273. N-*Substituted Amino-acids. Part II. The Reductive Alkylation of Amino-acids.*

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The alkylation of amino-acids by reductive condensation with higher aliphatic aldehydes has been studied. With straight-chain aldehydes at room temperature glycine and alanine furnish the corresponding *NN*-dialkylamino-acids, but other amino-acids undergo monoalkylation owing to steric hindrance brought about by the group R′ (cf. III). With aldehydes branched in the α-position, all the amino-acids which have so far been examined yielded *N*-monoalkyl derivatives.

It has been shown (preceding paper) that amino-acids (I) may be converted into their *NN*-dimethyl derivatives (IV; R = H) by catalytic reduction in the presence of formaldehyde (II; R = H).

$$\underset{\text{(I.)}}{NH_2\cdot\underset{R'}{CH}\cdot CO_2H} + \underset{\text{(II.)}}{R\cdot CHO} \xrightarrow[H_2\text{–Pd}]{} \underset{\text{(III.)}}{R\cdot CH_2\cdot NH\cdot\underset{R'}{CH}\cdot CO_2H} \xrightarrow[H_2\text{–Pd}]{R\cdot CHO} \underset{\text{(IV.)}}{\begin{matrix}R\cdot CH_2\\ R\cdot CH_2\end{matrix}\!\!>\!N\cdot\underset{R'}{CH}\cdot CO_2H}$$

In extending this reaction to the higher aldehydes, attention was first directed to the reductive alkylation of glycine. The reduction was carried out at ordinary temperature as described previously and from acetaldehyde, propaldehyde, *n*-butanal, *n*-heptanal, and furfuraldehyde the corresponding NN-*dialkyl* derivatives were obtained. The reactions took place as readily as those with formaldehyde, but difficulties were encountered in the purification of the alkyl derivatives owing to the presence of aldehyde polymerides.

In the case of valine reductive condensation with *n*-butanal in aqueous-ethanolic solution at ordinary temperature proceeded rapidly at first but almost ceased when 1 mol. of hydrogen had been taken up, the product being the monoalkylated amino-acid, N-n-*butylvaline* (III; R = Pr^n, R′ = Pr^i. In a similar manner, by use of the appropriate aldehydes, N-n-*ethyl*-, N-n-*propyl*-, N-n-*butyl*-, N-iso*butyl*-, and N-n-*heptyl-valine* were prepared. N-n-*Butyl-leucine* (III; R = Pr^n, R′ = Bu^i) and N-n-*butylamino-α-phenylacetic acid* (III; R = Pr^n, R′ = Ph) were obtained as the sole products of the reductive butylation of leucine and amino-α-phenylacetic acid, respectively.

The amino-acids in which monoalkylation occurs have a branched chain in the β- or γ-position to the carboxyl group and it therefore seemed probable that some steric effect connected with the branched chain was inhibiting further alkylation at ordinary temperature. Under more drastic conditions, *viz.*, at higher temperatures and with more prolonged reaction, the dialkyl derivatives were slowly produced. Thus, valine on reductive alkylation with *n*-heptanal at 54° furnished NN-*di*-n-*heptylvaline* in addition to the monoheptyl derivative. Furthermore, with amino-acids in which the group R′ is not so bulky, as in alanine, the reaction was markedly dependent on the temperature. Thus, at 11° alanine and *n*-butanal gave N-n-*butylalanine* as the main product, whilst at 50° the reaction proceeded further giving a mixture which consisted predominantly of NN-*di*-n-*butylalanine*; similar results were obtained with *n*-heptanal.

Experiments on the alkylation of glycine by means of acetaldehyde, propaldehyde, *n*-butanal, and *n*-heptanal under conditions favourable to the formation of monoalkyl derivatives failed to reveal any evidence of partial alkylation. It seemed possible that steric effects similar to those just described might be brought into operation by the employment of aldehydes having branched chains in positions adjacent to the aldehyde group. The most direct evidence of such an effect would be furnished if partial alkylation could be realised with an amino-acid such as glycine, which had previously been shown to be incapable of forming monoalkyl derivatives with straight-chain aldehydes. Indeed reductive alkylation of glycine with *iso*butanal at room temperature gave N-*mono*iso*butylglycine* (V) accompanied by a small quantity of the *dialkyl* derivative (VI).

