889. *Formation and Properties of Sydnone Imines, a New Class of Meso-ionic Compound, and Some Sydnones Related to Natural α-Amino-acids.*

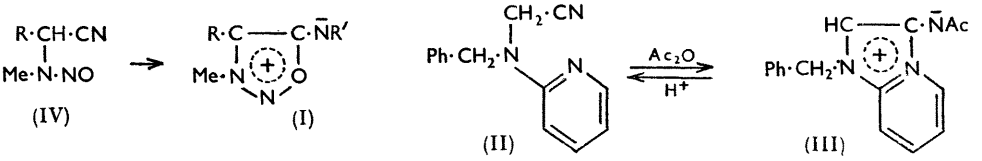
By Peter Brookes and James Walker.

When two representative α-methylamino-nitriles were treated with excess of nitrous fumes and the crude products were treated with acetic anhydride, sydnone nitroimines were formed by dehydration of the intermediate sydnone imine nitrates. Sydnone imine salts are formed with great ease from α-*N*-methyl-*N*-nitrosoamino-nitriles by reaction with an equivalent of nitric acid, or with hydrogen chloride in ether. The parent free sydnone imines were unstable and liberation from the salt gave the corresponding α-(*N*-methyl-*N*-nitrosoamino)-acid amide. Catalytic hydrogenation of 3-methyl-4-*iso*propylsydnone imine nitrate gave *N*-methylvaline amide and ammonia.

Besides their formation by dehydration with acetic anhydride, the sydnone nitroimines were also obtained by treatment of the nitrates with concentrated sulphuric acid. The nitroimines were stable to acid but decomposed immediately in presence of alkali with liberation of nitrous oxide and formation of the α-(*N*-methyl-*N*-nitrosoamino)-acid.

Several sydnones bearing side-chains characteristic of natural α-amino-acids have been prepared.

As a preliminary stage in the preparation of sydnones related to natural α-amino-acids, which is described below, α-methylamino*iso*valeronitrile and γ-methyl-α-methylaminovaleronitrile were prepared as intermediates in the preparation of *N*-methylvaline and *N*-methyl-leucine respectively. It therefore appeared of interest to nitrosate these two nitriles and to attempt the formation of the corresponding sydnone imines (I; R′ = H).

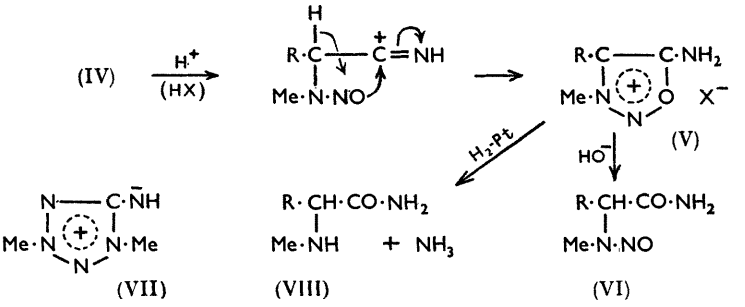


As a guide to the behaviour that might have been expected from this hitherto unknown type of compound * one may note that Bristow, Charlton, Peak, and Short [1] had shown that *N*-benzyl-*N*-2-pyridylamino-acetaldoxime and -acetonitrile (II) were both converted by acetic anhydride into " an acetyl derivative of the nitrile," which contained no cyano-group (from its infrared absorption spectrum) and was formulated as the meso-ionic compound (III). On cold acid hydrolysis the latter (III) was deacetylated and reverted to the nitrile (II). This behaviour of (III) suggested that it might not be possible to demonstrate the formation of the sydnone imine (I; R′ = H) unless steps were taken to stabilise the structure, as, for example, by acetylation to give the sydnone acetylimine (I; R′ = Ac), and the normal conditions used for sydnone formation from α-[*N*-alkyl(or aryl)-*N*-nitrosoamino]-acids, namely, the action of acetic anhydride, could be expected to lead to acetylated imines (I; R′ = Ac) when applied to α-(*N*-methyl-*N*-nitrosoamino)-nitriles (IV). Acetic anhydride, however, had no effect on pure α-(*N*-methyl-*N*-nitrosoamino)*iso*valeronitrile (IV; R = Pr^{i}), but treatment of α-methylamino*iso*valeronitrile with nitrous fumes in excess followed by treatment of the crude product with acetic anhydride at room temperature gave a crystalline solid $C_6H_{10}O_3N_4$, which appeared to contain no cyano-group from its infrared absorption spectrum and showed two strong bands in its ultraviolet

* Baker, Ollis, and Poole (*J.*, 1949, 311) had foreseen the possible existence of sydnone alkyl- or aryl-imines (I; R′ = alkyl or aryl), although none has so far been described.

