

CCCCLV.—*Search for Trypanocidal Activity. Derivatives of Dehydrothio-p-toluidinesulphonic Acid and of 3-Aminocarbazoledisulphonic Acid.*

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As regards its potency in the treatment of trypanosomiasis the drug Bayer 205 possesses a value far greater than that of compounds of closely related structure and the cause of this outstanding activity has not been correlated clearly with chemical constitution; for, so far as is known, any slight change in the structure leads to greatly diminished activity. The present work was undertaken with the object of ascertaining the effect of replacing the terminal α -naphthylaminetrisulphonic acid residues by other groups, and two symmetrical ureides (carbamides) of dehydrothio-*p*-toluidinesulphonic acid and three of 3-aminocarbazoledisulphonic acid have been prepared but in no case has trypanocidal action been detected. The arsonic acid obtained through the Bart reaction from dehydrothio-*p*-toluidinesulphonic acid was similarly inactive.

3-Nitrobenzoyldehydrothio-p-toluidinesulphonic Acid.—*m*-Nitrobenzoyl chloride (13 g.) was added with shaking to dehydrothio-*p*-toluidinesulphonic acid (10.3 g.) dissolved in 2*N*-sodium hydroxide (50 c.c.) and water (300 c.c.), additional alkali being slowly added (30 c.c.) in order to maintain a slight alkalinity. The yellow precipitate was recrystallised from water (Found: loss at 160° in a vacuum, 10.15. $C_{21}H_{14}O_6N_3S_2Na, 3H_2O$ requires H_2O , 9.9%. Found in anhydrous salt: Na, 4.5; N, 8.5. $C_{21}H_{14}O_6N_3S_2Na$

requires Na, 4.7; N, 8.55%). The *sodium* salt (M.L.D. > 100 mg.)* separated from water in sparingly soluble, microscopic needles (p_H , 7).

3-Aminobenzoyldehydrothio-p-toluidinesulphonic Acid.—The foregoing nitrobenzoyl derivative (7.9 g.) was reduced by iron in water containing a trace of hydrochloric acid. The mixture was rendered slightly alkaline and, after removal of iron oxides, the sodium salt was precipitated by addition of sodium chloride, from which it could not subsequently be freed and consequently the product was purified as free acid (Found: loss in a vacuum at 160°, 3.2. $C_{21}H_{17}O_4N_3S_2 \cdot H_2O$ requires H_2O , 3.1%. Found for anhydrous acid: N, 9.6%; 0.28 g. equivalent to 6.15 c.c. *N*/10-alkali. $C_{21}H_{17}O_4N_3S_2$ requires N, 9.6%; 6.17 c.c. *N*/10-alkali). The neutralised solution of acid showed a M.L.D. of 25 mg.

Ureidodehydrothio-p-toluidinesulphonic Acid.—Dehydrothio-*p*-toluidinesulphonic acid (8 g.), dissolved in water (250 c.c.) containing ten equivalents of sodium carbonate (13.5 g.), was treated with a slow stream of carbonyl chloride until the mixture became strongly acid, the whole treatment being repeated until the product no longer contained any primary base. The pasty yellow precipitate was converted into *sodium* salt and purified as such by repeated solution in water, concentration, and precipitation by alcohol (Found: loss at 150° in a vacuum, 13.2. $C_{29}H_{20}O_7N_4S_4Na_2 \cdot 6H_2O$ requires H_2O , 13.3%. Found in anhydrous salt: Na, 6.3; N, 7.5; S, 17.55. $C_{29}H_{20}O_7N_4S_4Na_2$ requires Na, 6.5; N, 7.9; S, 18.05%).

The sodium salt (M.L.D. = 20—40 mg.) became gelatinous when moistened with water and dissolved with difficulty in hot water, forming an intensely green fluorescent solution (p_H , 7.5).

