971. *Synthesis of* DL-p-*Trimethylsilylphenylalanine.*

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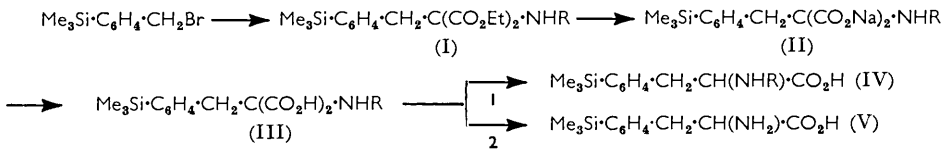
DL-*p*-Trimethylsilylphenylalanine has been prepared in good yield by condensation of 4-trimethylsilylbenzyl bromide with diethyl formamidomalonate, followed by mild hydrolysis and decarboxylation of the resulting disodium α-(4-trimethylsilylbenzyl)formamidomalonate. Its *N*-carboxyanhydride was obtained on reaction of the amino-acid with carbonyl chloride, and it has been polymerised in pyridine.

THE important role played by phenylalanine in the metabolism of various organisms has prompted the preparation of phenylalanine derivatives substituted in the benzene ring, with the intention of obtaining competitive antagonists of phenylalanine or tyrosine. Analogues of phenylalanine *para*-substituted by methyl,[1] nitro-,[2] amino-,[2] fluoro-,[3] or mercapto-,[4] or other sulphur-containing groups [5] have been prepared [6] and tested as antimetabolites. From this point of view it seemed interesting to prepare *p*-trimethylsilylphenylalanine as a potential antimetabolite for both phenylalanine and tyrosine, for it has been pointed out [7] that the relative sizes of substituting groups affects their antimetabolite activity. Moreover, the electronic effects of the trimethylsilyl group ($+I$ and $-M$) may also come into play.

Amino-acids have been prepared [8,9] containing a trialkylsilyl group attached to the carbon side-chain of aliphatic amino-acids such as glycine or alanine, as well as *N*-alkylsilyl derivatives and silyl esters.[10]

We have synthesised *N*-acetyl- and *N*-formyl-*p*-trimethylsilylphenylalanine from diethyl acylamidomalonate by the route summarised in the Chart. We failed to remove the acetyl group of *N*-acetyl-*p*-trimethylsilyl-DL-phenylalanine (IVa) under mild conditions. Heating with concentrated acids [11] led to loss of the trimethylsilyl group and formation of phenylalanine, as expected.[12] The *N*-formyl derivatives (Ib), (IIb), and (IVb) were



R = (a) Ac, (b) CHO. Me_3Si *para* to CH_2.

Reagents: 1, H·CO_2H. 2, HCl–MeOH.

prepared in high yields from diethyl formamidomalonate, and the formyl group was readily removed by use of methanolic hydrochloric acid [13,14] at room temperature, a procedure that, in this case, seemed simpler than the oxidative method.[15] The disodium

[1] Dakin, *J. Biol. Chem.*, 1911, **9**, 151; Herr, Enkoji, and Dailey, *J. Amer. Chem. Soc.*, 1957, **79**, 4229

[2] Erlenmeyer and Lipp, *Annalen*, 1883, **219**, 219; Burckhalter and Stephens, *J. Amer. Chem. Soc.*, 1951, **73**, 56.

[3] Bennett and Niemann, *J. Amer. Chem. Soc.*, 1950, **72**, 1800.

[4] Johnson and Brautlecht, *J. Biol. Chem.*, 1912, **12**, 175; Elliott and Harington, *J.*, 1949, 1374.

[5] Nevenzel, Shelberg, and Niemann, *J. Amer. Chem. Soc.*, 1949, **71**, 3024; Colescott, Herr, and Dailey, *ibid.*, 1957, **79**, 4232.

[6] Greenstein and Winitz, " Chemistry of the Amino Acids," John Wiley and Sons, New York, 1961, p. 2697.

