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Cyclodehydration of Acylated α-Amino Acid Amides

I. Saturated Amides

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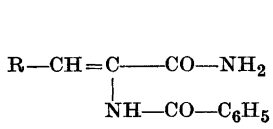
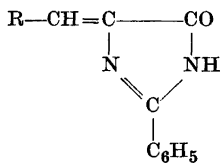
In 1900 Erlenmeyer [1] observed that α-benzamidocinnamamide (I, R = C_6H_5) underwent intramolecular dehydration to 2-phenyl-4-benzylidene-5-imidazolone (II, R = C_6H_5) on treatment with hot aqueous alkali.



I



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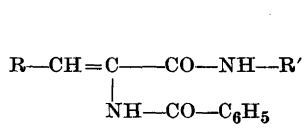
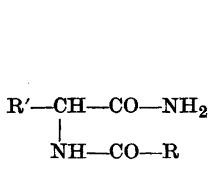


III

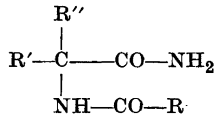
Additional examples in further communications [2-4] from the same laboratory demonstrated the general nature of this ring-closure reaction of unsaturated α-benzamido acid amides (I). Substituents in the amide-grouping, however, precluded ring-formation under the usual reaction conditions as evidenced from the stability of the corresponding anilides (III, R′ = C_6H_5). It remained for Gränacher *et al.*[5,6] to extend the reaction to N-substituted amides (III), although with certain limitations as to the nature of R′. They showed that heating of the amides *in vacuo* above the melting points would bring about the cyclisations desired. Narang and Rây [7] later reported that heating with phosphoryl chloride transformed various substituted α-benzamidocinnamanilides into the corresponding imidazolones. Still another, although more special modification, has recently been introduced through the observation by Shaw and McDowell [8] that certain unsaturated hydroxamic acids (III, R = C_6H_5, R′ = OH or $OCH_2C_6H_5$) undergo cyclisation in hot mineral acid.

Little attention has been given to studies of the analogous cyclisation of *saturated* α-acylamido amides (IV), a reaction which may be of interest for the discussion of the structure of alkali-treated proteins. Mohr [9] found that α-benzamido*iso*butyramide (V, R = C_6H_5, R′ = R″ = CH_3) readily suffered dehydration to the imidazolone (VI, R = C_6H_5, R′ = R″ = CH_3) in alkaline

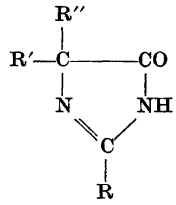
solution. Again, Gränacher and Mahler [5] reported two cases in which heating *in vacuo* of properly substituted α-benzamido*iso*butyramides yielded the corresponding imidazolones.



IV



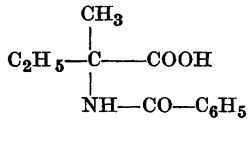
V



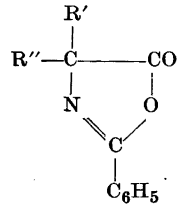
VI

As part of a broader investigation in the imidazolone series it became desirable to study more closely this dehydration reaction in order to determine its scope, synthetic potentialities and possible bearing on protein chemistry. Because Mohr [9] failed to achieve cyclisation of N-benzoylphenylalaninamide (IV, R = C_6H_5, R′ = $C_6H_5CH_2$) the behaviour of some amides of tertiary α-amino acids was first investigated in order to ascertain that the α-benzamido*iso*butyramides do no represent unique cases.

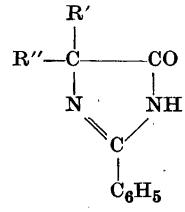
DL-*iso*Valine was benzoylated in 76 per cent yield following the general procedure of Steiger [10], a significant improvement over the 20—30 per cent yield previously reported by Slimmer [11]. Treatment of benzoyl*iso*valine (VII) with acetic anhydride gave the crystalline 2-phenyl-4-methyl-4-ethyl-5-oxazolone (VIII, R′ = CH_3, R″ = C_2H_5). The azlactone was characterised by its reactions with water, ammonia and aniline to give benzoyl*iso*valine, its amide and anilide, respectively.