Ureido-m-aminobenzoyldehydrothio-p-toluidinesulphonic Acid.—Carbonyl chloride was passed through a solution of the foregoing aminobenzoyl compound (3.5 g.), suspended in water containing sodium carbonate (8 g.), until separation of the carbamide was complete. The precipitate was redissolved in alkali and the treatment repeated; the product, which then became practically free from primary base, was dissolved in sodium hydroxide, the solution evaporated to dryness in a vacuum, and the *sodium* salt purified by solution in boiling 95% alcohol, from which it separated on cooling (Found: loss at 160° in a vacuum, 8.65. $C_{43}H_{30}O_9N_6S_4Na_2 \cdot 5H_2O$ requires H_2O , 8.8%. Found in anhydrous salt: Na, 5.0; N, 9.2. $C_{43}H_{30}O_9N_6S_4Na_2$ requires Na, 4.85; N, 8.9%). The sodium salt (M.L.D. > 100 mg.) is not readily soluble in water, but a 1% jelly (p_H 6.5) can be obtained by dissolving it in 300 parts of water with subsequent concentration to one-third.

* Minimum lethal dose for mouse of 20 g. = M.L.D.

Sulphodehydrothiotoluene-p-arsonic Acid.—Dehydrothio-*p*-toluidinesulphonic acid (18 g.), dissolved in water (200 c.c.) containing 2*N*-sodium hydroxide (30 c.c.), was treated simultaneously in the cold with 2*N*-hydrochloric acid (60 c.c.) and *N*-sodium nitrite (60 c.c.). The diazo-solution was poured into an alkaline solution of sodium arsenite (20 g. in 60 c.c. of 2*N*-sodium hydroxide) to which a little copper sulphate had been added. Nitrogen was rapidly evolved, and the reaction completed on the steam-bath. The solution, which was quite free from tar, was evaporated in a vacuum and on acidification the arsonic acid separated (21 g.). The *sodium* salt was precipitated from aqueous solution by absolute alcohol (Found in anhydrous salt: N, 3.2, 3.0; As, 15.7. $C_{14}H_{10}O_6NS_2AsNa_2$ requires N, 3.0; As, 15.8%). This reddish-brown sodium salt (M.L.D. 30—40 mg.) was very soluble in water (p_H 7.5) and moderately so in 95% alcohol.

3-Nitrocarbazoledisulphonic Acid.—Sulphonation of 3-nitrocarbazole by the use of 67% sulphuric acid (Schwalbe and Wolff, *Ber.*, 1911, 44, 237) at 130—140° led to charring and incomplete reaction with correspondingly small yields. When, however, nitrocarbazole (20 g.) in concentrated sulphuric acid (20 c.c.) was heated gradually to 70° and maintained at 70—75° for 4 hours, a clean solution was achieved. This solution was added to ice, filtered to remove unchanged nitrocarbazole (1.5 g.), and neutralised by calcium carbonate. The *calcium* salt, which showed no definite crystalline form, separated on concentration of the filtrate; it was fairly readily soluble in water, giving a solution neutral to litmus (Found in anhydrous salt: Ca, 9.6; S, 15.8. $C_{12}H_6O_8N_2S_2Ca$ requires Ca, 9.8; S, 15.6%).

3-Aminocarbazoledisulphonic Acid.—An aqueous solution of calcium 3-nitrocarbazoledisulphonate (14 g.) was heated on a steam-bath with iron filings (10 g.) and a trace of hydrochloric acid. After removal of iron oxides and evaporation of the filtrate in a vacuum, a faintly coloured calcium salt remained which on exposure to air assumed an intense purple colour and neither the calcium nor the sodium salt could be subsequently isolated in a colourless state. The free *acid*, obtained in poor yield by adding concentrated hydrochloric acid to a concentrated solution of the sodium salt, was purified by recrystallisation from water (Found in anhydrous acid: N, 8.0. $C_{12}H_{10}O_6N_2S_2$ requires N, 8.2%). In view of these experimental difficulties, the following method was adopted.

