# The Synthesis of 2,2,3,3-Tetramethyl-β-alanine

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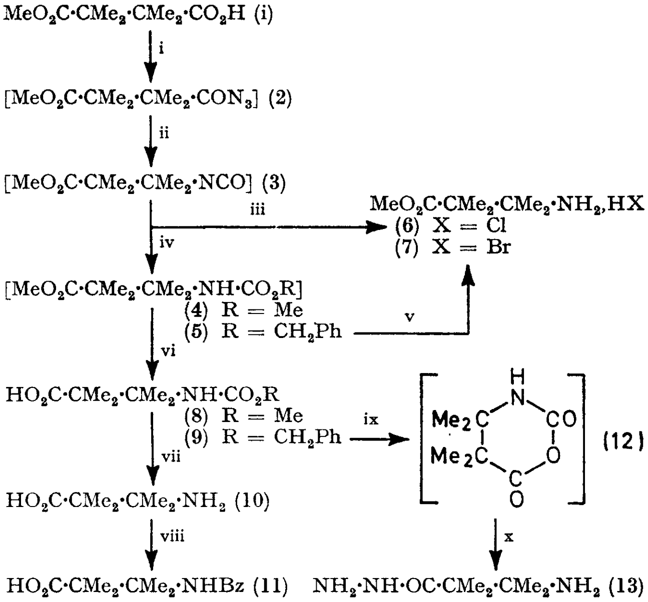
2,2,3,3-Tetramethyl-β-alanine was prepared from methyl hydrogen tetramethylsuccinate by a modified Curtius procedure. Conventional procedures were not suitable for making derivatives of this amino-acid.

ALTHOUGH various derivatives of β-alanine have been prepared from succinic acid derivatives *via* the Hofmann and Curtius reactions,[1] when the Hofmann reaction was applied to tetramethylsuccinimide little reaction occurred. However a modified Curtius procedure[2] applied to methyl hydrogen tetramethylsuccinate gave the required isocyanate (3). Acid hydrolysis of the isocyanate gave 2,2,3,3-tetramethyl-β-alanine methyl ester hydrochloride (6) (13%), and alkaline hydrolysis of the isocyanate gave *N*-(methoxycarbonyl)-2,2,3,3-tetramethyl-β-alanine (8) (14%).



Reagents: i, $Et_3N{-}ClCO_2Et$, then $NaN_3$; ii, heat; iii, HCl; iv, $ROH{-}OH^-$; v, HBr–AcOH; vi, $NaOH{-}MeOH{-}H_2O$; vii, where R = Me, NaOH and where $R = CH_2Ph$, $H_2{-}Pd{-}C$ or HBr–AcOH; viii, $PhCOCl{-}Et_3N$; ix, $SOCl_2$; x, $N_2H_4$.

In order to convert the isocyanate (3) into a urethane which could be easily cleaved, it was treated with benzyl alcohol in the presence of *N*-ethylmorpholine,[3] and the product was hydrolysed with alkali to give *N*-benzyloxycarbonyl-2,2,3,3-tetramethyl-β-alanine (9) in an overall yield of 28%. The benzyloxycarbonylamino-acid (9) gave 2,2,3,3-tetramethyl-β-alanine (10) on catalytic reduction, and with hydrogen bromide in acetic acid gave the corresponding hydrobromide.

Treatment of the amino-acid (10) with benzoyl chloride and triethylamine in dimethylformamide gave the *N*-benzoyl derivative (11), but this reaction failed in aqueous solution in the presence of sodium hydrogen carbonate.

*N*-Benzyloxycarbonyl-2,2,3,3-tetramethyl-β-alanine (9), when treated with thionyl chloride and then hydrazine, gave 2,2,3,3-tetramethyl-β-alanine hydrazide (13), presumably *via* the cyclic *N*-carboxy-β-amino-acid anhydride[4] (12). The hydrazide (13) was not formed when a mixed anhydride or cyanomethyl ester derived from the *N*-benzyloxycarbonylamino-acid (9) was treated with hydrazine, and 2,2,3,3-tetramethyl-β-alanine methyl ester did not react with hydrazine at 80°. Conventional coupling procedures have also been reported[5] to fail when applied to 3-benzamido-3-methylbutanoic acid, although the oxazinone prepared from this acid was suitable for the preparation of derivatives.

