273. *Derivatives of 6-Aminopenicillanic Acid. Part II.**
*Trisubstituted Acetyl Derivatives.*

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A number of new trisubstituted acetic acids and various derivatives thereof have been prepared. Reaction of the acid chlorides with 6-aminopenicillanic acid gave a series of new penicillins which differ from the conventional ones in being much less readily inactivated by penicillinase.

FOLLOWING the isolation [1] of 6-aminopenicillanic acid (I), we have synthesised many novel penicillins (II) by treating it with acylating agents. These included several analogues of benzylpenicillin (penicillin G: II; $R = Ph \cdot CH_2$) of which one, triphenylmethyl-penicillin (II; $R = Ph_3C$), unexpectedly proved to be essentially stable towards penicillinase, the enzyme which hydrolyses all previously known penicillins to the biologically inactive penicilloic acids (III). Hence, whereas benzylpenicillin is much less active against the clinically important penicillinase-producing staphylococci than against strains which do not produce the enzyme, triphenylmethylpenicillin was found to be equally active *in vitro* against both types. Since both diphenylmethylpenicillin (II; $R = Ph_2CH$) and $\beta\beta\beta$-triphenylethylpenicillin (II; $R = Ph_3C \cdot CH_2$) were found to be inactivated by penicillinase at approximately the same rate as benzylpenicillin, it seemed possible that resistance to the enzyme was characteristic of penicillins derived from trisubstituted acetic acids. A number of trisubstituted methylpenicillins were therefore prepared and, except for a few simple analogues such as trichloromethylpenicillin (II; $R = Cl_3C$) and t-butylpenicillin (II; $R = Me_3C$), they proved to be significantly more stable

H_2N·CH — CH S CMe_2 ... (I), (II), (III)
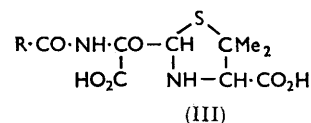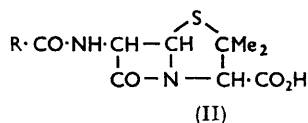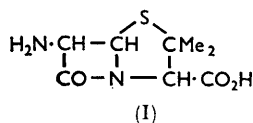
towards penicillinase than was benzylpenicillin, the effect being most marked when all three substituents were fairly bulky. Possibly steric hindrance around the side-chain amide linkage leads to molecular conformations which are not accommodated at the active sites of the enzyme. Details of the enzyme studies were reported to us by Dr. G. N. Rolinson, Mr. F. R. Batchelor, and their colleagues.

Many of the trisubstituted acids used in this work were known compounds, but a number of new examples are described here. Triphenylacetic acid is readily prepared from organo-metallic triphenylmethyl compounds, but this approach is of limited value for the preparation of analogues. Hydrogenation of triphenylacetic acid at high temperature and pressure over a rhodium catalyst gave successively $\alpha\alpha$-dicyclohexylphenylacetic acid and tricyclohexylacetic acid.

Several triarylacetic acids have been prepared previously by condensing benzilic acid with a suitably reactive aromatic compound in the presence of stannic chloride [2,3] or sulphuric acid.[4] The process was further exemplified by condensing benzilic acid with catechol and with phenoxyacetic acid to yield 3,4-dihydroxy- [IV; $Ar = (HO)_2C_6H_3$] and

* Part I, preceding paper.

[1] Batchelor, Doyle, Nayler, and Rolinson, *Nature*, 1959, **183**, 257; Doyle, Nayler, and Rolinson, B.P. Spec. 870,396/1961.
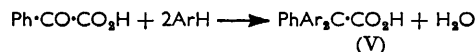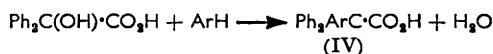[2] Bistrzycki and Nowakowski, *Ber.*, 1901, **34**, 3063.
[3] Bistrzycki and Kuba, *Helv. Chim. Acta*, 1921, **4**, 969.
[4] Ancizar-Sordo and Bistrzycki, *Helv. Chim. Acta*, 1931, **14**, 141; Bistrzycki and Krause, *ibid.*, 1933, **16**, 100.

p-carboxymethoxy-triphenylacetic acid (IV; Ar = HO$_2$C·CH$_2$·O·C$_6$H$_4$), respectively. Similarly di-p-methoxyphenylglycollic acid and anisole gave tri-(p-methoxyphenyl)acetic acid.
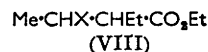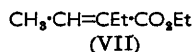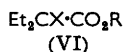
An extension of this reaction consists of the condensation under similar conditions of an α-keto-acid with two molecules of an aromatic compound.[5] Thus, phenylglyoxylic acid with phenol gave pp'-dihydroxytriphenylacetic acid (V; Ar = p-HO·C$_6$H$_4$), and with anisole and thioanisole it gave respectively pp'-dimethoxy- and pp'-di(methylthio)-triphenylacetic acids (V; Ar = p-MeO·C$_6$H$_4$ and p-MeS·C$_6$H$_4$). Unlike p-(methylthio)-triphenylacetic acid,[3] the pp'-dimethylthio-compound could not be oxidised to a sulphone without decarboxylation.

$$Ph_2C(OH)·CO_2H + ArH \longrightarrow Ph_2ArC·CO_2H + H_2O$$
$$(IV)$$

$$Ph·CO·CO_2H + 2ArH \longrightarrow PhAr_2C·CO_2H + H_2O$$
$$(V)$$

Several α-alkoxydiphenylacetic acids were prepared from α-chlorodiphenylacetyl chloride by way of the alkoxy-esters. Some alkylthio-analogues were conveniently obtained by condensing the appropriate thiols with benzilic acid in the presence of sulphuric acid.[6] A few of the α-(alkylthio)diphenylacetic acids were oxidised to the corresponding sulphones with hydrogen peroxide.

