# 272. N-*Substituted Amino-acids. Part I. A New Method of Preparation of Dimethylamino-acids.*

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Aliphatic and aromatic amino-acids can be converted into their *NN*-dimethyl derivatives by reductive condensation with formaldehyde and hydrogen in the presence of palladised charcoal. Aromatic nitro-acids can be reduced and *N*-methylated in one operation.

In connection with investigations on the relative configurations of the naturally occurring amino-acids, carried out several years ago in this laboratory under the direction of Dr. F. Barrow, it became necessary to prepare the *NN*-dimethyl derivatives of some of them in an optically active form. The methods hitherto employed for the resolution of the simple amino-acids are not directly applicable to their dimethyl derivatives, but in preliminary experiments *NN*-dimethylalanine was resolved by means of its (−)-menthyl ester (Halliday, Thesis, Univ. of London, 1938), and optically pure (+)-*dimethyl*-L-*alanine* was isolated. This method was, however, not so successful when extended to other dimethylamino-acids, and attention was therefore directed to their preparation by the direct methylation of the unsubstituted amino-acids.*

A review of the literature revealed that, although the behaviour of a large number of amino-acids towards all the usual methylating agents had been examined, there is at present no satisfactory method available for the conversion of amino-acids into their dimethyl derivatives: methyl iodide in the presence of alkali leads to betaines, occasionally accompanied by mono- or di-alkylamino-acids; diazomethane leads to the methyl esters or mixtures thereof with the corresponding betaines; formaldehyde in the presence of formic acid has little value except for glycine and α-amino*iso*butyric acid, whose *NN*-dimethyl derivatives were obtained in satisfactory yield (Clarke, Gillespie, and Weisshauss, *J. Amer. Chem. Soc.*, **1933**, **55**, 4571.

Reductive condensation of amines with aldehydes or ketones in the presence of hydrogen and a catalyst (Skita and his co-workers, *Ber.*, **1928**, **61**, 1151 *et seq.*) has been frequently employed in recent years for the alkylation of amines. It has now been applied to amino-acids and peptides, furnishing a simple and convenient method for the preparation of both their mono- and their di-alkyl derivatives.

The reaction was first applied to the methylation of DL-alanine, a mixture of the amino-acid and formaldehyde being submitted to catalytic reduction in aqueous solution in the presence of palladised charcoal. Reduction proceeded readily at ordinary temperature and pressure, and *NN*-dimethyl-DL-alanine was isolated in almost quantitative yield. This method was then subsequently extended, with complete success, to glycine and the inactive forms of valine, leucine, phenylglycine, and phenylalanine.

Aromatic amino-carboxylic and amino-sulphonic acids may also be thus methylated, anthranilic and sulphanilic acids being readily converted into their dimethyl derivatives. It is of interest that the aromatic amino-acids may be replaced by the corresponding nitro-acids which are reduced and then methylated in one operation; the three isomeric dimethylamino-benzoic acids have been prepared in this manner, and the sodium salt of *p*-nitrotoluene-2-sulphonic acid has been converted into *sodium 4-dimethylaminotoluene-2-sulphonate*.

Attention was then directed to the preparation of the *NN*-dimethyl derivatives of the optically active forms of some of the naturally occurring amino-acids. Methylation at ordinary temperature was not attended with racemisation and the NN-*dimethyl* derivatives of (−)-D-alanine, (+)-L-*valine*, (+)-D-*leucine*, (−)-L-*phenylalanine*, and (−)-L-*tyrosine* were isolated in almost quantitative yields. (−)-L-Cystine gave NN-*dimethylcysteine* owing to the simultaneous reduction of the disulphide group: this dimethyl derivative very readily undergoes atmospheric oxidation to (−)-NNN′N′-*tetramethyl*-L-*cystine*.

* The major part of the work described in this paper was carried out by (the late) H. H. Stroud and forms part of a thesis submitted by him for the degree of Ph.D. (Univ. of London) in June, 1939.

