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LACTAMS—I

THE SYNTHESIS AND ACID HYDROLYSIS OF 4- AND 5-SUBSTITUTED 1-BENZYL-2-PIPERIDONE DERIVATIVES[1]

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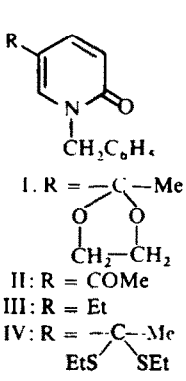
Abstract—In order to explain the difficulty in hydrolysing the lactam linkage of 1-benzyl-2-oxo-5-ethyl-4-piperidineacetic acid (XIV) under acid conditions, several model compounds such as 1-benzyl-2-piperidone (X), 1-benzyl-5-ethyl-2-piperidone (XI), 1-benzyl-4-ethyl-2-piperidone (XII), and 1-benzyl-2-oxo-4-piperidineacetic acid (XIII) were prepared and their hydrolysis in boiling 6N HCl was studied. For each of the lactams, the hydrolysis was found to proceed to an equilibrium as shown in Table 1. Substituents at the 4- and 5-positions of the piperidone ring seemed to favour the ring form in the equilibrium between piperidones (X–XIV) and ω-amino acid hydrochlorides (type XV).

IN PREVIOUS papers[2,3] it was reported that 1-benzyl-2-oxo-5-ethyl-4-piperidineacetic acid (XIV) was resistant to acid hydrolysis, contrary to what was expected from a simple lactam. This observation, together with that of interconversion between the two isomers of 2-oxo-5-ethyl-4-piperidineacetic acid (XVI) under similar hydrolytic conditions,[3] prompted us to investigate the effect of substituents at the 4- and 5-positions of the 2-piperidone ring on susceptibility of the lactam linkage to acid hydrolysis. Analysis of structural features in XIV suggested the selection of model compounds such as 1-benzyl-2-piperidone (X),[2] 1-benzyl-5-ethyl-2-piperidone (XI), 1-benzyl-4-ethyl-2-piperidone (XII), and 1-benzyl-2-oxo-4-piperidineacetic acid (XIII) in which the essential partial structures of XIV are obvious. Therefore, we synthesized compounds XI, XII, and XIII according to the method of Sugasawa and Kirisawa.[4–7]

For the synthesis of XI, 1-benzyl-5-(1,1-ethylenedioxyethyl)-2(1*H*)-pyridone (I)[5] was treated with a mixture of dilute hydrochloric acid and ethanol to produce 1-benzyl-5-acetyl-2(1*H*)-pyridone (II)[5] in a good yield. The reaction condition seemed preferable to the one used by Anderson and Berkelhammer.[5] Since difficulty was encountered in the conversion of methyl ketone II into 1-benzyl-5-ethyl-2(1*H*)-pyridone (III) by the Huang-Minlon modification of the Wolff-Kishner reduction, the diethylmercaptol (IV) was prepared from II, and desulfurized with Raney nickel to a mixture which was presumed to contain III and its partially and/or fully hydrogenated products. Hydrogenation of the mixture over Adams catalyst furnished XI[8] in a good overall yield.

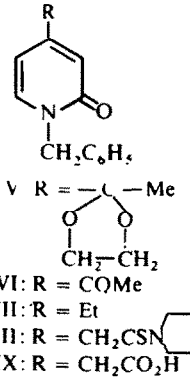
The synthesis of XII and XIII was accomplished through the common intermediate, 1-benzyl-4-acetyl-2(1*H*)-pyridone (VI), which was obtained by a reaction sequence [1-benzyl-4-(1,1-ethylenedioxyethyl)pyridinium bromide → 1-benzyl-4-(1,1-ethylenedioxyethyl)-2(1*H*)-pyridone (V) → VI] starting with 4-acetylpyridine ethylene ketal and according to the synthesis of II. The reduction of VI by the Huang-Minlon

method proceeded without difficulty and the resulting 1-benzyl-4-ethyl-2(1*H*)-pyridone (VII) was converted into XII by catalytic hydrogenation. On the other hand, 1-benzyl-4-morpholinothiocarbonylmethyl-2(1*H*)-pyridone (VIII) obtained from VI by a Kindler modification of the Willgerodt reaction afforded, after hydrolysis, 1-benzyl-2-oxo-1,2-dihydro-4-pyridineacetic acid (IX). Catalytic hydrogenation of IX to give XIII was effected over Raney nickel at 40–45° and atmospheric pressure.