Various trisubstituted acetic acids have been prepared by α-alkylation of acetonitrile, phenylacetonitrile, or diphenylacetonitrile in the presence of sodamide, followed by hydrolysis of the resulting trisubstituted acetonitriles.[7] Such hydrolysis becomes more difficult as the bulk of the alkyl substituents is increased,[8] and we were unable to hydrolyse nitriles containing more than one secondary alkyl substituent. Oxidation of αα-di-(2-methylthioethyl)phenylacetic acid with hydrogen peroxide gave the bis-sulphone.

α-Methyl-α-phenoxypropionic acid was conveniently prepared by the interaction of phenol, acetone, chloroform, and a base,[9,10] but we confirmed a previous report [10] that α-ethyl-α-phenoxybutyric acid (VI; R = H, X = OPh) could not be prepared in similar fashion by using diethyl ketone instead of acetone. Treatment of α-ethyl-α-hydroxybutyric acid (VI; R = H, X = OH) with acetyl chloride in pyridine gave the acetoxy-acid (VI; R = H, X = OAc). The ethoxy-analogue (VI; R = H, X = OEt) was prepared from ethyl αα-dichloro-α-ethoxyacetate and ethylzinc iodide,[11] with subsequent hydrolysis. It could not be prepared from ethyl α-bromo-α-ethylbutyrate (VI; R = Et, X = Br) and sodium ethoxide, the product being ethyl α-ethylcrotonate (VII).

$$Et_2CX·CO_2R \qquad CH_3·CH=CEt·CO_2Et \qquad Me·CHX·CHEt·CO_2Et$$
$$(VI) \qquad\qquad (VII) \qquad\qquad (VIII)$$

The tendency of the α-bromo-ester (VI; R = Et, X = Br) to undergo dehydrohalogenation in the presence of bases cast doubt on the identity of the product obtained by treating it with thiophenol in alcoholic sodium hydroxide. If the crotonate (VII) were an intermediate in this reaction, addition to the double bond could have given either ethyl α-ethyl-α-(phenylthio)butyrate (VI; R = Et, X = SPh) or the β-phenylthio-isomer (VIII; X = SPh). To clarify this point, the unsaturated ester (VII) was treated with hydrogen bromide in chloroform to give ethyl β-bromo-α-ethylbutyrate (VIII; X = Br), distinguished by infrared spectroscopy from the isomer (VI; R = Et, X = Br). However, when the β-bromo-ester (VIII; X = Br) was treated with thiophenol in alcoholic

[5] Dreyfuss and Coccuzza, *Gazzetta*, 1938, **68**, 95.
[6] Bistrzycki and Risi, *Helv. Chim. Acta*, 1925, **8**, 582; Barkenbus and Brower, *J. Amer. Chem. Soc.*, 1955, **77**, 579.
[7] Sperber, Papa, and Schwenk, *J. Amer. Chem. Soc.*, 1948, **70**, 3091.
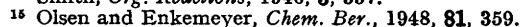[8] Newman, " Steric Effects in Organic Chemistry," Wiley, New York, 1956, p. 233.
[9] Bargellini, *Gazzetta*, 1906, **36**, 334.
[10] Julia, *Bull. Soc. chim. France*, 1956, 776.
[11] Blaise and Picard, *Bull. Soc. chim. France*, 1912, **11**, 589.

sodium hydroxide the only isolable product, after hydrolysis, was α-ethylcrotonic acid. The failure to obtain ethyl α-ethyl-β-(phenylthio)butyrate (VIII; X = SPh) in this way provides reasonable confirmation that the original product from the α-bromo-ester was ethyl α-ethyl-α-(phenylthio)butyrate (VI; R = Et, X = SPh). Larsson [12] has shown that α-bromo-α-methylpropionic acid similarly reacts with thiols without rearrangement.

Reaction of ethyl α-bromo-α-propylvalerate with thiophenol gave ethyl α-phenylthio-α-propylvalerate which, like its lower homologue (VI; R = Et, X = SPh), was readily hydrolysed by alkali to the free acid. α-Benzylthio-α-ethylbutyric acid (VI; R = H, X = S·CH₂Ph) was prepared in a single step from α-bromo-α-ethylbutyric acid (VI; R = H, X = Br) and the potassium derivative of toluene-ω-thiol in anhydrous alcohol.

The most convenient reactive derivatives of the various trisubstituted acetic acids for reaction with 6-aminopenicillanic acid were generally the acid chlorides. Several new acid chlorides are described in the Experimental section, but in some cases it was preferable to use the crude product from the acid and thionyl chloride without purification. This was especially advantageous when the chlorides were thermally unstable, as was the case when α-alkoxy-substituents were present. In such cases the crude chlorides were generally characterised by the preparation of the amide or anilide.

The use of the mixed ethoxyformic anhydrides (X), prepared *in situ* from the tri-ethylamine salt of the trisubstituted acetic acid and ethyl chloroformate, for the acylation of 6-aminopenicillanic acid appeared to be suitable only for the less highly hindered acids. Thus, although α-methylethyl-α-phenoxypenicillin (II; R = PhO·CMe₂) was readily obtained from α-methyl-α-phenoxypropionic acid by this procedure, a similar reaction with triphenylacetic acid yielded no trace of triphenylmethylpenicillin. The latter experiment did, however, yield some ethoxypenicillin (II; R = EtO) which was identified by paper chromatographic comparison with an authentic specimen prepared from 6-amino-penicillanic acid and ethyl chloroformate. The formation of ethoxypenicillin in the attempted triphenylacetylation of 6-aminopenicillanic acid could not be ascribed to failure of the ethyl chloroformate to react with triphenylacetic acid because, in a separate experiment, ethoxyformic triphenylacetic anhydride (IX; R = Ph₃C) was prepared and isolated in crystalline form. It suggests, rather, that reaction of the mixed anhydride (IX) with the amine proceeded in this case by path (*b*) rather than by the more usual path (*a*). A

$$\text{R·CO}_2\text{H} + \text{R'·NH·CO}_2\text{Et} \xleftarrow{\ b\ } \text{R·CO·O·CO}_2\text{Et} + \text{R'·NH}_2 \xrightarrow{\ a\ } \text{R·CO·NHR'} + \text{EtOH} + \text{CO}_2$$
$$\text{(XI)} \qquad\qquad\qquad \text{(IX)} \qquad\qquad\qquad \text{(X)}$$

model experiment supported this idea; treatment of ethoxyformic triphenylacetic an-hydride (IX; R = Ph₃C) with aniline gave triphenylacetic acid and ethyl N-phenyl-urethane (XI; R' = Ph), but no isolable triphenylacetanilide (X; R = Ph₃C, R' = Ph). The mode of interaction of a mixed ethoxyformic anhydride with an amine is known to depend considerably on the structure of the amine; for example, secondary amines often yield a considerable quantity of urethane in addition to the amide.[13] The present results suggest that it is similarly influenced by steric factors in the acid component.