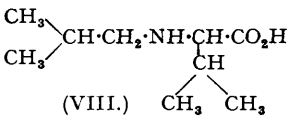
$$\underset{\text{(V.)}}{Bu^i\cdot NH\cdot CH_2\cdot CO_2H} \qquad \underset{\text{(VI.)}}{Bu^i_2N\cdot CH_2\cdot CO_2H} \qquad \underset{\text{(VII.)}}{Me_2CH\cdot[CH_2]_3\cdot CHMe\cdot CH_2\cdot CHO}$$

Further evidence was supplied by the reductive alkylation of glycine with 3 : 7-dimethyloctanal (VII), in which the relevant branching is in the β-position to the aldehyde group. This gave a mixture of N-3 : 7-*dimethyloctylglycine* and NN-*di*-(3 : 7-*dimethyloctyl*)*glycine* in which

the latter predominated: furthermore, *iso*butylation of alanine (I; R′ = Me) gave N-iso-*butylalanine* as the sole product (cf. reaction with *n*-butanal).

Two further aspects of this problem have been examined with the object of obtaining additional information concerning the nature of the steric forces. First, a series of monoalkylvalines having alkyl groups of gradually increasing complexity was submitted to reductive methylation in order to discover whether the different groups exercised varying effects on the rate of further alkylation. The *N*-ethyl, *N*-*n*-propyl, *N*-*n*-butyl, *N*-*n*-heptyl, and *N*-*iso*butyl derivatives of valine did not react with hydrogen, catalyst, and formaldehyde in ethanol at room temperature, but at 54° methylation proceeded to completion in all cases in almost quantitative yield. No appreciable differences in the rates of reduction were observed.

Secondly, *N*-*iso*butylvaline (VIII), in which the steric hindrance to further alkylation would be most pronounced on account of two branched chains, was submitted to reductive alkylation in ethanol by means of acetaldehyde, propaldehyde, *n*-butanal, and *iso*butanal. As in previous cases, no reaction occurred at room temperature, but at 54°, except in the case of *iso*butanal, further alkylation proceeded to completion. No reaction took place with *iso*butanal even at 54° after prolonged reaction. It is noteworthy that these reactions allow of the preparation of a large number of " mixed " dialkylamino-acids subject only to limitations disclosed by this last example.



(VIII.)

The properties of the alkylated amino-acids are of interest in that the monoalkyl derivatives resemble the original amino-acids in having high melting points, usually with decomposition, and in being sparingly soluble in organic solvents, whereas the dialkyl derivatives melt at much lower temperatures than the parent compounds and, on the whole, are readily soluble in organic solvents. The *N*-alkyl-*N*-*iso*butylvalines in particular form low-melting waxy solids which are very readily soluble even in hydrocarbon solvents such as light petroleum.

Experimental.

The general method of reductive alkylation has already been described in Part I.

Alkylation of Glycine.—The amino-acid (0·1 mol.) was stirred in an atmosphere of hydrogen at room temperature in ethanol or aqueous ethanol (100 ml.) in the presence of the requisite aldehyde (0·4 mol.) and palladised charcoal (3 g., containing 10% of Pd) until the absorption of hydrogen ceased (0·2 mol.). After filtration from the catalyst, the solution was evaporated to dryness *in vacuo* and the resulting solid amino-acid crystallised from an appropriate solvent. The following *N*-substituted *glycines* were prepared:

	Crystalline form and solvents used.	M. p.	N, %. Found.	N, %. Reqd.
NN-*Diethyl-*	Slender needles,[1] benzene	131°	10·5	10·7
NN-*Dipropyl-*	Prisms,[1] acetone–light petroleum (b. p. 40—60°)	130	8·4	8·8
NN-*Di*-n-*butyl-*	Needles, benzene–light petroleum (b. p. 40—60°)	134	7·5	7·5
NN-*Di*-n-*heptyl-*	Needles, acetone	131	5·1	5·2
NN-*Difurfuryl-*	Needles, ethanol	138	5·7	5·9[2]

[1] Hygroscopic. [2] Found: C, 61·0; H, 5·7. $C_{12}H_{13}O_4N$ requires C, 61·3; H, 5·5%.