I. R =

II: R = COMe
III: R = Et
IV: R =

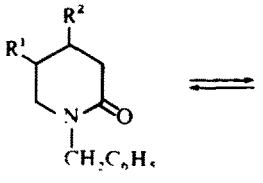


V R =

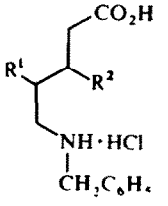
VI: R = COMe
VII: R = Et
VIII: R =
IX: R = CH_2CO_2H

Piperidone X possesses the parental carbon skeleton common to all the five test compounds, and has been known to undergo hydrolysis in hot hydrochloric acid to give 5-benzylaminovaleric acid hydrochloride (type XV).[2, 9, 10] Accordingly, we first followed the progress of the reaction in boiling 6·04N HCl by measuring the amount of the unchanged lactam X. The hydrolysis was found to proceed to an equilibrium and resulted in approximately 98% conversion into the ω-amino acid hydrochloride (type XV) in 20 hr. The attainment of equilibrium was checked by conducting the reverse experiment with 5-benzylaminovaleric acid hydrochloride (type XV).

The hydrolysis of XI, XII, XIII, and XIV (a mixture of the *cis* and *trans* isomers)[3, 8] was also studied separately under the identical reaction condition. For each of the first four of the group, the hydrolysis product (type XV) was characterized as the



X: $R^1 = R^2 = H$
XI: $R^1 = Et$; $R^2 = H$
XII: $R^1 = H$; $R^2 = Et$
XIII: $R^1 = H$; $R^2 = CH_2CO_2H$
XIV: $R^1 = Et$; $R^2 = CH_2CO_2H$



XV

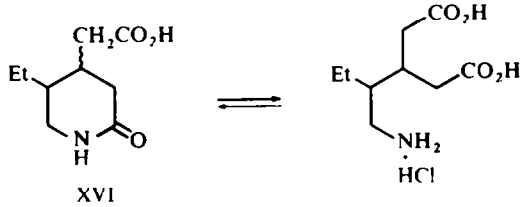
hydrochloride or N-tosylated ω-amino acid. In the case of XIV, either purification or N-tosylation of a hydrolysis product presumed to be 3-(1-benzylaminomethyl-propyl)glutaric acid hydrochloride (type XV) was unsuccessful, owing to great ease with which its recyclization to XIV took place during the procedure. In the hydrolysis

of XI, XII, and XIII, experiments with different initial concentrations of the piperidones also served to check the equilibrium. Table 1 summarizes the results.

TABLE 1. HYDROLYSIS OF 0·528M PIPERIDONES IN BOILING 6·04N HYDROCHLORIC ACID

Lactam	At equilibrium Time (hr)	Hydrolysis (%)
X	*ca* 20	98
XI	*ca* 20	74
XII	*ca* 25	83
XIII	*ca* 15	81
XIV	*ca* 30	14

It is of interest that the substituents at either the 4- or 5-positions caused to shift the equilibrium between lactam and ω-amino acid hydrochloride (type XV) to the left and the extent of the effect was larger on the 5-substituted piperidone (XI) than the 4-substituted ones (XII and XIII). Two substituents at the 4- and 5-positions of XIV co-operatively favoured the ring form in the equilibrium. This seems to be similar to the effect of alkyl substituents observed in other equilibria involving the opening and closing of rings, such as the equilibria between cyclic anhydrides and dicarboxylic acids in aqueous media.[11]



XVI XVII

Thus, the previously reported *cis-trans* isomerization of XVI in hot conc. hydrochloric acid[3] could be explained by assuming an analogous equilibrium between XVI and 3-(1-aminomethylpropyl)glutaric acid hydrochloride (XVII), in which a mechanism of ring opening followed by rotation and recyclization with another carboxyl group is possible. Several other reported observations of retention of the lactam linkage[12] and of formation of it[13–18] under acid hydrolytic condition might also be understandable in the light of the present study and that[19] of glutamic acid—pyroglutamic acid equilibrium.