[1] Bristow, Charlton, Peak, and Short, *J.*, 1954, 616.

absorption spectrum suggestive of an aromatic system. Similar treatment of γ-methyl-α-methylaminovaleronitrile afforded a homologous substance $C_7H_{12}O_3N_4$, having an almost identical ultraviolet absorption spectrum and showing many features in common with the preceding substance $C_6H_{10}O_3N_4$ in its infrared absorption spectrum. In a subsequent experiment the crude unwashed α-(*N*-methyl-*N*-nitrosoamino)*iso*valeronitrile, when left overnight, partly solidified and the solid after purification gave analytical figures indicative of the formula $C_6H_{12}O_4N_4$; the ultraviolet absorption spectrum of this substance showed a single maximum at 300 mμ and the infrared absorption spectrum showed a strong band at 1670 cm.$^{-1}$, with a subsidiary band at 1615 cm.$^{-1}$. Similar treatment of γ-methyl-α-methylaminovaleronitrile gave a substance $C_7H_{14}O_4N_4$ with closely similar light-absorption properties to those of the substance $C_6H_{12}O_4N_4$. As the substance $C_6H_{12}O_4N_4$ was a nitrate it was obviously derived from a base $C_6H_{11}ON_3$, and the similarity between the ultraviolet light absorption and that of 3-*cyclo*hexyl-[2] and 3-benzyl-sydnone [2,3] suggested that the substance $C_6H_{12}O_4N_4$ was, in fact, 3-methyl-4-*iso*propylsydnone imine nitrate (V; R = Pr^i, X = NO_3). It was then found to be more conveniently accessible by treating pure α-(*N*-methyl-*N*-nitrosoamino)*iso*valeronitrile (IV; R = Pr^i) with an equivalent amount of nitric acid, and the hydrochloride (V; R = Pr^i, X = Cl) was obtained by the action of hydrogen chloride in dry ether * on the methylnitrosoamino-nitrile (IV; R = Pr^i). Similarly the substance $C_7H_{14}O_4N_4$ was shown to be 4-*iso*butyl-3-methylsydnone imine nitrate (V; R = Bu^i, X = NO_3) by its ready formation from pure γ-methyl-α-(*N*-methyl-*N*-nitrosoamino)valeronitrile (IV; R = Bu^i) and nitric acid, and the hydrochloride (V; R = Bu^i, X = Cl) resulted from the action of dry hydrogen chloride in ether. The nitrate (V; R = Pr^i, X = NO_3) was converted into the hydrochloride (V; R = Pr^i, X = Cl) by treatment with the chloride form of an anion-exchange resin, but treatment with the hydroxyl form of the resin opened the heterocyclic ring and gave the α-(*N*-methyl-*N*-nitrosoamino)-acid amide (VI; R = Pr^i), which was also obtained when the neutral aqueous solution of the nitrate (V; R = Pr^i, X = NO_3) was basified in the



cold and extracted with chloroform. It thus appears that the sydnone imine (I; R = Pr^i, R′ = H) is incapable of existence as the free base in contrast, for example, with 5-imino-1 : 3-dimethyltetrazole (VII), a meso-ionic imine, which can be handled as the free base.[4] The conversion of the sydnone imine nitrate (V; R = Pr^i, X = NO_3) into the α-(*N*-methyl-*N*-nitrosoamino)-amide (VI; R = Pr^i) on treatment with alkali is formally analogous to the reversion,[5] under rather more vigorous alkaline conditions, of sydnones to their parent α-[*N*-alkyl(or aryl)-*N*-nitrosoamino]-acids. Also, as in the catalytic hydrogenation

* *Added, July 6th*, 1957.—Reference was made to the present work recently by Baker and Ollis (*Quart. Rev.*, 1957, **11**, 15), and, as a result, Professor M. Ohta (Tokyo) has written to say that he and his colleagues have obtained sydnone imine hydrochlorides by the action of ethanolic hydrogen chloride on suitably substituted nitriles (Kato, Hashimoto, and Ohta, *J. Chem. Soc. Japan*, 1957, **78**, 707).

[2] Baker, Ollis, and Poole, *J.*, 1949, 311.

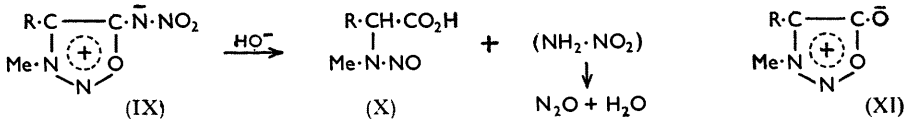
[3] Earl, Le Fèvre, and Wilson, *ibid.*, p. S 103.

[4] Bryden, Henry, Finnegan, Boschan, McEwan, and Van Dolah, *J. Amer. Chem. Soc.*, 1953, **75**, 4863; Henry, Finnegan, and Lieber, *ibid.*, 1954, **76**, 2894.

[5] Earl and Mackney, *J.*, 1935, 899.

of sydnones [2] to the α-*N*-alkyl(or aryl)amino-acid and ammonia, 3-methyl-4-*iso*propylsydnone imine nitrate (V; R = Pr^i, X = NO_3) took up two mols. of hydrogen rapidly and a third more slowly with formation of *N*-methylvaline amide (VIII; R = Pr^i) and ammonia.