[7] Woolley, " A Study of Antimetabolites," John Wiley and Sons, New York, 1950, p. 220.

[8] Birkofer and Ritter, *Annalen*, 1958, **612**, 22.

[9] Sommer, U.S.P. 2,774,778/1956; *Chem. Abs.*, 1958, **52**, 3851b.

[10] Rühlmann, Kaufmann, and Knopf, *J. prakt. Chem.*, 1962, **18**, 131; Birkofer and Ritter, *Chem. Ber.*, 1960, **93**, 424.

[11] Albertson and Archer, *J. Amer. Chem. Soc.*, 1945, **67**, 308.

[12] Cf. Eaborn, " Organosilicon Compounds," Butterworths Scientific Publns., London, 1960, p. 146.

[13] Waley, *Chem. and Ind.*, 1953, 107.

[14] Boissonnas and Preitner, *Helv. Chim. Acta*, 1953, **36**, 875.

[15] Losse and Zönnchen, *Annalen*, 1960, **636**, 140.

malonate derivative (IIb) was thus converted in one step into the pure amino-acid by simultaneous decarboxylation and deformylation.

DL-*p*-Trimethylsilylphenylalanine is insoluble in cold water and alcohol but soluble in acetic and formic acid. It has infrared bands at 8, 11·9, 13·25 ($SiMe_3$), 9 (Si–Ph), and 11·7 μ (*p*-disubstituted benzene).[16]

The *N*-carboxy-anhydride of *p*-trimethylsilylphenylalanine was obtained on passing carbonyl chloride into a suspension of the amino-acid in tetrahydrofuran at room temperature. The pure product had infrared absorption at 5·45 and 5·65 μ (*N*-carboxy-anhydride) besides that of the trimethylsilyl group. The freshly prepared crystalline anhydride was polymerised in pyridine solution.

Experimental

M. p.s were determined on a Fischer–Johns apparatus. Ascending paper partition chromatography in 80% aqueous phenol was used.

Trimethyl-p-*tolylsilane*.—This compound was previously prepared [17] in 56% yield starting from the *p*-bromotolyl Grignard reagent. The following method using the cheaper and lower-boiling *p*-chlorotoluene gives better yields and the product is more easily separated.

p-Chlorotoluene (190 g., 1·5 mole) in dry ether (350 ml.) was dropped during 2—3 hr. into a three-necked flask, fitted with a high speed stirrer, a gas adapter for introducing nitrogen, and a separatory funnel, on to lithium wire (22 g., excess) in dry ether (450 ml.) under nitrogen and cooled in ice–salt. Stirring was carried out for 8 hr. in the cold, and the mixture was then left overnight. Chlorotrimethylsilane (163 g., 1·5 mole) in dry ether (300 ml.) was dropped in during 2 hr., with cooling in ice–salt, and stirring continued for another 3 hr. The mixture was then left to warm to room temperature and refluxed for 4 hr., filtered through glass wool, and treated with water. The ethereal layer was separated and washed with water, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated. The residue, on fractionation, gave a small forerun of *p*-chlorotoluene, and trimethyl-*p*-tolylsilane (210 g., 85%) was collected at 185—187°/690 mm. Its infrared spectrum was as recorded.[17]