EXPERIMENTAL

All m.ps are corrected; b.ps, uncorrected. The UV spectra were recorded on a Hitachi EPS-2U spectrophotometer in 95% EtOH aq. The IR spectra were obtained with a JASCO-DS-301 or -402G spectrophotometer and the NMR spectra were determined with a JEOL-JNM-C-60H spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: m = multiplet, t = triplet, d = doublet, s = singlet, b = broad, sh = shoulder, DMSO = dimethyl sulfoxide.

1-*Benzyl*-5-*acetyl*-2(1H)-*pyridone* (II). A soln of I[5] (3·80 g, 0·014 mole) in EtOH (30 ml) and 10% HCl aq (11 ml) was refluxed for 1·5 hr, and then concentrated to a small volume under vacuum. The mixture was

diluted with H_2O, rendered basic (K_2CO_3), and extracted with $CHCl_3$. The extracts were washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo*. The residual solid (3·15 g, 99%), m.p. 72–75°, was recrystallized from benzene—hexane (1:2) to give colourless needles, m.p 83–84° (lit.[5] m.p. 77 78°); UV λ_{max} mμ (ε): 278·5 (18,400); λ_{min} 239 (2200); IR ν_{max}^{KBr} cm^{-1}: 1688 (C=O), 1646 (pyridone); NMR ($CDCl_3$) τ: 7·62 (3H, s, COMe), 4·82 (2H, s, $NCH_2C_6H_5$), 3·45 (1H, d, J = 9·5 c/s, $H_{(3)}$), 2·68 (5H, s, C_6H_5), 2·14 (1H, d-d, J = 9·5 and 3 c/s, $H_{(4)}$), 1·74 (1H, d, J = 3 c/s, $H_{(6)}$). (Found: C, 73·91; H, 5·68; N, 6·26. $C_{14}H_{13}O_2N$ requires: C, 73·99; H, 5·77; N, 6·16%).

The *semicarbazone* of II was prepared in the usual manner, and recrystallized from EtOH to afford colourless prisms, m.p. 233–236° (dec). (Found: C, 63·43; H, 5·72; N, 19·60. $C_{15}H_{16}O_2N_4$ requires: C, 63·36; H, 5·67; N, 19·71%).

1-*Benzyl*-5-*ethyl*-2-*piperidone* (XI). To a mixture of II (18·2 g, 0·08 mole), $ZnCl_2$ (12 g), which had been freshly fused and powdered, and anhyd Na_2SO_4 (8 g) was added EtSH (56 ml) under ice-cooling. The mixture was thoroughly mixed by shaking for 30 min with occasional cooling, kept standing at room temp for 96 hr, and then poured into H_2O (500 ml) to separate a yellow oil, which was extracted with benzene. The extracts were washed successively with H_2O, 10% NaOHaq, and H_2O, and dried over Na_2SO_4. Evaporation of the benzene *in vacuo* provided *diethylmercaptol* IV as a viscous oil (26 g), which was shown by TLC [Merck silica gel GF_{254}, benzene—EtOH (10:1)] to be contaminated with a trace of the unchanged II.