VII



VIII

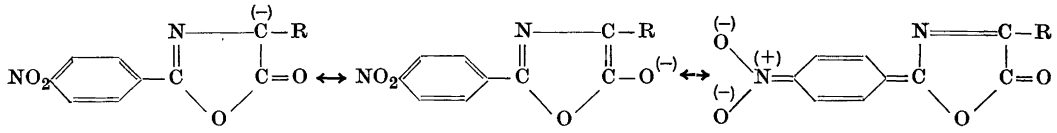


IX

Upon treatment with aqueous alkali at ordinary or slightly higher temperature, the amide lost the elements of water yielding a compound with all the characteristics of an imidazolone (IX, R′ = CH_3 R″ = C_2H_5). An example of an imidazolone, carrying an aromatic substituent in 4-position, was furnished by starting from α-benzamidohydratropic acid which yielded an oily azlactone (VIII, R′ = CH_3, R″ = C_6H_5). Ammonolysis of the latter gave α-benzamidohydratropamide, smoothly converted into 2,4-diphenyl-4-methyl-5-imidazolone (IX, R′ = CH_3, R″ = C_6H_5) under the usual conditions. The same sequence of reactions, carried out with α,α-diethylhippuric acid as the starting material, yielded the imidazolone (IX, R′ = R″ = C_2H_5).

That the nature of the acyl-grouping in the tertiary α-amino acid amides is no limiting factor in the cyclisations to imidazolones was demonstrated by the following examples. α-*p*-Nitrobenzamido*iso*butyric acid was prepared and transformed into its azlactone (X, R′ = R″ = CH_3, R = *p*-$NO_2C_6H_4$) as usual.

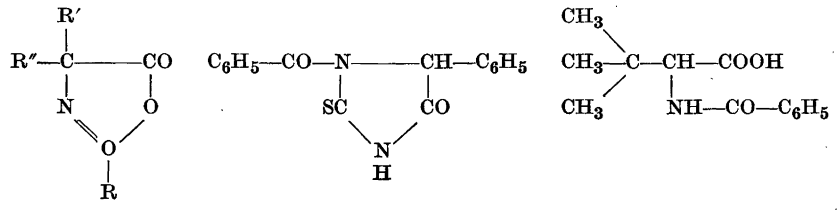
No colour was produced on treating this azlactone with alkali or pyridine, in contrast to the violet or blue colours observed when the ordinary, non-tertiary α-amino acids are treated with *p*-nitrobenzoyl chloride and aqueous alkali or pyridine (the *Waser*-reaction). Karrer and Keller [12] ascribed the formation of colour in this reaction to the presence of a resonance-stabilised anion of the oxazolone:



The failure of the nitrophenyl-oxazolone to produce the blue colour supports this explanation, because in the present case the requisite hydrogen-atom in 4-position is missing.

Ammonolysis of the oxazolone proceeded smoothly to give α-*p*-nitrobenzamido*iso*butyramide which readily afforded the imidazolone (VI, R = *p*-$NO_2C_6H_4$, R′ = R″ = CH_3) in alkali. Spectrophotometrically it could be shown that the introduction of the nitro-grouping in the molecule resulted in an increased rate of cyclisation (Fig. 1). A similar experiment with α-benzamido*iso*butyramide demonstrated that about 220 hours were required for the cyclisation to go to completion under similar conditions.

When α-phenacetamido*iso*butyric acid was treated with acetic anhydride, 2-benzyl-4,4-dimethyl-5-oxazolone resulted. Ammonolysis yielded the amide which easily cyclised in alkali to 2-benzyl-4,4-dimethyl-5-imidazolone (VI, R = $C_6H_5CH_2$, R′ = R″ = CH_3), crystallising as a monohydrate isomeric with the open amide. Removal of the water of crystallisation upon heating was accompanied by simultaneous destruction of the compound, but the imidazolone-structure could be definitely established on spectroscopical evidence (Fig. 2). Similarly, phenacetylation of DL-α-phenylalanine yielded the acylated, tertiary amino acid. Azlactonisation gave an oily oxazolone (X, R = $C_6H_5CH_2$, R′ = CH_3, R″ = C_6H_5) which could easily be opened with ammonia to α-phenacetamidohydratropamide. The facile ring-closure in alkaline solution to the imidazolone (VI, R = $C_6H_5CH_2$, R′ = CH_3, R″ = C_6H_5) points to the generality of this reaction of acylated, tertiary α-amino acid amides.



X XI XII

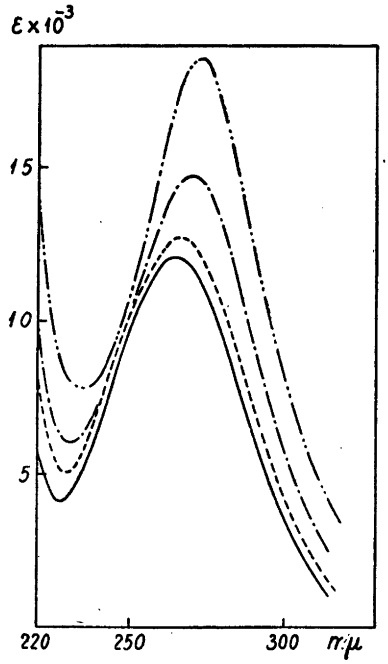


Fig. 1. UV-absorption spectra of a 0.08 M *solution of α-(*p*-nitrobenzamido)-isobutyramide in 0.01* N *methanolic KOH, measured immediately, and after standing at 23°. ——— Immediately after dissolution, — — — after 8 hours, — · — after 44 hours and — · · — after 140 hours. The latter curve is identical with the one obtained from authentic imidazolone in methanolic KOH.*