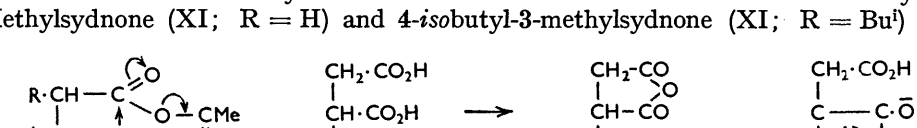
Returning to the compounds $C_6H_{10}O_3N_4$ and $C_7H_{12}O_3N_4$, it is obvious, in view of the ready formation of the sydnone imine nitrates (V; R = Pr^i, Bu^i, X = NO_3) from the α-(*N*-methyl-*N*-nitrosoamino)-nitriles (IV; R = Pr^i, Bu^i), that they were formed in the circumstances outlined above by dehydration of sydnone imine nitrates by the action of acetic anhydride analogously to the dehydration of aryl- [6] and alkyl-amine nitrates [7] by acetic anhydride to give aryl- or alkyl-nitramines. The same substances $C_6H_{10}O_3N_4$ and $C_7H_{12}O_3N_4$ were also obtained by the action of cold concentrated sulphuric acid on the sydnone imine nitrates (V; R = Pr^i or Bu^i, X = NO_3), similarly to the conversion of urea nitrate into nitrourea.[8] The substances $C_6H_{10}O_3N_4$ and $C_7H_{12}O_3N_4$ are therefore formulated as the meso-ionic 3-methyl-4-*iso*propylsydnone nitroimine (IX; R = Pr^i) and 4-*iso*butyl-3-methylsydnone nitroimine (IX; R = Bu^i) respectively. These substances were stable towards cold mineral acid and water but they were immediately decomposed by aqueous alkali, the products in the case of 3-methyl-4-*iso*propylsydnone nitroimine (IX; R = Pr^i) being identified as *N*-methyl-*N*-nitrosovaline and nitrous oxide. The latter product, identified by its infrared absorption spectrum, is presumably formed by way of nitramide.



(IX) (X) (XI)

No biological properties of sydnones appear to have been recorded, and, as it appeared probable that suitably substituted sydnones might act as amino-acid antagonists, a number of sydnones (XI) were prepared from *N*-methylamino-acids. The *N*-methylamino-acids employed were sarcosine, *N*-methylvaline, *N*-methyl-leucine, and *N*-methylphenylalanine. *N*-Methyl-leucine was prepared from *iso*valeraldehyde by the method used in the case of *N*-methylvaline,[9] and *N*-methylphenylalanine was prepared by a simplification of the method of Knoop and Oesterlin.[10]

Nitrosation was best carried out in aqueous solution with nitrous fumes, and sydnone formation from the *N*-methyl-*N*-nitrosoamino-acids was effected with acetic anhydride. 3-Methylsydnone (XI; R = H) and 4-*iso*butyl-3-methylsydnone (XI; R = Bu^i) could



(XII) (XIII) (XIV) (XV)

not be obtained solid at room temperature and distillation in a vacuum was accompanied by slight decomposition, but 3-methyl-4-*iso*propyl- (XI; R = Pr^i) and 4-benzyl-3-methylsydnone (XI; R = CH_2Ph) were obtained crystalline. The ultraviolet spectra of these four compounds were very similar; the 4-substituted compounds (XI; R = Pr^i, Bu^i, CH_2Ph) showed a single strong band at 292 mμ (log ε 3·89—3·98) in agreement with Baker, Ollis, and Poole,[2] who regard absorption at 292 mμ as characteristic of the sydnone ring, while in 3-methylsydnone (XI; R = H) the maximum was shifted to 286 mμ. The

[6] Bamberger, *Ber.*, 1895, **28**, 399; Hoff, *Annalen*, 1900, **311**, 99.
[7] Bamberger, *Ber.*, 1895, **28**, 535.
[8] Lachman and Thiele, *Ber.*, 1894, **27**, 1519.
[9] Cook and Cox, *J.*, 1949, 2334.
[10] Knoop and Oesterlin, *Z. physiol. Chem.*, 1925, **148**, 310.

infrared spectra showed multiple bands [11] in the 1650—1800 cm.$^{-1}$ region, the numbers, positions, and relative intensities of the maxima depending markedly on the media in which the spectra were observed (homogeneous film, $CHCl_3$, CCl_4, EtOH, or KCl disc).

Baker, Ollis, and Poole [12] have provided evidence to show that sydnone formation with acetic anhydride takes place by way of a mixed anhydride (XII), and that conversion of the latter into the sydnone occurs relatively slowly by attack by the anionoid nitroso-oxygen atom on the proximate cationoid carbonyl group. Particular interest therefore attached to the behaviour of an *N*-alkyl-*N*-nitrosoaspartic acid (XIII) under the conditions of sydnone formation with acetic anhydride. *N*-Methylaspartic acid, readily obtained by addition of methylamine to maleic acid, gave, however, an oily nitroso-derivative, and *N*-benzylaspartic acid was therefore used instead, as it gave a solid nitroso-derivative (XIII; R = CH_2Ph). Treatment of the latter with acetic anhydride gave a crystalline anhydro-compound $C_{11}H_{10}O_4N_2$, showing a single rather broad band in its ultraviolet absorption spectrum at 242 mμ and two strong typical carbonyl-stretching bands in its infrared absorption spectrum at 1785 and 1865 cm.$^{-1}$, indicative of the cyclic anhydride * structure (XIV), together with a band at 1400 cm.$^{-1}$ probably due to the >N·NO group.[11a] Obviously steric and polar constraints inhibiting approach of the nitroso-oxygen atom to the carbonyl-carbon atom prevent isomerisation of *N*-benzyl-*N*-nitrosoaspartic anhydride (XIV) to 3-benzyl-4-carboxymethylsydnone (XV).

