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THE FORMATION OF PEPTIDOKETONES FROM N-METHYLAMINO ACIDS

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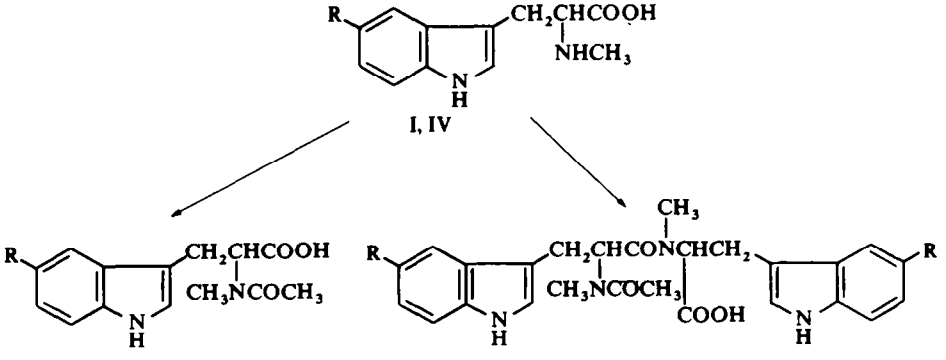
Abstract—Acylation of the N-methylamino acids with acetic anhydride in glacial acetic acid yields acetyl-dipeptides, as well as the acetylamino acids. On treatment with acetic anhydride N-methylamino acids produce bis-diamino ketones.

N-METHYLATED amino acids, many of which occur naturally are of particular interest as some enter into the structure of antibiotics.[1] Unfortunately, some simple reactions of these acids have not been studied. We found that whereas tryptophane is easily acetylated,[2] N-methyltryptophane (abrine; I) under similar conditions gives a mixture of acetylabrine (II) and acetylabrylabrine (III).

The acetyl derivative (II) forms only at low temperature (30–35°) and as the temperature is raised to 60–70° the acetylpeptide predominates.



I, IV

II, V

III, VI

I, II, III R = H; IV, V, VI R = OCH_3

Also treatment of 5-methoxyabrine‡ (IV) with acetic anhydride in glacial acetic acid produces acetyl-5-methoxyabryl-5-methoxyabrine (VI). Both the acetyl dipeptides are soluble in alkali, and are hydrolysed to the initial amino acids and show half the electrophoretic mobility of the corresponding acetylamino acids. Similar dipeptide formation takes place during acetylation of N-methyl and N-benzylphenylalanine.

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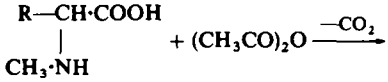
‡ Synthesis of abrine and 5-methoxyabrine see (3).

Acetic anhydride brings about ketonization in amino acids when heated under reflux in pyridine solution, the products being acetylaminoketones.[4] This reaction with N-methylvaline and N-methylleucine produces acetylmethylaminoketone in low yield, the major product being an unidentified resin.[5] Acetylsarcosine, gives acetylmethylaminoacetone and its enolacetate.[6]

We have found that vigorous heating of abrine, 5-methoxyabrine, N-methylphenylalanine or N-methylvaline with acetic anhydride causes intense evolution of carbon dioxide with the formation of acetylpeptidoketones (VII–X).



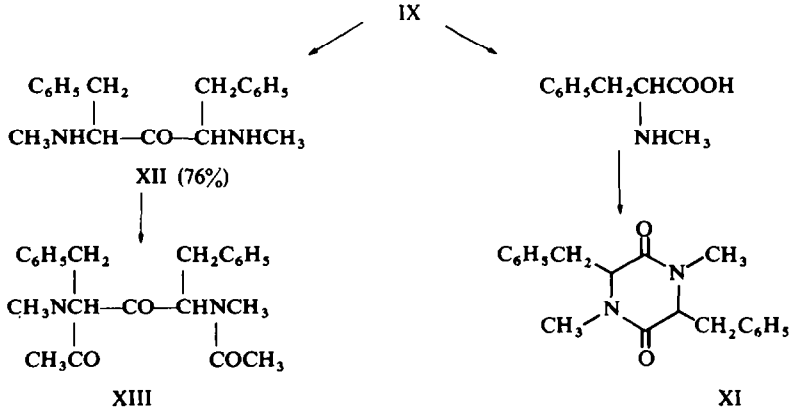
$$[CH_3CON(CH_3)CHRCON(CH_3)CHRCON(CH_3)CHR]_2CO$$

R = skatyl (VII), 5 methoxyskatyl (VIII), benzyl (IX), isopropyl (X).