The action of hydrazine under rather vigorous conditions on the readily available ethyl α-ethoxydiphenylacetate gave the hydrazide but this, unexpectedly, could not be con-verted into the penicillin (II; R = EtO·CPh₂) by way of the azide. Treatment with nitrous acid at 0—10° in the usual way [14] gave no azide but an excellent yield of α-ethoxy-diphenylacetamide. The action of nitrous acid on α-methoxydiphenyl- and on triphenyl-acethydrazides likewise gave the corresponding amides, and not the azides. The formation of an appreciable quantity of amide from the hydrazide and nitrous acid appears to have been observed before only in the case of hexahydrobenzhydrazide.[15] Amide formation

[12] Larsson, *Trans. Chalmers Univ. Technol., Gothenburg,* 1945, **47**, 9.
[13] Leicester and Tarbell, *J. Org. Chem.,* 1958, **23**, 1152.
[14] Smith, *Org. Reactions,* 1946, **3**, 337.
[15] Olsen and Enkemeyer, *Chem. Ber.,* 1948, **81**, 359.

has occasionally been noted in peptide syntheses by the azide method, but usually only as a minor side-reaction.[16]

Preparation of the new penicillins from the trisubstituted acetyl chlorides and 6-aminopenicillanic acid was carried out either in water containing a weak base such as sodium hydrogen carbonate or in an anhydrous solvent containing a tertiary base such as triethylamine. In either case partial purification was effected by partition between a water-immiscible solvent and an acidified aqueous phase. The penicillin was then re-extracted from the organic phase into the requisite quantity of aqueous sodium hydrogen carbonate, and the aqueous phase was evaporated at low temperature and pressure. The resulting sodium salt of the penicillin was sufficiently pure for preliminary biological and pharmacological tests. Complete purification of a penicillin is often tedious and was not usually attempted, but details for the preparation of the pure sodium and potassium salts of triphenylmethylpenicillin are given in the Experimental section. Further information on the other penicillins, which were not completely purified, is in a patent.[17]

Details of the testing of the new penicillins *in vitro* and *in vivo* were reported to us by Dr. G. N. Rolinson, Mr. D. M. Brown, and their respective colleagues.

Experimental

αα-Dicyclohexylphenylacetic Acid.—Triphenylacetic acid (14·4 g.) in ethanol (1 l.) was hydrogenated at 134°/160 atm. for 24 hr. in the presence of 5% rhodium–alumina (10 g.); the mixture was then cooled, filtered, and evaporated to dryness. Crystallisation from ethyl acetate gave αα-dicyclohexylphenylacetic acid (5·2 g.), m. p. 240—241° (Found: C, 80·0; H, 9·8. Calc. for $C_{20}H_{28}O_2$: C, 80·0; H, 9·4%). M. p.s of 242—244° and 250—252° have been given [18] for specimens prepared in other ways. Heating the acid at 230° with soda lime gave dicyclohexylphenylmethane, b. p. 115—120°/0·05 mm., having the same infrared absorption spectrum as an authentic specimen.

Tricyclohexylacetic Acid.—Triphenylacetic acid (14·4 g.) was reduced as described above and, after removal of catalyst and solvent, the crude tricyclohexyl compound was dissolved in cyclohexane (1 l.), treated with a further 10 g. of the same catalyst, and hydrogenated for a further 24 hr. at 200°/160 atm. The mixture was filtered and evaporated and the residue crystallised from ethanol to give *tricyclohexylacetic acid* (5·2 g.), m. p. 264—266° (Found: C, 78·3; H, 11·4. $C_{20}H_{34}O_2$ requires C, 78·4; H, 11·2%).

p-*Hydroxytriphenylacetic Acid.*—The product from benzilic acid, phenol, and stannic chloride [2] separated from aqueous alcohol as a colourless hydrate which gave the yellow anhydrous acid only after drying at 100°/1 mm. for some hours (Found: C, 79·2; H, 5·5. Calc. for $C_{20}H_{16}O_3$: C, 78·9; H, 5·3%).

The anhydrous acid in benzene was treated with an excess of thionyl chloride and a trace of pyridine at 60—70° for 1 hr., cooled, and filtered. Evaporation of the filtrate *in vacuo* gave the crude acid chloride as a viscous oil. A portion in acetone kept overnight with concentrated aqueous ammonia gave the *amide*, m. p. 214—216° (from ethanol) (Found: C, 78·9; H, 5·8; N, 4·5. $C_{20}H_{17}NO_2$ requires C, 79·2; H, 5·6; N, 4·6%). A further portion of the chloride in acetone was stirred with aniline and aqueous sodium hydrogen carbonate for 1 hr., to give the *anilide*, m. p. 158—159° (from carbon tetrachloride) (Found: C, 81·9; H, 5·6; N, 3·5. $C_{26}H_{21}NO_2$ requires C, 82·3; H, 5·5; N, 3·7%).

3,4-Dihydroxytriphenylacetic Acid.—Stannic chloride (24 ml.) was added during 10 min. to a refluxing solution of benzilic acid (45·6 g.) and catechol (22 g.) in dry benzene (240 ml.). At the end of the addition the dark mixture was refluxed for 15 min. more, then cooled and treated with 5N-hydrochloric acid (400 ml.). The purple product (35·5 g.) was collected and washed successively with dilute hydrochloric acid, water, and benzene. Recrystallisation from ethyl acetate–light petroleum and then from aqueous alcohol containing a little sodium dithionite gave pure *3,4-dihydroxytriphenylacetic acid* as a tan-coloured microcrystalline powder, m. p. 223—224° (Found: C, 74·6; H, 5·3. $C_{20}H_{16}O_4$ requires C, 75·0; H, 5·0%).

