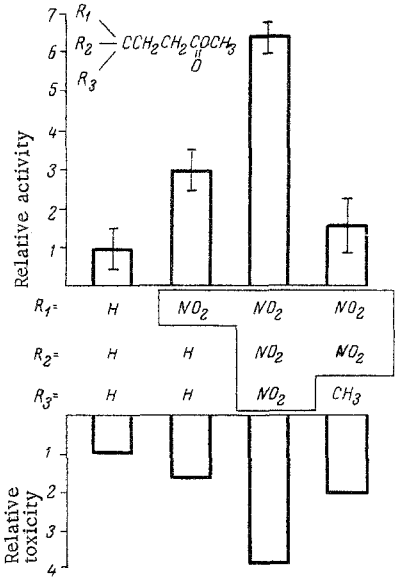

Fig. 3. Role of substituents in γ-position of an ester of butyric acid in manifestation of its antiedema and toxic action.

Similar patterns were observed when nitro groups were introduced in the γ-position into butyric acid amide. Introduction of one nitro group into butyric amide in the γ-position causes a marked decrease in its antiedema activity. Introduction of three nitro groups increases the antiedema activity considerably (by 10 times). However, the marked increase in antiedema activity of the compound is accompanied by a considerable increase in its toxicity (by 44 times).

Changes in the antiedema activity were most clearly revealed among the esters of butyric acid and their nitro-analogs.

The ability of esters of butyric acid to inhibit the development of edema is much less than the activity of the acid itself. However, the antiedema activity of esters of γ,γ,γ-trinitrobutyric acid is not less, but actually greater, than the activity of the corresponding nitro-acid (Fig. 2). Esters of both acids possess lower toxicity. For this reason, esters of γ,γ,γ,-tributyric acid, with their greater antiedema activity and their low toxicity, possess greater therapeutic latitude. However, despite this, the compounds described above possess a cumulative action in experiments of long duration, thus detracting from their practical value.

The importance of the number of introduced nitro groups and the role of the substituent introduced (methyl group) were studied in more detail in relation to the methyl ester of butyric acid. Introduction of one nitro group in the γ-position of the ester increased its antiedema activity (by three times). Introduction of three nitro groups gave a further increase in the ability of the ester to inhibit edema development (by 6 times).

Substitution of one nitro group by methyl was accompanied by a marked (by two-thirds) decrease in the antiedema activity and toxicity of the compounds (Fig. 3).

By introducing nitro groups into the carbon chain of butyric acid esters in a different position (in the ester group), compounds were obtained which also possessed marked antiedema activity and high toxicity. Changes in the antiedema activity of the nitroesters of butyric acid were studied on the example of the ethyl ester of butyric acid. Introduction of one nitro group into the alcohol residue of the ester was accompanied by a marked increase in the antiedema activity and toxicity of the compound. Introduction of three nitro groups in the same position led to a further increase in the antiedema activity and toxicity of the compound. After combined introduction of nitro groups in both positions of the carbon chain (i.e., 3 nitro groups in the γ-position and 1 nitro group into the ester group), a marked increase was obtained in the antiedema activity by comparison with the activity of the ethyl esters of γ,γ,γ-trinitrobutyric acid. Introduction of six-nitro groups in the same positions was not accompanied by any increase in the antiedema activity and toxicity. The compound with six nitro groups occupied an intermediate position in activity, being no more active than the ethyl ester of γ,γ,γ-trinitrobutyric acid and no less active than the compound with four nitro groups.

The following conclusion may be drawn from these findings. Introduction of nitro groups leads to changes in the antiedema action of butyric acid derivatives. The antiedema activity is increased most of all by introduction of three nitro groups. The position of the introduced nitro groups has no significant influence.

Besides intraperitoneal injection, in a series of experiments administration of the compounds by the enteral route was tested. These experiments showed that the antiedema properties of the most active nitro-derivatives of butyric acid were appreciably reduced when given enterally. The marked decreased in activity of the nitro-derivatives of butyric acid when given by the enteral route may be due to difficulty of penetration through the gastro-intestinal tract or to their destruction by enzyme action in the stomach. The most disadvantageous factor when assessing the effectiveness of nitro-derivatives of butyric acid is the increase in their toxicity during prolonged administration.

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