The *N*-methylamino-acids and the four sydnones were kindly examined by Dr. A. T. Fuller and Mr. J. Lee for inhibitory activity *in vitro* against *Strep. haemolyticus, Staph. aureus, Bact. coli*, and *Leuconostoc mesenteroides* but no activity was observed. The four sydnones, the sydnone imines, and nitroimines were kindly examined by Dr. R. J. Terry for activity in experimental filarial infections but none showed activity.

Experimental

*3-Methyl-4-iso**propylsydnone Imine Nitrate*** (V; R = Pr^i; X = NO_3).—(*a*) 2-Methylamino-*iso*valeronitrile [9] (11·2 g.) was dissolved in dry ether (50 c.c.), the solution was cooled in ice, and nitrous fumes, generated by the action of 25% sulphuric acid on solid sodium nitrite, were passed until the solution became deep blue-green in colour (1½—2 hr.). The solvent was removed at room temperature, giving a pale brown liquid (16·5 g.), which evolved nitrous fumes on warming. The liquid did not crystallise and the ultraviolet light absorption spectrum showed only end-absorption. When kept at room temperature for 3 days the liquid deposited crystals. Ether was added and the pale yellow solid (6·5 g.) was collected and crystallised from ethanol–ether, giving colourless needles of *3-methyl-4-iso**propylsydnone imine nitrate***, m. p. 135—136° (Found: C, 35·5; H, 6·0; N, 26·8. $C_6H_{11}ON_3,HNO_3$ requires C, 35·3; H, 5·9; N, 27·4%). Low nitrogen figures were regularly obtained with substances containing the NNO structure.

Nitrate ion was determined qualitatively and quantitatively as follows: (i) aqueous solutions of the above substance (0·2 g.) and *p*-acetylphenylguanidine hydrochloride [13] (0·21 g.) were mixed. *p*-Acetylphenylguanidine nitrate (0·24 g.) separated immediately and crystallised from water in colourless prisms, m. p. 242°, in agreement with King and Tonkin,[13] not depressed on admixture with an authentic specimen. (ii) A solution of the substance (217·7 mg.) in water (10 c.c.) and acetic acid (1 c.c.) was heated nearly to boiling and treated with a 10% solution of nitron in acetic acid (10 c.c.). The solution was cooled in ice for 1 hr. before collection of the precipitated nitron nitrate (410 mg.) in a tared crucible (Found: NO_3^-, 31·1. $C_6H_{11}ON_3,HNO_3$ requires NO_3^-, 30·4%).

(*b*) α-(*N*-Methyl-*N*-nitrosoamino)*iso*valeronitrile (2·8 g.) (see below) was mixed with 95% nitric acid (1·4 g.), and the mixture was kept at room temperature for 18 hr.; it set to a mass of

* Cf. succinic anhydride, $\nu_{max.}$ 1782 and 1865 cm.$^{-1}$ (Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1954, p. 111).

[11] Cf. (*a*) Earl, Le Fèvre, Pulford, and Walsh, *J.*, 1951, 2207; (*b*) Fugger, Tien, and Hunsberger, *J. Amer. Chem. Soc.*, 1955, **77**, 1843.

[12] Baker, Ollis, and Poole, *J.*, 1950, 1542.

[13] King and Tonkin, *J.*, 1946, 1063.

crystals. Recrystallisation from ethanol–ether gave colourless needles (3·56 g.) of 3-methyl-4-*iso*propylsydnone imine nitrate, m. p. 136°, identical (infrared absorption spectrum) with the substance prepared as in (*a*) (above). The ultraviolet absorption spectrum showed a single maximum at 300 mμ (log ε 3·97).

3-*Methyl*-4-iso*propylsydnone Imine Hydrochloride* (V; R = Pr^i, X = Cl).—(*a*) The above nitrate (0·2 g.), dissolved in water (10 c.c.), was passed slowly through a column (10 cm. × 0·5 cm.) of " Amberlite IRA-400 " in the chloride form. The effluent from the column remained neutral throughout and evaporation afforded the *hydrochloride* (0·17 g.), which separated from ethanol–ether in colourless needles, m. p. 185° (Found: C, 40·7; H, 6·4; Cl, 20·1. $C_6H_{11}ON_3$,HCl requires C, 40·6; H, 6·8; Cl, 20·0%). (*b*) α-(*N*-Methyl-*N*-nitrosoamino)*iso*valeronitrile (2·0 g.) was dissolved in dry ether (10 c.c.) and the solution was saturated with dry hydrogen chloride. White crystals (2·2 g.) separated immediately and recrystallisation from ethanol–ether gave the sydnone imine hydrochloride, m. p. 185°, identical with the substance prepared as in (*a*) (above).