A portion of the acid was refluxed with an excess of thionyl chloride for $2\frac{1}{2}$ hr., then

[16] Honzl and Rudinger, *Coll. Czech. Chem. Comm.*, 1961, **26**, 2333.
[17] Doyle and Nayler, B.P. Spec. 878,233/1961.
[18] Rosslander, Bock, and Marvel, *J. Amer. Chem. Soc.*, 1930, **52**, 2976; Ziegler and Herte, *Annalen*, 1942, **551**, 222.

evaporated *in vacuo*. The residual oily acid chloride with concentrated aqueous ammonia gave the *amide* which, when crystallised from ethanol and then from butanol, had m. p. 276—277° (decomp.) (Found: C, 74·8; H, 5·6; N, 4·0. $C_{20}H_{17}NO_3$ requires C, 75·3; H, 5·3; N, 4·4%).

p-*Carboxymethoxytriphenylacetic Acid.*—Stannic chloride (3 ml.) was added during 10 min. to a refluxing solution of benzilic acid (4·56 g.) and phenoxyacetic acid (3·04 g.) in dry benzene (25 ml.). The dark red mixture was refluxed for a further 20 min. and then cooled, whereupon a dark gum separated. Trituration of the mixture with 5N-hydrochloric acid discharged the colour and caused the gum to solidify. The cream-coloured solid (6·86 g.) was collected and washed successively with dilute hydrochloric acid, water, and benzene, then crystallised from aqueous alcohol, to give colourless p-*carboxymethoxytriphenylacetic acid*, m. p. 227—228° (Found: C, 73·1; H, 5·4. $C_{22}H_{18}O_5$ requires C, 72·9; H, 5·0%).

Tri-(p-*methoxyphenyl*)*acetic Acid.*—Concentrated sulphuric acid (20 ml.) was added during 1 hr. to a stirred mixture of di-(p-methoxyphenyl)glycollic acid (14·4 g.), anisole (5·95 g.), and acetic acid (60 ml.). Next morning the deep red solution was poured into ice, and the solid collected and washed well with cold water. *Tri*-(p-*methoxyphenyl*)*acetic acid* (14·4 g.), crystallised from ethanol, had m. p. 212—213° (Found: C, 72·6; H, 6·1. $C_{23}H_{22}O_5$ requires C, 73·0; H, 5·9%).

pp′-*Dihydroxytriphenylacetic Acid.*—Concentrated sulphuric acid (15 ml.) and acetic acid (25 ml.) were mixed and immediately added to a solution of phenylglyoxylic acid (3 g.) and phenol (3·8 g.) in acetic acid (40 ml.). After 24 hr. at room temperature the red solution was poured into water (500 ml.), affording an oil which soon solidified. The pink powder (3·95 g.) was collected, washed with water, dried *in vacuo*, and recrystallised from ethyl acetate–light petroleum and then from aqueous alcohol; this gave pale yellow pp′-*dihydroxytriphenylacetic acid* which, after drying at 110°/1 mm., had m. p. 253—254° (Found: C, 74·9; H, 5·4. $C_{20}H_{16}O_4$ requires C, 75·0; H, 5·0%).

The anhydrous acid was treated with an excess of thionyl chloride, refluxed for $2\frac{1}{2}$ hr., and evaporated *in vacuo*. The residual acid chloride was dissolved in acetone and stirred with aniline in the presence of aqueous sodium hydrogen carbonate, to give the *anilide*, m. p. 236—238° (from xylene) (Found: C, 78·4; H, 5·6; N, 3·2. $C_{26}H_{23}NO_3$ requires C, 78·6; H, 5·8; N, 3·5%).

pp′-*Dimethoxytriphenylacetic Acid.*—Stannic chloride (3 ml.) was added during 5 min. to a refluxing solution of phenylglyoxylic acid (3 g.) and anisole (4·4 ml.) in dry benzene (30 ml.). The dark red solution was refluxed for a further 10 min., then cooled and stirred for 30 min. with 5N-hydrochloric acid (80 ml.). The layers were separated and the benzene phase was washed with water, dried, and evaporated *in vacuo*. The pink residue was washed with light petroleum to leave the *dimethoxy-acid* (4·35 g.) which crystallised from alcohol in laths, m. p. 186—187° (Found: C, 76·0; H, 6·0. $C_{22}H_{20}O_4$ requires C, 75·8; H, 5·8%).

pp′-*Dimethylthiotriphenylacetic Acid.*—Concentrated sulphuric acid (30 ml.) was added dropwise to an ice-cold solution of phenylglyoxylic acid (15 g.) and thioanisole (48 g.) in acetic acid (60 ml.). The mixture was set aside at room temperature, rapidly separating into two layers and then slowly depositing a white solid. After 90 hr. it was poured into ice–water and then the crude product was collected and freed from oil by washing it with light petroleum. The *acid* (21·8 g.) was purified by crystallisation from acetic acid and then from alcohol; it had m. p. 210—211° (Found: C, 69·1; H, 5·5; S, 16·8. $C_{22}H_{20}O_2S_2$ requires C, 69·5; H, 5·3; S, 16·8%).