(+)-L-Aspartic and (+)-L-glutamic acids have also been methylated by this method. The *NN*-dimethyl derivative of aspartic acid is noteworthy in that it is rapidly racemised in aqueous solution at 100° and differs in this respect from all the other optically active dimethylamino-acids so far examined.

Melting points and specific rotations of the active *NN*-dimethylamino-acids are given in the Table, together with the corresponding data for the unmethylated acids :

| | $[\alpha]_D$ in water. | M. p. | | $[\alpha]_D$ in water. | M. p. (decomp.). |
|---|---|---|---|---|---|
| (−)-*Dimethyl*-D-*alanine* ..... | − 8·73° | 188° | (−)-D-Alanine ..... | − 2·7° | 297° |
| (+)-*Dimethyl*-L-*valine* ..... | + 40·6 | 153 | (+)-L-Valine ..... | + 6·4 | 315 |
| (−)-*Dimethyl*-D-*leucine* ..... | − 49·6 | 198 | (+)-D-Leucine ..... | + 10·3 | 293 |
| (+)-*Dimethyl*-L-*phenylalanine* | + 77·1 | 218 | (−)-L-Phenylalanine..... | − 35·3 | 283 |
| (+)-*Dimethyl*-L-*tyrosine* ..... | + 74·3 | 300 | (−)-L-Tyrosine ..... | − 8·7 * | 314 |
| (−)-*Tetramethyl*-L-*cystine* ... | −146 | 106 | (−)-L-Cystine ..... | −220 * | 258 |
| (+)-*Dimethyl*-L-*aspartic acid* | + 14·4 | 184 | (+)-L-Aspartic acid ..... | + 6·0 | 270 |
| (+)-*Dimethyl*-L-*glutamic acid* | + 40·3 | 192 | (+)-L-Glutamic acid ..... | + 12·6 | 213 |

* In hydrochloric acid solution.

It will be observed that the methylation is sometimes accompanied by a change in the sign of rotation, but with acids belonging to the same steric series the rotation is always displaced in the same direction. Thus, in the case of the naturally occurring amino-acids (L-series), methylation results in a displacement of the rotation in a positive direction. It is possible that this displacement might be utilised in assigning configurations to amino-acids of undetermined stereochemical structure.

The dimethyl derivatives of amino-acids show marked differences in properties from the parent compounds. Whereas the latter melt indefinitely at high temperatures with decomposition, the dimethyl derivatives (except dimethyltyrosine) melt without decomposition and generally at much lower temperatures. The dimethyl derivatives are also more readily volatile and many of them can be sublimed under diminished pressure at temperatures near their melting points. Methylation also markedly increases the solubility. In alcohol and acetone the unmethylated acids are practically insoluble but, with few exceptions, the dimethyl derivatives dissolve readily in alcohol and are also somewhat soluble in acetone. The methylated acids are also much more soluble in water; *NN*-dimethyltyrosine, for example, is over fifty times more soluble than tyrosine; dimethyl-glycine and -alanine are deliquescent.

It is noteworthy that in every case so far investigated the amino-acids have given their dimethyl derivatives : no evidence has been found of the formation of monomethyl derivatives. In the succeeding paper it is shown that alkylations effected by reductive condensation of amino-acids $R{\cdot}CH(NH_2){\cdot}CO_2H$ with homologues of formaldehyde are subject to steric influences exercised by the group R, monoalkylation being readily accomplished in the case of amino-acids which contain a branched-chain in the β- or γ-position. The possibility of preparing monomethyl derivatives, therefore, appeared to be more favourable in the case of valine and α-amino*cyclo*hexylacetic acid, which have branched chains in the β-position. However, even with these acids under conditions favourable to the formation of monomethyl derivatives, only the dimethyl derivatives and the unchanged amino-acids could be isolated.