Monoalkylation of Valine, Leucine, and Phenylglycine.—A mixture of the amino-acid (0·05 mol.) and the aldehyde (0·1 mol.) was reduced at room temperature in aqueous or ethanolic solution (100 ml.) in the presence of the catalyst (2 g.) until the absorption of hydrogen almost ceased. The monoalkylamino-acids are sparingly soluble in both solvents and in the earlier experiments, which were carried out in aqueous solution, the products were separated from the catalyst by repeated extraction with boiling water. In subsequent experiments it was found more convenient to carry out the reaction in absolute ethanol and to remove the alkylamino-acids from the catalyst by extraction with hot ethanol containing slightly more than the theoretical amount of concentrated hydrochloric acid. The free amino-acids were then liberated from the ethanolic solution of their hydrochlorides by addition of the calculated amount of pyridine or aqueous ammonia. The following amino-acids were prepared in this manner:

	Crystalline form.[1]	M. p.	N, %. Found.	N, %. Reqd.
N-n-*Ethylvaline*	Needles	286—287°	9·4	9·7
N-n-*Propylvaline*	Plates	287—288	8·7	8·8
N-n-*Butylvaline*	Plates	269	7·8	8·1
N-iso*Butylvaline*	Oblong prisms	253—254	8·2	8·1
N-n-*Heptylvaline*	Prisms	279	6·4	6·5
N-n-*Butyl-leucine*	Plates	267	7·3	7·5
N-n-*Butyl-α-phenylglycine*	Needles	260	6·8	6·7

[1] Crystallisations were effected from boiling water.

Diheptylvaline.—The reductive heptylation was carried out in ethanol at 54° until three-quarters of the amount of hydrogen required for dialkylation had been absorbed (16 hours for 0·05 g.-mol.). Evaporation of the ethanolic filtrate furnished a yellow viscid gum from which by cooling of its solution (10%) in acetone to −50° NN-*di*-n-*heptylvaline* was obtained crystalline, m. p. 35—37° (Found: N, 4·0. $C_{19}H_{39}O_2N$ requires N, 4·5%).

Alkylation of Alanine.—(a) *With* n-*butanal at room temperature.* A mixture of alanine (4·45 g.), *n*-butanal (9 g.), catalyst (1·5 g.), and aqueous ethanol (100 ml. of 50%) was stirred in an atmosphere of hydrogen at 11° until 1375 ml. of gas had been absorbed (theory for monoalkylation, 1120 ml. at N.T.P.). The reaction mixture was then heated to boiling and filtered. Evaporation of the filtrate *in vacuo* furnished N-n-*butylvaline* as a yellow crystalline mass which, after being washed with cold acetone, separated from boiling aqueous ethanol in slender white needles, m. p. 286° (Found: N, 9·7. $C_7H_{15}O_2N$ requires N, 9·7%).

(b) *With* n-*butanal at* 54°. In this case the hydrogenation proceeded to completion and furnished the crude dialkylamino-acid as a yellow gum which solidified when kept overnight. Crystallisation from benzene–light petroleum (b. p. 40—60°) yielded NN-*di*-n-*butylalanine* in macroscopic rosettes of needles, m. p. 89° (Found: N, 6·7. $C_{11}H_{23}O_2N$ requires N, 6·9%).

(c) *With* n-*heptanal.* Reduction at room temperature furnished N-n-*heptylalanine*, needles (from water), m. p. 277° (Found: N, 7·2. $C_{10}H_{21}O_2N$ requires N, 7·5%); at 54°, NN-*diheptylalanine*, a soft waxy solid, m. p. 42—44°, b. p. 170°/0·8 mm. (Found: N, 4·8. $C_{17}H_{35}O_2N$ requires N, 4·9%), was produced.

(d) *With* iso*butanal.* The reaction was carried out at 60° as described above. The catalyst was extracted with boiling water (100 ml.), and the combined filtrates were evaporated to dryness. The residue, thus obtained, was boiled with ethanol (50 ml.); N-iso*butylalanine* remained undissolved and was purified by crystallisation from boiling water, from which it separated in slender needles, m. p. 250° (Found: N, 9·7. $C_7H_{15}O_2N$ requires N, 9·7%).