4-iso*Butyl*-3-*methylsydnone Imine Nitrate* (V; R = Bu^i, X = NO_3).—(*a*) γ-Methyl-α-methylaminovaleronitrile (2·0 g.) was treated with nitrous fumes in the manner described above in the case of the lower homologue (*a*) (above). Recrystallisation of the product from ethanol–ether afforded colourless prisms (1·5 g.) of 4-iso*butyl*-3-*methylsydnone imine nitrate*, m. p. 91—93° (Found: C, 38·8; H, 6·5. $C_7H_{13}ON_3$,HNO_3 requires C, 38·5; H, 6·4%). The ultraviolet absorption spectrum showed a single maximum at 300 mμ (log ε 3·96).

(*b*) γ-Methyl-α-(*N*-methyl-*N*-nitrosoamino)valeronitrile (1·55 g.) was mixed with 95% nitric acid (0·67 g.) and kept at room temperature for 18 hr. The mixture solidified when scratched. Recrystallisation of the resulting solid from ethanol–ether afforded prisms (1·8 g.) of the nitrate, m. p. 91—93°, identical (infrared absorption spectrum) with the substance prepared as in (*a*) (above).

4-iso*Butyl*-3-*methylsydnone Imine Hydrochloride* (V; R = Bu^i, X = Cl).—A solution of γ-methyl-α-(*N*-methyl-*N*-nitrosoamino)valeronitrile (1·5 g.) in dry ether (5 c.c.) was saturated with dry hydrogen chloride. The precipitated *hydrochloride* (1·65 g.) separated from methanol–ethyl acetate in colourless needles, m. p. 165° (Found: C, 43·8; H, 7·2. $C_7H_{13}ON_3$,HCl requires C, 43·9; H, 7·3%). The ultraviolet absorption spectrum showed a single maximum at 300 mμ (log ε 3·96).

α-(N-*Methyl*-N-*nitrosoamino*)iso*valeronitrile* (IV; R = Pr^i).—α-Methylamino*iso*valeronitrile [9] (11·2 g.) was dissolved in dry ether, and nitrous fumes were passed in until the solution became pale green (*ca.* 1 hr.). The solution was washed with water, dried, and fractionated, affording α-(N-*methyl*-N-*nitrosoamino*)iso*valeronitrile* as a pale yellow oil (11·0 g.), b. p. 57—58°/0·3 mm., n_D^{21} 1·4580 (Found: C, 51·2; H, 7·7; N, 29·4. $C_6H_{11}ON_3$ requires C, 51·1; H, 7·8; N, 29·8%).

The substance was recovered unchanged (b. p., n_D) after treatment in the cold for 6 days with 3 parts of acetic anhydride and after 4 hr. on the steam-bath with 4 parts of acetic anhydride.

γ-*Methyl*-α-(N-*methyl*-N-*nitrosoamino*)*valeronitrile* (IV; R = Bu^i).—(i) *iso*Valeraldehyde (43 g.) was added with stirring to a solution of sodium metabisulphite (48 g.) in water (125 c.c.), the mixture being cooled in melting ice. After 30 min. 33% w/v aqueous methylamine (70 c.c.) was added, followed, after a further 30 min., by finely powdered potassium cyanide (33 g.). Stirring was continued for 1 hr., an oil separating. Extraction with ether and fractionation of the dried extract gave γ-methyl-α-methylaminovaleronitrile as a pale yellow oil (40 g.), b. p. 82—85°/15 mm., n_D^{21} 1·4351.

(ii) The preceding nitrile (6·0 g.) was treated with nitrous fumes in the manner described for the lower homologue (above), affording γ-*methyl*-α-(N-*methyl*-N-*nitrosoamino*)*valeronitrile* as a pale yellow oil (6·2 g.), b. p. 74°/0·4 mm., n_D^{21} 1·4594 (Found: C, 54·3; H, 8·5. $C_7H_{13}ON_3$ requires C, 54·3; H, 8·4%).

Attempted Preparation of 3-*Methyl*-4-iso*propylsydnone Imine Free Base.*—(*a*) 3-Methyl-4-*iso*propylsydnone imine nitrate (0·25 g.) was dissolved in water (10 c.c.) and applied to a column of " Amberlite IRA-400 " in the hydroxyl form. The effluent from the column was neutral throughout and evaporation gave a white solid (0·2 g.), affording on crystallisation from chloroform–light petroleum colourless needles of α-(N-*methyl*-N-*nitrosoamino*)iso*valeramide*, m. p. and mixed m. p. 159—161° (Found: C, 45·4; H, 8·0. $C_6H_{13}O_2N_3$ requires C, 45·3; H, 8·2%); an authentic specimen, obtained by esterification of *N*-methyl-*N*-nitrosovaline (see below) with diazomethane and shaking the resulting ester with concentrated aqueous ammonia for 24 hr.,

had m. p. 158—161° after recrystallisation from chloroform–light petroleum (Found: C, 45·3; H, 7·9%). (*b*) A solution of the nitrate (1·0 g.) in water (10 c.c.) was basified by the addition of 40% aqueous sodium hydroxide (0·5 c.c.). The solution was extracted with ether (3 × 10 c.c.) and evaporation of the dried extract gave α-(*N*-methyl-*N*-nitrosoamino)*iso*valeramide (0·7 g.), m. p. 159—161° after recrystallisation from chloroform–light petroleum (Found: C, 45·7; H, 8·1%).