Reductive condensation with formaldehyde may also be applied to the hydrochlorides and the esters. Thus DL-lysine hydrochloride was readily converted into NNN′N′-*tetramethyl*-DL-*lysine*; and DL-alanine hydrochloride gave its dimethyl derivative, although somewhat more slowly than the free amino-acid. Glycine ethyl ester hydrochloride was also converted into its NN-*dimethyl* derivative, provided that the methylation was carried out under anhydrous conditions, *i.e.*, in the presence of dry paraformaldehyde and anhydrous magnesium sulphate in absolute ethanol.

## Experimental.

Formaldehyde employed was the commercial aqueous solution (*ca.* 40%). Polarimetric determinations were made in 2-dm. tubes.

*Methylation of Amino-acids.*—Unless otherwise stated, methylations were carried out by stirring a solution or suspension of the amino-acid (5 g.) in water (200 ml.) containing twice the theoretical amount of aqueous formaldehyde with palladised charcoal (5 g. of 10%) in an atmosphere of hydrogen at ordinary pressure and temperature until either reduction ceased or slightly more than the theoretical amount of hydrogen had been absorbed; with the free amino-acids the period of reduction varied from 3 to 12 hours. The mixture was then heated to boiling and filtered, and any amino-acids remaining with the catalyst extracted with hot water. Evaporation of the combined filtrates furnished the dimethylamino-acids in almost quantitative yield, together with some paraformaldehyde which was removed by re-evaporation with water.

NN-*Dimethylglycine*. This crystallised from ethanol–acetone in very deliquescent prisms, m. p. 176—178°; sublimation at 110—120°/0·5 mm. raised the m. p. to 182—183°, a value much higher than any previously recorded (Found: N, 13·6. Calc. for $C_4H_9O_2N$: N, 13·6%). NN-*Dimethylglycine ethyl ester hydrochloride* was prepared by methylation of glycine ester hydrochloride (14 g.) under anhydrous conditions in absolute ethanol (150 ml.) with paraformaldehyde (20 g.) in the presence of palladised charcoal (5 g. of 10%) and anhydrous magnesium sulphate (10 g.). Reduction was slow at room temperature but much more rapid at 54°, the theoretical volume of hydrogen being then absorbed in 8 hours. After filtration, the solution was evaporated to dryness. The residue slowly solidified when kept *in vacuo* over sulphuric acid and then crystallised from acetone–ether in extremely deliquescent slender needles, m. p. 88—90° (Found: Cl, 20·0. $C_6H_{13}O_2N$,HCl requires Cl, 21·1%).

NN-*Dimethyl*-DL-*alanine*, prepared from DL-alanine, crystallised from aqueous acetone as a *monohydrate*, prisms, m. p. 182° (Found: N, 10·4. $C_5H_{11}O_2N$,$H_2O$ requires N, 10·4%). Evaporation of its ethanolic solution to dryness on the steam-bath, followed by crystallisation of the residue from ethanolic acetone, furnished the anhydrous amino-acid in deliquescent, colourless prisms, m. p. 185° (cf. Duvillier, *Bull. Soc. chim.*, 1892, [iii], 7, 99) (Found: N, 12·0. Calc. for $C_5H_{11}O_2N$: N, 12·0%). The *hydrochloride* crystallised from ethanol–light petroleum (b. p. 40—60°) in hygroscopic prisms, m. p. 148° (Found: N, 9·2; Cl, 23·1. $C_5H_{11}O_2N$,HCl requires N, 9·1; Cl, 23·1%). The *copper* salt, prepared by digesting an aqueous solution of the amino-acid with freshly precipitated copper hydroxide, separated from ethanol as the *dihydrate*, in blue, non-efflorescent prisms [Found: N, 8·5; Cu, 19·2. $(C_5H_{10}O_2N)_2Cu,2H_2O$ requires N, 8·5; Cu, 19·2%]; an efflorescent heptahydrate has been described by Duvillier (*loc. cit.*).

