973. *The Formation of Cyclic Lactams from Derivatives of Basic Amino-acids.*

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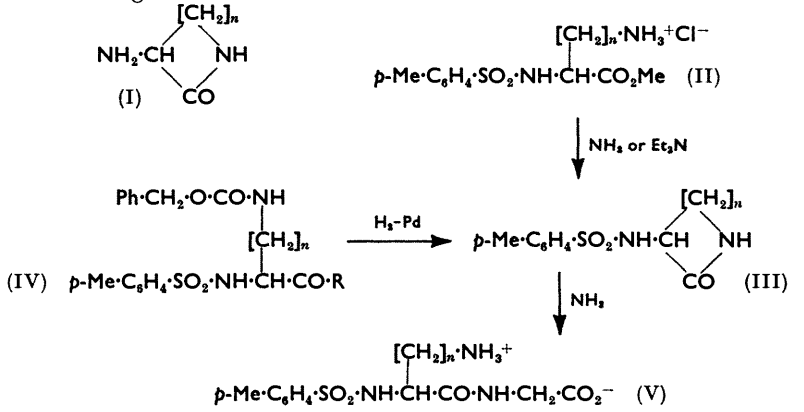
Cyclic 3-toluene-*p*-sulphonamidolactams (III; $n = 2$, 3, and 4) are formed by the action of ammonia or triethylamine on the methyl ester hydrochlorides of α-*N*-toluene-*p*-sulphonyldiamino-acids (II; $n = 2$, 3, and 4), and by hydrogenolysis of ω-*N*-benzyloxycarbonyl-α-*N*-toluene-*p*-sulphonyldiamino-acid amides (IV; R = NH_2, $n = 2$, 3, and 4). The peptide linkages of α-*N*-toluene-*p*-sulphonylornithylglycine (V; $n = 3$) and γ-amino-α-toluene-*p*-sulphonamidobutyrylglycine (V; $n = 2$) are partly cleaved by methanolic or ethanolic ammonia at room temperature. α-*N*-Toluene-*p*-sulphonyl-lysylglycine (V; $n = 4$) is stable under these conditions, but is partly degraded in liquid ammonia at 100°. The infrared spectra of the lactams (III) are briefly discussed.

Ester hydrochlorides of lysine [1] and αγ-diaminobutyric acid [1,2] in presence of sodium alkoxides at room temperature readily afforded the cyclic 3-amino-lactams (I; $n = 4$ and 2 respectively). In addition, Rudinger [3] found that Curtius degradation of *N*-toluene-*p*-sulphonyl-L-glutamic acid γ-hydrazide gave 3-toluene-*p*-sulphonamidopyrrolid-2-one (III; $n = 2$). It has now been observed that methyl ester hydrochlorides of α-*N*-toluene-*p*-sulphonyldiamino-acids (II; $n = 2$, 3, and 4) in methanolic ammonia produce the cyclic 3-toluene-*p*-sulphonamido-lactams (III; $n = 2$, 3, and 4). The yields (88, 82, and 49% respectively) indicate that the seven-membered ring is less readily formed than the other two. A good yield of 3-toluene-*p*-sulphonamidopiperid-2-one (III; $n = 3$) also resulted from treatment of the ester hydrochloride (II; $n = 3$) with triethylamine in methanol at room temperature. The foregoing lactams were also afforded by the hydrogenolysis of ω-*N*-benzyloxycarbonyl-α-*N*-toluene-*p*-sulphonyldiamino-amides (IV; R = NH_2, $n = 2$, 3, and 4) in methanol containing acetic acid. Both methods presumably involve nucleophilic attack by the uncharged ω-amino-group on the carbonyl-carbon atom. The second procedure gave theoretical yields of the pyrrolid-2-one (III; $n = 2$) and piperid-2-one (III; $n = 3$), whereas only 7% of the homopiperid-2-one (III; $n = 4$) was obtained, thereby emphasising even more markedly the relative difficulty of closing the seven-membered ring.