3-(3'-Nitro-4'-methylbenzamido)carbazoledisulphonic Acid.—Calcium 3-nitrocarbazoledisulphonate (16 g.), dissolved in water (100 c.c.), was reduced by iron filings (16 g.) in presence of a trace of hydrochloric acid, and the filtrate from iron oxides treated forthwith with

2-nitro-*p*-toluoyl chloride (16 g.) while 10% aqueous sodium hydroxide was run into the cooled and stirred solution. A yellow precipitate separated slowly and was purified as *sodium* salt by precipitation from water by alcohol (Found in anhydrous salt: Na, 8.5; N, 7.8. $C_{20}H_{13}O_9N_3S_2Na_2$ requires Na, 8.4; N, 7.7%). The sodium salt dissolved readily in hot water and separated on cooling as a curdy precipitate.

3-(3'-3''-Nitrobenzamido-4'-methylbenzamido)carbazoledisulphonic Acid.—The nitrotoluoyl derivative (9.6 g.) was reduced as in the foregoing preparation, the filtrate from iron oxides being treated with 3-nitrobenzoyl chloride (6 g.) in presence of sodium hydroxide (4 g.). The resulting *sodium* salt was recrystallised from water (Found in anhydrous salt: Na, 6.8; S, 7.0. $C_{27}H_{18}O_{10}N_4S_2Na_2$ requires Na, 6.9; S, 7.2%).

Ureido-3-aminocarbazoledisulphonic Acid.—A slow stream of carbonyl chloride was passed through an aqueous solution (50 c.c.) of 3-aminocarbazoledisulphonic acid (2 g.) containing ten equivalents of sodium carbonate (6.2 g.) until the liquid was strongly acid; the phosgenation was then repeated in presence of five equivalents of alkali. The product separated slowly as a gelatinous precipitate, which was converted into *sodium* salt, purification of the latter being effected by repeated precipitation from water by alcohol (Found in anhydrous salt: Na, 11.5. $C_{25}H_{14}O_{13}N_4S_4Na_4$ requires Na, 11.5%). The sodium salt exhibited no definite crystalline form; it was soluble to the extent of at least 6 parts in 10 at room temperature (p_H 6; M.L.D. = 2 mg.).

Ureido-3-(3'-amino-4'-methylbenzamido)carbazoledisulphonic Acid.—Sodium 3-(3'-nitro-4'-methylbenzamido)carbazoledisulphonate (5.5 g.), dissolved in cold water, was reduced by simultaneous addition of solutions of ferrous chloride (14 g.) and sodium hydroxide (6 g.), the reaction being promoted by stirring. After removal of iron oxides the filtrate was phosgenated as in the preceding preparation. The acid was converted into the *sodium* salt, which was purified by precipitation from concentrated aqueous solutions by alcohol (Found in anhydrous salt: Na, 8.3. $C_{41}H_{28}O_{15}N_6S_4Na_4$ requires Na, 8.6%). The sodium salt had no definite crystalline form, it dissolved readily in water to a neutral solution (p_H 7; M.L.D. = 18 mg.), and gave only a very slight diazo-reaction.

Ureido-3-(3'-3''-aminobenzamido-4'-methylbenzamido)carbazoledisulphonic Acid.—Sodium 3-(3'-3''-nitrobenzamido-4'-methylbenzamido)carbazoledisulphonate (4 g.) was reduced by iron filings in presence of a trace of hydrochloric acid. The filtrate was treated with carbonyl chloride in presence of sodium carbonate until no free primary amine remained. The product separated as a gelatinous

paste (2.1 g.), convertible into *sodium* salt, which separated in filtrable form on addition of alcohol to its concentrated solution (Found in anhydrous salt: Na, 7.25. $C_{55}H_{38}O_{17}N_8S_4Na_4$ requires Na, 7.1%). This sodium salt (M.L.D. = 10 mg.) gelatinised on addition of water but did not appear to pass readily into solution. On warming in water the substance dispersed, forming a viscous fluid which set to a jelly on cooling; even a 3% solution (p_H 9) behaved in this way. The compound gave a very faint diazo-reaction.

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