Compounds VII and VIII are very resistant to alkaline hydrolysis while after heating IX and X with 5% sodium hydroxide (at 140° for 30 hr) gives N-methylphenylalanine and N-methylvaline, respectively. In compounds VII–X, the insolubility in mineral acids and alkalis, non-mobility in electrophoresis in both alkaline (borate buffer pH 8·9) and acid (30% AcOH) media, and mobility in chromatography on neutral alumina proved the absence of free amino or hydroxy terminal groups. Moreover, evolution of carbon dioxide during the reaction indicated decarboxylation.

The IR spectra of VII–X display intense bands at 1632, 1630–1640, 1643 and 1636–1642 cm^{-1} (amide carbonyl) and at 1707–1720 cm^{-1} (keto group). The ketonic structure is supported by the formation of the corresponding 2,4-dinitrophenylhydrazones.

Acid hydrolysis of IX gives N-methylphenylalanine in 90% yield and a small amount of 2,5-dimethyl-3,6-dibenzyldiketopiperazine, XI). On extracting the reaction mixture with ammoniacal ether the base XII is obtained in good yield. This compound, gives a purple color with ninhydrin and rapidly decomposes in air and on contact with alumina.



Compound XII on acetylation gives a product identical with N,N'-dimethyl-2,4-diacetamido-1,5-diphenylphentan-3-one which was synthesized by an independent route.[8]

The mass spectra of acetylpeptidoketones IX and X (Fig. 1) show no molecular ion peaks. Apparently the molecular ion decomposes immediately according to

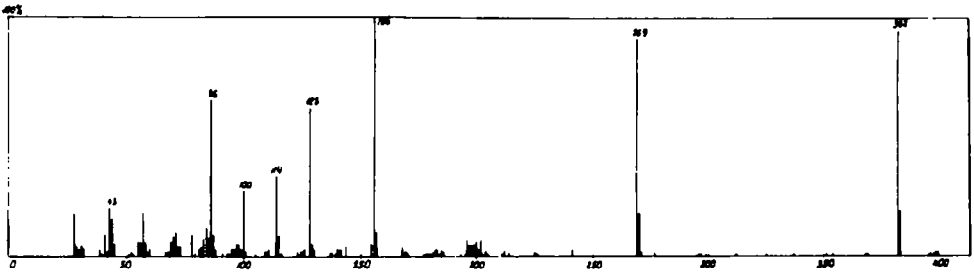


FIG. 1 Mass spectrum of acetylpeptidoketone X.

α-type fragmentation giving rise to a linear peptide with a positive charge on the C-terminal and an acetyl protecting group on the N-terminal, or alkylideneimine fragment. Peaks corresponding to both these fragments are observed in the mass spectrum. Further degradation of the peptide fragment takes place[9] with consecutive elimination of amino acid residues (starting from the C-terminal) with loss of the CO group to form alkylideneimine fragments.

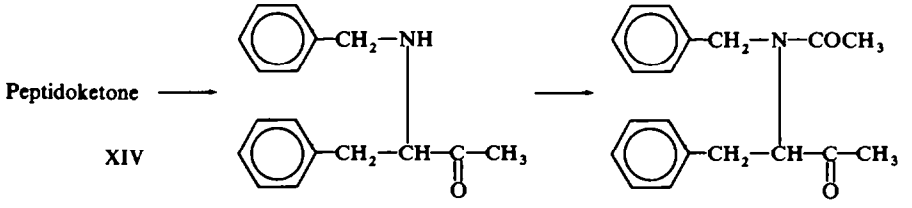
The same picture is observed in the mass spectra of the model acetyliminoketone (XIII) containing peaks at *m/e* 204, 176, 162 and 134.