In view of the success of the foregoing reactions, the α-*N*-toluene-*p*-sulphonyl-peptides [4] (V; $n = 2$, 3, and 4) were kept in methanolic or ethanolic ammonia at room temperature

[1] Adamson, *J.*, 1943, 39.
[2] Wilkinson, *J.*, 1951, 104.
[3] Rudinger, *Coll. Czech. Chem. Comm.*, 1954, **19**, 365.
[4] Barrass and Elmore, *J.*, 1957, 3134.

for various lengths of time. Paper chromatography of the products revealed that the derivatives of αγ-diaminobutyric acid (V; $n = 2$) and ornithine (V; $n = 3$) were partly cleaved to glycine. In addition, the piperid-2-one (III; $n = 3$) was isolated from the products resulting from the degradation of the ornithine derivative (V; $n = 3$). α-*N*-Toluene-*p*-sulphonyl-lysylglycine (V; $n = 4$), however, was unchanged by this treatment and also by exposure to ethanolic ammonia at 60°. In liquid ammonia at 100°, on the other hand, some cleavage occurred, although chromatography revealed that an additional unknown ninhydrin-reacting substance was also formed. The greater stability of the lysine derivative than of the compounds of αγ-diaminobutyric acid and ornithine is consonant with the observations recorded above. It is interesting that Zaoral and Rudinger [5] have successfully reduced α-*N*-toluene-*p*-sulphonyl-L-ornithylglycine (V; $n = 3$) with sodium in liquid ammonia; presumably the desired reaction is much faster than the competing cyclisation and degradation at the b. p. of liquid ammonia.

In order to ascertain whether other basic peptides could be similarly degraded, tyrocidine was treated with ammonia under various conditions. In each case, the products were brought into reaction with 1-fluoro-2 : 4-dinitrobenzene,[6] then hydrolysed by acid, and the resulting 2 : 4-dinitrophenylamino-acids were identified by paper chromatography.[7] By this method, tyrocidine was found to be unaffected by ethanolic ammonia at room temperature or at 60°, or by liquid ammonia at 100°. This disappointing result would not seem to depend entirely on the electrophilic character of the carbonyl-carbon atom of the peptide linkage, since the $-I$ effect of the toluene-*p*-sulphonamido-group is apparently not much greater than that of an acylamino-group. Thus, the pK_a of *N*-acetylglycine [8] is 3·60, while that of *N*-toluene-*p*-sulphonylglycine [9] is 3·46. It is possible that the side-chain of the amino-acid linked to the carboxyl group of the basic amino-acid sterically hinders ring-closure. This is very likely in the case of tyrocidine [10] where the relevant amino-acid sequence is -orn.leu-.

The infrared spectra of the three cyclic lactams are of some interest. The νC=O band of 3-toluene-*p*-sulphonamido-L-pyrrolid-2-one is at 1698 cm.$^{-1}$, but for the two other compounds at 1658 cm.$^{-1}$, in general agreement with the spectra of unsubstituted cyclic lactams [11] and numerous cyclic ketones.[12] Further, there is no band which can be assigned to the amide-II vibration; this seems to be a characteristic property of cyclic lactams.[11,13] The weak band near 1600 cm.$^{-1}$ is attributed to skeletal vibrations of the aromatic ring. Finally, the two strong bands at 1168 and 1334—1339 cm.$^{-1}$ are doubtless due to the sulphonamide group, as reported earlier by several workers.[14]

Experimental

Optical rotations are quoted with 99% confidence limits. Infrared spectra were measured in pressed discs of potassium bromide with a Grubb-Parsons double-beam spectrometer and a rock-salt prism.

