## 727. *A Search for New Trypanocides. Part III.* Some Analogues of Suramin.*

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Some symmetrical ureas are descibed, which are based on the structure of Suramin but contain thiazol-2-yl, 2-pyridyl, 5-sulpho-2-pyridyl, and 4-carboxy-3-hydroxyphenyl groups, instead of the naphthalenetrisulphonic acid grouping. All the compounds were inactive against *Trypanosoma congolense* and *T. rhodesiense* infections in mice.

Suramin has been used for many years in the treatment of the early stages of human trypanosomiasis, and since the structure of this drug was established as (I) by Fourneau [1] and his collaborators many analogous ureas have been prepared. None of these had any appreciable trypanocidal activity (cf., *inter alia*, Fourneau *et al.*[1] and Fischl and Schlossberger [2]), and it was concluded that any deviation, however slight, from the structure (I) reduced the activity very considerably or gave an inactive compound.

Since analogues prepared by other workers were based on naphthalene substituted by various sulphonic acid residues, it was decided, when the present work was started some years ago, to make a more drastic change, and synthesise ureas of type (VIII), based on heterocyclic systems. Wills and Wormall [3] recently examined the enzyme-inhibiting capacity of Suramin and various analogues of it. One of these was the related sulphonamide (II). Spinks [4] also studied a series of compounds including the product (III), which was stated to have only a trace of trypanocidal activity. Pratesi and Raffa [5] also prepared analogues such as the symmetrical ureas derived from 1-[*p*-(*p*-aminobenzenesulphonamido)benzenesulphonamido]naphthalene-6-sulphonic acid and 1-(*m*-aminobenzenesulphonamido)naphthalene-3 : 6 : 8-trisulphonic acid, in which all the amido-groups of the Suramin type of

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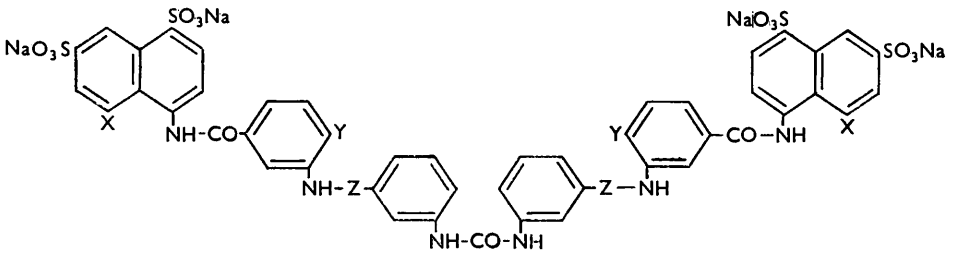
[1] Fourneau, Trefouel, Trefouel, and Vallée, *Compt. rend.*, 1924, **178**, 675; *Ann. Inst. Pasteur*, 1924, **38**, 81.
[2] Fischl and Schlossberger, "Handbook of Chemotherapy," Roebuck & Son, Baltimore, 1933.
[3] Wills and Wormall, *Biochem. J.*, 1950, **47**, 158.
[4] Spinks, *ibid.*, 1948, **42**, 109.
[5] Pratesi and Raffa, *Farmaco. sci. e tec. (Pavia)*, 1946, **1**, 21; *Chem. Abs.*, 1946, **40**, 4360.