In the case of abrine, 5-methoxyabrine and N-methylphenylalanine, yields of the acetylated peptidoketones were 75·5, 62 and 84% respectively. Since the mixture of compounds obtained as by products are immobile on neutral alumina they are probably acetylated amino acids and peptides. N-Methylvaline gives only a 16% yield of acetylpeptidodiketone, the main product being an acetylated linear polypeptide. The above reaction does not take place with the corresponding unmethylated amino acids e.g. tryptophane or valine. Similar ketonization occur with sarcosine but without the formation of peptide chains, while proline gives only the N-acetyl derivative.[13, 14]

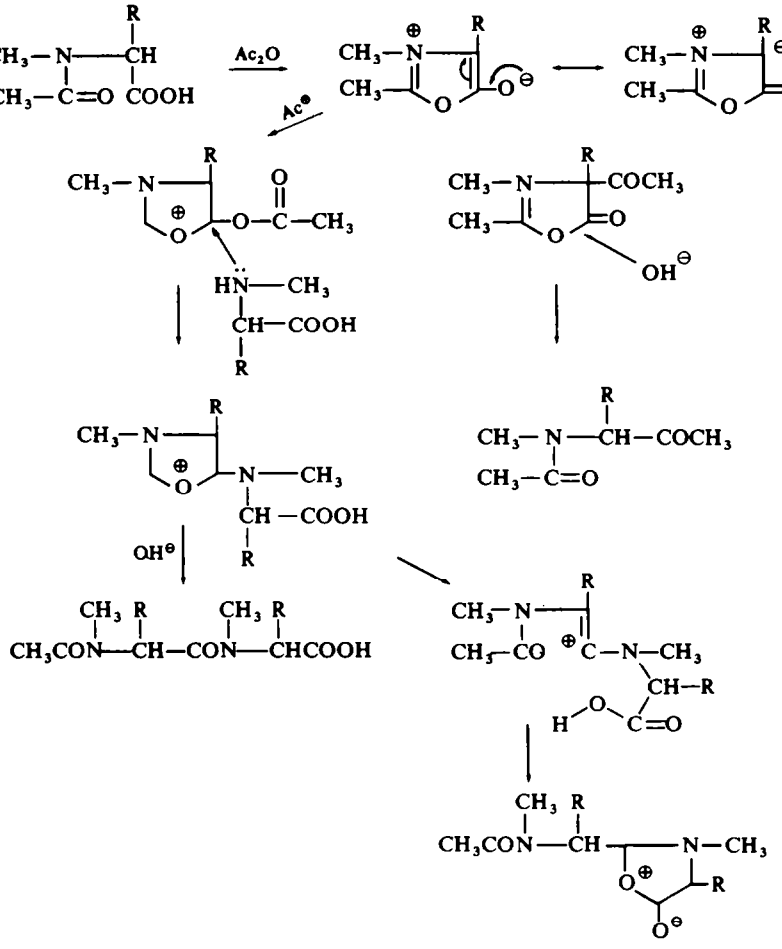
Formation of peptide chains is due to the action of mixed anhydrides, which are generated during the reaction. The anhydrides favour the formation of peptide bonds rather than the acetylation of amino group. Further, the peptide chain ceases to grow after reaching the tripeptide stage (possibly due to steric hindrance), then symmetrical tripeptide anhydride and ketonization occurs.

N-Benzylphenylalanine reacts slowly with acetic anhydride in the same way as N-methylamino acids. The peptidoketone (XIV) m.p. 120–124° obtained from this reaction does not move in electrophoresis either in alkaline or in acidic medium. It has the mol wt 1044 and its IR spectrum shows the absorption maxima 1636 (amide) and 1702–1726 cm^{-1} (keto group). It has 4 amino acid residues as shown by analysis It is hydrolysed by ethanolic hydrochloric acid to N-benzylphenylalanine and the aminoketone (XV). The acetyl derivative of the latter is identical with 1-phenyl-2-(N-benzylacetamido) butanone-3 (XVI). Hence the peptide ketone (XIV) possesses

an unsymmetrical structure and this fact is further supported by its mass spectrum. However its high mol wt did not permit a full spectrum. The amino ketone (XV) has the molecular ion peak 295 and other peaks 252, 210 (due to loss of CH_3CO- and CH_2CO- groups respectively), 162 (M-42-91) and 91 (benzyl cation). However the amino group can be acetylated in good yield (85–90%) without the formation of any by products if the COOH group is protected by esterification.