The fact that derivatives of 2,2,3,3-tetramethyl-β-alanine (10) are difficult both to form and to cleave can be understood by examining molecular models, which show that the four methyl groups force the amino- and carboxy-groups into close proximity so that substitution of the amino- or the carboxy-group is likely to decrease the reactivity of the other group by steric hindrance.

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## EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 237 instrument.

N-*Benzyloxycarbonyl*-2,2,3,3-*tetramethyl*-β-*alanine* (9).—Methyl hydrogen tetramethylsuccinate[6] (1) (18·6 g.) was converted into the crude isocyanate (3) (11·0 g.), $\nu_{max.}$ 2260 and 1730 cm.$^{-1}$, by a procedure similar to that previously described for an indane acid.[2] Heating the isocyanate with benzyl alcohol (11 ml.) and *N*-ethylmorpholine (2 ml.) at 180° for 2 hr. and distillation gave a fraction (10·8 g.), b.p. 129—135°/0·1 mm., $\nu_{max.}$ 3330 and 1730 cm.$^{-1}$. The oil (5) (10·8 g.), methanol (80 ml.), and 2N-sodium hydroxide (25 ml.) were stirred at 20° for 56 hr., then heated under reflux for 3 hr. The mixture was evaporated, cooled, and acidified (2N-HCl), and the oil was extracted with ether. The extract was washed ($H_2O$), dried ($MgSO_4$), and evaporated, and the residue was collected with light petroleum (b.p. 40—60°); m.p. 116—117° (7·7 g., 28%). A sample recrystallised twice from aqueous methanol gave the *benzyloxycarbonylamino-acid* (9), m.p. 122·5—123·5° (Found: C, 64·8; H, 7·6; N, 4·8. $C_{15}H_{21}NO_4$ requires C, 64·5; H, 7·6; N, 5·0%), $\nu_{max.}$ (Nujol) 3430, 1725, and 1680 cm.$^{-1}$.

2,2,3,3-*Tetramethyl*-β-*alanine* (10) *Hydrochloride and* N-(*Methoxycarbonyl*-2,2,3,3-*tetramethyl*-β-*alanine* (8).—The isocyanate (3) (3·65 g.), methanol (50 ml.), and 40% sodium hydroxide solution (15 ml.) after 16 hr. at room temperature were heated under reflux for 3 hr. The methanol was removed and the aqueous solution was acidified. The solid (1·65 g.) gave the N-*methoxycarbonylamino-acid* (8) (1·0 g.), m.p. 139—140° (from aqueous ethanol) (Found: C, 53·3; H, 8·6; N, 6·7. $C_9H_7NO_4$ requires C, 53·2; H, 8·4; N, 6·9%), $\nu_{max.}$ (Nujol) 3380, 1705, and 1670 cm.$^{-1}$.

The acidic filtrate was evaporated and the residue was extracted with propan-2-ol. The extract was evaporated with several further additions of propan-2-ol and the residue yielded the *amino-acid hydrochloride* (0·2 g.), m.p. 244—245° (decomp.) (from propan-2-ol–ethyl acetate) (Found: C, 46·3; H, 8·95; N, 7·5. $C_7H_6ClNO_2$ requires C, 46·25; H, 8·9; N, 7·7%), $\nu_{max.}$ (Nujol) 3250, 3190, 2530, 2020, and 1755 cm.$^{-1}$.

2,2,3,3-*Tetramethyl*-β-*alanine Methyl Ester Hydrochloride* (6).—The isocyanate (3) (2·2 g.) and 5N-hydrochloric acid (20 ml.) were heated on a steam-bath for 2 hr. The solution was evaporated with additions of propan-2-ol and the product was isolated with ether. Recrystallisation from propan-2-ol–ethyl acetate gave the *ester hydrochloride* (6) (0·52 g.), m.p. 170·5—172·0° (Found: C, 48·75; H, 9·4; N, 6·9. $C_8H_{18}ClNO_2$ requires C, 49·0; H, 9·3; N, 7·15%), $\nu_{max.}$ (Nujol) 2590, 2510, 2040, and 1725 cm.$^{-1}$.

