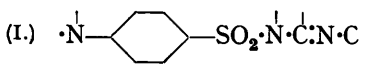
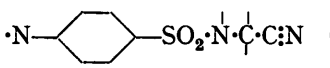
297. *The Preparation of Some Derivatives of Sulphanilamide.*

By Wesley Cocker.

A series of compounds of the type $X{\cdot}NH{\cdot}C_6H_4{\cdot}SO_2{\cdot}NY{\cdot}CH_2Z$ (*p*) have been prepared in which X is H or acetyl, Y is H or alkyl, and Z is CN, $CO{\cdot}NH_2$ or CO_2R. These substances have been examined for useful therapeutic properties, but so far the majority of them have proved of little value.

The success which has attended the use of 2-sulphanilamidopyridine* (M. & B. 693) and its derivatives in chemotherapy prompted the preparation of a series of compounds differing from it only slightly in atomic arrangement. This compound has the skeleton (I) and it was felt that compounds of the type (II) should have interesting and possibly useful therapeutic properties. The latter expectation has not been realised, but it has been

(I.)  (II.) 

found that these nitriles have toxic properties which increase as the substituent at N^1 is varied from H to CH_3 and then to C_2H_5. On the other hand, this change gives an increase in therapeutic value, but insufficient to counterbalance the increase in toxicity. Thus in tests on mice the compound $CH_3{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}SO_2{\cdot}NR{\cdot}CH_2{\cdot}CN$ when R = H is comparable in toxicity with " sulphanilamide," but the latter is seven times more active than the former in mice infected with a virulent culture of group A, hæmolytic *streptococcus*. When $R = CH_3$ or C_2H_5, the activity of the nitriles is greater than that of " sulphanilamide " but the therapeutic dose is unfortunately near the lethal dose.

The corresponding amides are neither toxic nor of therapeutic value.

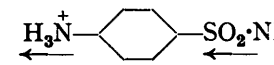
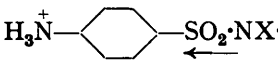
These nitriles and amides are easily converted into the corresponding esters. For instance, in an early experiment designed to give sulphanilamidoacetic acid, N^4-acetylsulphanilamidoacetonitrile was hydrolysed on the water-bath with concentrated hydrochloric acid for one hour, the solution evaporated to dryness, and the residue left overnight over caustic soda in an evacuated desiccator to remove traces of water and entrained hydrochloric and acetic acids. The required amino-acid hydrochloride was then separated from ammonium chloride, produced in the hydrolysis, by extraction with boiling absolute alcohol during five minutes. The alcoholic extract was evaporated to dryness and it was then intended to use the calculated quantity of caustic soda to decompose the hydrochloride. It was, however, noticed that this could be performed by using even an excess of sodium bicarbonate without the product dissolving as its sodium salt, and in fact the

* Nomenclature and numbering are due to Crossley, Northey, and Hultquist (*J. Amer. Chem. Soc.*, 1928, **60**, 2217).

product was proved to be ethyl sulphanilamidoacetate. Similar results were obtained by treatment of N^4-*acetyl*-N^1-*methyl*- and *-ethyl-sulphanilamidoacetonitriles* in like manner and the *methyl* esters are also produced by this method. Thus esterification of the amino-acid hydrochlorides takes only a few minutes.

It was also discovered that the hydrolysis of these esters is not easy, and those in which the substituent at N^1 is alkyl were only completely soluble in 2N-sodium hydroxide after heating for one hour on the water-bath. Interchange of ester group from ethyl to methyl can be performed, however, by hydrolysis of the ethyl ester with concentrated hydrochloric acid, followed by the esterification process indicated above.

This ease of esterification is doubtless associated with the acidic strength of the hydrochlorides of the amino-acids, which, owing to the presence of two kationoid groups within the molecule (III), must be quite strongly acidic.

(III.)  (IV.) 