α-N-*Toluene*-p-*sulphonyl*-L-*lysine*.—This was obtained from ε-*N*-benzyloxycarbonyl-α-*N*-toluene-*p*-sulphonyl-L-lysine [4] by hydrogenolysis (90%) or by the action of hydrogen bromide

[5] Zaoral and Rudinger, *Proc. Chem. Soc.*, 1957, 176.
[6] Sanger, *Biochem. J.*, 1945, **39**, 507.
[7] Blackburn and Lowther, *ibid.*, 1951, **48**, 126.
[8] Zief and Edsall, *J. Amer. Chem. Soc.*, 1937, **59**, 2245.
[9] Lovén, *Z. phys. Chem.*, 1896, **19**, 456.
[10] Paladini and Craig, *J. Amer. Chem. Soc.*, 1954, **76**, 688; King and Craig, *ibid.*, 1955, **77**, 6627.
[11] Mecke and Mecke, *Chem. Ber.*, 1956, **89**, 343.
[12] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen & Co. Ltd., London, 1954, pp. 127—128.
[13] Lenormant, *Bull. Soc. chim. France*, 1948, **15**, 33; Randall, Fowler, Fuson, and Dangl, " Infra-red Determination of Organic Structures," Van Nostrand, New York, 1949, p. 11; " The Chemistry of Penicillin," Princeton Univ. Press, Princeton, 1949, p. 390.
[14] Adams and Tjepkema, *J. Amer. Chem. Soc.*, 1948, **70**, 4204; Schreiber, *Analyt. Chem.*, 1949, **21**, 1168; Barnes, Gore, Liddel, and Williams, " Infra-red Spectroscopy," Reinhold Publ. Corp., New York, 1944, p. 87.

in acetic acid (46%). After recrystallisation from water, it had m. p. 263—264° (decomp.) [Kucherov and Ivanov [15] record m. p. 244° (decomp.)] (Found: C, 51·9; H, 6·7; N, 9·5. Calc. for $C_{13}H_{20}O_4N_2S$: C, 52·0; H, 6·7; N, 9·3%). The *hydrochloride* had m. p. 187—188° after recrystallisation from ethanol–ether (Found: C, 46·4; H, 6·2; N, 7·9; Cl, 10·4. $C_{13}H_{20}O_4N_2S$,HCl requires C, 46·4; H, 6·3; N, 8·3; Cl, 10·5%).

α-N-*Toluene*-p-*sulphonyl*-L-*ornithine* (97%), prepared as described for the racemate,[4] had m. p. 212—213° (decomp.) after recrystallisation from water (Found: C, 48·6; H, 6·7; N, 9·2; S, 10·9. $C_{12}H_{18}O_4N_4S,\frac{1}{2}H_2O$ requires C, 48·8; H, 6·5; N, 9·5; S, 10·9%).

γ-Amino-L-α-*toluene*-p-*sulphonamidobutyric Acid.*—Hydrogenolysis of γ-benzyloxycarboxyamido-L-α-toluene-*p*-sulphonamidobutyric acid [3,4] in methanol containing a few drops of acetic acid afforded this *compound* (97%), m. p. 257—259° (decomp.) after recrystallisation from water (Found: C, 48·4; H, 5·8; N, 9·8. $C_{11}H_{16}O_4N_2S$ requires C, 48·5; H, 5·9; N, 10·3%).

α-N-*Toluene*-p-*sulphonyl*-L-*lysine methyl ester hydrochloride* (II; $n = 4$) was prepared (65%) from α-*N*-toluene-*p*-sulphonyl-L-lysine by the Fischer–Speier method. Recrystallised from ethanol–ether, it had m. p. 146—147° (Found: C, 47·7; H, 6·3; N, 8·3; S, 8·7; Cl, 9·6. $C_{14}H_{22}O_4N_2S$,HCl requires C, 47·9; H, 6·6; N, 8·0; S, 9·1; Cl, 10·1%).