It has been found that N-phenyl substituted amino acids undergo a Dakin West reaction.[15,16] Therefore, probably peptide formation or peptide ketone synthesis takes place through ylide formation, which can be acetylated by the attack by the



acetic cation. If O-acetylation takes place an ester is obtained which can interact with amino acid giving rise to a peptide. On the other hand, if C-acetylation occurs then the reaction yields an α-aminoketone.*

EXPERIMENTAL

For TLC Motier and Potter's modification of Mistryukov's method[11] was used. Brockmann alumina of grade II–III, sifted through a caprone sieve, and KSK silica gel of 100–150 mm grains were employed as absorbents, layer thickness being 0·8 mm and plate size 13 × 18 cm. Depending on the nature of the substances, spots were detected by UV light, by iodine vapour or by nin-hydrin or fluorescence. All determinations were carried out at room temp. For electrophoresis the vertical procedure was followed at 300 V using "Leningrad B" paper with a borate buffer system 19·07 g/l $Na_2B_4O_7$ + 10 g/l H_3BO_3 or 30% acetic acid.

Acetyl groups were determined using 55% orthophosphoric acid instead of sulphuric acid. OMe groups were estimated by the Zeisel Pregl method and the mol wts by Rast titration with alkali (phenolphthalein as indicator) isothermal distillation or thermoelectrically using Signer's method modified by Clark.[7] Methyl acetate and di-n-octyl ketone were used as solvent and reference substance respectively.

Mass spectra were obtained on mass spectrometer MX-1303 at ionizing voltage of 30–50 V. Samples were volatilized in the ion source in the immediate proximity to the ionizing region at 100–150° or directly in the ion source (~230°).

Acetylabrine (II). To a soln of abrine (1 g) in glacial AcOH (20 ml) was added with stirring a mixture of Ac_2O (1 ml) and AcOH (5 ml). After 2 hr the mixture was heated for ½ hr at 30–35° and kept overnight at room temp. The solvent was evaporated in vacuum, water (20 ml) and a drop of conc HCl was added and heated to 50°. On cooling a light brown oil was obtained which was decanted and dried in a vacuum dessicator; yield 0·2 g. The soln was evaporated to ½ its volume and extracted twice with EtOAc. The extract was evaporated to dryness when more (0·3 g) of acetylabrine was obtained, m.p. 80–81, R_f 0·74 on TLC (silica gel and gypsum, n-propanol-ammonia 7:3, Ehrlich's reagent).

The acid soln remaining after extraction on neutralization with ammonia precipitated unchanged abrine (0·32 g).

Acetylabrilabrine (III). To a soln of abrine (2·18 g) in glacial AcOH (25 ml) at 60–70° Ac_2O (1·02 g) in glacial AcOH (20 ml) was added dropwise with stirring. Heating and stirring was continued for another 30 min, and the solvent distilled off in vacuum. The residue dissolved in 5% NaOH and acidified (Congo red) with dil HCl yielded acetylabrylabrine as an amorphous powder. It was washed with water and dried in a vacuum dessicator yield 0·44 g. The filtrate was concentrated in vacuum to a small volume, neutralized with NaOH to yield the unreacted abrine (0·52 g). The acetylabrylabrine was purified by dissolving in 2% NaOH and regeneration by acidification with 2N HCl after extracting with ether, m.p. 140–160°. (Found: C, 65·24, 65·51; H, 6·51, 6·03; MeCO, 9·65, 9·51; M.W. (Rast) 488, (titration) 435. Calc for $C_{26}H_{28}N_4O_4 \cdot H_2O$: C, 65·27; H, 6·31; MeCO, 9·00% M.W. 479·5).

Acetyl-N-benzylphenylalanine. N-Benzylphenylalanine (5 g) was dissolved in warm glacial AcOH (100 ml) and treated with Ac_2O (4 g) at 25°. The temp of the reaction mixture was slowly raised to 70° during the course of 2 hr. It was then evaporated to dryness in vacuum at 40°. Ether (90 ml) was added to the residue (5·5 g) and the unreacted N-benzylphenyl alanine (1·3 g) separated. The filtrate after washing with NaOH (2% soln) followed by acidification with HCl yielded an oil, which was extracted with ether, dried over $MgSO_4$ and the solvent removed under vacuum. The oil obtained was dissolved in THF and treated with pet ether. After long standing in the refrigerator the acetylated product separated as white crystals m.p. 145–147° from THF and pet ether mixture. (Found: C, 72·50; H, 6·45, 6·57; $C_{18}H_{19}NO_3$ requires: C, 72·69; H, 6·46%).