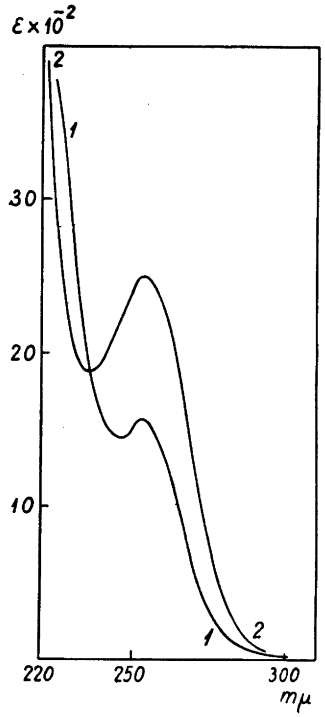


Fig. 2. UV-absorption spectra of: 1. 2-Benzyl-4,4-dimethyl-5-imidazolone in methanol; 2. The same in 0.1 N *methanolic KOH.*

Despite numerous attempts, no crystalline imidazolone could be obtained from ring-closure reactions of DL-α-acetamidohydratropamide (V, R = R′ = CH_3, R″ = C_6H_5). Undoubtedly, however, the oily product represented essentially pure imidazolone (VI, R = R′ = CH_3, R″ = C_6H_5) as inferred from analysis and general chemical properties. This result is consistent with the observation by Steiger [13] who previously described the oily imidazolone, although without analytical data. Both α-amino*iso*butyric acid and α-phenylalanine were formylated, but the further processing to the corresponding amides and imidazolones was abolished owing to the rather labile nature of the formamido-grouping of these substances.

The saturated imidazolones reported above are all colourless compounds with relatively high melting points. They are readily soluble in dilute alkali, less so in acid, rather soluble in alcohol, but sparingly soluble in ether, benzene and chloroform. In addition to the spectroscopical evidence, discussed in

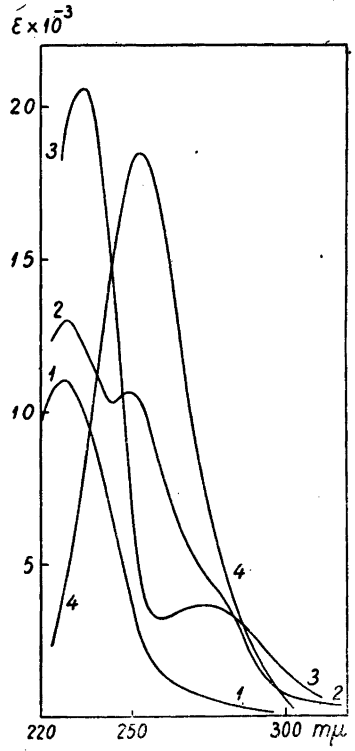
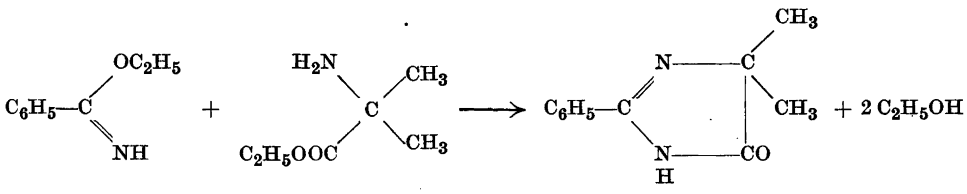
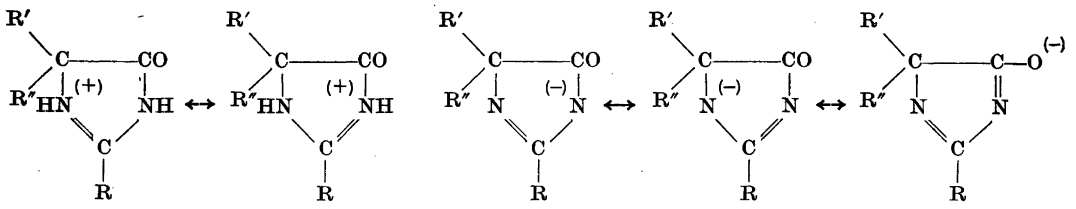


Fig. 3. UV-absorption spectra of: 1. α-Benzamidoisobutyramide in methanol; 2. 2-Phenyl-4,4-dimethyl-5-imidazolone in methanol; 3. The same in 0.1 N *methanolic KOH; 4. The same in 0.08* N *methanolic HCl.*

the following, an independent synthesis of a typical representative, *viz.* 2-phenyl-4,4-dimethyl-5-imidazolone, served to confirm the structure. Upon heating in xylene of ethyl iminobenzoate and ethyl α-amino*iso*butyrate a crystalline substance formed, which proved identical with Mohr's compound, resulting from the intramolecular dehydration of α-benzamido*iso*butyramide.