α-N-*Toluene*-p-*sulphonyl*-L-*ornithine methyl ester hydrochloride* (II; $n = 3$), prepared by the same method (84% yield), had m. p. 152—153° after recrystallisation from ethanol–ether (Found: C, 45·9; H, 6·7; N, 8·2; S, 9·2. $C_{13}H_{20}O_4N_2S$,HCl requires C, 46·4; H, 6·2; N, 8·3; S, 9·5%). The DL-*compound* had m. p. 184·5—185·5° (Found: C, 46·5; H, 6·2; N, 8·4; S, 9·4%).

Methyl γ-Amino-L-α-*toluene*-p-*sulphonamidobutyrate Hydrochloride* (II; $n = 2$).—Obtained in almost theoretical yield by the same method, this *compound* had m. p. 199·5—200·5° after recrystallisation from methanol–ether (Found: C, 44·3; H, 6·1; N, 8·8; S, 9·4. $C_{12}H_{18}O_4N_2S$,HCl requires C, 44·6; H, 5·9; N, 8·7; S, 9·9%).

ε-N-*Benzyloxycarbonyl*-α-N-*toluene*-p-*sulphonyl*-L-*lysine Methyl Ester* (IV; R = OMe, $n = 4$).—ε-*N*-Benzyloxycarbonyl-α-*N*-toluene-*p*-sulphonyl-L-lysine (1 g.) was dissolved in methanol (10 c.c.) and benzene (10 c.c.) containing toluene-*p*-sulphonic acid (0·1 g.). The solution was slowly distilled during 6 hr., more methanol–benzene being added as required. Solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The solution was washed successively with 10% aqueous sodium hydrogen carbonate and water, dried, and evaporated under reduced pressure. The *ester* (0·92 g., 90%), crystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 80—81° (Found: C, 59·0; H, 6·3; N, 5·6. $C_{22}H_{28}O_6N_2S$ requires C, 58·9; H, 6·2; N, 6·2%).

δ-N-*Benzyloxycarbonyl*-α-N-*toluene*-p-*sulphonyl*-L-*ornithine methyl ester* (IV; R = OMe, $n = 3$) was prepared by the same method (90%). It crystallised from ether–light petroleum (b. p. 40—60°), and had m. p. 97—98° (Found: C, 57·7; H, 5·9; N, 6·4. $C_{21}H_{26}O_6N_2S$ requires C, 58·0; H, 6·0; N, 6·4%). The DL-*compound* had m. p. 93·5—94·5° [from benzene–light petroleum (b. p. 40—60°)] (Found: C, 58·3; H, 6·3; N, 6·1%).

Methyl γ-Benzyloxycarboxyamido-L-α-*toluene*-p-*sulphonamidobutyrate* (IV; R = OMe, $n = 2$).—Prepared by the same method (91%), this *ester* crystallised from benzene–ether–light petroleum (b. p. 40—60°) and had m. p. 103·5—104·0° (Found: C, 57·0; H, 5·9; N, 7·0. $C_{20}H_{24}O_6N_2S$ requires C, 57·1; H, 5·8; N, 6·7%).

ε-N-*Benzyloxycarbonyl*-α-N-*toluene*-p-*sulphonyl*-L-*lysine amide* (IV; R = NH_2, $n = 4$) was afforded (79%) by treatment of the methyl ester (IV; R = OMe, $n = 4$) with ethanolic ammonia at room temperature for 2 days. Crystallised from ethanol or dioxan–light petroleum (b. p. 60—80°), it had m. p. 157—158° (Found: C, 57·8; H, 6·3; N, 10·3; S, 6·9. $C_{21}H_{27}O_5N_3S$ requires C, 58·2; H, 6·2; N, 9·7; S, 7·4%).

δ-N-*Benzyloxycarbonyl*-α-N-*toluene*-p-*sulphonyl*-L-*ornithine amide* (IV; R = NH_2, $n = 3$), obtained in theoretical yield and crystallised from propan-1-ol, had m. p. 135—136° (Found: C, 56·8; H, 6·0; N, 10·1. $C_{20}H_{25}O_5N_3S$ requires C, 57·3; H, 6·0; N, 10·0%). The DL-*compound* had m. p. 143—144° [from acetone–light petroleum (b. p. 60—80°)] (Found: C, 56·9; H, 5·9; N, 10·4%).