Catalytic Hydrogenation of 3-*Methyl*-4-iso*propylsydnone Imine Nitrate.*—The nitrate (0·28 g.) in methanol (10 c.c.) was shaken with hydrogen at room temperature and atmospheric pressure in presence of previously reduced Adams catalyst (50 mg.). Uptake of hydrogen proceeded rapidly during the first 15 min. (Found: 75 c.c. Calc. for $2H_2$: 67 c.c.), and continued for a further hour [Found (total): 96 c.c. Calc. for $3H_2$: 100 c.c.]. The catalyst was removed and the odour of ammonia was apparent during evaporation of the solvent. Crystallisation of the residue (0·17 g.) from methanol–ether afforded colourless needles of N-*methylvaline amide nitrate*, m. p. 169—172° (Found: C, 37·4; H, 7·6; N, 21·2. $C_6H_{14}ON_2,HNO_3$ requires C, 37·3; H, 7·8; N, 21·7%). An aqueous solution (193 mg. in 2 c.c.) was basified with 40% aqueous sodium hydroxide (0·3 c.c.) and extracted with chloroform (3 × 5 c.c.). The residue (90 mg.) obtained on evaporation of the dried chloroform extract crystallised from ether–light petroleum in colourless prisms, m. p. 90° (Found: C, 55·2; H, 10·8; N, 21·2. Calc. for $C_6H_{14}ON_2$: C, 55·4; H, 10·7; N, 21·6%), identical with an authentic specimen of *N*-methylvaline amide, prepared as described by Cook and Cox.[9]

The ammonia produced during the catalytic hydrogenation was estimated in a separate experiment. 3-Methyl-4-*iso*propylsydnone imine nitrate (49·2 mg.) was hydrogenated as above. The catalyst was removed and the filtrate was made alkaline with aqueous sodium hydroxide. The solvent and ammonia were distilled into 0·1N-hydrochloric acid (10 c.c.), and excess of acid was back-titrated (Found: 2·4 c.c. Calc. for 1NH_3 per $C_6H_{11}ON_3,HNO_3$: 2·4 c.c.).

3-*Methyl*-4-iso*propylsydnone Nitroimine* (IX; R = Pr^i).—(*a*) α-Methylamino*iso*valeronitrile (11·2 g.) was nitrosated in dry ether in the usual way and the solvent was removed at room temperature without prior washing. The residual crude brown oil was treated with ice-cold acetic anhydride (40 g.), and the mixture was kept at room temperature for several days. The solution was then poured on crushed ice (100 g.), neutralised with ammonia, and extracted with chloroform. Evaporation of the dried extract gave an oil (2·4 g.), which crystallised when cooled and scratched. Recrystallisation from chloroform–light petroleum afforded 3-*methyl*-4-iso*propylsydnone nitroimine* as colourless needles, m. p. 147—148° (Found: C, 38·8; H, 5·4; N, 29·5. $C_6H_{10}O_3N_4$ requires C, 38·7; H, 5·4; N, 30·1%).

(*b*) 3-Methyl-4-*iso*propylsydnone imine nitrate (2·04 g.) was added in small portions to concentrated sulphuric acid (10 c.c.) cooled in ice. When all the solid had been added the solution was kept at room temperature for 30 min. before being poured on crushed ice (50 g.). The precipitate was collected, and the filtrate was extracted with chloroform, yielding a further quantity of the same product. On crystallisation from ethanol the combined product (1·55 g.) afforded colourless needles, m. p. 146—148°, identical with the product obtained in (*a*) (above). The ultraviolet light absorption spectrum showed maxima at 270 and 345 mμ with log ε 3·89 and 4·26 respectively.

4-iso*Butyl*-3-*methylsydnone Nitroimine* (IX; R = Bu^i).—(*a*) Nitrosation of γ-methyl-α-methylaminovaleronitrile followed by treatment with acetic anhydride was carried out as described above for the preparation (*a*) of the lower homologue. 4-iso*Butyl*-3-*methylsydnone nitroimine* separated from chloroform–light petroleum in pale yellow plates, m. p. 127—128° (Found: C, 42·4; H, 5·9. $C_7H_{12}O_3N_4$ requires C, 42·0; H, 6·0%). The ultraviolet light absorption spectrum showed maxima at 270 and 345 mμ with log ε 3·82 and 4·16 respectively.

(*b*) 4-*iso*Butyl-3-methylsydnone imine nitrate (0·55 g.) was added to concentrated sulphuric acid (3 c.c.) as described above for the preparation (*b*) of the lower homologue. Crystallisation of the product from chloroform–light petroleum afforded 4-*iso*butyl-3-methylsydnone nitroimine, m. p. 127—128°, identical with the substance obtained in (*a*) (above) (Found: C, 41·7; H, 6·0%).