(−)-NN-*Dimethyl*-D-*alanine*.—(−)-Benzoyl-D-alanine, prepared by the resolution of the inactive compound (Pope and Gibson, *J.*, 1912, **101**, 939), was hydrolysed with hydrochloric acid and the resulting (−)-D-alanine hydrochloride (3·8 g.), $[\alpha]_D^{18}$ −9·13° in water (*c*, 13·1), was methylated with formaldehyde (15 ml.) at ordinary temperature, the reduction being complete in 12 hours. The hydrochloride was purified as above and converted into the free *dimethylamino-acid via* the silver salt in the usual manner. Crystallised from acetone–ethanol, this formed very deliquescent prisms having m. p. 184°, $[\alpha]_D^{16\cdot5}$ −3·5°, $[\alpha]_{5461}^{16\cdot5}$ −4·2° (*c*, 5·10 in ethanol), and $[\alpha]_D^{17\cdot5}$ −8·7°, $[\alpha]_{5461}^{17\cdot5}$ −10·5° (*c*, 5·12 in water) (Found: N, 12·0. $C_5H_{11}O_2N$ requires N, 12·0%).

(+)-NN-*Dimethyl*-L-*valine*, prepared from (+)-L-valine, $[\alpha]_D^{18}$ + 6·4° (*c*, 4·5 in water), crystallised from acetone–ethanol in long slender, slightly hydroscopic needles, m. p. 154°, and had $[\alpha]_D^{16}$ + 34·1°, $[\alpha]_{5461}^{16}$ + 40·1° (*c*, 2·02 in ethanol), and $[\alpha]_D^{14}$ + 40·6°, $[\alpha]_{5461}^{14}$ + 48·2° (*c*, 2·15 in water) (Found: N, 9·7. $C_7H_{15}O_2N$ requires N, 9·7%).

*NN*-Dimethyl-DL-valine, previously obtained by Karrer *et al.* (*Helv. Chim. Acta*, 1922, **5**, 469) as a crystalline hygroscopic mass (m. p. not stated) by interaction of dimethylamine and (±)-α-bromo*iso*valeric acid, was readily prepared in a pure condition by the methylation of DL-valine. It crystallised from acetone–ethanol in slightly hygroscopic prisms, m. p. 152° (Found: N, 9·6%), and formed a *hydrochloride* which separated from the same solvent in slender needles, m. p. 164° (Found: Cl, 19·5. $C_7H_{15}O_2N$,HCl requires Cl, 19·5%); the *copper* salt crystallised as a *monohydrate* in ruby-red, rhombic prisms when its aqueous solution was evaporated at *ca.* 60° (Found: Cu, 17·3; N, 7·6; loss on drying at 100°/2 mm., 4·5. $C_{14}H_{28}O_4N_2Cu,H_2O$ requires Cu, 17·2; N, 7·6; $H_2O$, 4·9%). When the monohydrate remained in contact with the mother-liquor for 2 days at room temperature, it was transformed into a *dihydrate*, which crystallised in lustrous, deep-blue prisms (Found: Cu, 16·3; N, 7·2; loss on drying at 100°/2 mm., 10·0. $C_{14}H_{28}O_4N_2Cu,2H_2O$ requires Cu, 16·4; N, 7·4; $H_2O$, 9·3%), the anhydrous salt forms a bronze coloured powder.

(−)-NN-*Dimethyl*-D-*leucine*, prepared from (+)-D-leucine having $[\alpha]_D^{20}$ +10·3° (*c*, 2·02 in water), crystallised from ethanol–acetone in long needles, m. p. 210°, and had $[\alpha]_D^{20}$ −35·8°, $[\alpha]_{5461}^{20}$ −42·4° (*c*, 3·15 in ethanol) and $[\alpha]_D^{20}$ −49·6°, $[\alpha]_{5461}^{20}$ −58·2° (*c*, 3·15 in water) (Found: C, 60·6; H, 10·7; N, 8·7. $C_8H_{17}O_2N$ requires C, 60·3; H, 10·8; N, 8·8%).