Another point of theoretical interest concerning the hydrochlorides of the esters of the type (IV) is the ease of dissociation in water of that in which X and R = C_2H_5. This compound, when stirred into water, yields the free base, but when X = C_2H_5 and R = CH_3 or when X = CH_3 and R = C_2H_5 this is not the case. Obviously all these esters must be weakly basic, but certainly on the theoretical order of electron-releasing effects of alkyl groups ($C_2H_5 > CH_3 > H$) it would be expected that those bases in which X and R = C_2H_5 would be most basic and their salts should show the least tendency to dissociate in water. It appears that we have another instance of alkyl groups failing to follow the theoretical order.

Experimental.

N^4-*Acetylsulphanilamidoacetonitrile.*—Acetylsulphanilyl chloride (70 g.) (Stewart, J., 1922, **121**, 2558; " Organic Syntheses," **5**, 3) was ground to a paste with water (150 c.c.) and added all at once to a concentrated aqueous solution of aminoacetonitrile hydrogen sulphate (40 g.) (Anslow and King, J., 1929, 2463). The mixture was thoroughly agitated, and 3N-sodium hydroxide (350 c.c.) slowly added during 3 hours. The clear solution obtained was filtered, cooled with ice, and acidified with concentrated hydrochloric acid. The precipitate was freed from acid by washing with water. On crystallisation from hot water the required *nitrile* (54 g.) was obtained in flat, silvery plates, m. p. 194—195° (Found : C, 47·5; H, 4·7. $C_{10}H_{11}O_3N_3S$ requires C, 47·4; H, 4·4%).

N^4-*Acetylsulphanilamidoacetamide.*—The above nitrile (5 g.) was added little by little to concentrated sulphuric acid (10 c.c.), the mixture being agitated during each addition. The temperature slowly rose to 45°, and was then raised to 85° for 5 minutes. The straw-coloured solution was cooled and poured on ice, and the precipitate washed free from acid. It crystallised from hot water in long, colourless, rectangular prisms (5·2 g.), m. p. 224—225° (Found : C, 44·9; H, 5·0. $C_{10}H_{13}O_4N_3S$ requires C, 44·3; H, 4·8%).

Ethyl Sulphanilamidoacetate.—The nitrile previously described (3 g.) was heated for 2 hours with concentrated hydrochloric acid (20 c.c.) on the water-bath, and the mixture then evaporated to dryness. The residue was extracted during 5 minutes with boiling absolute alcohol, and the extract filtered from ammonium chloride. On concentration it yielded *ethyl sulphanilamidoacetate hydrochloride* (3 g.), which crystallised from a small volume of absolute alcohol in tufts of pointed prisms, m. p. 175° (Found : C, 41·2; H, 5·5. $C_{10}H_{14}O_4N_2S$,HCl requires C, 40·8; H, 5·1%). The hydrochloride, dissolved in water, was neutralised with sodium bicarbonate and the free *ester* which separated was washed with water and crystallised from dilute alcohol, forming long, colourless needles, m. p. 92° (Found : C, 46·6; H, 5·4. $C_{10}H_{14}O_4N_2S$ requires C, 46·5; H, 5·4%). This ester is readily obtained from its amide by a similar process. The *acetyl* derivative of the above ester was prepared by heating the ester (0·5 g.) with acetic anhydride (0·2 g.) for 1 hour on the water-bath. The excess of the anhydride was removed in a vacuum, and the residue poured into water. The oil which was deposited soon became solid; after being washed with water, it crystallised from dilute alcohol in long, colourless, feathery needles, m. p. 128° (Found : C, 47·7; H, 5·1. $C_{12}H_{16}O_5N_2S$ requires C, 48·0; H, 5·3%).

Methyl Sulphanilamidoacetate.—The ethyl ester (0·5 g.) was hydrolysed for 1 hour on the water-bath with concentrated hydrochloric acid (10 c.c.); the residue, after evaporation to dryness, was esterified by boiling methyl alcohol (30 c.c.) for 10 minutes, and the *methyl* ester

obtained from its hydrochloride by neutralisation with sodium bicarbonate. The ester crystallised from dilute methyl alcohol in large, colourless plates (0·3 g.), m. p. 88·5—89° (Found : C, 43·9; H, 4·7. $C_9H_{12}O_4N_2S$ requires C, 44·2; H, 4·9%).