Action of Alkali on 3-*Methyl*-4-iso*propylsydnone Nitroimine.*—The nitroimine (0·93 g.) was dissolved in hot water (20 c.c.) and treated dropwise with 40% aqueous sodium hydroxide (0·5 c.c.). Each addition of alkali caused the evolution of a colourless, odourless gas, which rekindled a glowing splint. When all the alkali had been added the solution was strongly acidified with concentrated hydrochloric acid and extracted with ether. The colourless oil

(0·65 g.) recovered from the dried extract failed to crystallise promptly; it was acidic, and the S-*benzylthiuronium salt* crystallised from aqueous ethanol in needles, m. p. 141—143° (Found: C, 51·6; H, 6·4; N, 17·5. $C_6H_{12}O_3N_2,C_8H_{10}N_2S$ requires C, 51·5; H, 6·7; N, 17·2%). This derivative was identical with an authentic specimen of the benzylthiuronium salt of *N*-methyl-*N*-nitrosovaline (see below).

The nitroimine (0·6 g.), dissolved in hot water (20 c.c.), was treated dropwise with 3N-sodium hydroxide (5 c.c.) while a slow stream of air was passed through the solution. The gas evolved was washed with 20% aqueous sodium hydroxide and concentrated sulphuric acid before being passed through a glass spiral immersed in liquid air. The inlet to the spiral was closed and the exit was connected to the previously evacuated gas cell of the infrared spectrophotometer. The liquid air was removed and the contents of the spiral were allowed to evaporate. The infrared spectrum of the gas, measured over the range 4000—1000 cm.$^{-1}$, was identical with that of nitrous oxide.

N-*Methyl-leucine*.—γ-Methyl-α-methylaminovaleronitrile (40 g.) was added slowly to ice-cold concentrated sulphuric acid (60 g.). The solution was heated at 100°, then cooled, and poured on crushed ice (50 g.). The resulting solution was refluxed for 24 hr., cooled, and neutralised with 50% aqueous sodium hydroxide. The precipitate was removed and the filtrate was taken to dryness. The combined solids were extracted with boiling methanol (4 × 500 c.c.). Concentration and cooling afforded *N*-methyl-leucine (24·5 g.), and further crude material (7 g.) on further concentration of the mother-liquors; the substance crystallised from methanol in colourless prisms which sublimed at 255—256° (Found: C, 57·8; H, 10·6; N, 9·8. Calc. for $C_7H_{15}O_2N$: C, 57·9; H, 10·3; N, 9·7%).

N-*Methylphenylalanine*.—Phenylpyruvic acid [14] (3·3 g.) was dissolved in 70% aqueous ethanol (30 c.c.), and 25% w/v aqueous methylamine (4·8 c.c.) was added. The mixture was shaken in hydrogen at 3 atm. and room temperature for 22 hr. in presence of 5% palladised charcoal (100 mg.). The solution was filtered and the residue was washed with alcohol, filtrate and washings yielding further crude crystalline product on evaporation. The catalyst was separated by solution of the combined solids in the minimum volume of boiling water and filtering. On cooling, *N*-methylphenylalanine separated in colourless plates (2·5 g.), m. p. (sublimes) 235—240° (Found: C, 67·2; H, 7·3; N, 7·7. Calc. for $C_{10}H_{13}O_2N$: C, 67·0; H, 7·3; N, 7·8%).

N-*Methylaspartic Acid*.—A mixture of maleic anhydride (9·8 g.) and water (25 c.c.) was boiled under reflux for 30 min., cooled in melting ice, and treated slowly with 25% w/v aqueous methylamine solution (25 c.c.). After 1 hr. at the b. p. the solution was concentrated to small bulk and then boiled with 25% aqueous sodium hydroxide (40 c.c.), methylamine being removed in a stream of air. The resulting solution was concentrated (to *ca.* 25 c.c.) and acidified with concentrated hydrochloric acid to pH 2. The precipitate (12·6 g.) obtained by the addition of an equal volume of ethanol was crystallised from aqueous ethanol, affording *N*-methyl-aspartic acid monohydrate as needles, m. p. 134°, which gave the anhydrous acid, m. p. 184°, at 100° in a vacuum (Found: C, 40·5; H, 6·1; N, 9·5. Calc. for $C_5H_9O_4N$: C, 40·8; H, 6·1; N, 9·5%).

N-Methylvaline was prepared by the method of Cook and Cox,[9] and *N*-benzylaspartic acid by that of Frankel, Liwschitz, and Amiel.[15]

Nitrosation.—The *N*-alkylamino-acids were dissolved in water with slight warming only, if necessary, and nitrous fumes, generated as described above, were passed to saturation. The crude products were recovered by extraction with ether and concentration of the dried extracts. *N*-Nitrososarcosine, *N*-methyl-*N*-nitrosoleucine, and *N*-methyl-*N*-nitrosoaspartic acid were obtained as brown oils. *N*-Methyl-*N*-nitrosovaline was obtained as a brown oil but the *S*-benzylthiuronium salt crystallised from aqueous ethanol in needles, m. p. 142—143° (Found: C, 51·2; H, 6·5. Calc. for $C_6H_{12}O_3N_2,C_8H_{10}N_2S$: C, 51·5; H, 6·7%).

