Synthesis of β-Amino-acid Peptides. Part 2.[1] Preparation of Peptides of 3-Amino-2,2-dimethylpropionic Acid by Means of Conventional Coupling Reagents and with Oxazin-6-one Derivatives

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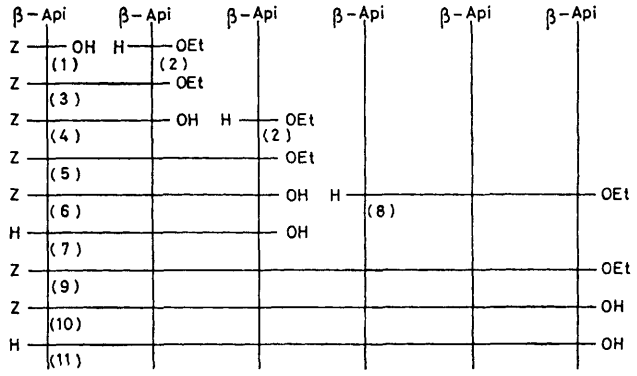
Side reactions were encountered during the coupling of 3-amino-2,2-dimethylpropionic acid (β-Api) derivatives, some of which could be directly ascribed to steric hindrance at the carboxy-group. Protected and deprotected tri- and hexa-peptides were prepared using dicyclohexylcarbodi-imide and hydroxybenzotriazole. Alternative procedures employing oxazin-6-ones were not as useful as expected.

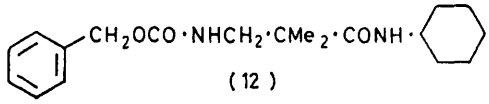
FOLLOWING from earlier work with sterically hindered β-amino-acids,[1] we turned to a study of 3-amino-2,2-dimethylpropionic acid [2] (β-aminopivalic acid; β-Api) to examine problems that might be encountered with selective protection and coupling procedures.[3] It has been assumed that steric hindrance at the amino-group is of greater importance than that associated with the carboxy-group,[4] a difficult premise to evaluate but one which may be amenable to study with this amino-acid. An additional aim included the preparation of tri- and hexa-peptides suitable for cyclisation reactions.

Preparation of the title amino-acid, isolated as the hydrochloride, was achieved by published procedures.[5,6] Protecting groups were confined to benzyloxycarbonyl and benzoyl for *N*-protection and methyl or ethyl esters for *C*-protection. Peptides were prepared by *C*-terminal elongation by using carbonic mixed anhydrides (CMA), dicyclohexylcarbodi-imide (DCCI) and DCCI with the additive 1-hydroxybenzotriazole (Hbt). Low yields of di- and tri-peptides were obtained with CMA activation consistent with the isolation of isobutyloxycarbonyl



SCHEME 1

derivatives.[7] Attempts to prepare the dipeptide (3) using DCCI were likewise not promising, resulting in mixtures. The crude dipeptide (3) was saponified in the hope that the dipeptide acid (4) could be retrieved more readily. Extraction of the hydrolysate afforded a compound formulated as 3-benzyloxycarbonylamino-*N*-cyclohexyl-2,2-dimethylpropionamide (12). At this point it was not clear whether the amide (12) was a genuine DCCI secondary degradation product. Chromatography of the original reaction mixture gave the required dipeptide (3) in addition to the *N*-acylurea (13),



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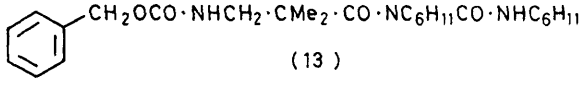

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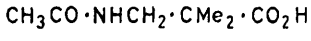

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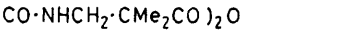

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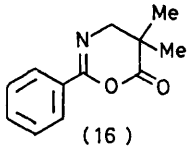

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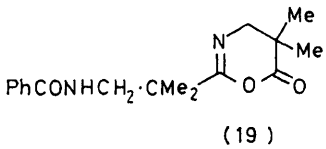

(19)

but there was no trace of the amide (12). On treatment of the urea (13) with base a high yield of the amide (12) could be recovered (Table). This result may be ascribed to the stereoelectronic efforts of the *gem*-dimethyl group of the amino-acid, allowing an otherwise unlikely reaction pathway to intervene. Recently [8] a similar product has been isolated from a DCCI coupling reaction, with a hindered amine.