N-Benzylphenylalanine hydrochloride. A soln of N-benzylphenylalanine (2·6 g) in abs MeOH (40 ml) was treated with dry HCl gas for 0·5 hr. The mixture was evaporated in vacuum after standing for 12 hr and the hydrochloride obtained was purified by the usual method, yield, 2·7 g, m.p. 170° (subl). (Found: C, 66·29, 66·94; H, 6·64, 6·76; Calc for $C_{17}H_{19}NO_2 \cdot HCl$: C, 66·76, H, 6·61%).

To a suspension of the above salt (16·7 g) in $CHCl_3$ (120 ml) a mixture of Et_3N (18·5 ml) and Ac_2O (5·9 ml) was added and after standing for 12 hr it was poured into water. The $CHCl_3$ layer separated and was washed with 3% $NaHCO_3$aq, dried over K_2CO_3 and evaporated in vacuum; MeOH (15 ml) was

* In the case of phenylglycine the corresponding diaminoketone is also obtained but in low yield.[17]

added to the residue and evaporated again. The residue was then dissolved in a mixture of MeOH (50 ml) and 5% NaOH aq (120 ml) and heated for 50 min on a steam bath. MeOH was removed and the aqueous soln filtered. On acidification (congo red) with HCl a crystalline material separated which was washed with water and dried in vacuum, yield 14·1 g, m.p. 149–150° identical with acetyl N-benzylphenylalanine obtained in an earlier experiment.

Acetyl-5-methoxyabrine (V) *and acetyl-5-methoxyabryl-5-methoxyabrine* (VI). To a warm soln of 5-methoxyabrine (3 g) in glacial AcOH (30 ml) was added Ac_2O (3 ml) and AcOH (15 ml). Heating (50–60°) and stirring continued for another 30 min and the major portion of AcOH was distilled off in vacuum. The residue was poured into water and allowed to stand overnight. A brown oil was separated by decantation. A few drops of HCl was added to the transparent soln and left in refrigerator for several days when colourless crystals (0·4 g) of V were obtained. The above oil was dissolved in alkali and precipitated by HCl. A light brown substance (3 g) consisting of a mixture of V and VI was obtained The two were separated by fractional precipitation using alcohol–water mixture, yield of V 1·75 g, m.p. 165–170° (aqueous alcohol). (Found: C, 62·7; 62·14; H, 6·15; 6·22. Calc for $C_{15}H_{18}N_2O_4$: C, 62·10; H, 6·24%).

The other product was a non-crystallizing oil which was dissolved in dil NaOH, washed with benzene and filtered and carefully acidified with 2N HCl. An amorphous powder precipitated which was washed with water and dried, yield of VI 1·5 g (48%), m.p. 143–153°. (Found: C, 64·52, 64·61; H, 6·26, 6·21; N, 11·36; MeCO 7·2, 7·1 M.W. (Rast) 596 (isothermal distillation) 537, (titration) 606, 532 Calc for $C_{28}H_{32}N_4O_6$: C, 64·60; H, 6·20; N, 10·76; MeCO 8·06%, M.W. 520·5).

*Bis-*N,N′*-(acetylabrylabryl)* N,N′*-dimethyl-α,α′-diaminodiskatylacetone* (VII). Abrine (2 g) was refluxed with Ac_2O (10 ml) for 1 hr. During the reaction a brisk evolution of CO_2 was observed. The mixture was poured into water (50 ml) and stirred. A brown oil separated which solidified on standing overnight. It was triturated with water (30 ml), filtered and washed with water (30 ml). It was purified by passing a soln in dioxan through a column of alumina. On evaporation of the dioxan, the product was obtained as a foamed glass, yield 1·45 g. A small portion of VII crystallized from a mixture of dioxan and ether as a pale yellow solid. It was carefully washed with ether and dried in vacuum at 100°, m.p. 175–185° (darkening at 166°). (Found: C, 71·37; H, 6·65; N, 13·14; M.W. (thermoelectric method) 1239, 1194. Calc for $C_{75}H_{78}N_{12}O_7$: C, 71·54; H, 6·24, N, 13·34%, M.W. 1259·5), IR-spectra (Nujol) 1632, 1707–1719 cm^{-1}.