The total amount of IV above was heated under reflux in 70% EtOHaq (2 l.) with Raney Ni* (280 ml of the settled catalyst in a suspension in abs EtOH) for 4 hr. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to a small volume (*ca* 200 ml). After dilution with H_2O, the residue was extracted with benzene. The benzene soln was washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo* to yield a faintly yellowish, viscous oil (15·2 g), which was presumed from its IR spectrum (ν_{max}^{film} cm^{-1} 1680, 1650, 1640, 1610, 1592) and TLC to be a mixture of III and its partially and/or fully hydrogenated products. The crude oil in EtOH (140 ml) was hydrogenated over Adams catalyst (340 mg) at room temp and atm press; the reaction ceased after having taken 49% of the theoretical amount of H_2, based on assumption that the oil were composed of pure pyridone III, during 7 hr. Filtration of the catalyst and evaporation of the filtrate left a slightly yellowish oil (15·1 g) shown to be homogeneous by a single spot on a TLC plate. Distillation of the oil under reduced press yielded piperidone XI as a colourless oil (14·2 g, 82% from II), b.p. 163–164°/3 mm Hg (lit.[8] b.p. 161–162°/3 mm Hg); UV λ_{max} mμ (ε): 252·5 (166), 258·5 (194), 264·5 (150); IR ν_{max}^{film} cm^{-1}: 1643 (lactam); NMR (CCl_4) τ: 9·15 (3H, t, J = 5·5 c/s, CH_2CH_3), 5·54 (2H, s, $NCH_2C_6H_5$), 2·82 (5H, s, C_6H_5). (Found: C, 77·18; H, 9·17; N, 6·52. $C_{14}H_{19}ON$ requires: C, 77·38; H, 8·81; N, 6·45%).

1-*Benzyl*-4-(1,1-*ethylenedioxyethyl*)-2(1H)-*pyridone* (V). To a chilled soln of 2-(4-pyridyl)-2-methyl-1,3-dioxolane[6, 21] (57·6 g, 0·349 mole) in $HCONMe_2$ (120 ml) was added a soln of benzyl bromide (71·3 g, 0·417 mole) in $HCONMe_2$ (50 ml). The mixture was allowed to stand at room temp for 40 hr, and then evaporated *in vacuo* to leave a brown oil. The oil was dissolved in H_2O (800 ml), washed with benzene, and combined with a soln of $K_3Fe(CN)_6$ (335 g, 1·02 moles) in H_2O (1·61.) To the well-stirred mixture was added dropwise a soln of KOH (200 g) in H_2O (400 ml) under cooling with ice-water over a period of 30 min. Benzene (600 ml) was added and the mixture was stirred under cooling for 1 hr, then at room temp for 2 hr, and allowed to stand overnight. The benzene layer was separated, washed with sat NaClaq, and dried over Na_2SO_4. Removal of the benzene *in vacuo* provided the crude pyridone V (79·2 g, 84%), m.p. 85–88°, which was recrystallized from hexane—benzene (10:1) to give colourless needles, m.p. 90 92°; UV λ_{max} mμ (ε): 231 (sh) (6350), 307 (5180); λ_{min}; 250 (560); IR ν_{max}^{KBr} cm^{-1}; 1669 (pyridone), 1202, 1040 (ketal); NMR (DMSO) τ: 8·48 (3H, s, Me), 6·13 (m, b, OCH_2CH_2O), 4·88 (2H, s, $NCH_2C_6H_5$), 3·75 (1H, d-d, $H_{(5)}$), 3·55 (1H, b, $H_{(3)}$), 2·66 (5H, s, C_6H_5), 2·20 (1H, d, J = 7 c/s, $H_{(6)}$). (Found: C, 70·94; H, 6·29; N, 5·26 $C_{16}H_{17}O_3N$ requires: C, 70·83; H, 6·32; N, 5·16%).