Alkylation of Glycine with Branched-chain Aldehydes.—(a) *With* iso*butanal.* A suspension of glycine (5 g.) and catalyst (3 g.) in aqueous ethanol (200 ml. of 50%) containing *iso*butanal (10 g.) was stirred in an atmosphere of hydrogen at 21° until 1660 ml. of gas had been absorbed (theory for monoalkylation, 1493 ml. at N.T.P.). The reaction mixture was then boiled and filtered, and the catalyst extracted with boiling water (25 ml.). The combined ethanolic and aqueous solutions were evaporated to dryness and the residue was extracted with hot ethanol (25 ml.), unchanged glycine (0·8 g.) remaining undissolved. Final evaporation of the ethanolic extract, followed by extraction with boiling benzene, furnished N-iso*butylglycine* as a crystalline solid which separated from hot ethanol in small white prisms, m. p. 203° (Found: N, 10·6. $C_6H_{13}O_2N$ requires N, 10·7%). Removal of the solvent from the benzene solution furnished a red gum which on crystallisation from hot light petroleum (b. p. 40—60°) yielded NN-*di*iso*butylglycine* as clusters of needles, m. p. 94° (Found: N, 7·7. $C_{10}H_{21}O_2N$ requires N, 7·5%).

(b) *With* 3 : 7-*dimethyloctanal.* Citronellal (17·2 g.) was reduced to its dihydro-derivative by stirring it with palladised charcoal (4 g. of 10%) in ethanolic solution at room temperature. When the required volume of hydrogen (2420 ml.) had been absorbed, an aqueous solution of glycine (3·75 g. in 75 ml.) was introduced, and reduction continued until a further 1620 ml. had been taken up (theory for monoalkylation, 1120 ml. at N.T.P.). Fractional crystallisation, from acetone, of the residue obtained by evaporating the aqueous-ethanolic solution yielded, as a more sparingly soluble fraction, N-3 : 7-*dimethyloctylglycine* as colourless prisms, m. p. 178° (Found: N, 6·1. $C_{12}H_{25}O_2N$ requires N, 6·5%). The more soluble fraction consisted of NN-*di*-3 : 7-*dimethyloctylglycine* and crystallised in filamentous aggregates of long slender needles resembling cotton wool, m. p. 129° (Found: N, 4·2. $C_{22}H_{45}O_2N$ requires N, 3·9%).

Methylation of N-*Alkylvalines.*—A mixture of the *N*-alkylvaline (2·0 g.), catalyst (2 g.), formaldehyde (2 ml. of 40%), and absolute ethanol (100 ml.) was stirred in hydrogen at 54°, whereupon a fairly rapid absorption of hydrogen took place, the theoretical volume being taken up in 3 hours. The solution, after filtration, was evaporated to dryness and the residue re-evaporated with water until the vapours were free from formaldehyde. Final evaporation of the water furnished the *NN*-disubstituted *valines* in quantitative yield and almost pure:

N-*Methyl*-N-*alkylvalines.*

	Crystalline form and solvent.	M. p.	N, %. Found.	Reqd.
N-*Methyl*-N-*ethylvaline*	Prisms, ethanol–acetone	128°	8·8	8·8
N-*Methyl*-N-n-*propylvaline* ...	Prisms, acetone	118	8·3	8·1
N-*Methyl*-N-n-*butylvaline*	Feathery clusters, benzene–light petroleum (b. p. 40—60°)	104	7·7	7·5
N-*Methyl*-N-iso*butylvaline* ...	Plates, *cyclo*hexane–carbon tetrachloride	93	7·2	7·5
N-*Methyl*-N-n-*heptylvaline* ...	Prisms, light petroleum (b. p. 40—60°)	94	6·5	6·1

Alkylation of N-iso*Butylvaline.*—A mixture of *N-iso*butylvaline (2·6 g.), catalyst (2 g.), and the requisite aldehyde [acetaldehyde (1·5 g.), propaldehyde or *n*-butanal (2·5 g.)], was smoothly reduced at 54° (after failure at room temperature) in 3—4 hours. The products were worked up as in the previous

	B. p./0·6 mm.	M. p.[1]	N, %. Found.	Reqd.
N-*Ethyl*-N-iso*butylvaline*	103—106°	50—54°	6·7	6·9
N-n-*Propyl*-N-iso*butylvaline*	104—107	63—65	6·6	6·5
N-n-*Butyl*-N-iso*butylvaline*	108—110	51—54	5·9	6·1

[1] Previous softening took place about 2—4° below the m. p.

example except that final purification was effected by distillation *in vacuo*. The melting-point ranges and the waxy nature of the resulting *dialkylvalines* appear to indicate that the purification was not complete; further purification by crystallisation was impracticable on account of the extreme solubility of the products in all the common organic solvents. Attempts to force further alkylation of *N-iso*-butylvaline by means of *iso*butanal failed.

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