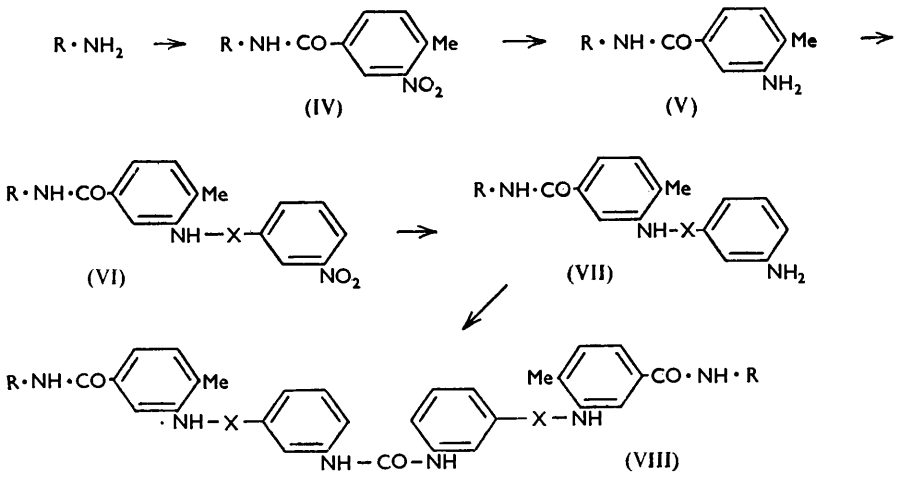
compound were replaced by sulphonamido-linkages. Although no information regarding trypanocidal activity of these products was given, we thought it of interest to include some ureas containing sulphonamido-linkages amongst those prepared by us.



(I): X = $SO_3Na$, Y = Me, Z = CO. (II): X = $SO_3Na$, Y = H, Z = $SO_2$

(III): X = OH, Y = Me, Z = $SO_2$

The terminal groups R of the ureas (VIII) prepared were thiazol-2-yl, 2-pyridyl, 5-sulpho-2-pyridyl, and 4-carboxy-3-hydroxyphenyl. Condensations of the amines $R{\cdot}NH_2$ and (V) with substituted benzoyl chlorides were easily performed in dry pyridine, in preference to use of the Schotten–Baumann conditions (cf. previous authors), and very good yields (75—95%) of the amides (IV) and (VI) were obtained. This method failed only in the case of 4-aminosalicylic acid from which unidentifiable low-melting products were obtained. Attempted condensation of this acid with 4-methyl-3-nitrobenzoyl chloride under Schotten–Baumann conditions gave *ON*-di-(4-methyl-3-nitrobenzoyl)-*m*-aminophenol, the salt derived from 4-aminosalicylic acid, and 4-methyl-3-nitrobenzoic acid. The desired amide (IVg) was finally prepared in good yield by boiling the reactants in acetone. This compound, together with others in the series, was unusual in that it did not decompose, or dissolve in, saturated aqueous sodium hydrogen carbonate. However, boiling aqueous

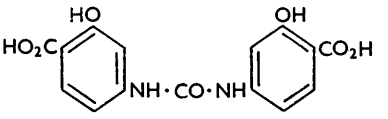


a, X = CO, R = thiazol-2-yl.
b, X = $SO_2$, R = ,,
c, X = CO, R = 2-pyridyl.
d, X = $SO_2$, R = ,,
e, X = CO, R = 5-sulpho-2-pyridyl.
f, X = $SO_2$, R = ,,
g, X = CO, R = 4-carboxy-3-hydroxyphenyl.

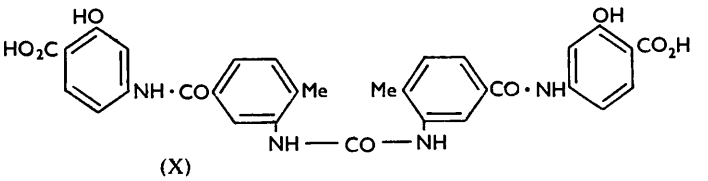
sodium carbonate gave a sodium salt, insoluble in cold and only slightly soluble in boiling water.

