132. *Experiments in the Glutamic Acid Series.*

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A proposed synthesis of *l*-α-amino-β-4-methylthiazolyl-5-propionic acid involved as a first step the action of dehydrating agents on *p*-toluenesulphonylglutamic acid. Such action was found to give not a normal anhydride but *5-keto*-1-p-*toluenesulphonyl-pyrrolidine-2-carboxylic acid*. Evidence is presented in favour of the latter structure. Two new characteristic reactions of α-*p*-toluenesulphonamido-ketones have been observed, of which one involves the reductive fission of a C–N link.

In our last communication (J., 1939, 443) we described a synthesis of α-amino-β-4-methylthiazolyl-5-propionic acid. For certain experiments with a biological bearing it was desir-

able to have in our hands the optically active form of this compound of configuration corresponding to that of the naturally occurring amino-acids. This could probably be accomplished by a direct resolution; it was thought, however, that a synthesis of the active amino-acid might be found using *l*-(+)glutamic acid as starting material. Such a synthesis would have the advantage of settling unequivocally which of the optical isomers of the thiazole amino-acid was the "natural" form.

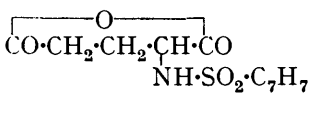
The proposed synthesis would start from an *N*-acylglutamic α-ester (I): this should be capable of conversion into a chloromethyl ketone (II), by the action of diazomethane on the acid chloride; on dehalogenation and subsequent bromination a compound (III) should be obtained, which, on condensation with thioformamide, would give the *N*-acyl ester of the required thiazole amino-acid.

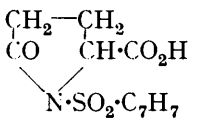
$RO_2C{\cdot}\underset{\displaystyle NHR'}{\underset{|}{C}}H{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$ (I.) $\quad RO_2C{\cdot}\underset{\displaystyle NHR'}{\underset{|}{C}}H{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2Cl$ (II.) $\quad RO_2C{\cdot}\underset{\displaystyle NHR'}{\underset{|}{C}}H{\cdot}CH_2{\cdot}CHBr{\cdot}CO{\cdot}CH_3$ (III.)

In the first attempt α-benzyl *N*-carbobenzyloxyglutamate (I; $R = CH_2{\cdot}C_6H_5$, $R' = CO{\cdot}O{\cdot}CH_2{\cdot}C_6H_5$) was used as the starting material: the chloromethyl ketone (II; $R = CH_2{\cdot}C_6H_5$, $R' = CO{\cdot}O{\cdot}CH_2{\cdot}C_6H_5$) was obtained successfully: but all attempts to replace the halogen by hydrogen led also to reductive fission of the carbobenzyloxy-residue.

Attention was now turned to derivatives of N-p-*toluenesulphonylglutamic acid*: it was hoped that these would behave like the carbobenzyloxy-derivatives, except that the *p*-toluenesulphonyl group would be more stable to reduction. Anomalous behaviour was, however, immediately encountered which has made it impossible to carry out the synthesis planned. The chemistry of the reactions involved has been studied in some detail and points have emerged which seem to be of sufficient interest to merit publication.

There are three ways in which *p*-toluenesulphonylglutamic acid might be expected to lose water, namely, to form an anhydride (IV), a pyrrolidone derivative (V), or a compound with a ring of an azlactone type (VI).


(IV.)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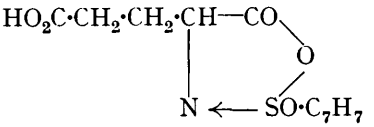
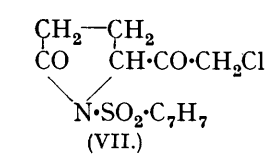

(VI.)

It was expected by analogy with *N*-carbobenzyloxyglutamic acid that the normal anhydride (IV) would be formed. When, however, *N*-*p*-toluenesulphonylglutamic acid, obtained readily by the usual method, was treated with acetyl chloride or acetic anhydride, the product proved to be an acetylated anhydride; and the compound obtained by removal of the acetyl group was not the anhydride (IV), since it possessed a free carboxyl group which could be titrated, and which would react with phosphorus pentachloride to give an acid chloride. It must therefore be either (V) or (VI): in either case the acetyl derivative first formed would be a mixed anhydride with acetic acid. Of the two structures (V and VI) the pyrrolidone (V) was considered the more probable in view of the readiness with which glutamic acid itself can be converted into 5-ketopyrrolidine-2-carboxylic acid. A further analogy is given by the conversion of δ-benzamidobutyric acid into 5-keto-1-benzoylpyrrolidine by the action of acetic anhydride (Kanevskaya, *Ber.*, 1936, **69**, 266). It was felt, however, that further evidence was necessary before structure (VI) could be rigidly excluded. The problem had an added interest in that, if structure (VI) should prove correct, the compound would serve admirably as a starting point for the synthesis of α-amino-β-4-methylthiazolyl-5-propionic acid on the lines indicated above. An attempt to settle the matter by the *p*-toluenesulphonation of 5-ketopyrrolidine-2-carboxylic acid to give compound (V) met with failure, and less direct methods had to be employed.