Tri- [(5), (6), (7)] and hexa-peptides [(9), (10), (11)] (Scheme 1) were eventually made by *C*-terminal elongation and a '3 + 3' block coupling using DCCI in conjunction with Hbt. Peptides were recovered in high yield, albeit in each step traces of NAU were still detectable.

It was anticipated that the oxazinones (16) and (19) should be applicable to the synthesis of β-aminopivalic acid peptides.[1] Dehydration with acetic anhydride [9] led to the isolation of the transacylated acetylamino-acid (14). Alternative reagents including thionyl chloride and CMAs provided the crystalline oxazine (16) in high

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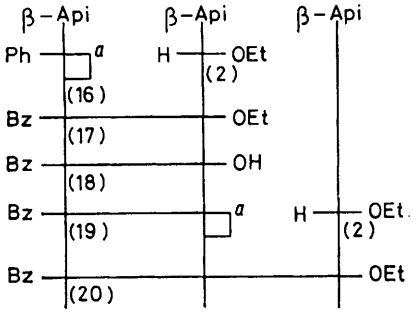
Isolation of by-products

Z-Api	Api-OEt	Triethyl-amine	Coupling reagent	Ethyl acetate	Time/Temp		Product
2.2 g, 8.8 mol	1.75 g [a] 9.6 mmol	0.97 g, 9.6 mmol	DCCI (1.99 g, 9.6 mmol)	40 ml	30 min 2 days	0 °C room temp.	3-*Benzyloxycarbonylamino*-N-*cyclohexyl*-2,2-*dimethylpropionamide* (12) isolated after hydrolysis as for (4), (0.37 g, 13%), m.p. 95—96 °C (from ethyl acetate–light petroleum) (Found: C, 68.5; H, 8.6; N, 8.8. $C_{12}H_{28}N_2O_3$ requires C, 68.6; H, 8.5; N, 8.4%)
2.74 g, 11.8 mmol	1.76 g, 12.2 mmol		DCCI (2.52 g, 12.2 mmol)	200 ml	30 min 2 days	0 °C room temp.	N-(β-*Benzyloxycarbonylaminopivaloyl*)-N,N′-*dicyclohexylurea* [c] (13), (0.31 g, 31%) m.p. 77—78 °C (from light petroleum) (Found: C, 68.5; H, 8.7; N, 9.3. $C_{26}H_{39}N_3O_4$ requires C, 68.2; H, 8.6; N, 9.2%)
1.4 g, 5.6 mmol	0.89 g, 6.1 mmol	0.56 g, 5.6 mmol	IBC [b] (0.76 g, 5.6 mmol)	50 ml	5 min 4 h 18 h	−5 °C 0 °C room temp.	β-*Isobutyloxycarbonylaminopivalic acid dicyclohexylammonium salt*; crude ester (6.5 g) hydrolysed as for (4); acid converted into the crystalline salt, m.p. 139.5—140.5 °C (from ethyl acetate–light petroleum) (Found: C, 66.5; H, 10.6; N, 7.0. $C_{22}H_{42}N_2O_4$ requires C, 66.3; H, 10.6; 7.0%)

[a] As the hydrochloride. [b] IBC = Isobutyl chloroformate. [c] Hydrolysis of (13) provided (12) in 59% yield.

yield.[10] Occasionally the same reaction gave rise to the symmetrical anhydride (15). We noted that if the triethylamine was not dried and purified immediately prior to use, the alternative reaction was favoured. That compound (16) is an oxazinone and not the isomeric acyl-lactam has been established elsewhere.[10,11]

Reaction of aniline with (16) provided the corresponding anilide in high yield. Under similar conditions, treatment of (16) with ethyl aminopivaloate (2) afforded the dipeptide (17) hemihydrate in good yield. Cyclisation of (18) using thionyl chloride proved rather unsatisfactory as manipulation of the reaction products led to



Scheme 2

[a] Represents the dihydro-oxazinone system

decomposition of the required oxazinone (19), although the isolated material was stable on storage at room temperature. Subsequently, reaction of the crude product with ethyl aminopivaloate (2) provided a very mediocre yield of the tripeptide (20) (Scheme 2).