Reduction of the nitro-amides had previously been carried out by iron in acetic acid. In the present work the nitro-amides (IV) and (VI) were reduced catalytically in solution or suspension in a convenient solvent, with Adams platinum catalyst. In some cases the

choice of solvents was important. Thus reductions of the nitro-compounds (IVa and c) could be performed in acetic acid, but gave mixtures when attempted in ethanol, whilst that of (VIb) proceeded smoothly in aqueous sodium hydroxide at 20 atmospheres but only to a limited extent in acetic acid and not at all in ethanol. On the other hand, reduction of the compound (VIc) was successful in ethanol, whereas no solid product could be isolated when acetic acid was used. Compounds containing sulphonic or carboxylic acid groups were reduced in solution or suspension in aqueous sodium hydroxide, at room temperature and 20 atmospheres.




(IX)




(X)

The amines (VIIa, c, and d) which did not contain free acidic substituents reacted with carbonyl chloride in aqueous acetic acid, in presence of sodium acetate. These reactions were usually carried out at room temperature, but in the case of (VIId) a temperature of 90° was necessary. Those amines containing carboxy- or sulpho-substituents (VIIe, f, and g), and (VIIb) which was insoluble in aqueous acetic acid, were treated with carbonyl chloride in aqueous sodium hydroxide at room temperature, to give the ureas (VIIIe, f, g, and b) in good yield. Higher yields were obtained when carbonyl chloride was introduced slowly, and the reaction temperature was kept at 0°, thus avoiding any fission of the amide linkages in the alkaline medium. This method was also used to prepare the symmetrical ureas (IX) and (X) from 4-aminosalicylic acid and *p*-(3-amino-4-methylbenzamido)salicylic acid (Vg).

All the ureas were inactive against *T. congolense* and *T. rhodesiense* infections in mice.

## Experimental

*2-(4-Methyl-3-nitrobenzamido)thiazole* (IVa).—4-Methyl-3-nitrobenzoyl chloride (21 g.) was slowly added with stirring and cooling to 2-aminothiazole (10·5 g.) dissolved in dry pyridine (30 c.c.) and cooled to 0°, after which the mixture was heated on the steam-bath for 10 min. The solid mass was added to water (1 l.), and the finely divided product was filtered off, washed with water, and dried (24·3 g., 88%). Recrystallisation from ethanol gave 2-(4-*methyl*-3-*nitrobenzamido*)*thiazole*, colourless hexagonal plates, m. p. 192° (Found: C, 50·2; H, 3·6; N, 15·8. $C_{11}H_9O_3N_3S$ requires C, 50·2; H, 3·4; N, 16·0%).

*4-(4-Methyl-3-nitrobenzamido)salicylic Acid* (IVg).—4-Aminosalicylic acid (153 g., 1 mol.) and 4-methyl-3-nitrobenzoyl chloride (100 g., 0·5 mol.) in acetone (1 l.) were boiled under reflux for 1 hr. The solid product was filtered off and stirred for 10 min. with a solution of anhydrous sodium carbonate (110 g.) in water (1500 c.c.) to remove excess of aminosalicylic acid. The residual sodium salt was washed with water and stirred with N-hydrochloric acid (1500 c.c.). Recrystallisation of the resulting solid from pyridine gave 4-(4-*methyl*-3-*nitrobenzamido*)*salicylic acid* (146 g., 92%) as short white needles, m. p. 264—265° (decomp.) [Found: C, 57·0; H, 3·9; N, 8·9; $CO_2$, lost on decomp. at m. p., 14·0%; equiv. (by titration), 319. $C_{15}H_{12}O_6N_2$ requires C, 57·0; H, 3·8; N, 8·9; $CO_2$, 13·9%; equiv., 316·4]. The acid gave a violet colour with aqueous ferric chloride, but did not affect saturated aqueous sodium hydrogen carbonate, though it was slightly soluble in hot 2N-sodium carbonate from which the sodium salt crystallised in fine needles, m. p. >300°.

