259. *Search for Trypanocidal Activity. Part II. Derivatives of β-Naphthylamine-4 : 6 : 8-Trisulphonic Acid.*

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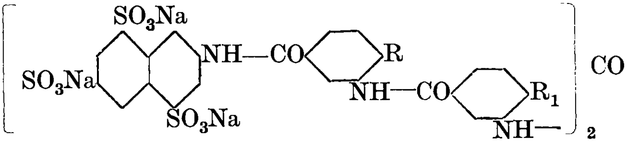
Since there appeared to be no published information regarding the trypanocidal activity of compounds in which the terminal α-naphthylamine-4 : 6 : 8-trisulphonic acid residue of Bayer 205 (R = CH_3; R_1 = H) is replaced by the corresponding β-naphthylamine derivative the following compounds were prepared.

The first substance, which may be termed the toluoylbenzoyl derivative (R = CH_3; R_1 = H), is an isomeride of Bayer 205 differing only in the point of attachment of the centre chain to the two terminal nuclei; it displayed some curative action against trypanosomiasis for 1 week in doses of 0·2 mg. per g. body weight (minimum lethal dose in mg. for mouse of 20 g., 8—10). The benzoyltoluoyl derivative (R = H; R_1 = CH_3) (M.L.D. 7·5) exhibited a slight therapeutic action, and the toluoyltoluoyl (R = CH_3; R_1 = CH_3) carbamide (M.L.D. 10) had no effect. These tests for therapeutic activity were carried out under the auspices of the Medical Research Council.



The acid sodium salt of β-naphthylamine-4 : 8-disulphonic acid (24 g.) was converted into the 4 : 6 : 8-trisulphonic acid with 60% fuming sulphuric acid (50 c.c.) first at 98—100° for 10 hours and finally at 120° for 2 hours. Neutralisation of the solution by barium carbonate gave the barium sodium salt, from which barium was removed by sodium carbonate. On addition of hydrochloric acid to the solution the acid disodium salt (20 g.) separated as microscopic needles. Its solution exhibited a brilliant blue fluorescence (Found in anhydrous salt: Na, 11·0; S, 22·5; N, 2·65. $C_{10}H_7O_9NS_3Na_2$ requires Na, 10·8; S, 22·5; N, 3·3%. 0·5419 G. required 13·77 c.c. of *N*/10-sodium carbonate. Calc., 13·5 c.c.).

3-*Nitro*-4-*methylbenzoyl*-β-*naphthylamine*-4 : 6 : 8-*trisulphonic Acid.* —β-Naphthylamine-4 : 6 : 8-trisulphonic acid (11 g.), suspended in water (30 c.c.), was treated with 2-nitro-*p*-toluoyl chloride (12 g.; 2 mols.), 20% sodium hydroxide solution being added in portions to preserve a slight alkalinity. The reaction mixture was acidified, excess of nitrotoluic acid removed, and the solution, after neutralisation by sodium carbonate, concentrated in a vacuum (Found in anhydrous salt: Na, 11·5; N, 4·4; S, 15·9. $C_{18}H_{11}O_{12}N_2S_3Na_3$ requires Na, 11·3; N, 4·6; S, 15·7%). The *trisodium* salt crystallised from water on addition of alcohol in microscopic needles; it gave no diazo-reaction and the solution (p_H 7) exhibited no fluorescence.

3-*Nitrobenzoyl*-β-*naphthylamine*-4 : 6 : 8-*trisulphonic Acid.*—The foregoing method was also employed to obtain the corresponding nitrobenzoyl compound. The *trisodium* salt was readily soluble in water (p_H 7) and separated on addition of alcohol (Found in anhydrous salt: Na, 11·7; N, 4·6. $C_{17}H_9O_{12}N_2S_3Na_3$ requires Na, 11·5; N, 4·7%).

3′-*Nitrobenzoyl*-3-*amino*-4-*methylbenzoyl*-β-*naphthylamine*-4 : 6 : 8-*trisulphonic Acid.*—The nitrotoluoyl derivative (10 g.) was reduced in aqueous solution by iron filings and a trace of hydrochloric acid, the iron oxides removed, and the solution treated with 3-nitrobenzoyl chloride in alkaline solution. Excess of nitrobenzoic acid was removed by ether, and the neutralised solution evaporated in a vacuum until the *trisodium* salt separated. This salt was soluble in water to the extent of 9% (p_H 7) at room temperature (Found in anhydrous salt: Na, 9·4; N, 5·75. $C_{25}H_{16}O_{13}N_3S_3Na_3$ requires Na, 9·4; N, 5·75%).