Preparation of *N*-benzoylamino-peptides *via* DCCI–Hbt coupling reactions proceeded uneventfully and are not described in this paper. Consideration has been given to *in situ* formation of oxazinone intermediates during the latter coupling reactions. I.r. spectral studies of the reaction between β-benzoylaminopivalic acid and DCCI in acetonitrile at 0 °C unequivocally demonstrated that the sole product was the oxazinone (16). Under these conditions the time of half-reaction was some minutes. Repetition of the reaction with the inclusion of Hbt did not accord with the previous findings, the only products identified being the symmetrical anhydride (15).

EXPERIMENTAL

M.p.s were recorded on a Gallenkamp apparatus. Solvents were purified by standard methods.[12] Light petroleum refers to the fraction of b.p. 60—80 °C. I.r. spectra were recorded for liquids or Nujol mulls using a Perkin-Elmer 137 or 457 spectrophotometer. ^{1}H N.m.r. spectra (60 MHz) were recorded on a Perkin-Elmer R12 or a Varian A60 instrument with tetramethylsilane as internal standard. Unless otherwise stated neutral products were isolated by washing in ethyl acetate with 1M-hydrochloric acid (3 aliquots), 5% sodium hydrogencarbonate solution (3 aliquots) and then water or saturated sodium chloride solution to neutrality. Organic solutions were dried with either anhydrous magnesium sulphate or sodium sulphate and all evaporations were carried out under reduced pressure on a rotary evaporator. Hydrogenations were performed in methanol over 10% palladium–charcoal as catalyst. Hydrolyses in general were carried out in aqueous methanol or acetone solution at 0 °C using a 10% excess of sodium hydroxide (1M). Products were isolated by evaporation of the organic solvent followed by standard extraction and wash procedures. *N*-Benzyloxycarbonyl derivatives were prepared by conventional procedures. Silica gel (60—120 mesh) was used for column chromatography after washing with 6M-hydrochloric acid, water to neutrality, methanol, and then drying overnight at 100 °C. T.l.c. on Merck Kieselgel G (0.25 mm) employed the following solvent systems (v/v): (A) cyclohexane–chloroform–acetic acid (2 : 8 : 1), (B) ethyl acetate, (C) chloroform, (D) ethanol–ammonia–water (8 : 1 : 1), (E) chloroform–ethyl acetate (24 : 1), (F), (G) and (H) benzene–ethyl acetate (84 : 16),

(92 : 8) and (68 : 32), (I) butan-1-ol–water–acetic acid (4 : 1 : 1), (*J*) methanol–chloroform–acetic acid (5 : 20 : 1).

Synthesis of the Di-, Tri- and Hexa-peptides of β-Aminopivalic acid via *Benzyloxycarbonyl Derivatives.*—*β-Benzyloxycarbonylaminopivalic acid* (1) *dicyclohexylammonium salt.* β-Aminopivalic acid hydrochloride [2a,c] (6 g, 33 mmol) was treated with benzylchloroformate (22 ml, 22 mmol) using the standard procedure. The product (7.6 g, 78%), an oil, was dissolved in ethyl acetate, and dicyclohexylamine (5.5 g, 30 mmol) was added at 0 °C. Evaporation of the solvent and recrystallisation of the residue from ethyl acetate–light petroleum yielded the *dicyclohexylammonium salt* of (1) (11 g, 65%), m.p. 152.5—154 °C (raised to 153.5—154 °C on further crystallisation) (Found: C, 69.7; H, 9.2; N, 6.3. $C_{25}H_{40}N_2O_4$ requires C, 69.4; H, 9.3; N, 6.5%).