α-*Isopropoxy*-αα-*diphenylacetic Acid.*—α-Chloro-αα-diphenylacetyl chloride (53 g.) was refluxed with an excess of anhydrous isopropanol for 18 hr., and then for a further 10 hr. with an excess of sodium isopropoxide in the same solvent. After evaporation *in vacuo*, the residue was dissolved in ether, washed with water, dried, and distilled to give isopropyl α-isopropoxy-αα-diphenylacetate (26·5 g.), b. p. 116—118°/0·2 mm. (lit.,[19] b. p. 105°/0·01 mm.), n_D^{25} 1·5275 (Found: C, 76·7; H, 8·0. Calc. for $C_{20}H_{24}O_3$: C, 76·9; H, 7·7%). This was refluxed with potassium hydroxide in ethanol for 24 hr., giving, after concentration and acidification, α-isopropoxy-αα-diphenylacetic acid (50%), m. p. 129·5—130·5° (from heptane) (Found: C, 75·3; H, 6·9. Calc. for $C_{17}H_{18}O_3$: C, 75·6; H, 6·7%). The acid has been prepared by three other methods,[19-21] reported m. p.s ranging from 143—144° to 153—155°.

[19] Büchi, Lauener, Meyer, and Lieberherr, *Helv. Chim. Acta*, 1951, **34**, 373.
[20] Holmberg, *Acta Chem. Scand.*, 1951, **5**, 1093.
[21] Klosa, *Arch. Pharm.*, 1955, **288**, 42.

The acid (1·35 g.) in benzene (30 ml.) was treated with thionyl chloride (0·38 g., 1 mol.) and triethylamine (1·01 g., 2 mol.) at room temperature for 3 hr. Aniline (0·47 g., 1 mol.) and more triethylamine (1·01 g., 2 mol.) were then added and the mixture was set aside for 24 hr. Triethylamine hydrochloride was removed and the filtrate was diluted with ether and washed with dilute acid, dilute sodium hydroxide, and water, then dried and evaporated. The residual *anilide* (70%) (from light petroleum) had m. p. 82·5—83·5° (Found: C, 80·4; H, 7·0; N, 4·1. $C_{23}H_{23}NO_2$ requires C, 79·9; H, 6·7; N, 4·1%).

α-n-Butoxy-αα-diphenylacetic Acid.—Refluxing α-chloro-αα-diphenylacetyl chloride in butan-1-ol for 24 hr. gave, after alkaline hydrolysis of the ester, α-butoxy-αα-diphenylacetic acid, m. p. 130—133° (lit.,[21] m. p. 128—130°). The acid in benzene was refluxed for 2 hr. with thionyl chloride (1·1 mol.), then evaporated *in vacuo* to leave the crude oily acid chloride which with anhydrous ammonia in benzene gave the *amide*, m. p. 136—138° (from ethanol) (Found: C, 76·5; H, 7·5; N, 4·8. $C_{18}H_{21}NO_2$ requires C, 76·3; H, 7·4; N, 4·9%).

α-Alkylthio-αα-diphenylacetic Acids.—The new *sulphides* listed in Table 1 were prepared by slow addition of concentrated sulphuric acid (200 ml.) to a stirred mixture of benzilic acid (115 g.), the appropriate thiol (0·5 mole), and acetic acid (400 ml.), the temperature being maintained between 40° and 60° by a cooling-bath. The mixture was stirred at room temperature for 1 hr., then poured on ice. Each product was collected, washed with water, dried, and purified as indicated in the Table.

α-Alkylsulphonyl-αα-diphenylacetic Acids.—The new *sulphones* listed at the botton of Table 1 were each prepared by treating the corresponding sulphide (0·37 mole) in a mixture of acetic acid (16 ml.) and acetic anhydride (16 ml.) with 30% hydrogen peroxide (10 g.), the temperature

TABLE 1.

α-Alkylthio- and α-alkylsulphonyl-αα-diphenylacetic acids, $R \cdot CPh_2 \cdot CO_2H$.

R	Yield (%)	Cryst. from *	M. p.	Found (%) C	H	S	Formula	Required (%) C	H	S
EtS	46	Toluene	131—132°	70·2	6·3	11·6	$C_{16}H_{16}O_2S$	70·6	5·9	11·8
PrⁿS	31	AcOH	116—118	70·8	6·3	11·2	$C_{17}H_{18}O_2S$	71·3	6·3	11·2
PrⁱS	55	AcOH	130—132	70·6	6·6	11·5	$C_{17}H_{18}O_2S$	71·3	6·3	11·2
BuˢS	39	Pet.	95—96·5	72·6	7·2	10·7	$C_{18}H_{20}O_2S$	72·0	6·7	10·7
n-C₇H₁₅S	66	Pet.	81—83	73·5	7·9	9·6	$C_{21}H_{26}O_2S$	73·6	7·7	9·4
n-C₁₂H₂₅S ...	26	Pet.	77—79	75·5	8·8	7·7	$C_{26}H_{36}O_2S$	75·7	8·8	7·8
n-C₁₆H₃₃S ...	35	AcOH	81—82	76·6	9·6	6·5	$C_{30}H_{44}O_2S$	76·9	9·5	6·8
2-Pyridylthio	34	EtOH	121—122	70·8	5·1	10·0	$C_{19}H_{15}NO_2S$	71·0	4·7	10·0
Et·SO₂	31	EtOAc–Pet.	129—130	63·2	5·6	10·2	$C_{16}H_{16}O_4S$	63·1	5·3	10·5
n-C₇H₁₅·SO₂...	32	,,	137—139	67·0	7·1	8·6	$C_{21}H_{26}O_4S$	67·3	7·0	8·6
Ph·CH₂·SO₂...	41	,,	162—164	69·0	5·3	9·0	$C_{21}H_{18}O_4S$	68·8	5·0	8·8

* Pet. = light petroleum.

being kept below 35°. Next morning the product was collected, washed, dried, and recrystallised from 1 : 1 ethyl acetate–light petroleum.

αα-Di-(2-methylthioethyl)-α-phenylacetonitrile.—Phenylacetonitrile (39 g.) was added dropwise to a stirred suspension of sodamide (28 g.) in ether (300 ml.), and the mixture was refluxed for 4 hr. to complete the formation of the sodio-derivative. 2-Methylthioethyl chloride (89 g.) in ether (100 ml.) was added dropwise and the mixture was refluxed with stirring for a further 24 hr. Water (150 ml.) was added to the cooled mixture, the layers were separated, and the aqueous phase was extracted with more ether (3 × 100 ml.). The combined ether solutions were dried and distilled, yielding *αα-di-(2-methylthioethyl)-α-phenylacetontrile* (58 g.), b. p. 184—186°/2 mm., n_D^{20} 1·5631 (Found: C, 62·9; H, 7·2; S, 23·8. $C_{14}H_{19}NS_2$ requires C, 63·4; H, 7·2; S, 24·1%).