Diethyl DL-*Acetamido*-α-(4-*trimethylsilylbenzyl*)*malonate* (Ia).—To a solution from sodium (1·15 g., 0·05 mole) in absolute ethanol (100 ml.) was added with stirring diethyl acetamidomalonate [18] (10·9 g., 0·05 mole). After a few minutes 4-trimethylsilylbenzyl bromide (12·1 g., 0·05 mole), prepared from trimethyl-*p*-tolylsilane, *N*-bromosuccinimide, and 5 mol. % of benzoyl peroxide,[19] were added, and the mixture was stirred for 4 hr. at room temperature and left overnight, then evaporated *in vacuo*. The residue was taken up in ether (100 ml.) and water (50 ml.). The ether layer was separated and the water layer was extracted with ether three times. The combined ether extracts were dried ($MgSO_4$) and evaporated. The residue was dissolved in a minimum amount of ethanol and, after addition of water to incipient cloudiness, left to crystallise at 0° (yield, 11·2 g.; m. p. 88—89°). From the filtrate another crop (6·2 g.; m. p. 85°) was obtained on further addition of water (total yield 92%). The m. p. was raised to 90° on recrystallisation from 2 : 3 aqueous ethanol. The *product* is soluble in acetone and slightly soluble in light petroleum and had $\nu_{max.}$ 8, 11·9, 13·15 ($SiMe_3$), and 9 μ (Si–Ph) (Found: C, 60·4; H, 7·6; N, 3·7; Si, 7·6. $C_{19}H_{29}NO_5Si$ requires C, 60·2; H, 7·7; N, 3·7; Si, 7·4%).

Hydrolysis of the Amide (Ia) *with Hydrobromic Acid*.—The amide (0·48 g.) was heated with 48% hydrobromic acid [11] (1·5 ml.) at 130—140° for 7·5 hr. This gave DL-phenylalanine, identified by its nitrogen content, infrared spectrum, and R_F value.

Disodium DL-α-*Acetamido*-α-(4-*trimethylsilylbenzyl*)*malonate* (IIa).—The amide (Ia) (3·8 g.) was dissolved in a solution from sodium (0·5 g.) in absolute ethanol (20 ml.). Water (0·5 ml.) was added, and the solution boiled for 5 min. The precipitated *disodium salt* (3·4 g., 92%) was collected and washed with ethanol. It does not melt below 300° (Found: N, 3·7. $C_{15}H_{19}NNa_2O_5Si$ requires N, 3·8%).

DL-α-*Acetamido*-α-(4-*trimethylsilylbenzyl*)*malonic Acid* (IIIa).—A solution of freshly prepared disodium salt (IIa) (0·5 g.) in water (20 ml.) was cautiously acidified with hydrochloric acid.

[16] Cross, "Introduction to Practical Infrared Spectroscopy," Butterworths Scientific Publns., London, 1960, p. 74.
[17] Clark, Gordon, Young, and Hunter, *J. Amer. Chem. Soc.*, 1951, **73**, 3798.
[18] Shaw and Nolan, *J. Org. Chem.*, 1957, **22**, 1668.
[19] Severson, Rosscup, Lindberg, and Engberg, *J. Amer. Chem. Soc.*, 1957, **79**, 6540.

The precipitated *acid* (yield almost quantitative), m. p. 128°, was recrystallised from ether–light petroleum, then having m. p. 131° (Found: C, 55·0; H, 6·5; N, 4·6. $C_{15}H_{21}NO_5Si$ requires C, 55·6; H, 6·5; N, 4·3%).

DL-N-*Acetyl*-p-*trimethylsilylphenylalanine* (IVa).—The sodium salt (IIa) (1·0 g.) was added to 90% formic acid (5 ml.) and heated to the b. p., diluted with water and cooled. The precipitate (0·53 g., 70%), when recrystallised from 1 : 3 aqueous ethanol, melted at 190° (Found: C, 59·7; H, 7·3; N, 4·9. $C_{14}H_{21}NO_3Si$ requires C, 60·2; H, 7·5; N, 5·0). The same *product* was obtained on heating the salt (IIa) for several hours with dilute hydrochloric acid.

Diethyl DL-α-*Formamido*-α-(4-*trimethylsilylbenzyl*)*malonate* (Ib).—The *compound* obtained in 93% yield from diethyl formamidomalonate [18] and 4-trimethylsilylbenzyl bromide by the procedure given for the acetyl derivative (Ia) and recrystallised from dilute alcohol (40%) had m. p. 81—82°; its infrared spectrum showed the absorption of the trimethylsilyl group (Found: C, 59·0; H, 7·4; N, 3·6. $C_{18}H_{27}NO_5Si$ requires C, 59·2; H, 7·4; N, 3·8%).