*Bis-*N,N′*-(acetyl-5-methoxyabryl-5-methoxyabryl)* N,N′*-dimethyl-α,α′-diaminodi-5-methoxyskatylacetone* (VIII). Similarly, the reaction of 5-methoxyabrine with Ac_2O yielded VIII. EtOAc was used as solvent for chromatography and a mixture of EtOAc and ether was used for crystallization of the product, yield 0·3 g, m.p. 190–205°. (Found: C, 66·81; H, 6·95, 7·14; N, 11·31, 11·48; MeO 12·0; 12·1; MeCO 6·92. M.W. Signer–Clark method 1328. Calc for $C_{81}H_{90}N_{12}O_{13}$: C, 7·58, H, 6·30, N, 11·68, MeO 12·9, MeCO 5·97%, M.W. 1440), IR spectrum (LiBr) 1630–1640, 1715–1720 cm^{-1}.

*Bis-*N,N′*-(acetyl-*N*-methylphenylalanyl-*N*-methylphenylalanyl)*-N,N′*-α,α′-diaminodibenzyl acetone* (IX). A mixture of N-methylphenylalanine (2 g) and Ac_2O (8 ml) was refluxed for 1 hr and IX was isolated. It crystallized from a mixture of ether–pet ether as a white powder (dec. 55–65°). (Found: C, 73·90, 74·15, H, 7·51, 7·61, N, 7·98, 7·94, M.W. Singer–Clark method 1048, (thermoelectric method) 1000 and 1036. Calc. for $C_{63}H_{72}N_6O_7$: C, 73·80, H, 7·08, N, 8·19%, M.W. 1025·2).

The 2,4*-dinitrophenylhydrazone* was prepared from 500 mg of IX by the usual method. The hydrazone was purified by passing through an alumina column, yield 380 mg, m.p. 115–118°; R_f 0·33 TLC Al_2O_3, pet ether: EtOAc 2:1). (Found: C, 68·84; 69·03; H, 6·81, 6·79; N, 11·19; M.W. (Signer–Clark method) 1208. Calc. for $C_{69}H_{76}N_{10}O_{10}$: C, 68·75, H, 6·35, N, 11·62%, M.W. 1205), IR spectra (KBr): 1640 cm^{-1}.

*Hydrolysis of bis-*N,N′*-(acetyl-*N*-methylphenylalanyl)* N,N′*-dimethyl-α,α′-diaminodibenzylacetone* (IX). The ketone IX (1 g) was refluxed with 6N HCl (10 ml) for 4·5 hr and then diluted to twice the volume with water. It was evaporated to dryness and the residue was heated with water (25 ml) till it dissolved. It was filtered and kept overnight in the refrigerator until XI, 0·65 g separated, m.p. 150–152° (benzene–hexane). (Found: C, 74·93, 74·72, H, 7·05, 7·22, N, 8·04. Calc. for $C_{20}H_{22}N_2O_2$: C, 74·51, H, 6·86, N, 8·68%), IR spectra (KBr, UR-10) 1050, 1082, 1258, 1350, 1400, 1460, 1487–1497, 1630–1660 cm^{-1}.

The filtrate was evaporated to dryness, the residue dissolved in 10% ammonia and extracted with water. The ether extract was dried over potash, filtered and evaporated to dryness. The residue (220 mg), 76% XII was an oil rapidly darkening in air. It gave the picrate, m.p. 151–152° (from benzene). Immediately after its isolation the diaminoketone was acetylated with Ac_2O in glacial AcOH and part of the diacetyl derivative was purified by TLC on alumina (benzene:acetone 5:1). Compound XIII was chromatographically and IR spectroscopically identical with N,N′-dimethyl-2,4-diacetamido-1,5-diphenylpentan-3-one synthesized by another route. The aqueous ammonia soln after isolation of the aminoketone was evapo-

rated to dryness in vacuum. The residue recrystallized from water and was found to be nylalanine, yield, 0·63 g. The 2,4-dinitrophenyl hydrazones of the two samples prepared by the usual method were identical in every respect (m.p. 124–127° and their IR spectra were superimposable.)