2-Allyl-2-phenylpent-4-enenitrile.—Phenylacetonitrile was alkylated by the method of the previous experiment with two mol. of allyl bromide, to give 2-allyl-2-phenylpent-4-enenitrile (59%), b. p. 93°/0·2 mm., n_D^{20} 1·5242 (Found: N, 7·0. Calc. for $C_{14}H_{15}N$: N, 7·1%). The nitrile has been reported [22] as an intermediate but its physical properties were not recorded.

α-s-Butyl-β-methyl-α-phenylvaleronitrile.—Alkylation of phenylacetonitrile as before with two mol. of s-butyl bromide gave the *nitrile* (84%), b. p. 118—120°/3 mm. (Found: C, 84·1; H, 10·1; N, 6·4. $C_{16}H_{23}N$ requires C, 83·9; H, 10·1; N, 6·1%).

[22] Ramart and Amagat, *Ann. chim.*, 1927, **8**, 272; Pflugk, G.P. 959,015/1957.

α-Isopropyl-α-phenylvaleronitrile.—Phenylacetonitrile (58·5 g.) was refluxed for 2 hr. with a stirred suspension of sodamide (19·5 g.) in ether (400 ml.), then treated with n-propyl bromide (67·6 g.) in ether (250 ml.) at such a rate as to maintain gentle refluxing. The stirred mixture was refluxed for 5 hr. more, cooled, and cautiously treated with water (150 ml.). Distillation of the dried ether layer gave α-phenylvaleronitrile (42·5 g.), b. p. 68—76°/0·1 mm. This was then treated with more sodamide and alkylated, this time with isopropyl bromide, to give *α-isopropyl-α-phenylvaleronitrile* (44·6 g.), b. p. 76°/0·01 mm., n_D^{23} 1·5015 (Found: C, 83·6; H, 9·2; N, 7·1. $C_{14}H_{19}N$ requires C, 83·6; H, 9·4; N, 7·0%).

Hydrolysis of Hindered Nitriles.—Each nitrile (0·2 mole) was heated in an autoclave with a solution of potassium hydroxide (60 g.) in methanol (400 ml.) containing water (10 ml.). The solution was cooled and evaporated, then the residue was dissolved in water, washed with ether, and acidified. The hindered acid was isolated by filtration or ether-extraction. Details for individual compounds are as follows:

(*a*) Hydrolysis of α-phenyl-α-propylvaleronitrile [23] at 145° for 18 hr. gave α-phenyl-α-propylvaleric acid (90%), m. p. 103—105° (from light petroleum) (lit.,[24] b. p. 167°/5 mm.) (Found: C, 76·3; H, 9·2. Calc. for $C_{14}H_{20}O_2$: C, 76·4; H, 9·1%). A portion was converted *via* the acid chloride into the amide, m. p. 88—89° (from heptane) (lit.,[25] m. p. 95°) (Found: C, 76·4; H, 9·5; N, 6·1. Calc. for $C_{14}H_{21}NO$: C, 76·7; H, 9·6; N, 6·4%).

(*b*) Hydrolysis of α-isobutyl-γ-methyl-α-phenylvaleronitrile [23] at 180° for 24 hr. gave a α-isobutyl-γ-methyl-α-phenylvaleric acid (50%), m. p. 78—79°. Bodroux [26] obtained only a small yield of this acid, m. p. 75—76°, by hydrolysis in boiling pentyl alcohol. In our hands moderate hydrolysis conditions gave chiefly the *amide*, m. p. 75·5° (from light petroleum) (Found: C, 77·5; H, 10·0; N, 5·9. $C_{16}H_{25}NO$ requires C, 77·7; H, 10·3; N, 5·7%). The *anilide*, prepared *via* the acid chloride, had m. p. 147·5—148·5° (from light petroleum) (Found: C, 81·8; H, 8·9; N, 4·2. $C_{22}H_{29}NO$ requires C, 81·7; H, 8·9; N, 4·3%).

(*c*) Hydrolysis of α-isopropyl-α-phenylvaleronitrile at 185—195° for 24 hr. gave *α-isopropyl-α-phenylvaleric acid* (52%), b. p. 128°/0·3 mm., n_D^{20} 1·5166 (Found: C, 76·6; H, 9·1. $C_{14}H_{20}O_2$ requires C, 76·4; H, 9·1%). Treatment with an excess of thionyl chloride (2 hours' refluxing) gave the *acid chloride* (63%), b. p. 81—86°/0·5 mm. (Found: Cl, 14·9. $C_{14}H_{19}ClO$ requires Cl, 14·9%). This with concentrated aqueous ammonia gave the *amide*, m. p. 93—94° (from light petroleum) (Found: C, 76·7; H, 9·6; N, 6·4. $C_{14}H_{21}NO$ requires C, 76·7; H, 9·6; N, 6·4%).

(*d*) The semi-solid acid from the hydrolysis of αα-di-(2-methylthioethyl)-α-phenylacetonitrile (58 g.) at 140—150° for 24 hr. was treated in ethyl acetate with benzylamine (20 ml.), giving *benzylammonium αα-di-(2-methylthioethyl)phenylacetate* (44·2 g.), m. p. 123·5—124·5° (from benzene–light petroleum) (Found: C, 64·5; H, 7·5; S, 15·8. $C_{21}H_{29}NO_2S_2$ requires C, 64·5; H, 7·4; S, 16·4%).