3′-*Nitro*-4′-*methylbenzoyl*-3-*amino*-4-*methylbenzoyl*-β-*naphthylamine*-4 : 6 : 8-*trisulphonic Acid.*—The nitrotoluoyl derivative (17 g.) was reduced with iron as above, and the solution of the aminotoluoyl derivative treated directly with 2-nitro-*p*-toluoyl chloride and sodium hydroxide. On concentration in a vacuum the *trisodium* salt separated in microscopic rods (p_H 6·5—7) (Found in anhydrous salt: Na, 9·2; N, 5·5. $C_{26}H_{18}O_{13}N_3S_3Na_3$ requires Na, 9·3; N, 5·6%).

3′-*Nitro*-4′-*methylbenzoyl*-3-*aminobenzoyl*-β-*naphthylamine*-4 : 6 : 8-*trisulphonic Acid.*—The 3-nitrotoluoyl derivative (6·8 g.) in aqueous solution was reduced by iron filings and a trace of hydrochloric acid. Treatment of the solution with 2-nitro-*p*-toluoyl chloride in presence of alkali gave the required derivative. The *trisodium* salt separated from water (p_H 6·5) in microscopic needles (Found in anhydrous salt: Na, 9·7; N, 5·5. $C_{25}H_{16}O_{13}N_3S_3Na_3$ requires Na 9·4; N, 5·75%).

Ureido-3′-*aminobenzoyl*-3-*amino*-4-*methylbenzoyl*-β-*naphthylamine*-4 : 6 : 8-*trisulphonic Acid.*—The nitrobenzoylaminotoluoyl derivative, after reduction by iron filings and a trace of hydrochloric acid, was subjected to a slow stream of carbonyl chloride, sodium carbonate being added at intervals to maintain alkalinity (50 c.c. 2*N*-solution). The acid mixture was neutralised, evaporated to dryness in a vacuum, and the *sodium* salt of the carbamide extracted by methyl alcohol. The sodium salt when purified by repeated precipitation from water by alcohol until free from chloride gave no diazo-reaction (Found : loss in a vacuum at 160°, 13·45. $C_{51}H_{34}O_{23}N_6S_6Na_6,12H_2O$ requires H_2O, 13·2%. Found in anhydrous salt : Na, 9·7 ; N, 5·9. $C_{51}H_{34}O_{23}N_6S_6Na_6$ requires Na, 9·7 ; N, 5·8%). On addition of water the sodium salt gelatinised before passing into solution.

Ureido-3'-amino-4'-methylbenzoyl-3-aminobenzoyl-β-naphthylamine-4 : 6 : 8-trisulphonic Acid.—The nitrotoluoylaminobenzoyl derivative (5·7 g.) was similarly converted into *s*-carbamide. The *sodium* salt was readily soluble in water and in methyl alcohol (Found : loss in a vacuum at 160°, 6·0. $C_{51}H_{34}O_{23}N_6S_6Na_6,5H_2O$ requires H_2O, 5·7%. Found in anhydrous salt : Na, 9·6 ; N, 5·9%).

Ureido-3'-amino-4'-methylbenzoyl-3-amino-4-methylbenzoyl-β-naphthylamine-4 : 6 : 8-trisulphonic Acid.—The nitrotoluoylaminotuluoyl derivative (10 g.) was also converted into carbamide (Found : loss in a vacuum at 160°, 9·9. $C_{53}H_{38}O_{23}N_6S_6Na_6,9H_2O$ requires H_2O, 10·0%. Found in anhydrous salt : Na, 9·25 ; N, 5·7. $C_{53}H_{38}O_{23}N_6S_6Na_6$ requires Na, 9·5 ; N, 5·8%). The *sodium* salt gelatinised on addition of water but dissolved readily (p_H 7) ; it was soluble in methyl alcohol but only sparingly soluble in ethyl alcohol.

We desire to record our thanks to the Imperial Chemical Industries Limited for a gift of β-naphthylamine-4 : 8-disulphonic acid.

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