Bis-N,N'-(*acetyl*-N-*methylvalyl*-N-*methylvalyl*)-N,N'-*dimethyl*-α,α'-*diaminodiisopropylacetone* (X). A mixture of N-methylvaline (2 g) and Ac_2O (8 ml) was refluxed for 1 hr but unlike earlier reactions the CO_2 liberated was negligible. The reaction mixture on working up as described earlier gave a solid product, yield 1·2 g. It was chromatographed over a column of alumina (16·5 × 1·4) using dioxan as the solvent and separated into three fractions. The first fraction (A; 40 ml) containing X was evaporated and well dried in vacuum, yield, 0·36 g, 16%. It was a glassy mass with softening temp around 55°. (Found: C, 63·59, 63·76, H, 9·80, 9·93, M.W. (Signer–Clark method) 740. Calc. for $C_{39}H_{72}N_6O_7$: C, 63·55, H, 9·85%; M.W. 737), IR spectra (Nujol) 1642–1636, 1718 cm^{-1}.

The column was then washed with alcohol (40 ml) and the washings containing (B) fraction were evaporated to dryness in vacuum; the residue resembling foamed glass melted from 121 to 131°, yield 0·28 g. The column was then washed with a mixture of alcohol–ammonia (10:1) when the fraction (C) was eluted, which was evaporated to dryness; yield, 0·61 g, m.p. 110–121°. The substances isolated as fraction B and C were separately hydrolysed with 6N HCl for 5–8 hr. The aqueous soln was evaporated to dryness in vacuum after washing with ether. The residue on paper chromatography (BuOH:AcOH:water 4:1:5) gave a single spot corresponding to N-methylvaline; (R_f, 0·49), no other ninhydrin coloured spots were detected.

Reaction of N-*benzylphenylalanine with acetic anhydride.* A mixture of N-benzylphenylalanine (15 g) and Ac_2O was left overnight. A solid separated and was dried in vacuum at 30°, yield 15·1 g. It was dissolved in benzene and adsorbed over a column of alumina and fractions eluted using benzene, benzene + EtOAc (20:1) EtOAc, isopropanol and isopropanol + ammonia (20:1) successively. 30 Fractions were collected in all using TLC as control. Fractions eluted by benzene–EtOAc were purified by further column chromatography and crystallized from benzene–pet ether, yielding XIV as a white solid, yield 5·2 g. m.p. 120–124°. (Found: C, 79·64, 80·20, H, 6·77, 6·79, N, 5·39, 5·53, M.W. (isothermic distillation) 1044, Calc for $C_{64}H_{66}N_4O_6$; C, 79·88, H, 6·62, N, 5·56%, M.W. 1007·5), IR spectra (nujol, UR-10) 1720–1726, 1636 cm^{-1}.

The last eluate (isopropanol–ammonia mixture) gave acetylated peptide, yield 3 g, m.p. 165–157° (from MeOH). (Found: C, 78·50, 78·67, H, 6·44, 6·57. Calc for $C_{67}H_{64}N_4O_6$ C, 78·71, H, 6·34%). Acid hydrolysis of $C_{67}H_{64}N_4O_6$ gave only N-benzylphenylalanine (paper chromatography in two different systems).

The above ketone (XIV; 1 g) was boiled with a mixture of 10% HCl (30 ml) and EtOH (30 ml) for 4 hr. EtOH was distilled off and the aqueous soln extracted with ether. The soln was then made basic (pH 10) and extracted thrice with ether. The extract on evaporation of the solvent in vacuum gave a residue which was acetylated by Ac_2O and AcOH yielding XVI as a dark brown oil, yield 0·25 g. TLC on alumina in 3 different solvent systems (benzene–EtOAc (10:1), benzene–acetone (15:1); cyclohexane–acetone (2:1) proved its identity as 1-phenyl-2-(N-benzyl acetamido) butan-3-one, the authentic sample of which was prepared as described below. The basic aqueous soln left after extraction with ether was acidified to give N-benzylphenylalanine, yield 0·3 g, and identified by paper chromatography using 2 different solvent systems.

1-*Phenyl*-2(N-*benzylacetamido*)*butanone*-3 (XVI). A mixture of acetyl-N-benzylalanine (1 g) and Ac_2O (2·7 g) was boiled for 1·5 hr. The reaction was eluted with water (6 ml) and allowed to stand for 12 hr. It was then evaporated to dryness. The residue was a dark brown oil which was purified by column chromatography using alumina (eluent, benzene–EtOAc 5:1). The amidoketone XVI was obtained as a solid. It first crystallized from alcohol and then from benzene pet ether mixture as colourless needles m.p. 69–70°. (Found: C, 77·23, 77·37; H, 7·21, 7·26, Calc for $C_{19}H_{21}NO_2$; C, 77·25; H, 7·17%).

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