2,2,3,3-*Tetramethyl*-β-*alanine* (10).—(*a*) *N*-Benzyloxycarbonyl-2,2,3,3-tetramethyl-β-alanine (9) (5·0 g.), 90% acetic acid (50 ml.), and 10% palladium–charcoal (0·5 g.) were shaken in hydrogen until no more hydrogen was absorbed. The solution was filtered and evaporated with two additions of propan-2-ol and the product was collected with ether to give the *amino-acid* (10) (2·2 g., 86%), m.p. 280—283° (decomp.) (Found: C, 58·1; H, 10·35; N, 9·4. $C_7H_{15}NO_2$ requires C, 57·9; H, 10·4; N, 9·65%).

(*b*) *N*-Benzyloxycarbonyl-2,2,3,3-tetramethyl-β-alanine (5·0 g.) and 50% hydrogen bromide in acetic acid (20 ml.) were set aside for 1 hr. Dilution with ether gave the *amino-acid* (10) *hydrobromide* (3·2 g., 78%), m.p. 238—239° (decomp.) (Found: C, 36·95; H, 7·15; N, 6·0. $C_7H_{16}BrNO_2$ requires C, 37·15; H, 7·1; N, 6·2%).

N-*Benzoyl*-2,2,3,3-*tetramethyl*-β-*alanine* (11).—The amino-acid (10) (0·71 g.), dimethylformamide (20 ml.), triethylamine (3·0 ml.), and benzoyl chloride (1·16 ml.) were heated on a steam-bath for 2 hr. The solution was evaporated and water (150 ml.) and 2N-sodium hydroxide (20 ml.) were added to the residue. The solution was stirred for 15 min., acidified, and extracted with ether (×2), and the extract was dried ($MgSO_4$) and evaporated. The residue was recrystallised from light petroleum (b.p. 100—120°) to give the N-*benzoyl derivative* (11) (0·27 g., 22%), m.p. 154—155° (Found: C, 67·5; H, 7·8; N, 5·45. $C_{14}H_{19}NO_3$ requires C, 67·4; H, 7·7; N, 5·6%), $\nu_{max.}$ (Nujol) 3450, 1730, and 1630 cm.$^{-1}$.

2,2,3,3-*Tetramethyl*-β-*alanine Methyl Ester Hydrobromide* (7).—Crude *N*-benzyloxycarbonyl-2,2,3,3-tetramethyl-β-alanine methyl ester (2·93 g.) and 50% hydrogen bromide in acetic acid (10 ml.) were set aside for 45 min. Dilution with ether gave the *ester hydrobromide* (7) (1·3 g.), m.p. 156—158° (Found: C, 39·5; H, 7·6; N, 5·9. $C_8H_{18}BrNO_2$ requires C, 40·0; H, 7·5; N, 5·8%). The ester was isolated by treatment of the hydrobromide (7) with sodium hydroxide and extraction with ether.

2,2,3,3-*Tetramethyl*-β-*alanine Hydrazide* (13).—*N*-Benzyloxycarbonyl-2,2,3,3-tetramethyl-β-alanine (1·4 g.) and thionyl chloride (6 ml.) were heated at 60° for 30 min. The solution was evaporated with two additions of methylene chloride. Tetrahydrofuran (10 ml.) and hydrazine hydrate (1·0 ml.) were added to the residue, the mixture was stirred for 16 hr., and excess of sodium carbonate was added. The mixture was evaporated and the residue was extracted with propan-2-ol. The extract was evaporated and the residue was crystallised from light petroleum (b.p. 80—100°) to give the *hydrazide* (13) (350 mg.), m.p. 93·5—94·0° (Found: C, 52·9; H, 10·9; N, 26·2. $C_7H_{17}N_3O$ requires C, 52·8; H, 10·8; N, 26·4%).

In a previous experiment in which sodium carbonate was not added the hydrazide was isolated as the *hydrochloride* (from methanol–ether), m.p. 250° (decomp.) (Found: C, 42·6; H, 9·4; N, 21·2. $C_7H_{18}ClN_3O$ requires C, 43·0; H, 9·2; N, 21·5%).

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[6] K. Auwers, Th. Schiffer, and F. Schlosser, *Annalen*, 1896, **292**, 175.