The protolytic nature of the imidazolones is clearly reflected in their UV-spectra. In Fig. 3 the spectra of 2-phenyl-4,4-dimethyl-5-imidazolone in neutral, alkaline and acidic solution are reproduced. They can be regarded as typical for this class of compounds. For comparison, the spectrum in methanol of the corresponding α-benzamido*iso*butyramide is presented also. The amide is devoid of notable acidic or basic properties, while the pronounced and reversible shift of the absorption curves for the imidazolones with changes in pH, reflects the important contribution of resonance-structures such as



in acidic and alkaline solutions, respectively. Other charged structures may of course be implied also, but their contributions will most likely be of minor importance.

Attention was next turned to acylated α-amino acid amides containing a hydrogen atom in the α-position (IV). In a previous communication [14] we demonstrated the report by Karrer and Gränacher [15] on the cyclisation of hippuramide to 2-phenyl-5-imidazolone to be incorrect, owing to a misinterpretation of the structure of the reaction product. No positive results attended numerous experiments to cyclise N-benzoylphenylalaninamide and N-benzoylalaninamide under widely varied reaction conditions, the straightforward hydrolysis to acid and ammonia being in most cases the predominant reaction. It was thought that an aromatic substituent on the α-carbon atom might facilitate the cyclisation. DL-α-Benzamidophenylacetic acid was transformed into its yellow azlactone (VIII, R′ = H, R″ = C_6H_5) which was characterised through its reactions with water, aniline and ammonia to give the acid, its anilide and amide (IV, R = R′ = C_6H_5), respectively. The Komatsu-Johnson reaction of the azlactone with ammonium thiocyanate and acetic anhydride led to the unknown 1-benzoyl-5-phenyl-2-thiohydantoin (XI). All attempts to cyclise α-benzamidophenylacetamide proved abortive, regardless of the conditions selected (alkali, acid, heat, dehydrating agents).

Next it was reasoned that steric factors might be implied. In order to test this possibility the preparation of the unknown N-benzoyl-DL-*pseudo*leucinamide was undertaken from *pseudo*leucine *via* its N-benzoyl-derivative (XII) and the corresponding azlactone. The latter was characterised by its reactions with methylamine, morpholine and aniline. Again, no indications of ring-closure were observed despite numerous efforts, demonstrating that the presence of a bulky substituent on the α-carbon atom is not *per se* sufficient to bring about cyclisation.

The findings above suggest a rather fundamental difference in the chemical behaviour of α-acylamido amides of non-tertiary and tertiary acids, the latter resembling in many respects the amides of unsaturated acids. These have been further studied in the hope of gaining more insight in the structural requirements for ring-closure. The results are presented in the following paper.

EXPERIMENTAL *

N-Benzoyl-DL-iso*valine*. DL-*iso*Valine (13.7 g) was treated with benzoyl chloride (13.6 ml) and a total amount of 120 ml of 2 *N* NaOH, according to the directions given by

* All melting points are uncorrected and determined in capillary tubes in an electrically heated block, those below 80° in a water-bath.

Steiger[10]. The yield was 19.8 g (76 %) of the colourless benzoyl-derivative. M.p. 192—193°. An analytical sample was obtained as platelets from aqueous acetone, containing some ethanol. M.p. 196°.

$C_{12}H_{15}O_3N$ (221.3) Calc. N 6.33
Found » 6.48

2-Phenyl-4-ethyl-4-methyl-5-oxazolone. Finely pulverised benzoyl*iso*valine (5.0 g) was suspended in 40 ml of freshly distilled acetic anhydride and shaken into solution at 70—80° within 12 minutes. Removal *in vacuo* of volatile material gave a slightly yellow oil, rapidly crystallising in the ice-box. Recrystallisation from *n*-hexane yielded the azlactone (3.65 g) as colourless rhombic plates, m.p. 48°.

$C_{12}H_{13}O_2N$ (203.2) Calc. C 70.93 H 6.45 N 6.90
Found » 71.03 » 6.41 » 6.98

On reaction with water containing a trace of alkali the azlactone afforded benzoyl-*iso*valine, identified by mixed melting point determination.