1-*Benzyl*-4-*acetyl*-2(1H)-*pyridone* (VI). Compound V was hydrolysed in the same way as I and the crude ketone VI formed was extracted with $CHCl_3$, yield 98%. Recrystallizations from benzene furnished colourless prisms, m p. 92 94°; UV λ_{max} mμ (ε): 345 (3750); λ_{min} 278 (430); IR ν_{max}^{KBr} cm^{-1}: 1685 (C=O), 1670 (pyridone); NMR ($CDCl_3$) τ· 7·52 (3H, s, COMe), 4·89 (2H, s, $NCH_2C_6H_5$), 3·47 (1H, d-d, J = 7 and 3 c/s, $H_{(5)}$), 2·98 (1H, d, J = 3 c/s, $H_{(3)}$), 2·73 (5H, s, C_6H_5), 2·64 (1H, d, J = 7 c/s, $H_{(6)}$). (Found: C, 74·27; H, 5·84; N, 6·17. $C_{14}H_{13}O_2N$ requires· C, 73·99; H, 5·77; N, 6·16%).

1-*Benzyl*-4-*ethyl*-2(1H)-*pyridone* (VII). In a 3-l. 3-necked flask equipped with a descending condenser and a mechanical stirrer was placed a mixture of VI (45·5 g, 0·2 mole), ethylene glycol (400 ml), 80% aqueous

* Prepared according to the direction given by R. Mozingo, but the final temp and duration employed in digestion were 50–55° and 1 hr.[20]

hydrazine hydrate (25 g) and KOH (26 g). The mixture was heated with stirring in an oil bath at 120° for 1·5 hr. Then, the temp of the oil bath was slowly raised to 190° in 30 min. The mixture was further heated with stirring at 190–195° (bath temp) for 2 hr to give *ca* 14 ml of a colourless distillate. After having been cooled, the soln was poured into H_2O (1·2 l.) to separate a brown oil, which was extracted with benzene, washed with H_2O, and dried over Na_2SO_4. Evaporation of the solvent and distillation of the residue *in vacuo* provided VII as a colourless oil (37·4 g, 88%), b.p. 182–185°/2 mm Hg, which solidified on standing at room temp. Recrystallizations from hexane gave colourless needles, m.p. 42–44°; UV λ_{max} mμ (ε): 233·5 (sh) (4550), 302 (4700); λ_{min} 250 (500); IR ν_{max}^{KBr} cm^{-1}: 1658 (pyridone); NMR ($CDCl_3$) τ: 8·83 (3H, t, J = 7·5 c/s, CH_2CH_3), 7·57 (2H, q, J = 7·5 c/s, CH_2CH_3), 4·95 (2H, s, $NCH_2C_6H_5$), 4·03 (1H, d-d, J = 7 and 2 c/s, $H_{(5)}$), 3·63 (1H, b, $H_{(3)}$), 2·88 (1H, d, J = 7 c/s, $H_{(6)}$), 2·77 (5H, s, C_6H_5). (Found: C, 79·13; H, 7·25; N, 6·53. $C_{14}H_{15}ON$ requires: C, 78·84; H, 7·06; N, 6·57%).

The *picrate* of VII was prepared from a portion of the pyridone by dissolving it in a small amount of Et_2O and adding a sat soln of picric acid in Et_2O. After recrystallizations from EtOH, yellow needles of m.p. 96–98° were obtained. (Found: C, 54·03; H, 4·07; N, 12·72 $C_{20}H_{18}O_8N_4$ requires: C, 54·30; H, 4·10; N, 12·67%).

1-*Benzyl*-4-*ethyl*-2-*piperidone* (XII). Pyridone VII (41·4 g) in EtOH (400 ml) was hydrogenated over Adams catalyst (500 mg) at room temp and atm press. When the reaction was complete, the catalyst was filtered and the filtrate was evaporated to leave an oil, which was distilled *in vacuo* to give XII as a colourless oil (38·5 g, 91%), b.p. 158–159°/1·5 mm Hg; UV λ_{max} mμ (ε): 252·5 (156), 258·5 (182), 264·5 (140); IR ν_{max}^{film} cm^{-1} 1644 (lactam); NMR (CCl_4) τ: 9·10 (3H, t, J = 5·5 c/s, CH_2CH_3), 5·55 (2H, s, $NCH_2C_6H_5$), 2·84 (5H, s, C_6H_5). (Found: C, 77·40; H, 8·92; N, 6·62. $C_{14}H_{19}ON$ requires: C, 77·38; H, 8·81, N, 6·45%).