It was first decided to attempt the differentiation between the two structures by the following scheme. The acid chloride derived from the anhydro-acid (V or VI) should give a chloromethyl ketone on treatment with diazomethane: this should be easily reduced to

the corresponding methyl ketone, which, on opening of the anhydro-ring, would give either γ-toluenesulphonamido-δ-ketohexoic acid (from V) or α-toluenesulphonamido-δ-ketohexoic acid (from VI). If this compound could be reduced and the toluenesulphonyl residue removed, the product would be γ-aminohexoic acid or norleucine, two compounds which could easily be distinguished. The first part of this programme was successfully carried out, γ(or α)-*toluenesulphonamido-δ-ketohexoic acid* being obtained. The *bromo*-derivatives of both this compound and the methyl ketone from which it was obtained were also prepared with a view to condensation with thioformamide, should structure (VI) prove correct. Attempts to reduce the γ(or α)-toluenesulphonamido-δ-ketohexoic acid with zinc amalgam and hydrochloric acid resulted, however, in the formation in good yield of *p*-toluenesulphonamide. This result is all the more remarkable because the compound is stable to hydrolysis, either by alkali, or under acid conditions analogous to those of the reduction. It appears, therefore, that we have here a reductive fission of a C–N link. Another unexpected property of the γ(or α)-*p*-toluenesulphonamido-δ-ketohexoic acid is its power to reduce Fehling's solution. That the structure of the compound is in fact what we have assumed is shown by the excellent analyses obtained through the whole series, and by the fact that on oxidation with hypobromite it yielded *dl-p*-toluenesulphonylglutamic acid.


(VII.)

The racemisation was found to have occurred mainly during the reduction of the chloro-ketone (VII if structure V is assumed for the anhydro-acid) to the corresponding methyl ketone, the latter compound being obtained with a very low optical activity. Further investigation showed that the chloromethyl ketone (VII) reduced Fehling's solution, and gave *p*-toluenesulphonamide on reduction; neither reaction was given by *p*-toluenesulphonylglutamic acid, or by the anhydro-acid (V or VI). Two authentic α-*p*-toluenesulphonamido-ketones were now prepared; α'-*chloro*-α-p-*toluenesulphonamidoacetone*, by the action of diazomethane on *N-p*-toluenesulphonylglycyl chloride; and ω-p-*toluenesulphonamidoacetophenone*, by the interaction of ω-bromoacetophenone and the *potassium* salt of *p*-toluenesulphonamide. Both these compounds reduced Fehling's solution, and both gave *p*-toluenesulphonamide on Clemmensen reduction. It seems probable, therefore, that these two reactions are general properties of α-*p*-toluenesulphonamido-ketones, and are therefore not inconsistent with the structures derived from (V). It seems less likely that they should be given by the α-*p*-toluenesulphonamido-δ-ketohexoic acid derived from (VI), but this improbability cannot be regarded as proof of structure (V) in the absence of any method of reduction.

It was now decided to investigate the *amide* derived from the anhydro-acid (V or VI). If this compound were treated with alkaline hypobromite, the first product, formed by the opening of the anhydride ring by alkali, should be *N-p*-toluenesulphonylglutamic acid-α(or γ)-amide. The γ-amide (from VI) should give γ-amino-α-*p*-toluenesulphonamidohexoic acid without difficulty. The α-amide (from V) should give in the first instance an α-amino-α'-*p*-toluenesulphonamido-derivative; this compound would be expected to be unstable, decomposing to give *p*-toluenesulphonamide, ammonia and succinic half-aldehyde which might be further oxidised to succinic acid (cf. Kanevskaya, *loc. cit.*, who isolated benzamide when hippuramide was treated with hypobromite).

When in fact the amide was treated with hypobromite a far-reaching oxidation occurred, as was shown by the immediate formation of bromoform. If two equivalents of bromine were used, as calculated for the simple oxidation of amide to amine, the products isolated were *p*-toluenesulphonamide (35%) and *N-p*-toluenesulphonylglutamic acid-α(or γ)-amide (50%). If the bromine used was increased to 6 equivalents, the yield of *p*-toluenesulphonamide rose to 85%. No succinic acid or other product was isolated and it seems likely that the molecule has been oxidised to units of very small molecular weight. The results are strongly in favour of structure (V).