*2-(3-Amino-4-methylbenzamido)thiazole* (Va).—A suspension of the nitro-amide (IVa) (105·2 g.) in acetic acid (2 l.) was hydrogenated at room temperature and atmospheric pressure

in the presence of Adams catalyst (5 g.). Hydrogenation required 20 hr. during which grey crystals separated. These were dissolved by warming and the catalyst was then filtered off. After addition of an equal volume of water and basification with aqueous sodium hydroxide, the precipitate (76·8 g., 82%) was filtered off; recrystallisation from ethanol gave 2-(3-*amino*-4-*methylbenzamido*)*thiazole* in fine, colourless needles, m. p. 208° (Found: C, 56·8; H, 4·8; N, 17·9. $C_{11}H_{11}ON_3S$ requires C, 56·65; H, 4·7; N, 18·0%).

2-(4-*Methyl*-3-m-*nitrobenzamidobenzamido*)*thiazole* (VIa).—This was prepared similarly to the simpler analogue (IVa) from *m*-nitrobenzoyl chloride and 2-(3-amino-4-methylbenzamido)-thiazole (Va) in pyridine. Recrystallisation of the product (46·9 g., 94%) from aqueous pyridine gave 2-(4-*methyl*-3-m-*nitrobenzamidobenzamido*)*thiazole* in fine, colourless needles, m. p. 283—285° (Found: C, 56·9; H, 3·9; N, 14·7. $C_{18}H_{14}O_4N_4S$ requires C, 56·5; H, 3·7; N, 14·7%).

4-(4-*Methyl*-3-m-*nitrobenzamidobenzamido*)*salicylic Acid* (VIg).—The amine (Vg) (143 g.) was heated under reflux for 3 hr. with *m*-nitrobenzoyl chloride (93 g.) and acetone (2 l.). The product was filtered off, washed with acetone, and dried (183 g.). It was stirred for 10 min. with a solution of sodium hydrogen carbonate (100 g.) in water (3 l.); the solid was filtered off, washed with water, stirred for 1 hr. with 2N-sodium hydroxide (4 l.), and kept overnight. The mixture was filtered, and the filtrate diluted with ethanol (1 l.) and acidified with acetic acid. Purification of the product by the sodium hydroxide–ethanol–hydrochloric acid treatment (see footnote *d*, Table 1) gave fawn prisms (108 g., 50%), m. p. 271—272° (decomp.) (Found: C, 60·5; H, 4·1; N, 9·8. $C_{22}H_{17}O_7N_3$ requires C, 60·7; H, 3·9; N, 9·65%).

*Symmetrical Urea* (VIIIa) *from* 2-(3-m-*Aminobenzamido*-4-*methylbenzamido*)*thiazole*.—The amine (VIIa) (11·6 g.) was dissolved in warm acetic acid (200 c.c.). After cooling, a solution of sodium acetate trihydrate (11·6 g.) in water (11·6 c.c.) was added, and a slow stream of carbonyl chloride was passed into the mixture. An exothermic reaction occurred, and after 30 min. the mixture was poured into water (1·5 l.) and kept overnight. The product, which was gelatinous, darkened during attempted drying at 100°; the remainder of the urea was therefore dissolved in boiling pyridine (500 c.c.). The solution was treated with charcoal, filtered, and poured into cold water (3 l.), and the milky precipitate coagulated by warming on the steam-bath. The product was then filtered off, washed with water, and dried at 100°. Recrystallisation from aqueous pyridine or aqueous acetic acid gave the *product* (6·8 g., 56%) in short, colourless needles, m. p. 305—307° (Found: C, 56·2; H, 5·0; N, 14·0; loss at 115°/vac., 7·6. $C_{37}H_{30}O_5N_8S_2,3H_2O$ requires C, 56·6; H, 4·6; N, 14·3; $H_2O$, 7·0%).