*NN*-Dimethyl-DL-leucine, obtained by methylating inactive leucine, has m. p. 187—188°. A *NN*-dimethyl-leucine showing a lævorotation (value not stated) has been obtained by Karrer *et al.* (*Helv. Chim. Acta*, 1921, **4**, 76) as a hygroscopic mass, m. p. 185°, by the interaction of dimethylamine with (−)-α-bromo*iso*hexoic acid. Since neither of the dimethyl-leucines described above is hygroscopic, Karrer's product was impure and, from its m. p., appears to have consisted mainly of the inactive form.

(+)-NN-*Dimethyl*-L-*phenylalanine*, prepared from (−)-L-phenylalanine having $[\alpha]_D^{20}$ −35·3° (*c*, 2·01 in water), separated from aqueous ethanol in needles, m. p. 218°, $[\alpha]_D^{20}$ +77·1°, $[\alpha]_{5461}^{20}$ +91·7° (*c*, 1·32 in water) (Found: N, 7·1. $C_{11}H_{15}O_2N$ requires N, 7·2%).

NN-*Dimethylphenyl*-DL-*alanine* crystallised from methanol in small prisms, m. p. 228° (Found: N, 7·2%), and furnished a *copper* salt which separated from water as a light-blue crystalline powder (Found: N, 5·9; Cu, 13·8. $C_{22}H_{28}O_4N_2Cu$ requires N, 6·3; Cu, 13·9%).

(+)-NN-*Dimethyl*-L-*tyrosine*.—The methylation of natural (−)-L-tyrosine in aqueous suspension (5 g. in 250 ml.) proceeded very slowly at ordinary temperature, but was complete in 5·5 hours at 65°. It crystallised from water in felted masses of filamentous needles, which slowly changed into short stout prisms when allowed to remain in contact with the mother-liquor. Both *forms* had the same rotation, *viz.*, $[\alpha]_D^{19}$ +74·3°, $[\alpha]_{5461}^{19}$ +89·7° (*c*, 2·07 in water), and showed a similar behaviour when heated. They became brown at *ca.* 220° and had m. p. varying from 246° to 290° (decomp.) according to the rate of heating; when rapidly heated after being plunged in a bath at 295° they both melt at 300° (decomp.) (Found: C, 63·3; H, 7·2; N, 6·6. $C_{11}H_{15}O_3N$ requires C, 63·1; H, 7·2; N, 6·7%).

(−)-L-Cystine, $[\alpha]_D^{22}$ −220° (*c*, 1·832 in N-HCl), on methylation absorbed slightly more than 5 molecular proportions of hydrogen indicating that simultaneous reduction to *NN*-dimethylcysteine had taken place. The latter was isolated as a colourless gum which could not be obtained in a crystalline condition, but after oxidative exposure to air, followed by crystallisation from acetone, it furnished (−)-NNN′N′-*tetramethyl*-L-*cystine* in needles, m. p. 105—107° after softening at 95°, $[\alpha]_D^{20}$ −121°, $[\alpha]_{5461}^{20}$ −146° (*c*, 0·50 in ethanol), $[\alpha]_D^{22}$ −146°, $[\alpha]_{5461}^{22}$ −170° (*c*, 0·543 in water) (Found: C, 40·7; H, 6·7; N, 9·6. $C_{10}H_{20}O_4N_2S_2$ requires C, 40·5; H, 6·8; N, 9·5%).

NNN′N′-*Tetramethyl*-DL-*lysine hydrochloride*, prepared from DL-lysine hydrochloride in the usual

manner, separated from acetone–ethanol in extremely hygroscopic prisms, m. p. 203—204° after prolonged drying over sulphuric acid (Found : N, 11·6. $C_{10}H_{25}O_2N_2Cl$ requires N, 11·7%).