β-Benzyloxycarbonylaminopivaloyl-β-aminopivalic acid (4). 1-Hydroxybenzotriazole (1.61 g, 12 mmol), β-benzyloxycarbonylaminopivalic acid (3 g, 12 mmol), ethyl β-aminopivaloate hydrochloride [2a,c] (2.39 g, 13 mmol), and triethylamine (1.33 g, 13 mmol) were added to acetonitrile (25 ml). The mixture was cooled (0 °C) and a precooled (0 °C) solution of DCCI (2.71 g, 13 mmol) in acetonitrile (15 ml) was added. The mixture was stirred for 1 h at 0 °C and 1 h at room temperature, and then filtered. The filtrate, after the solvent had been changed to ethyl acetate, was washed in the usual way and evaporated to give an oil (4.4 g, 98%). A solution of the foregoing crude ester (3) (3.2 g, 8.5 mmol) in acetone (30 ml) was cooled to 0 °C and sodium hydroxide solution (1M; 9 ml) was added gradually. The mixture was stirred overnight at room temperature, then neutralised (2M; HCl), and the acetone evaporated. The aqueous solution was made alkaline again (2M; NaOH), reacidified to Congo Red, and again extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried, and evaporated. The residue, after recrystallision from ethyl acetate–light petroleum, afforded the *dipeptide acid* (4) (2.3 g, 77%), m.p. 106.5—108 °C, R_{FD} 0.55 (Found: C, 61.5; H, 7.5; N, 7.9. $C_{18}H_{26}N_2O_5$ requires C, 61.7; H, 7.5; N, 8.0%).

β-Benzyloxycarbonylaminopivaloyl-β-aminopivaloyl-β-aminopivalic acid ethyl ester (5). β-Benzyloxycarbonylaminopivaloyl-β-aminopivalic acid (4) (14.9 g, 43.0 mmol) and ethyl β-aminopivaloate [2a,c] (6.82 g, 47.0 mmol; derived from the hydrochloride) were coupled using DCCI (9.9 g, 47.0 mmol) and 1-hydroxybenzotriazole (5.18 g, 43 mmol) in an analogous procedure to the one detailed above for the preparation of the dipeptide derivative (3). Recrystallisation from ethyl acetate–light petroleum gave the *tripeptide ester* (14.6 g, 80%), m.p. 89.5—90.5 °C (Found: C, 62.8; H, 8.0; N, 8.7. $C_{25}H_{39}N_3O_6$ requires C, 62.9; H, 8.2; N, 8.8%).

β-Benzyloxycarbonylaminopivaloyl-β-aminopivaloyl-β-aminopivalic acid (6) *dicyclohexylammonium salt.* The foregoing tripeptide ethyl ester (5) (11.5 g, 24 mmol) in acetone (90 ml) was cooled to 0 °C and treated with sodium hydroxide solution (1M; 25 ml) as for the dipeptide acid (4). The peptide was isolated as a viscous oil (11.0 g), R_{FA} 0.33. Dissolution of the oil in ethyl acetate and addition of dicyclohexylamine (4.36 g, 24 mmol) afforded the *dicyclohexylammonium salt* of (6) (11.7 g, 78%), m.p. 80—82 °C (Found: C, 66.8; H, 9.2; N, 9.1. $C_{35}H_{58}N_4O_6$ requires C, 66.6; H, 9.3; N, 8.9%).

β-Aminopivaloyl-β-aminopivaloyl-β-aminopivalic acid (7). The aforementioned oily benzyloxycarbonyl-tripeptide acid (6) (5.8 g, 13 mmol) was hydrogenated in methanol (60 ml) over 10% palladium–charcoal (0.75 g) for 6 h and worked up in the usual way to furnish the *free tripeptide* (7) (3.4 g, 83%), m.p. 209—212 °C (from methanol–ether) (Found: C, 56.9; H, 9.2; N, 13.1. $C_{15}H_{29}N_3O_4$ requires C, 57.1; H, 9.3; N, 13.3%).

β-Benzyloxycarbonylaminopivaloyl-β-aminopivaloyl-β-aminopivaloyl-β-aminopivaloyl-β-aminopivaloyl-β-aminopivalic acid ethyl ester (9). A solution of the aforementioned oily tripeptide acid (6) (2.6 g, 5.8 mmol) and the tripeptide ester (8) (2.2 g, 6.4 mmol) [obtained by hydrogenolysis of (5) (3.14 g, 6.4 mmol)] (used without purification) in acetonitrile (15 ml) was treated with 1-hydroxybenzotriazole (0.78 g, 5.8 mmol) and a solution of DCCI (1.31 g, 6.4 mmol) in acetonitrile (10 ml) as described previously for the preparation of the dipeptide ester (3). The residue from initial filtration of the reaction mixture was dissolved in methanol–acetone (1 : 1 v/v, 100 ml), then cooled to −70 °C. The precipitate was filtered off and the filtrate was evaporated. The crude product was recrystallised from ethanol–water giving the *hexapeptide derivative* (9) (3.58 g, 79%), m.p. 160—162 °C (raised to 164—165 °C on further recrystallisation) (Found: C, 61.9; H, 8.4; N, 11.0. $C_{40}H_{66}N_6O_9$ requires C, 62.0; H, 8.6; N, 10.9%).