2-(4-*Methyl*-3-m-*nitrobenzensulphonamidobenzamido*)*thiazole* (VIb).—*m*-Nitrobenzene-sulphonyl chloride (28·5 g.) was added to a solution of 2-(3-amino-4-methylbenzamido)thiazole (Va) (30 g.) in pyridine (155 c.c.) which was then heated on the steam-bath for 1 hr. The solution was poured, with stirring, into water (5 l.) and kept overnight, by which time the sticky precipitate had solidified. Recrystallisation of the solid from aqueous pyridine gave 2-(4-*methyl*-3-m-*nitrobenzenesulphonamidobenzamido*)*thiazole*, straw-coloured needles, m. p. 215—217° (Found: C, 48·5; H, 3·3; N, 13·3. $C_{17}H_{14}O_5N_4S_2$ requires C, 48·8; H, 3·3; N, 13·4%).

The other *ureas* and *intermediates* were prepared by methods similar to those recorded above and are recorded in Tables 1—3.

*Salt of* 4-*Aminosalicylic Acid with* 4-*Methyl*-3-*nitrobenzoic Acid.—Method I.* 4-Methyl-3-nitrobenzoyl chloride (15·5 g.) was added to 4-aminosalicylic acid (11·9 g.) in 3% aqueous sodium hydroxide (200 c.c.), and the mixture was shaken for 1 hr. The solid was filtered off, washed with water, and dried. It was stirred for 10 min. with N-sodium hydroxide (50 c.c.), and the

TABLE 1. *Nitroamides* (IV) *and amino-amides* (V).

| Subst. | | Yield (%) | M. p. | Formula | Found (%) C | H | N | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| *Nitro-amides* | | | | | | | | | | |
| IVc | Plates [e] | 96 | 152—153° | $C_{13}H_{11}O_3N_3$ | 60·9 | 4·3 | 16·6 | 60·7 | 4·3 | 16·3 |
| IVe | Needles [a] | 78 | 316 * | $C_{13}H_{11}O_6N_3S$ | 46·6 | 3·6 | 12·55 | 46·25 | 3·3 | 12·5 |
| *Amino-amides* | | | | | | | | | | |
| Vc | Rectangular prisms [f] | 64 | 182·5—183 | $C_{13}H_{13}ON_3$ | 68·6 | 6·2 | 18·65 | 68·7 | 5·7 | 18·5 |
| Ve | Needles [a] | 70 [b] | 306 | $C_{13}H_{13}O_4N_3S$ [c] | 48·3 | 4·6 | 13·15 | 48·7 | 4·2 | 13·1 |
| Vg | Fawn prisms [d] | 91 | 251 * | $C_{15}H_{14}O_4N_2$ | 62·8 | 5·0 | 9·8 | 62·9 | 4·9 | 9·8 |

* With decomp. [a] Pptd. by acid from solution in dil. NaOH. [b] Reduction carried out in dil. NaOH at 25°/20 atm. [c] $+H_2O$ (Loss at 100°/vac., 4·5. Required: $H_2O$, 4·2%). [d] Pptd. by acid from solution in dil. NaOH–EtOH. [e] From EtOH or $C_6H_6$. [f] From EtOH.

TABLE 2. *Nitro-amides* (VI) *and amino-amides* (VII).