αα-Di-(2-methylsulphonylethyl)-α-phenylacetic Acid.—Benzylammonium αα-di-(2-methylthioethyl)-α-phenylacetate (20 g.) was dissolved in acetic acid (60 ml.) and acetic anhydride (60 ml.), cooled to 0°, and treated with 30% hydrogen peroxide (90 ml.). After 90 min. the ice-bath was removed and the mixture set aside for 8 days, then concentrated *in vacuo*. The residual syrup was dissolved in 10% sodium hydroxide solution, washed with ether, and treated with hydrochloric acid to precipitate the crude acid. One crystallisation from ethyl acetate–light petroleum gave *αα-di-(2-methylsulphonylethyl)-α-phenylacetic acid* (11 g.), m. p. 188—190° not increased by further crystallisation from acetic acid (Found: C, 47·9; H, 5·9; S, 18·1. $C_{14}H_{20}O_6S_2$ requires C, 48·3; H, 5·7; S, 18·4%). This acid gave a *benzylamine salt*, m. p. 156—157° (from ethanol–light petroleum) (Found: C, 55·1; H, 6·7; N, 3·3; S, 14·1. $C_{21}H_{29}NO_6S_2$ requires C, 55·4; H, 6·4; N, 3·1; S, 14·1%).

α-Acetoxy-α-ethylbutyric Acid.—Acetyl chloride (5 g.) was added to an ice-cooled solution of α-ethyl-α-hydroxybutyric acid (6·6 g.) in pyridine (6 ml.). The mixture was set aside overnight, then diluted with ether, filtered to remove pyridine hydrochloride, and shaken with sodium hydrogen carbonate solution. The aqueous phase was separated, acidified, and extracted with ether. The final extracts were dried and evaporated to an oil which solidified.

[23] Bodroux and Taboury, *Bull. Soc. chim. France*, 1910, **7**, 734.
[24] Mndzhoyan, Tatevosyan, and Agbalyan, *Doklady Akad. Nauk Armyan, S.S.R.*, 1957, **25**, No. 1, 11; *Chem. Abs.*, 1958, **52**, 2798.
[25] Lumière and Perrin, *Compt. rend.*, 1926, **183**, 617.
[26] Bodroux, *Bull. Soc. chim. France*, 1910, [4], **7**, 848.

Recrystallisation from light petroleum gave α-*acetoxy-α-ethylbutyric acid* (5·5 g.), m. p. 67·5—68·5° (Found: C, 55·0; H, 7·7. $C_8H_{14}O_4$ requires C, 55·2; H, 8·0%). With thionyl chloride in light petroleum at room temperature (18 hr.) this gave the *acid chloride* (82%), b. p. 82°/9 mm., n_D^{22} 1·4398 (Found: Cl, 18·3. $C_8H_{13}ClO_3$ requires Cl, 18·4%).

α-*Ethoxy-α-ethylbutyramide.*—α-Ethoxy-α-ethylbutyric acid [11] (2 g.) and triethylamine (3·6 ml.) in chloroform (20 ml.) were treated with thionyl chloride (0·92 ml., 1 mol.) in chloroform (5 ml.) at 0° for 20 min. Ammonia was then passed into the solution, still at 0°, for 30 min., after which the mixture was diluted with ether and washed with dilute acid, dilute alkali, and water. Evaporation of the dried solvent phase left α-*ethoxy-α-ethylbutyramide* (65%), m. p. 73·5—74° (from light petroleum) (Found: N, 9·1. $C_8H_{17}NO_2$ requires N, 8·8%). Attempts to prepare the intermediate α-ethoxy-α-ethylbutyryl chloride under more vigorous conditions caused decomposition.

α-*Ethyl-α-(phenylthio)butyric Acid.*—Sodium hydroxide (28 g.) in 50% aqueous ethanol (60 ml.) was added to a stirred mixture of ethyl α-bromo-α-ethylbutyrate (44·8 g.), thiophenol (24 g.), and ethanol (120 ml.) at <10°. Next morning, the mixture was diluted with ethanol (70 ml.) and sufficient water to give a clear solution, then refluxed for 8 hr. Unchanged thiophenol was removed from the acidified mixture by steam-distillation and the residue was cooled and extracted with ether. Evaporation of the dried extracts left α-*ethyl-α-(phenylthio)-butyric acid* (33%), having m. p. 76—77° after crystallisation from light petroleum (Found: C, 64·2; H, 7·2; S, 14·5. $C_{12}H_{16}O_2S$ requires C, 64·3; H, 7·2; S, 14·3%). With thionyl chloride in benzene (2 hours' refluxing) it gave the *acid chloride* (72%), b. p. 86°/0·05 mm., n_D^{21} 1·5535 (Found: Cl, 14·4. $C_{12}H_{15}ClOS$ requires Cl, 14·6%).

α-*Phenylthio-α-propylvaleric Acid.*—Similarly prepared from ethyl α-bromo-α-propylvalerate and thiophenol, then crystallised from benzene–light petroleum, this *acid* had m. p. 118° (Found: C, 67·0; H, 7·9; S, 12·4. $C_{14}H_{20}O_2S$ requires C, 66·7; H, 7·9; S, 12·7%).

α-*Benzylthio-α-ethylbutyric Acid.*—Toluene-ω-thiol (27·3 ml.) was added to a solution prepared from potassium (16·9 g.) and ethanol (200 ml.), then the mixture was kept at 15—20° whilst α-bromo-α-ethylbutyric acid (139 g.) was added dropwise. Next morning, potassium bromide was removed and the filtrate was refluxed for 30 min., acidified with hydrochloric acid, and concentrated to remove ethanol. The product was extracted in ether, washed, dried, evaporated, and heated under reduced pressure to remove residual toluene-ω-thiol. α-*Benzyl-thio-α-ethylbutyric acid* (18 g.) solidified on cooling and, recrystallised from light petroleum, melted at 76° (Found: C, 65·2; H, 7·6; S, 13·5. $C_{13}H_{18}O_2S$ requires C, 65·5; H, 7·6; S, 13·8%). It gave, as above, the *acid chloride* (82%), b. p. 124°/0·1 mm. (Found: Cl, 14·1; S, 12·8. $C_{13}H_{17}ClOS$ requires Cl, 14·0; S, 12·5%), and *amide*, m. p. 83·5° (from light petroleum) (Found: N, 6·1; S, 13·7. $C_{13}H_{19}NOS$ requires N, 5·9; S, 13·5%).