1-*Benzyl*-4-*morpholinothiocarbonylmethyl*-2(1H)-*pyridone* (VIII). A mixture of *p*-toluenesulfonic acid monohydrate (0·22 g) and toluene (50 ml) was evaporated to dryness under slightly reduced press to obtain the anhyd acid.* To it were added morpholine (7·32 g, 0·084 mole), ketone VI (9·09 g, 0·04 mole), and sulfur (1·36 g, 0·0424 mole). The mixture was heated at 135–140° (bath temp) for 3 hr, and then evaporated *in vacuo* to leave a dark, hard oil, which solidified when triturated with a small amount of EtOH. The solid was recrystallized from EtOH to yield light yellow needles (6·75 g, 52%), m.p. 145–147°. Recrystallizations from EtOH gave VIII as colourless micro-needles, m.p. 149–150°; UV λ_{max} mμ (ε): 236 (sh) (7140), 285 (17,100), λ_{min} 248·5 (3800); IR ν_{max}^{KBr} cm^{-1}: 1661(pyridone); NMR ($CDCl_3$) τ: 6·44 (2H, s, $\underline{CH_2}CSN$), 6·35 (4H, m, CH_2NCH_2), 5·85 (4H, m, CH_2OCH_2), 4·95 (2H, s, $NCH_2C_6H_5$), 3·82 (1H, d-d, J = 7 and 2 c/s, $H_{(5)}$), 3·62 (1H, b, $H_{(3)}$), 2·78 (1H, d, $H_{(6)}$), 2·77 (5H, s, C_6H_5). (Found: C, 65·61; H, 6·06; N, 8·82 $C_{18}H_{20}O_2N_2S$ requires: C, 65·82; H, 6·14; N, 8·53%).

1-*Benzyl*-2-*oxo*-1,2-*dihydro*-4-*pyridineacetic acid* (IX). A mixture of VIII (3·35 g, 0·0102 mole) and a soln of KOH (6·7 g) in H_2O (51 ml) was refluxed for 5 hr. The mixture was treated with charcoal and filtered. The pH of the filtrate was made to 2 to precipitate colourless crystals, which were filtered, washed with H_2O, and dried. The crude IX (2·30 g, 93%), m.p. 158–159° (dec), was recrystallized from EtOH to furnish colourless pillars, m.p. 160–161° (dec) (m.p. was variable depending on a rate of raising temp); UV λ_{max} mμ (ε): 305 (4900); λ_{min} 254 (690); IR ν_{max}^{KBr} cm^{-1}: 3000–2500, 1737 (CO_2H), 1645 (pyridone); NMR (DMSO-d_6) τ: 6·55 (2H, s, CH_2CO_2H), 4·93 (2H, s, $NCH_2C_6H_5$), 3·80 (1H, d-d, J = 7 and 2 c/s, $H_{(5)}$), 3·61 (1H, b, $H_{(3)}$), 2·72 (5H, s, C_6H_5), 2·32 (1H, d, J = 7 c/s, $H_{(6)}$), −1·95 (1H, very b, $CO_2\underline{H}$). (Found: C, 68·89; H, 5·28; N, 6·02 $C_{14}H_{13}O_3N$ requires: C, 69·12; H, 5·39, N, 5·76%).