N-*Methyl*-N-*nitrosophenylalanine*, obtained in 95% yield, crystallised from aqueous ethanol in colourless prisms, m. p. 148—150° (Found: C, 57·7; H, 5·8; N, 13·4. $C_{10}H_{12}O_3N_2$ requires C, 57·7; H, 5·8; N, 13·4%).

N-*Benzyl*-N-*nitrosoaspartic acid* (XIII; R = CH_2PH), as first obtained, crystallised from ether–light petroleum in colourless needles of a *dihydrate*, which lost its solvent of crystallisation above 80° and then melted sharply at 146—147° (Found: C, 45·9; H, 5·7; N, 9·4; loss in a

[14] *Org. Synth.*, Coll. Vol. II, p. 519.
[15] Frankel, Liwschitz, and Amiel, *J. Amer. Chem. Soc.*, 1953, **75**, 331.

vacuum at 80°, 13·4. $C_{11}H_{12}O_5N_2,2H_2O$ requires C, 45·8; H, 5·6; N, 9·7; H_2O, 13·4%). The anhydrous *compound* separated on crystallisation of the dried material from ether–light petroleum as colourless needles, m. p. **146—147°** (Found: C, 52·4; H, 4·6; N, 11·0. $C_{11}H_{12}O_5N_2$ requires C, 52·4; H, 4·8; N, 11·0%).

Sydnone Formation.—In each case the *N*-methyl-*N*-nitrosoamino-acid was dissolved in acetic anhydride and kept at room temperature for several days. The mixture was then poured into water and extracted with chloroform, the extracts being dried and evaporated to give the sydnone.

3-Methylsydnone (XI; R = H) obtained as an oil in 65% yield, crystallised at 0° in needles and melted again at room temperature. Recrystallisation from chloroform–light petroleum at a low temperature failed to raise the m. p. sufficiently to give a product solid at room temperature. The substance distilled at **140—142°/0·2** mm. (n_D^{25} 1·5163), with slight decomposition which is reflected in the analytical figures (Found: C, 37·5; H, 4·4. Calc. for $C_3H_4O_2N_2$: C, 36·0; H, 4·0%). Ultraviolet light absorption: $\lambda_{max.}$ 286 mμ (log ε 3·81). Hammick and Voaden [16] have mentioned this substance as having m. p. 36°, but no further details have been published.

3-*Methyl*-4-iso*propyl sydnone* (XI; R = Pr^i), obtained in 60% yield, separated from ether–light petroleum in colourless needles, m. p. **55—57°** (Found: C, 50·6; H, 7·3; N, 19·4. $C_6H_{10}O_2N_2$ requires C, 50·7; H, 7·0; N, 19·7%). Ultraviolet light absorption: $\lambda_{max.}$ 296 mμ (log ε 3·93).

4-iso*Butyl*-3-*methylsydnone* (XI; R = Bu^i), obtained as an oil in 65% yield, crystallised at −5°; it distilled with slight decomposition at **120—121°/0·2** mm. and had n_D^{25} 1·5043 (Found: C, 52·8; H, 7·6. $C_7H_{12}O_2N_2$ requires C, 53·8; H, 7·7%). Ultraviolet light absorption: $\lambda_{max.}$ 292 mμ (log ε 3·89).

4-*Benzyl*-3-*methylsydnone* (XI; R = CH_2Ph), obtained in 80% yield, crystallised from water in colourless needles, m. p. **108—110°** (Found: C, 63·0; H, 5·3; N, 14·4. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·2; N, 14·7%). Ultraviolet light absorption: $\lambda_{max.}$ 292 mμ (log ε 3·96).

N-*Benzyl*-N-*nitrosoaspartic Anhydride* (XIV).—Anhydrous *N*-benzyl-*N*-nitrosoaspartic acid (7·5 g.) was dissolved in acetic anhydride (20 c.c.), and the mixture was kept at room temperature for 4 days, then shaken vigorously with ice-cold water (50 c.c.); a white solid (3·6 g.) separated. Extraction of the aqueous solution with chloroform gave a further crop (1·1 g.) of the same substance. Crystallisation from chloroform–light petroleum afforded N-*benzyl*-N-*nitrosoaspartic anhydride* as colourless plates, m. p. **136—138°** (Found: C, 56·1; H, 4·2; N, 11·9. $C_{11}H_{10}O_4N_2$ requires C, 56·4; H, 4·3; N, 12·0%). Ultraviolet light absorption: $\lambda_{max.}$ 242 mμ (log ε 3·86).

National Institute for Medical Research,
The Ridgeway, Mill Hill, London, N.W.7.

[*Received, May* 22*nd*, 1957.]

[16] Hammick and Voaden, *Chem. and Ind.*, 1956, 739.