Conclusive evidence for structure (V) was now obtained as follows: the toluenesulphonyl residue was removed from the *N-p*-toluenesulphonylglutamic acid-α(or γ)-amide by reduction with sodium in liquid ammonia (du Vigneaud and Behrens, *J. Biol. Chem.*, 1937, **117**, 27). The crude product, on treatment with benzyl chloroformate, gave a good yield of *N*-carbobenzyloxy*iso*glutamine, which could only arise from structure (V).

A collateral argument for structure (V) is based on comparison with the behaviour of *N*-*p*-toluenesulphonylaspartic acid, which on treatment with acetyl chloride or acetic anhydride gives a normal anhydride of type (IV); this compound has no free carboxyl group, as is shown by its refusal to react with phosphorus pentachloride; and on treatment with sodium methoxide gives a monomethyl ester, behaviour exactly analogous to that of *N*-carbobenzyloxy-glutamic and -aspartic anhydrides. It is hard to explain this difference between the glutamic and aspartic series on any other assumption than that the anhydro-acid obtained in the glutamic series has the structure (V); for while the formation of a compound of type (VI) should be as easy for aspartic as for glutamic derivatives, the aspartic compound corresponding to (V) could not be expected to be formed, as it would have a four-membered ring.

We may conclude, therefore, that the product obtained by dehydration of *N*-*p*-toluene-sulphonylglutamic acid is in fact 5-*keto*-1-p-*toluenesulphonylpyrrolidine*-2-*carboxylic acid*.

Experimental.

Benzyl ε-Chloro-α-carbobenzyloxyamido-δ-ketohexoate.—α-Benzyl *N*-carbobenzyloxyglutamate (Bergmann and Zervas, *Ber.*, **1933**, **66**, 1288) (3·7 g.) was suspended in dry ether and treated with powdered phosphorus pentachloride (2·2 g.). After a few minutes the clear solution was decanted from residual phosphorus pentachloride. On addition of light petroleum the acid chloride was precipitated as an oil; it was washed with petroleum, dissolved in dry ether, and treated with an ethereal solution of diazomethane (from nitrosomethylurea, 5 g.). After 15 minutes the solution was ice-cooled while hydrogen chloride was passed in: the product separated in 20% yield and formed needles from alcohol, m. p. 125° (Found: N, 3·7; Cl, 8·9. $C_{21}H_{22}O_5NCl$ requires N, 3·5; Cl, 8·8%). The *compound* was readily decomposed by alkali, chlorine ions being liberated. In attempts to replace the chlorine by hydrogen the compound was shaken in alcoholic solution in an atmosphere of hydrogen with both palladised calcium carbonate and palladised barium sulphate. In both cases the amounts of hydrogen absorbed were extremely large, and the resulting solutions gave positive ninhydrin reactions.

Attempted p-*Toluenesulphonation of* 5-*Ketopyrrolidine*-2-*carboxylic Acid*.—The acid (McIlwain, *Biochem. J.*, **1939**, **33**, 1942) was treated with *p*-toluenesulphonyl chloride under the following conditions without any evidence of interaction being obtained: (a) in pyridine solution, both in the cold and with heating: (b) in an ether-aqueous sodium carbonate emulsion, with shaking for 24 hours at room temperature; (c) both in boiling benzene and in boiling xylene, with a current of nitrogen to remove any hydrogen chloride formed. With the latter solvent consider-able charring occurred, but no hydrogen chloride was formed.

N-p-*Toluenesulphonylglutamic Acid*.—This compound was prepared by the following method, which was found more convenient than those of Knoop and Oesterlin (*Z. physiol. Chem.*, **1927**, **170**, 186) and Bergell (*ibid.*, **1919**, **104**, 182). Glutamic acid (29·4 g.), *p*-toluenesulphonyl chloride (38 g.), and 2N-sodium hydroxide (300 c.c.) were warmed to about 70° and shaken till a clear solution was obtained: this was cooled, acidified, and extracted four times with ethyl acetate. The dried extract was concentrated in a vacuum to a low bulk: crystallisation set in on cooling and was completed by the addition of light petroleum. Yield, 80%. The acid formed prisms from ethyl acetate, m. p. 131°, $[\alpha]_D$ + 22° (*c* = 1 in ethyl acetate) (Found: C, 48·1; H, 5·0; N, 4·6; equiv., by titration, 151. Calc. for $C_{12}H_{15}O_6NS$: C, 47·8; H, 5·0; N, 4·65%; equiv., 150·5).