β-Benzyloxycarbonylaminopivaloyl-β-aminopivaloyl-β-aminopivaloyl-β-aminopivaloyl-β-aminopivaloyl-β-aminopivalic acid (10). The above benzyloxycarbonylhexapeptide ester (9) (3.3 g, 4.3 mmol) was hydrolysed and isolated as for the dipeptide acid (4). Recrystallisation from ethyl acetate raised the m.p. to 114—116 °C (1.8 g, 56%), giving the *acid* (10) (Found: C, 61.0; H, 8.2; N, 11.4. $C_{38}H_{62}N_6O_9$ requires C, 61.1; H, 8.4; N, 11.3%).

β-Aminopivaloyl-β-aminopivaloyl-β-aminopivaloyl-β-aminopivaloyl-β-aminopivaloyl-β-aminopivalic acid (11). A solution of (10) (800 mg, 1.1 mmol) in methanol (25 ml) was hydrogenated in the usual way. Evaporation of the solvent yielded the *hexapeptide* (11) *trihydrate* (360 mg, 50%), m.p. 203—208 °C (raised on recrystallisation from methanol–ether to 207.5—210.5 °C) (Found: C, 53.7; H, 8.7; N, 12.6%; $M^{+\bullet}$, 612. $C_{30}H_{56}N_6O_7 \cdot 3H_2O$ requires C, 54.0; H, 9.4; N, 12.6%; $M^{+\bullet}$, 612).

Synthesis of β-Benzoylaminopivaloyl-β-aminopivaloyl-β-aminopivalic Acid Ethyl Ester (20) via *N-Benzoyl-protected Derivatives.*—*β-Benzoylaminopivalic acid.* β-Aminopivalic acid hydrochloride [2a,c] (10 g, 65 mmol) was converted into the *benzoyl derivative* using the Schotten–Baumann method (13.3 g, 92%), m.p. 150.5—152 °C (changed to 151—152 °C on recrystallisation from ethyl acetate) (Found: C, 65.1; H, 6.8; N, 6.6. $C_{12}H_{15}NO_3$ requires C, 65.1; H, 6.8; N, 6.3%).

Attempted preparation of 4,5-dihydro-5,5-dimethyl-2-phenyl-1,3-oxazin-6-one [10] (16). *Isolation of β-acetylaminopivalic acid* (14). A solution of β-benzoylaminopivalic acid (1.11 g, 5 mmol) in acetic anhydride (16 ml) was heated under reflux for 10 h and evaporated. The oily residue was extracted with dry toluene (3 × 10 ml) and re-evaporated; a brown oil remained which crystallised on heating at 100 °C *in vacuo* for 12 h. The solid, R_{FD} 0.33 and 0.86 (benzoic acid), was triturated twice with boiling carbon tetrachloride giving the *acetyl derivative* (14) (0.63 g, 79%), m.p. 151—154 °C (raised to 154.5—155.5 °C on recrystallisation from ethanol–ethyl acetate) (Found: C, 52.7; H, 8.1; N, 8.9. $C_7H_{13}NO_3$ requires C, 52.8; H, 8.2; N, 8.8%).

Isolation of β-Benzoylaminopivalic acid anhydride (15). The procedure used to obtain (16) [10] was repeated, except

that the reaction was stirred at room temperature for 30 min. Recrystallisation of the crude product from dry ethyl acetate–light petroleum gave the *symmetrical anhydride* (15) (0.45 g, 42%), m.p. 127.5—129 °C (Found: C, 68.0; H, 6.7; N, 6.4. $C_{21}H_{28}N_2O_5$ requires C, 67.9; H, 6.7; N, 6.6%).