1-*Benzyl*-2-*oxo*-4-*piperidineacetic acid* (XIII). Pyridone IX (19·6 g, 0·08 mole) in 10% Na_2CO_3 aq (50 ml) and H_2O (200 ml) was hydrogenated over Raney Ni W-2 catalyst (10 g) at 40–50° and atm press. When the reaction was complete, the catalyst was removed by filtration and the filtrate was acidified with conc HCl aq to precipitate colourless crystals. The mixture was extracted with $CHCl_3$ and the $CHCl_3$ soln was washed with H_2O, and dried over Na_2SO_4. Removal of the solvent *in vacuo* provided colourless crystals (18·0 g, 91%), m.p. 144–146°. Recrystallization from 10% EtOH aq gave XIII as colourless needles of the same m.p.; UV λ_{max} mμ (ε): 252·5 (158), 258·5 (196), 264·5 (188); IR ν_{max}^{KBr} cm^{-1}: 3000–2500, 1718 (CO_2H), 1598 (lactam); NMR ($CDCl_3$) τ: 5·47 and 5·33 (2H, a pair of AB type d, J = 15 c/s, $NCH_2C_6H_5$), 2·72 (5H, s, C_6H_5), −1·19 (1H, s, $CO_2\underline{H}$). (Found: C, 68·08; H, 6·87; N, 5·49. $C_{14}H_{17}O_3N$ requires: C, 67·99; H, 6·93; N, 5·66%).

Hydrolysis of piperidones X, XI, XII, XIII *and* XIV (Table 1). The procedure employed for X will be described in detail. Other piperidones were handled similarly.

Piperidone X[2] was dissolved in 6·04N HCl aq at 0·528M concentration and 10-ml aliquots of the soln were refluxed in an oil bath kept at 140°. At intervals the reaction was quenched by removing and cooling

* For the use of *p*-TsOH in the Willgerodt–Kindler reaction as a catalyst, see Ref 22

the flasks. The soln was evaporated *in vacuo* and H_2O (20 ml) was added to the residue. The mixture was extracted with four 10-ml portions of $CHCl_3$. The $CHCl_3$ soln was dried over Na_2SO_4 and evaporated *in vacuo* to dryness. The residual oil (the unchanged X) was weighed, and identified by IR spectrum. A blank experiment showed that the recovery of X was 99%. On the other hand, the aqueous layer separated from the $CHCl_3$ layer was evaporated *in vacuo* to leave colourless solid, which was recrystallized and identified with 5-benzylaminovaleric acid hydrochloride (type XV).[2] The salt had two modifications of crystals of m.p. 155–157°[2] and of m.p. 120–122° (lit.[9] m.p. 120°), which were interconvertible by recrystallization.

The reverse experiments with 5-benzylaminovaleric acid hydrochloride (type XV) and 6·04N HClaq were also run in the same way.

In the cases of XI and XII, the aqueous layer presumed to contain the hydrochloride of ω-amino acid (type XV) was stirred with an excess of *p*-TsCl under alkaline (NaOH) condition. When the *p*-TsCl was consumed, the soln was washed with Et_2O, acidified with 10% HClaq, and extracted with $CHCl_3$. The $CHCl_3$ soln was dried over Na_2SO_4, and evaporated *in vacuo* to leave a colourless solid, which was recrystallized from benzene–hexane (4:6): 5-(N-*benzyl*-p-*toluenesulfonamido*)-4-*ethylvaleric acid*, m.p. 102–103°. (Found: C, 64·46; H, 7·10; N, 3·86. $C_{21}H_{27}O_4NS$ requires: C, 64·76; H, 6·99; N, 3·60%); 5-(N-*benzyl*-p-*toluenesulfonamido*)-3-*ethylvaleric acid*, m.p. 102·5–103°. (Found: C, 64·80; H, 7·17; N, 3·45%).

In the hydrolysis of XIII, the product was characterized as 3-(2-*benzylaminoethyl*)*glutaric acid hydrochloride monohydrate*. It was recrystallized from 96% aqueous dioxane and dried over P_2O_5 at 50°/3 mm Hg, m.p. 100–101°; IR ν_{max}^{KBr} cm^{-1}: 3330 (H_2O), 3000–2200 (CO_2H, NH_2N), 1700 (b, CO_2H). (Found: C, 52·57; H, 6·92; N, 4·68 $C_{14}H_{20}O_4NCl{\cdot}H_2O$ requires: C, 52·58; H, 6·93, N, 4·38%).

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