N-Benzoyl-iso*valinanilide.* This substance was readily isolated after treatment of the oxazolone with aniline in dry benzene. It separated from ethanol in thin needles. M.p. 199—200°.

$C_{18}H_{20}O_2N_2$ (296.4) Calc. C 72.93 H 6.80 N 9.45
Found » 73.02 » 6.78 » 9.40

N-Benzoyl-iso*valinamide.* When the azlactone above was treated for 5 minutes at 60° with 15 % aqueous ammonia, a clear solution remained which on cooling deposited the crystalline amide. Colourless prisms were obtained from water, m.p. 161—162°.

$C_{12}H_{16}O_2N_2$ (220.3) Calc. C 65.41 H 7.32 N 12.72
Found » 65.54 » 7.22 » 12.75

2-Phenyl-4-ethyl-4-methyl-5-imidazolone. The amide (161 mg) was dissolved within about 5 minutes in 2.5 ml of 1 *N* NaOH at *ca.* 85°. On addition of a few drops of glacial acetic acid a colourless oil separated which rapidly solidified. Recrystallisation of the product from water yielded 115 mg (78 %) of the imidazolone as colourless needles, m.p. 146—147°.

$C_{12}H_{14}ON_2$ (202.3) Calc. C 71.23 H 6.98 N 13.85
Found » 70.99 » 6.68 » 13.87

The UV-absorption spectrum in methanol showed three maxima at 230 mμ, 236 mμ and 250 mμ with molecular extinction values of 12 000, 11 900 and 11 000, respectively. Minima were found at 234 mμ and 242 mμ with ε-values of 11 750 and 10 600. An inflection point around 280 mμ (ε *ca.* 4 200) was also apparent.

DL-*α-Benzamidohydratropic acid.* Six grams of DL-α-amino-α-phenylpropionic acid[16] were benzoylated as described above for *iso*valine. The reaction product (5.5 g) tended to form an oil upon recrystallisation. By carefully adding petroleum ether to a solution in ethyl acetate, colourless rhombic platelets were obtained. M.p. 146—147°.

$C_{16}H_{15}O_3N$ (269.3) Calc. C 71.35 H 5.61 N 5.20
Found » 71.32 » 5.55 » 5.21

α-Benzamidohydratropamide. When the above acid was treated with acetic anhydride as usual, a pale yellow, oily azlactone remained after removal of excess reagents *in vacuo*. The oil did not crystallise on prolonged keeping in the ice-box and no attempts were made to purify it further.

Treatment of the product with ethanolic ammonia resulted in an 85 % yield of the crystalline amide, separating from aqueous ethanol as clusters of fine needles. M.p. 129—130°.

$C_{16}H_{16}O_2N_2$ (268.3) Calc. C 71.63 H 6.01 N 10.44
Found » 71.76 » 6.08 » 10.31

2,4-Diphenyl-4-methyl-5-imidazolone. Within 15 minutes 572 mg of the above amide went into solution in 10 ml of 1 *N* NaOH at 75—85°. No formation of ammonia was noticeable. After cooling and acidification, a crystalline mass was obtained and recrystallised from aqueous ethanol, giving 385 mg of fine needles. M.p. 151—152°.

$C_{16}H_{14}ON_2$ (250.3) Calc. C 76.79 H 5.64 N 11.20
Found » 76.96 » 5.60 » 11.23

α,α-Diethylhippuric acid. α-Aminodiethylacetic acid[17] (4.6 g) was benzoylated according to the general method. A sample for analysis was recrystallised twice from 30 % ethanol, m.p. 210°.

$C_{13}H_{17}O_3N$ (235.3) Calc. C 66.34 H 7.28 N 5.95
Found » 66.12 » 7.47 » 6.07

α,α-Diethylhippuramide. The acid was transformed into its azlactone as usual. This showed no signs of crystallisation and was submitted to ammonolysis without further purification. The amide was recrystallised from 50 % ethanol and melted at 198—200°.

$C_{13}H_{18}O_2N_2$ (234.3)	Calc.	C	66.63	H	7.74	N	11.96
	Found	»	66.47	»	7.50	»	11.92

2-Phenyl-4,4-diethyl-5-imidazolone. Upon treatment of the amide with alkali at moderate temperature, the imidazolone was obtained as a crystalline substance after scratching and cooling. M.p. 189—190°, after recrystallisation from aqueous ethanol.

$C_{13}H_{16}ON_2$ (216.3)	Calc.	C	72.18	H	7.46	H	12.95
	Found	»	72.41	»	7.10	»	12.90

The UV-absorption spectrum in methanol showed two maxima at 235 mμ and 250 mμ with the extinction values 12 250 and 12 600. A minimum was noticed at 245 mμ (ε 11 900). The usual inflection at 280 mμ was quite prominent (*cf.* Fig. 3).