Disodium DL-α-*Formamido*-α-(4-*trimethylsilylbenzyl*)*malonate* (IIb).—The above procedure for the hydrolysis of the acetyl derivative was followed. The *disodium salt* was precipitated in 85% yield. The yield was increased to theoretical by evaporation of the mother-liquor which yields the disodium salt slightly contaminated with sodium ethoxide. This crude product can be used for the preparation of the amino-acid without further purification. The salt does not melt below 300° (Found: N, 3·8. $C_{14}H_{17}NNa_2O_5Si$ requires N, 4·0%).

N-*Formyl*-DL-*p*-*trimethylsilylphenylalanine* (IVb).—The procedure for the *N*-acetyl derivative (IVa) was followed. The crude *product* (75%) melted at 175° and, recrystallised from 1 : 4 aqueous ethanol at 183° [Found: C, 59·1; H, 7·2; N, 5·4; *N*(Van Slyke), 0·0. $C_{13}H_{19}NO_3Si$ requires C, 58·9; H, 7·2; N, 5·3%].

The same product was obtained on heating the disodium salt (IIb) with dilute hydrochloric acid.

DL-p-*Trimethylsilylphenylalanine* (V).—Disodium formamido-4-trimethylsilylbenzylmalonate (14 g.) was added to methanolic 1·5N-hydrochloric acid (160 ml.) and left for 20 hr. The mixture was evaporated *in vacuo*, absolute methanol was added, and the whole evaporated again to remove hydrochloric acid. This process was repeated twice. The residue was triturated with water, filtered, and washed with cold water (yield, 8·1 g., 86%). The product was purified by boiling ethanol (92% recovery; m. p. 213°) and was free from chlorine. Neutralisation of the mother-liquor and washing with sodium hydrogen carbonate to pH 6—7 yielded a further 0·9 g. of impure material, m. p. 180—185°. The main product, recrystallised from 15% acetic acid, had m. p. 223°, R_F 0·95 (phenylalanine 0·85). Titration of the DL-p-*trimethylsilylphenylalanine* in acetic acid with anhydrous perchloric acid (Thymol Blue as indicator) gave mol. wt. 232 (calc. 237) (Found: C, 60·9; H, 8·0; N, 6·0; Si, 11·8. $C_{12}H_{19}NO_2Si$ requires C, 60·8; H, 8·0; N, 5·9; Si, 11·8%).

N-*Carboxy-anhydride*.—Carbonyl chloride was passed with stirring into a suspension of DL-*p*-trimethylsilylphenylalanine (1 g.) in tetrahydrofuran (100 ml.) at room temperature for 90 min. The solution was evaporated *in vacuo*, and the residue was left overnight in a vacuum-desiccator over phosphoric oxide. The N-*carboxy-anhydride*, on recrystallisation from ether–light petroleum, had m. p. 99° (Found: C, 58·4; H, 6·5; N, 5·3. $C_{13}H_{17}NO_3Si$ requires C, 59·3: H, 6·5; N, 5·3%).

Fresh *N*-carboxy-anhydride (0·3 g.) was left in dry pyridine (3 ml.), for 2 days at room temperature, then heated on a water-bath for a few hours. The pyridine was driven off *in vacuo*, water added to the residue, and the whole evaporated. The residual *polymer* further purified by washing it with water, followed by ethanol [Found: C, 64·4; H, 7·7; N, 6·0. $(C_{12}H_{17}NOSi)_x$ requires C, 65·7; H, 7·8; N, 6·4%]. It is soluble in cold chloroform, nitrobenzene, hot trifluoroacetic acid, *m*-cresol, and dichloroacetic acid. It is partially soluble in hot glacial acetic acid. The infrared spectrum showed the characteristic absorption for the trimethylsilyl group, $\lambda_{max.}$ 8, 11·9, and 13·25 μ.

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