| Subst. | X | | Yield (%) | M. p. | Formula | Found (%) C | H | N | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Nitro-amides* | | | | | | | | | | | |
| VIc | CO | Needles [f] | 90 | 228·5° | $C_{20}H_{16}O_4N_4$ | 63·8 | 4·35 | 14·75 | 63·8 | 4·25 | 14·9 |
| VId | $SO_2$ | Pale yellow prisms [j] | 90 | 192—193 | $C_{19}H_{16}O_5N_4S$ | 55·5 | 4·1 | 13·6 | 55·3 | 3·9 | 13·6 |
| VIe | CO | Colourless [a] | 74 | 312 | $C_{20}H_{16}O_7N_4S$ | 52·9 | 4·0 | — | 52·6 | 3·5 | — |
| VIf | $SO_2$ | Plates [a] | 44 | 223 | $C_{19}H_{16}O_8N_4S_2,H_2O$ | 44·9 | 3·7 | 10·5 | 44·7 | 3·5 | 10·95 |
| *Amino-amides* | | | | | | | | | | | |
| VIIa | CO | Needles [j] | 90 [b] | 270—270·5 | $C_{18}H_{16}O_2N_4S$ | 61·4 | 4·7 | 15·7 | 61·4 | 4·55 | 15·9 |
| VIIb | $SO_2$ | Fawn prisms [j] | 94 [c] | 287—289 | $C_{17}H_{16}O_3N_4S_2$ | 52·8 | 4·2 | 14·6 | 52·6 | 4·1 | 14·4 |
| VIIc | CO | Needles [k] | 90 [d] | 217 | $C_{20}H_{18}O_2N_4$ | 69·4 | 5·3 | 16·0 | 69·4 | 5·2 | 16·2 |
| VIId | $SO_2$ | ,, | 80 [d] | 206—207 | $C_{19}H_{18}O_3N_4S$ [e] | 59·5 | 4·8 | 14·45 | 59·7 | 4·7 | 14·7 |
| VIIe | CO | Cream-coloured [a] | 74 [f] | 287 * | $C_{20}H_{18}O_5N_4S,H_2O$ | 53·8 | 4·8 | 12·6 | 54·05 | 4·5 | 12·6 |
| VIIf | $SO_2$ | Colourless [a] | 83 [c] | 240—250 * | $C_{19}H_{18}O_6N_4S_2,H_2O$ [g h] | 47·5 | 4·8 | 11·55 | 47·5 | 4·2 | 11·7 |
| VIIg | CO | Fawn prisms [l] | 50 | 243—244 * | $C_{22}H_{19}O_5N_3$ | 64·7 | 4·8 | 10·1 | 65·2 | 4·7 | 10·4 |

* With decomp. [a] Pptd. by acid from solution in dil. NaOH–EtOH. [b] Reduction in acetic acid at 68°/20 atm. [c] Reduction in dil. NaOH at 25°/21 atm. [d] Reduction in EtOH. [e] Found : S, 8·5. Required : S, 8·4%. [f] Reduction in suspension in dil. NaOH. [g] Found : S, 13·5. Required : S, 13·3%. [h] Loss at 110°/vac., 3·6. Required : $H_2O$, 3·8%. [i] From MeOH or dil. pyridine. [j] From dil. pyridine. [k] From EtOH. [l] From pyridine.

TABLE 3. *Ureas* (VIII).

| Subst. | | Yield (%) | M. p. | Formula | Found (%) C | H | N | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| VIIIb | Pale yellow prisms [a] | 70 | 240—245° * | $C_{35}H_{30}O_7N_8S_1,H_2O$ [b] | 51·4 | 4·0 | 13·6 | 51·2 | 3·9 | 13·7 |
| VIIIc | Needles [j] | 53 | 266 | $C_{41}H_{34}O_5N_8,0·5H_2O$ [c] | 67·8 | 4·9 | 15·45 | 67·7 | 4·8 | 15·4 |
| VIIId | Cream-coloured [d] | 60 | 220 * | $C_{39}H_{34}O_7N_8S_2,4H_2O$ [e] | 54·2 | 4·8 | 12·9 | 54·3 | 4·9 | 13·0 |
| VIIIe | [a] | 91 | 300 * | $C_{41}H_{34}O_{11}N_8S_2,4H_2O$ [b] | 52·3 | 4·8 | 11·55 | 51·8 | 4·4 | 11·8 |
| VIIIf | [a] | 84 | [g] | $C_{39}H_{34}O_{13}N_8S_4,3H_2O$ [h] | 46·1 | 4·3 | 10·8 | 46·6 | 4·0 | 11·15 |
| VIIIg | Pale brown | 65 | 250—253 * | $C_{45}H_{36}O_{11}N_6,2H_2O$ [i] | 61·7 | 4·6 | 9·5 | 61·8 | 4·6 | 9·6 |