γ-Benzyloxycarboxyamido-α-*toluene*-p-*sulphonamido*-L-*butyramide* (IV; R = NH_2, $n = 2$).—Prepared in the same manner, this *compound* (92%) had m. p. 165—166° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 55·8; H, 5·6; N, 10·6. $C_{19}H_{23}O_5N_3S$ requires C, 56·3; H, 5·7; N, 10·4%).

[15] Kucherov and Ivanov, *J. Gen. Chem.* (*U.S.S.R.*), 1951, **21**, 1243.

3-*Toluene*-p-*sulphonamido*-L-*homopiperid*-2-*one* (III; $n = 4$).—(*a*) α-*N*-Toluene-*p*-sulphonyl-L-lysine methyl ester hydrochloride (2·5 g.) in methanol (5 c.c.) and chloroform (20 c.c.) was treated with a saturated solution of ammonia in chloroform (250 c.c.). The resulting suspension was shaken for 5 min., then filtered, and the filtrate was evaporated to small bulk under reduced pressure. The residue was left in saturated methanolic ammonia (100 c.c.) at room temperature for 2 days. After concentration under reduced pressure, the *product* recrystallised from methanol, then having m. p. 210—212°, $[\alpha]_D^{23}$ +111·5° ± 0·5° (*c* 1·15 in dimethylformamide) (Found: C, 54·9; H, 6·4; N, 10·2; S, 11·5. $C_{13}H_{18}O_3N_2S$ requires C, 55·3; H, 6·4; N, 9·9; S, 11·4%). The infrared spectrum had bands at 3370 m, 3210 m, 3030 w, 2905 m, 2845 m, 1658 s, 1599 m, 1496 m, 1443 s, 1414 m, 1376 m, 1336 s, 1294 m, 1279 m, 1251 w, 1225 w, 1168 s, 1116 w, 1086 s, 1068 s, 1034 w, 1025 w, 982 w, 953 w, 927 s, 888 m, 850 w, 829 m, 821 s, 805 m, 775 m cm.$^{-1}$.

(*b*) ε-*N*-Benzyloxycarbonyl-α-*N*-toluene-*p*-sulphonyl-L-lysine amide (2·87 g.) was hydrogenolysed over palladous oxide (0·3 g.) in methanol (50 c.c.) and acetic acid (1 c.c.). After filtration and evaporation under reduced pressure, the residual lactam (0·13 g., 7%) was recrystallised first from ethanol–ether and then methanol; it had m. p. 210—212°, undepressed by admixture with the above sample. The infrared spectra were identical.

3-*Toluene*-p-*sulphonamido*-L-*piperid*-2-*one* (III; $n = 3$).—(*a*) and (*b*). This *lactam* was prepared from both α-*N*-toluene-*p*-sulphonyl-L-ornithine methyl ester hydrochloride (82%) and δ-*N*-benzyloxycarbonyl-α-*N*-toluene-*p*-sulphonyl-L-ornithine amide (~100%) by the methods given for the homopiperid-2-one analogue. Recrystallised from methanol, it had m. p. 184—185°, $[\alpha]_D^{24}$ +60·5° ± 0·3° (*c* 1·8 in dimethylformamide) (Found: C, 53·4; H, 5·8; N, 10·4; S, 11·9. $C_{12}H_{16}O_3N_2S$ requires C, 53·7; H, 6·0; N, 10·4; S, 11·9%). The infrared spectra of the two samples were identical and had bands at 3190 m, 3100 m, 2905 m, 2850 m, 1658 s, 1599 w, 1505 w, 1459 m, 1432 m, 1334 s, 1320 m, 1289 w, 1268 w, 1214 w, 1168 s, 1135 m, 1099 s, 1025 w, 989 w, 951 m, 937 sh, 902 w, 871 w, 855 w, 818 m, 812 m, 798 m, 709 w cm.$^{-1}$.