N-(p-Nitrobenzoyl)-isobutyric acid. α-Amino*iso*butyric acid (10.3 g) was nitrobenzoylated, following the general procedure by Wright *et al.*[18]. After one recrystallisation from dilute ethanol the yield amounted to 17.1 g (68 %). An analytical sample was produced by two additional recrystallisations and appeared as small, pale yellow needles, m.p. 183.5°.

$C_{11}H_{12}O_5N_2$ (252.2)	Calc.	C	52.38	H	4.80	N	11.11
	Found	»	52.10	»	4.76	»	11.04

2-(p-Nitrophenyl)-4,4-dimethyl-5-oxazolone. When treated with acetic anhydride as usual, the acid above readily yielded the yellowish, crystalline azlactone. This recrystallised from anhydrous acetone as thin needles, m.p. 201—202°.

$C_{11}H_{10}O_4N_2$ (234.2)	Calc.	C	56.41	H	4.30	N	11.96
	Found	»	56.52	»	4.20	»	11.81

The UV-spectrum in methanol was characteristic of an aromatic nitro-compound with a broad maximum at 270 mμ (ε 12 100) and minimum at 230 mμ (ε 3 300), agreeing with the spectroscopical data previously reported [12] for similar compounds.

α-(p-Nitrobenzamido)-isobutyramide. This was obtained in 95 % yield from the oxazolone with ethanolic ammonia at room temperature as colourless needles with m.p. 223—225°.

$C_{11}H_{13}O_4N_3$ (251.2)	Calc.	C	52.58	H	5.22	N	16.73
	Found	»	52.42	»	4.79	»	16.70

In Fig. 1 the UV-spectrum in 0.01 *N* methanolic KOH is presented. When measured immediately after the preparation of the solution, this spectrum differs only slightly from that in pure methanol.

2-(p-Nitrophenyl)-4,4-dimethyl-5-imidazolone. The amide above was readily transformed in alkaline solution into the imidazolone, which crystallised from ethanol in colourless prisms with m.p. 216—217°.

$C_{11}H_{11}O_3N_3$ (233.2)	Calc.	C	56.65	H	4.75	N	18.02
	Found	»	56.72	»	4.54	»	18.07

In Fig. 1 the spectrum in 0.01 *N* methanolic KOH is reproduced together with some intermediate curves determined at different times in order to follow the cyclisation. The spectrum in pure methanol is quite different from the one here reported and reminiscent of the general imidazolone-spectrum in Fig. 3.

α-Phenacetamidoisobutyramide. α-Phenacetamido*iso*butyric acid [19] was transformed into its azlactone [19] as usual. Ammonolysis of the latter yielded the amide as long, colourless needles which were recrystallised from water. M.p. 184—185°.

$C_{12}H_{16}O_2N_2$ (220.3)	Calc.	C	65.45	H	7.32	N	12.72
	Found	»	65.43	»	7.24	»	12.65

2-Benzyl-4,4-dimethyl-5-imidazolone. The amide readily dissolved in 2 *N* NaOH. After acidification with glacial acetic acid, an oil separated which solidified on keeping in the ice-box overnight. On recrystallisation from water beautiful crystals were obtained which sintered from about 80° and gave analytical figures indicating a monohydrate.

$C_{12}H_{14}ON_2$, H_2O (220.3)	Calc.	C	65.45	H	7.32	N	12.72
	Found	»	65.24	»	7.25	»	12.75

Attempts to dehydrate the compound over P_2O_5 *in vacuo* at 56° resulted in slow sublimation and inconclusive analytical results on the residue. The imidazolone-structure was confirmed by the UV-spectra in methanol and methanolic KOH (Fig. 2).

DL-*α-Phenacetamidohydratropic acid.* Phenacetylation of 5.0 g of DL-α-amino-α-

phenylpropionic acid [16] by the Schotten-Baumann method gave 5.2 g (61 %) of the acylamido acid. Recrystallisation from aqueous ethanol yielded colourless needles. M.p. 184—185°.

$C_{17}H_{17}O_3N$ (283.3)	Calc.	C	72.06	H	6.05	N	4.94
	Found	»	71.96	»	5.96	»	4.93

α-Phenacetamidohydratropamide. Upon treatment of the above acid with acetic anhydride, the azlactone was obtained as a viscous oil which did not crystallise. Without further purification it was ammonolysed in the ordinary way to give the amide which crystallised from dilute ethanol as dense, colourless crystals, m.p. 130—132°.