(+)-NN-*Dimethyl*-L-*aspartic acid* was isolated from the aqueous solution resulting from the methylation of natural (+)-L-aspartic acid, by evaporation under diminished pressure below 30° in order to avoid racemisation. It crystallised from aqueous ethanol in slender prisms, m. p. 184°, $[\alpha]_D^{18}$ +14·4°, $[\alpha]_{5461}^{14\cdot4}$ +17·5° (*c*, 3·06 in water) and showed no change in rotation when its aqueous solution was kept at room temperature for 13 hours; but it underwent racemisation when the solution was heated at 100°, the initial value, $[\alpha]_D^{18}$ +14·4° (*c*, 3·06), falling to +8·5°, +5·0°, and +2·3° after 2, 4, and 8 hours, respectively (Found : N, 8·7. $C_6H_{11}O_4N$ requires N, 8·7%).

*NN*-Dimethyl-DL-aspartic acid, previously obtained by Korner and Menozzi (*Atti R. Accad. Lincei*, 1896, [v], I, 457), was readily obtained by heating an aqueous solution of the active dimethylamino-acid on the steam-bath for 24 hours. It crystallised from aqueous ethanol in small prisms, m. p. 175° (Found : N, 8·6%), and formed a *hydrochloride*, prisms, m. p. 160°, from acetone–ethanol (Found : N, 7·1; Cl, 17·9. $C_6H_{12}O_4NCl$ requires N, 7·1; Cl, 17·9%); the *copper* salt separated as a bluish-green microcrystalline *monohydrate*, when its aqueous solution was allowed to evaporate spontaneously at ordinary temperature (Found : N, 5·5; Cu, 26·0; loss over $P_2O_5$ at 95°/1·5 mm., 6·8. $C_6H_9O_4NCu,H_2O$ requires N, 5·8; Cu, 26·4; $H_2O$, 7·5%).

(+)-*Dimethyl*-L-*glutamic acid*, prepared from the natural (+)-L-glutamic acid, crystallised from aqueous ethanol in short prisms, m. p. 192°, $[\alpha]_D^{16}$ +40·3°, $[\alpha]_{5461}^{16}$ +48·3° (*c*, 3·71 in water); these values of $[\alpha]$ were unchanged after the solution had been heated for 5 hours at 100° (Found : C, 48·1; H, 7·5; N, 7·9. $C_7H_{13}O_4N$ requires C, 48·0; H, 7·5; N, 8·0%).

*Experiments on Partial Methylation.*—(a) *With valine.* Methylation of the inactive acid (5·9 g.) in ethanol (100 ml.) with aqueous formaldehyde (7·5 ml.) in the presence of palladised charcoal (4 g. : 10% of Pd) was carried out at room temperature and interrupted after 2 hours when the volume of hydrogen taken up amounted to 20% above that required for monomethylation. Working up as usual and crystallisation from acetone–ethanol gave *NN*-dimethylvaline (3 g.), m. p. (and mixed m. p.) 152°. The amino-acid remaining with the catalyst was extracted with hot ethanol (30 ml.) containing concentrated hydrochloric acid (3 ml.) and then liberated by the addition of pyridine (5 ml.). It weighed 2·4 g. and consisted of unchanged valine, m. p. (and mixed m. p.) 291°.

(b) *With α-amino*cyclo*hexylacetic acid.* The methylation of the amino-acid (1·97 g.) was carried out at 56° under the same conditions as those described for valine, and the products were isolated in a similar manner. The amino-acid (0·52 g.) insoluble in ethanol consisted of unchanged α-amino*cyclo*hexylacetic acid, m. p. (and mixed m. p.) 297° whilst the soluble portion (1·42 g.), after crystallisation from dioxan, furnished *α-dimethylamino*cyclo*hexylacetic acid* in rosettes of small needles, m. p. 176—177° (Found : N, 7·6. $C_{10}H_{19}O_2N$ requires N, 7·6%).