Ethoxyformic Triphenylacetic Anhydride.—Ethyl chloroformate (0·19 ml.) in dry acetone (5 ml.) was added to triphenylacetic acid (0·58 g.) and triethylamine (0·28 ml.) in dry ice-cold acetone (20 ml.), and the mixture was stirred at 10° for 30 min. Triethylamine hydrochloride was collected and the filtrate was evaporated *in vacuo*. Recrystallisation of the residue from light petroleum (25 ml., b. p. 40—60°) gave needles of the *ethoxyformic anhydride* (0·42 g.), m. p. 98—100° (Found: C, 76·4; H, 5·5. $C_{23}H_{20}O_4$ requires C, 76·7; H, 5·6%).

A similar reaction with s-butyl chloroformate gave the *s-butoxyformic anhydride* (needles from light petroleum), m. p. 82—84° (Found: C, 77·3; H, 6·4. $C_{25}H_{24}O_4$ requires C, 77·3; H, 6·2%).

Reaction of Ethoxyformic Triphenylacetic Anhydride with Aniline.—The anhydride (360 mg.) in acetone (2 ml.) was added to aniline (93 mg.) and water (2 ml.), and the mixture was set aside for 30 min. with occasional stirring, then diluted with water. The solid was collected and extracted with hot water (2 × 50 ml.), the extracts affording ethyl N-phenylurethane (70 mg.) which was identified by mixed m. p. determination. The water-insoluble residue was purified by dissolution in warm dilute sodium hydroxide followed by acidification, to give triphenylacetic acid (150 mg.), which was similarly identified.

α-*Ethoxydiphenylacethydrazide.*—A solution of ethyl α-ethoxydiphenylacetate (11·4 g.) and anhydrous hydrazine (8 ml.) in butanol (30 ml.) was refluxed for 24 hr., then evaporated *in vacuo*. The residue was treated with N-hydrochloric acid and extracted with ether. Basification of the aqueous solution gave α-*ethoxydiphenylacethydrazide* (7·82 g.) which crystallised from aqueous alcohol in needles, m. p. 123—124° (Found: C, 71·1; H, 7·0; N, 10·2. $C_{16}H_{18}N_2O_2$ requires C, 71·1; H, 6·7; N, 10·4%).

α-*Methoxydiphenylacethydrazide*, similarly prepared in 43% yield, crystallised from benzene–light petroleum in plates, m. p. 109—111° (Found: C, 70·4; H, 6·5; N, 10·9. $C_{15}H_{16}N_2O_2$ requires C, 70·3; H, 6·3; N, 10·9%).

Action of Nitrous Acid on Trisubstituted Acethydrazides.—(a) α-Ethoxydiphenylacethydrazide (2 g.) was dissolved in water (20 ml.) and 5N-hydrochloric acid (10 ml.), cooled to 0°, covered with ether (50 ml.), and stirred whilst sodium nitrite (0·7 g.) in water (10 ml.) was added at <10°. After 10 min. the layers were separated and the aqueous phase was extracted with ether (2 × 25 ml.). The combined ether solutions were washed, dried, and evaporated, to leave α-*ethoxydiphenylacetamide* (1·58 g., 83%) which crystallised from aqueous alcohol in laths, m. p. 145—146°, not depressed on admixture with a specimen prepared from the acid chloride and ammonia (Found: C, 74·9; H, 6·9; N, 5·4. $C_{16}H_{17}NO_2$ requires C, 75·3; H, 6·7; N, 5·5%).

(b) A similar experiment with α-methoxydiphenylacethydrazide gave α-*methoxydiphenyl-acetamide* (62%), needles (from alcohol), m. p. and mixed m. p. 153—155° (Found: C, 74·6; H, 6·4; N, 5·5. $C_{15}H_{15}NO_2$ requires C, 74·7; H, 6·3; N, 5·8%).

(c) Triphenylacethydrazide similarly gave triphenylacetamide (82%), plates (from butanol), m. p. and mixed m. p. 241—242° (Found: N, 5·0. Calc. for $C_{20}H_{17}NO$: N, 4·9%).

Triphenylmethylpenicillin.—(a) *Sodium salt.* Triphenylacetyl chloride (18·4 g.) in acetone (360 ml.) was added during 15 min. to a stirred solution of 6-aminopenicillanic acid (13 g.) in a mixture of 3% aqueous sodium hydrogen carbonate (500 ml.) and acetone (150 ml.). The mixture was stirred at room temperature for 3 hr., then washed with ether (2 × 600 ml.). The aqueous layer was filtered to remove a little suspended solid and then cooled to −6°, whereupon the product crystallised (plates). It was collected (refrigerated centrifuge) and recrystallised by dissolution in 80% aqueous acetone (300 ml.) at room temperature, following by cooling to −6°. Drying in a vacuum-desiccator gave a white powder (17·1 g.; m. p. 100—120°) which appeared to be essentially the monohydrate. Further drying over phosphorus pentoxide at 80°/0·4 mm. gave the anhydrous *sodium salt*, m. p. 183—190° (decomp.), $[\alpha]_D^{19}$ +81° (c 1·5 in H_2O) (Found: C, 65·9; H, 5·2; N, 5·2; S, 6·2; Na, 4·4. $C_{28}H_{25}N_2O_4SNa$ requires C, 66·1; H, 5·0; N, 5·5; S, 6·4; Na, 4·5%), but on exposure to air this rapidly reverted to the hydrate, m. p. 100—120°.

(b) *Potassium salt.* Substitution of the equivalent quantity of potassium hydrogen carbonate for the sodium salt in the above experiment gave the *potassium salt*, m. p. 199—201° (decomp.), of triphenylmethylpenicillin (Found: C, 63·7; H, 4·8; N, 5·1; S, 5·8; K, 7·4. $C_{28}H_{25}N_2O_4SK$ requires C, 64·1; H, 4·8; N, 5·3; S, 6·1; K, 7·4%).