$C_{17}H_{18}O_2N_2$ (282.3)	Calc.	C	72.33	H	6.43	N	9.93
	Found	»	72.30	»	6.52	»	10.06

2-Benzyl-4-methyl-4-phenyl-5-imidazolone. Alkali-treatment of the above amide brought about the cyclisation, and an 83 % yield of the crystalline imidazolone was obtained. It formed colourless, spear-formed prisms on recrystallisation from dilute ethanol. M.p. 163—165°.

$C_{17}H_{16}ON_2$ (264.3)	Calc.	C	77.25	H	6.10	N	10.60
	Found	»	77.38	»	6.21	»	10.64

2,4-Dimethyl-4-phenyl-5-imidazolone. When α-acetamidohydratropamide [20] was carefully heated in 1 *N* NaOH at 75—85° a clear solution was obtained within 8 minutes with no detectable evolution of ammonia. The mixture was acidified with glacial acetic acid and concentrated *in vacuo* to half its volume. On keeping at 0° an oil separated which was washed with cold water and thoroughly dried before analysis.

$C_{11}H_{12}ON_2$ (188.2)	Calc.	C	70.28	H	6.43	N	14.88
	Found	»	69.91	»	6.20	»	14.98

α-Formamidoisobutyric acid. Finely pulverised α-amino*iso*butyric acid (8.1 g) was dissolved in 10 ml of anhydrous formic acid on the steam bath. 17 g of the mixed anhydride, prepared from equimolecular amounts of formic acid and acetic anhydride, were added. A slightly exothermic reaction with evolution of gas (CO), was noticed. Next day the volatile contents were removed *in vacuo* at low temperature and the residue recrystallised from water. Clusters of flat prisms were obtained, (5.2 g, 51 %). M.p. 143—144°.

$C_5H_9O_3N$ (131.1)	Calc.	C	45.80	H	6.92	N	10.68
	Found	»	46.06	»	6.94	»	10.69

DL-*α-Formamidohydratropic acid.* Following the procedure above, an 84 % yield was obtained from DL-α-amino-α-phenylpropionic acid [16]. An analytical sample, recrystallised from hot water, melted at 178°.

$C_{10}H_{11}O_3N$ (193.2)	Calc.	C	62.16	H	5.74	N	7.25
	Found	»	62.20	»	5.90	»	7.22

DL-*α-Phenylhippuramide.* DL-α-Aminophenylacetic acid was benzoylated according to Steiger [10], and the α-phenylhippuric acid transformed into its slightly yellow azlactone, crystallising in thin needles [21]. The latter reacted with water to give α-phenylhippuric acid and with aniline to give the corresponding anilide, m.p. 214—215° (Ref. [21] 208—210° and 210—212°).

Reaction with ammonia gave α-phenylhippuramide in 88 % yield. It separated as colourless crystals from ethanol, m.p. 197°.

$C_{15}H_{14}O_2N_2$ (254.3)	Calc.	C	70.85	H	5.55	N	11.02
	Found	»	71.02	»	5.53	»	11.04

Numerous attempts were made to effect cyclisation of the amide, but all unsuccessful. Upon heating *in vacuo* the amide sublimed unchanged. Trituration with hot alkali or acid resulted in hydrolysis to the acid, whereas treatment with acetic anhydride or phosphorus pentachloride gave unchanged material contaminated with gummy products which could not be brought into a tractable form.

1-Benzoyl-5-phenyl-2-thiohydantoin. By following the general procedure of Johnson and Nicolet [22] for the reaction between azlactones and ammonium thiocyanate, an 87 % yield of crystalline thiohydantoin was obtained from the crude 2,4-diphenyl-5-oxazolone above. Very pale yellow needles separated from ethanol, m.p. 200—201°.

$C_{16}H_{12}O_2N_2S$ (296.3)	Calc.	C	64.86	H	4.08	N	9.46
	Found	»	64.68	»	4.40	»	9.24

DL-pseudo*Leucine (α-amino-β,β-dimethylbutyric acid).* Pinacolone (157.1 g) was oxidised in three portions with alkaline potassium permanganate. The method was that of

Richard [23] with minor modifications. Acidification, followed by ether extraction and distillation *in vacuo*, gave a total of 199.2 g (97 %) of analytically pure trimethylpyruvic acid as a viscous, colourless oil, b.p. 73.5—75° at 10 mm. (Ref.[23] 80 %).

When 53.4 g of trimethylpyruvic acid, 42.0 g of hydroxylamine hydrochloride and 50 g of anhydrous potassium carbonate in 140 ml of water were kept at room temperature for 20 hours, a thick suspension of crystalline material resulted. Further amounts of the same product separated upon addition of conc. hydrochloric acid. The crystals were taken up in ether and the aqueous phase repeatedly extracted with portions of fresh ether. Concentration *in vacuo*, followed by repeated evaporations with benzene in order to remove the last traces of water, gave a crystalline residue (55.0 g, 92 %) of the oxime, m.p. 112—115° (dec.). The anhydrous substance separated in colourless prisms from toluene. M.p. 116—117° (dec.). (Ref.[23] gives m.p. 85° for the monohydrate.)