(c) *With α-amino*iso*butyric acid.* After methylation at room temperature, slightly less than half of the amino-acid was recovered unchanged, m. p. 290°, the remainder being converted into *α-dimethylamino*iso*butyric acid*, which crystallised from ethanol–dioxan in needles, m. p. 275° with previous partial sublimation (Found : N, 11·0. $C_6H_{13}O_2N$ requires N, 10·7%), and gave a hydrochloride, m. p. 264°, in agreement with the value given by Clarke *et al.* (*loc. cit.*).

*Methylation of Aromatic Amino-acids.*—The isomeric dimethylaminobenzoic acids were prepared in acetic acid, preliminary experiments with anthranilic acid having shown that the methylation could not be effected in aqueous or aqueous–ethanolic solution on account of the separation of a resinous mass consisting, presumably, of a methylene derivative, which enclosed the catalyst and prevented further reduction. In acetic acid solution (75 ml.) the reduction of anthranilic acid (7 g.) with aqueous formaldehyde (25 ml.) in the presence of palladised charcoal (2·5 g. of 10%) at room temperature was complete in 13 hours. The residue, obtained by evaporating the solution, slowly solidified and on crystallisation from ether furnished *NN*-dimethylanthranilic acid in prisms, m. p. 72° (Found : C, 65·4; H, 6·6; N, 8·6. Calc. for $C_9H_{11}O_2N$ : C, 65·4; H, 6·7; N, 8·5%) (cf. Cohen and Dudley, *J.*, 1910, **97**, 1746).

The dimethylaminobenzoic acids were also prepared from the corresponding nitro-acids by simultaneous reduction and methylation in ethanolic solution. Thus, the reduction of *m*-nitrobenzoic acid (16·7 g.) in aqueous ethanol (80 ml. of 80%) in the presence of aqueous formaldehyde (50 ml.) occupied 3 hours and furnished *m*-dimethylaminobenzoic acid, m. p. 150°, in almost theoretical yield (Found : C, 65·6; H, 6·6; N, 8·5%).

In one experiment in which *p*-nitrobenzoic acid was employed, the preparation of the catalyst, the reduction of the nitro-compound, and the methylation of the resulting amino-acid were accomplished in one operation by stirring a mixture containing aqueous formaldehyde (25 ml.), ethanol (100 ml.), water (125 ml.), *p*-nitrobenzoic acid (10 g.), sodium acetate (5 g.), charcoal (5 g.), and palladium chloride (1 g. dissolved in 5 ml. of 2N-hydrochloric acid), in hydrogen at room temperature; reduction was complete in 45 minutes. After filtration and extraction of the catalyst with ethanol, the combined solutions were concentrated by evaporation until crystallisation commenced, *p*-dimethylaminobenzoic acid (8 g.) separating in needles, m. p. 240° (Found : C, 65·7; H, 6·8; N, 8·6%); previous values given for the m. p. vary from 234—243·5°.

Sulphanilic acid was also methylated in aqueous solution, and the resulting *NN*-dimethyl derivative isolated as of the monohydrate described by Bamberger and Tschirner (*Ber.*, 1899, **32**, 1892).

*Sodium* NN-*dimethyl*-p-*toluidine*-2-*sulphonate*, prepared by reducing the sodium salt of *p*-nitrotoluene-2-sulphonic acid in aqueous solution (11 g. in 100 ml.) containing aqueous formaldehyde (25 ml.), separated from ethanol as a *dihydrate* in the form of a white crystalline powder from which the water was not completely removed after 3 hours at 160°/2 mm. (Found : N, 5·1; Na, 8·4. $C_9H_{12}O_3NSNa,2H_2O$ requires N, 5·1; Na, 8·4%).

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