* With decomp. [a] Pptd. by acid from solution in dil. NaOH–EtOH. [b] Loss at 112°/vac., 2·05. Required : $H_2O$, 2·2%. [c] Loss at 115°/vac., 7·6. Required : $H_2O$, 7·0%. [d] Pptd. from EtOH by ether. [e] Found : S, 7·6. Required : S, 7·4%. [f] Found : S, 6·65. Required : S, 6·7%. [g] Slowly darkens above 295°. [h] Loss at 112°/vac., 5·0. Required : $H_2O$, 5·4%. [i] Loss at 112°/vac., 4·6. Required : $H_2O$, 4·1%. [j] From dil. pyridine.

mixture was filtered. Addition of acetic acid to the filtrate gave 4-methyl-3-nitrobenzoic acid (2·9 g.), m. p. 190°. The residue left after stirring with aqueous sodium hydroxide was washed with water and dried (5·9 g., m. p. 178—183°). Recrystallisation from toluene gave *ON-di-(4-methyl-3-nitrobenzoyl)-m-aminophenol*, white needles, m. p. 167—168°, then resolidifies, and remelts at 191°. The product gave no colour with aqueous ferric chloride; neither did it couple with β-naphthol after attempted diazotisation, or decompose aqueous sodium carbonate. The compound did not depress the m. p. of a specimen prepared from 4-methyl-3-nitrobenzoyl chloride and *m*-aminophenol by the Schotten–Baumann method (Found : C, 60·7; H, 4·0; N, 9·7. $C_{22}H_{17}O_7N_3$ requires C, 60·7; H, 3·9; N, 9·65%).

The filtrate from the original reaction was acidified with acetic acid and afforded a solid which after crystallisation from toluene gave the *salt* (7·7 g.) of 4-aminosalicylic acid and 4-methyl-3-nitrobenzoic acid as pale yellow prisms, m. p. and mixed m. p. with an authentic specimen (method II), 165° (decomp.) [Found : C, 54·5; H, 4·4; N, 8·2%; equiv., 168·5 (by titration). $C_7H_7O_3N,C_8H_7O_4N$ requires C, 53·9; H, 4·2; N, 8·4%; equiv., 167·1]. The product was acid to litmus, and liberated carbon dioxide from saturated aqueous sodium hydrogen carbonate. It gave a violet colour with aqueous ferric chloride and a red colour after diazotisation and coupling with β-naphthol.

*Method II.* Sodium 4-aminosalicylate (2·11 g.) in water (10 c.c.) was added to 4-methyl-3-nitrobenzoic acid (1·81 g.) in N-sodium hydroxide (10 c.c.). The clear yellow mixture was

acidified with acetic acid, and the cream-coloured precipitate was recrystallised from toluene to give the salt (3·2 g.), pale yellow prisms, m. p. 165° (decomp.).

*Symmetrical Urea* (IX) *from* 4-*Aminosalicylic Acid*.—Sodium 4-aminosalicylate dihydrate (10 g.), dissolved in a mixture of 2N-sodium hydroxide and acetone (1 : 1; 100 c.c.), was treated with carbonyl chloride as described above. The *product*, purified by the sodium hydroxide–ethanol–hydrochloric acid treatment, formed white crystals (83%), m. p. 300° (Found: C, 53·0; H, 3·6; N, 8·3; loss at 112°/vac., 2·3. $C_{15}H_{12}O_7N_2,0{\cdot}5H_2O$ requires C, 52·8; H, 3·8; N, 8·2; $H_2O$, 2·6%).

*Symmetrical Urea* (X) *from* 4-(3-*Amino*-4-*methylbenzamido*)*salicylic Acid*.—This *urea* was prepared (80%) similarly and crystallised from pyridine in white needles, m. p. 289—290° (decomp.) (Found: C, 62·2; H, 4·6; N, 9·3. $C_{31}H_{26}O_9N_4$ requires C, 62·2; H, 4·4; N, 9·4%).

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