β-*Benzoylaminopivalic acid anilide*. The oxazinone [10] (16) (300 mg, 1.5 mmol) mixed with aniline (137 mg, 1.5 mmol) in dry ether (10 ml) was stirred at room temperature overnight. The *anilide* (350 mg, 80%), m.p. 131.5—132.5 °C, precipitated from the reaction solution and was filtered off. A sample recrystallised from ethyl acetate had m.p. 133—134 °C (Found: C, 72.8; H, 6.8; N, 9.2. $C_{18}H_{20}N_2O_2$ requires C, 73.0; H, 6.8; N, 9.5%).

Ethyl β-*benzoylaminopivaloyl*-β-*aminopivaloate* (17). A mixture of the ester (2) hydrochloride [2a,c] (521 mg, 2.9 mmol) and triethylamine (290 mg, 2.9 mmol) in dry ether (10 ml) was added to (16) (530 mg, 2.6 mmol) in dry ether (10 ml). The mixture was stirred overnight at room temperature, filtered, and then the solvent was changed to ethyl acetate. The usual washing procedure led to the isolation of an oil which crystallised at 0 °C. Trituration with light petroleum yielded the *hemihydrate* of (17) (670 mg, 74%), m.p. 60—61.5 °C (raised to 61.5—62.5 °C on recrystallisation from ethyl acetate–light petroleum), R_{FB} 0.74, R_{FC} 0.12 (Found: C, 63.9; H, 8.2; N, 7.9. $C_{19}H_{28}N_2O_4 \cdot \frac{1}{2}H_2O$ requires C, 63.8; H, 8.2; N, 7.8%).

β-*Benzoylaminopivaloyl*-β-*aminopivalic acid* (18). A solution of the dipeptide derivative (17) (1.2 g, 3.5 mmol) in acetone (15 ml) was hydrolysed as for (4). The residue was recrystallised from ethyl acetate–light petroleum yielding the dipeptide (18) (0.88 g, 80%), m.p. 102.5—104 °C (changed to 102—103 °C after recrystallisation from ethyl acetate) (Found: C, 63.7; H, 7.6; N, 8.7. $C_{17}H_{24}N_2O_4$ requires C, 63.7; H, 7.55; N, 8.7%).

2-(2-*Benzoylamino*-1,1-*dimethylethyl*)-4,5-*dihydro*-5,5-*dimethyl*-1,3-*oxazin*-6-*one* (19). Triethylamine (556 mg, 5.5 mmol) was added to a suspension of (18) (800 mg, 2.5 mmol) in dry ethyl acetate (20 ml). The resulting solution was cooled (0 °C) and a solution of thionyl chloride (298 mg, 2.5 mmol) in dry ethyl acetate (10 ml) was added dropwise over 5 min with stirring. After the mixture had been stirred without cooling during 20 min, triethylamine hydrochloride was filtered off and triturated with hot ethyl acetate (3 × 10 ml). The material extracted was recrystallised from ethyl acetate providing the *oxazinone* (19) (80 mg, 11%), m.p. 139.5—148 °C (raised to 146—154 °C on further recrystallisation) (Found: C, 67.7; H, 7.4; N, 9.5. $C_{17}H_{22}N_2O_3$ requires C, 67.5; H, 7.3; N, 9.3%).

β-*Benzoylaminopivaloyl*-β-*aminopivaloyl*-β-*aminopivalic acid ethyl ester* (20). The oil (780 mg) from the previous reaction was dissolved in acetonitrile (10 ml) and added to a mixture of ethyl β-aminopivaloate hydrochloride [2a,c] (500 mg, 2.8 mmol) and triethylamine (278 mg, 2.8 mmol) in acetonitrile (10 ml). The mixture was heated under reflux for 3 h, filtered, then the solvent was changed to ethyl acetate. The solution was washed in the normal way to afford an oil; crystallisation from ethyl acetate–light petroleum gave the *protected tripeptide* (20) (226 mg, 20%), m.p. 125.5—128 °C (raised to 127.5—129 °C after recrystallisation), R_{FB} 0.42 (Found: C, 64.6; H, 8.3; N, 9.2. $C_{24}H_{37}N_3O_5$ requires C, 64.4; H, 8.3; N, 9.4%).

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