(*c*) α-*N*-Toluene-*p*-sulphonyl-L-ornithine methyl ester hydrochloride (0·337 g.) and triethylamine (0·101 g.) in methanol (5 c.c.) gave the same lactam (0·200 g., 75%) during 4 days at room temperature. Recrystallised from methanol, it had m. p. and mixed m. p. 184—185°.

The DL-*compound* (80%) was prepared by method (*a*). Recrystallised from methanol–light petroleum (b. p. 40—60°), it had m. p. 183·5—184·0° (Found: C, 53·4; H, 6·1; N, 10·0%).

3-Toluene-*p*-sulphonamido-L-pyrrolid-2-one (III; $n = 2$) was prepared by methods (*a*) (88% yield) and (*b*) (~100% yield). Recrystallised from methanol, it had m. p. 206—207° (in agreement with Rudinger [3]), $[\alpha]_D^{23}$ +14·6° ± 0·3° (*c* 1·27 in dimethylformamide) (Found: C, 51·6; H, 5·5; N, 10·6; S, 12·3. Calc. for $C_{11}H_{14}O_3N_2S$: C, 51·9; H, 5·6; N, 11·0; S, 12·6%). The infrared spectra of the two samples were identical and had bands at 3230 m, 3100 m, 2890 m, 1698 s, 1610 w, 1482 sh, 1462 m, 1448 m, 1383 w, 1339 s, 1322 sh, 1308 m, 1290 m, 1255 w, 1209 w, 1196 w, 1168 s, 1148 s, 1100 m, 1065 w, 1025 w, 1006 w, 947 w, 916 m, 896 m, 858 w, 842 w, 818 m, 801 w cm.$^{-1}$.

Action of Ammonia on α-N-*Toluene*-p-*sulphonylpeptides*.—(*a*) α-*N*-Toluene-*p*-sulphonyl-DL-ornithylglycine [4] (V; $n = 3$) (170 mg.) in saturated methanolic ammonia (50 c.c.) was kept in a sealed tube at room temperature for a week. After evaporation under reduced pressure, paper chromatography of a sample in butan-1-ol–acetic acid–water (4 : 1 : 5) revealed glycine as well as some starting material. The residue was extracted with dilute hydrochloric acid and filtered. The insoluble fraction (45 mg.) was dried *in vacuo* over phosphoric oxide. Recrystallised from aqueous methanol and then from methanol–light petroleum (b. p. 40—60°), it had m. p. 182—183° alone and in admixture with 3-toluene-*p*-sulphonamido-DL-piperid-2-one described above. The infrared spectra were identical, but slightly different from that of the L-stereoisomer.

(*b*) γ-Amino-α-toluene-*p*-sulphonamido-L-butyrylglycine [4] (V; $n = 2$) in saturated methanolic ammonia (10 c.c.) was left in a stoppered tube at room temperature for 1 day. Paper chromatography revealed that some degradation to glycine had occurred.

(*c*) α-*N*-Toluene-*p*-sulphonyl-L-lysylglycine [4] (V; $n = 4$) (100 mg.) in liquid ammonia (4 c.c.) was heated at 100° for 20 hr. in an open tube enclosed in a small stainless steel bomb. After ammonia had been allowed to evaporate, the residue was dissolved in aqueous ethanol and examined by paper chromatography. Two ninhydrin-positive spots were identified as glycine (R_F 0·11) and α-*N*-toluene-*p*-sulphonyl-L-lysylglycine (R_F 0·36); a further spot (R_F 0·47) was not identified, but was distinguished from α-*N*-toluene-*p*-sulphonyl-L-lysine (R_F 0·51). No

degradation of α-*N*-toluene-*p*-sulphonyl-L-lysylglycine occurred in saturated methanolic ammonia at room temperature or at 60° during 24 hr.

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