N^4-*Acetyl*-N^1-*methylsulphanilamidoacetonitrile.*—N^4-Acetylsulphanilamidoacetonitrile (10 g.), dissolved in methyl alcohol, was treated with sodium methoxide (1·5 g. of sodium in 20 c.c. of methyl alcohol) and the resultant solution was refluxed overnight with methyl iodide (18 g.; 3 mols.). The alcohol was distilled off, and the residue made alkaline with sodium hydroxide and poured into a large volume of water. The oil deposited rapidly solidified; after being washed with water, it crystallised from hot water (charcoal) in flat, colourless needles or plates (4 g.), m. p. 158—159° (Found : C, 49·4; H, 5·0. $C_{11}H_{13}O_3N_3S$ requires C, 49·4; H, 4·9%). The *nitrile* (1·4 g.), treated with concentrated sulphuric acid (5 c.c.) in the manner previously described, yielded N^4-*acetyl*-N^1-*methylsulphilamidoacetamide* (1·1 g.), which crystallised from hot water in large, flat colourless plates, m. p. 185—186° (Found : C, 46·3; H, 5·5. $C_{11}H_{15}O_4N_3S$ requires C, 46·3; H, 5·3%).

Ethyl N^1-*methylsulphanilamidoacetate* was prepared from N^4-acetyl-N^1-methylsulphanilamidoacetonitrile (5 g.) by hydrolysis with concentrated hydrochloric acid (20 c.c.), followed by treatment with absolute alcohol as described for the lower homologue. The product crystallised from dilute alcohol in colourless needles or long prisms (1·5 g.), m. p. 115° (Found : C, 48·9; H, 6·0; N, 11·1. $C_{11}H_{16}O_4N_2S$ requires C, 48·5; H, 5·9; N, 10·3%).

Methyl N^1-*methylsulphanilamidoacetate* crystallised from dilute methyl alcohol in long colourless needles, m. p. 105—106° (Found : C, 46·1; H, 5·3. $C_{10}H_{14}O_4N_2S$ requires C, 46·5· H, 5·4%).

N^4-*Acetyl*-N^1-*ethylsulphanilamidoacetonitrile* was obtained by the ethylation of N^4-acetylsulphanilamidoacetonitrile with ethyl iodide in presence of sodium ethoxide. It crystallised from dilute alcohol in colourless plates, m. p. 128—128·5° (Found : C, 51·2; H, 5·2. $C_{12}H_{15}O_3N_3S$ requires C, 51·2; H, 5·3%). The corresponding *amide*, prepared as previously described, crystallised from hot water in long, colourless prisms, m. p. 167—168° (Found : C, 48·0; H, 5·6; N, 13·7. $C_{12}H_{17}O_4N_3S$ requires C, 48·1; H, 5·7; N, 14·0%).

Ethyl N^1-*ethylsulphanilamidoacetate*, prepared from the above nitrile (2 g.), crystallised from alcohol in needles or long prisms (1·5 g.), m. p. 88—89° (Found : C, 50·5; H, 6·1; N, 10·2, 9·9. $C_{12}H_{18}O_4N_2S$ requires C, 50·35; H, 6·3; N, 9·8%). The *methyl* ester obtained in a corresponding manner, crystallised from dilute methyl alcohol in flat, colourless prisms, m. p. 85° (Found : C, 48·3; H, 5·6. $C_{11}H_{16}O_4N_2S$ requires C, 48·5; H, 6·0%).

The author desires to express his thanks to Professor W. N. Haworth, F.R.S., for arranging for some of the analyses to be performed in the Chemistry Department of the University of Birmingham, to Mr. A. Campbell of this Department for the remainder of the analyses, and to Mr. W. W. Cocker of Messrs. Dickinson and Son, Accrington, for his help in arranging for the therapeutic tests by Messrs. Evans Sons, Lescher and Webb, Ltd., of Runcorn.

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[*Received, October 28th,* 1940.]