After only discouraging results were obtained with various catalytic hydrogenations of the oxime, recourse was taken to the reduction with aluminium amalgam, previously mentioned in the literature [24]. A 40 % yield of pure *pseudo*leucine was obtained after repeated recrystallisations from aqueous acetone. The amino acid gave a deep-blue colour with ninhydrin, but only after heating for some time on the steam bath.

N-Benzoyl-DL-pseudo*leucine*. This was obtained in 70 % yield by the usual Schotten-Baumann benzoylation. An analytical sample separated from dilute ethanol in colourless plates, m.p. 164—166°.

$C_{13}H_{17}O_3N$ (235.3)	Calc.	C	66.34	H	7.28	N	5.95
	Found	»	66.37	»	7.53	»	5.71

*2-Phenyl-4-*tert.*-butyl-5-oxazolone*. This azlactone was readily produced from benzoyl-*pseudo*leucine and acetic anhydride as usual. Recrystallisation from hexane afforded colourless prisms, m.p. 73—74°.

$C_{13}H_{15}O_2N$ (217.3)	Calc.	C	71.85	H	6.96	N	6.45
	Found	»	72.04	»	7.33	»	6.21

*N-Benzoyl*pseudo*leucinmethylamide*. Produced from the azlactone and aqueous methylamine at room temperature. It separated as colourless prisms from aqueous ethanol, m.p. 202—203°.

$C_{14}H_{20}O_2N_2$ (248.3)	Calc.	C	67.71	H	8.12	N	11.29
	Found	»	67.42	»	7.87	»	11.45

*N-Benzoyl*pseudo*leucinmorpholide*. A solution of the azlactone above and morpholine in dry benzene was kept at room temperature overnight. Addition of hexane precipitated an oil which rapidly crystallised. Slender, colourless needles were obtained from aqueous ethanol. M.p. 181°.

$C_{17}H_{24}O_3N_2$ (304.3)	Calc.	C	67.06	H	7.95	N	9.20
	Found	»	66.91	»	7.99	»	9.40

*N-Benzoyl*pseudo*leucinanilide*. The azlactone was readily ring-opened on standing at room temperature in benzene solution containing a slight excess of aniline. When hexane was added, the anilide separated and was recrystallised from ethanol as colourless prisms, m.p. 223—225° after gradual sintering from *ca.* 170°.

$C_{19}H_{22}O_2N_2$ (310.4)	Calc.	C	73.50	H	7.15	N	9.03
	Found	»	73.58	»	7.20	»	9.12

*N-Benzoyl*pseudo*leucinamide*. One gram of the azlactone was added to 5 ml of ethanol, saturated at 0° with ammonia. A clear solution resulted from which the separation of prisms started in less than one minute. After standing, 0.97 g (89 %) of the amide could be collected. An analytical sample was obtained from ethanol. M.p. 202° (dec.).

$C_{13}H_{18}O_2N_2$ (234.3)	Calc.	C	66.63	H	7.57	N	11.96
	Found	»	66.40	»	7.68	»	12.19

Neither heating *in vacuo* nor treatment with the usual reagents afforded any indication of imidazolone-formation.

2-Phenyl-4,4-dimethyl-5-imidazolone. A solution of ethyl iminobenzoate (4.2 g) and ethyl α-amino*iso*butyrate (3.8 g) in 10 ml of anhydrous xylene was refluxed for 3 hours. After standing at room temperature for a few days, a crop of beautiful crystals (0.6 g) separated. The substance was recrystallised from water, m.p. 201—202°, alone or in admixture with a specimen prepared by the alkali-induced cyclodehydration of α-benzamido*iso*butyramide.

Ultraviolet absorption spectra. The UV-absorption spectra reported in this paper were determined in 1 cm cells on a model DU Beckman quartz spectrophotometer.

SUMMARY

A series of amides of acylated, tertiary α-amino acids has been prepared and their facile cyclisation to imidazolones demonstrated. The nature of the acyl-grouping and of the substituents on the α-carbon atom seems to play no decisive rôle, although considerable variation in the rate of the cyclisation-reaction has been observed.

Despite numerous attempts under widely varying conditions, no example has been found of a similar cyclisation within the class of non-tertiary α-acylamido acid amides.

An improved preparation of DL-*pseudo*leucine is reported and numerous new compounds described.

Microanalyses were carried out in this laboratory by Mr. A. Grossmann.

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