Mixed Anhydride of Acetic and 5-*Keto*-1-p-*toluenesulphonylpyrrolidine*-2-*carboxylic Acids*.—(a) *N*-*p*-Toluenesulphonylglutamic acid (5 g.) and acetic anhydride (14 c.c.) were refluxed for 10 minutes. The residue obtained after removal of the solvent in a vacuum was recrystallised from ethyl acetate, forming prisms, m. p. 148°, in 50% yield.

(b) The acid was suspended in freshly distilled acetyl chloride (100 c.c.) and refluxed till a clear solution was obtained (10—15 mins.). The acetyl chloride was removed in a vacuum, and the residue recrystallised from ethyl acetate. Yield, 60% of a product identical with that obtained above (Found: C, 52·0; H, 4·5; N, 4·35; S, 10·0; acetyl, 13·6. $C_{14}H_{15}O_6NS$ requires C, 51·7; H, 4·6; N, 4·3; S, 9·85; acetyl, 13·2%). The *compound* is unstable to long exposure to moist air.

5-*Keto*-1-p-*toluenesulphonylpyrrolidine*-2-*carboxylic Acid*.—The mixed anhydride (10 g.) in 70% aqueous dioxan (100 c.c.) was heated on the water-bath for 15 minutes. The solvent was then removed in a vacuum; acetic acid could be detected in the distillate by the lanthanum test. The residue was taken up in aqueous bicarbonate and extracted with ether; the aqueous layer

on acidification deposited an oil that slowly hardened to a crystalline hydrate of the desired product. This was collected, dried in a vacuum, and finally dissolved in benzene and freed from water by distillation. The product crystallised from the residual benzene, on cooling, in needles, m. p. 130°, $[\alpha]_D$ − 28° (*c* = 1·5 in ethyl acetate). Yield, 80% (Found: C, 51·55, 51·6; H, 4·6, 4·7; N, 4·8; S, 11·4; equiv., 284. $C_{12}H_{13}O_5NS$ requires C, 50·9; H, 4·6; N, 4·9; S, 11·3%; equiv., 283). In the preparation of this *compound* it is not necessary to isolate the mixed anhydride; the residue obtained after the removal of acetyl chloride can be treated direct with aqueous dioxan, and the product obtained as above. Yield (from *p*-toluenesulphonylglutamic acid), 75%. The compound is stable to aqueous sodium carbonate in the cold, but is readily hydrolysed by hot sodium carbonate, cold sodium hydroxide, or by boiling with concentrated hydrochloric acid. In one hydrolysis experiment the acid (265 mg.) and N-sodium hydroxide (2·0 c.c.) were heated on the water-bath for 5 minutes. The product (245 mg.), obtained by acidification and extraction into ethyl acetate, had, after recrystallisation, m. p. 131°; $[\alpha]_D$ + 24·5° (Found: N, 4·6%). A mixed m. p. determination showed it to be identical with *p*-toluenesulphonylglutamic acid.

5-Keto-1-*p*-toluenesulphonylpyrrolidine-2-carboxylic acid could be reconverted into the mixed acetic anhydride by refluxing with acetyl chloride (10 parts) for 15 minutes.

5-*Keto*-1-p-*toluenesulphonyl*-2-*chloroacetylpyrrolidine*.—5-Keto-1-*p*-toluenesulphonylpyrrolidine-2-carboxylic acid (5 g.) was suspended in dry ether (25 c.c.) and ice-cooled while powdered phosphorus pentachloride (4 g.) was added. After being shaken for a few minutes at room temperature, the clear solution was decanted from residual phosphorus pentachloride. On cooling, crystallisation of the acid chloride set in, and was completed by the addition of an equal volume of ligroin. The solid was collected with exclusion of atmospheric moisture, and washed through the filter with dry chloroform; the filtrate was treated with an ethereal solution of diazomethane (from nitrosomethylurea, 5 g.). After standing for 15 minutes at room temperature, the solution was ice-cooled while hydrogen chloride was passed in. The product separated in 60% yield and formed prisms from ethyl acetate, m. p. 141°, $[\alpha]_{5461}$ − 18·5° (*c* = 5 in dioxan) [Found: N, 4·5; S, 10·3; Cl, 11·25; *M* (Rast), 287. $C_{13}H_{14}O_4ClNS$ requires N, 4·4; S, 10·15; Cl, 11·3%; *M*, 315·5]. The *compound* reduced Fehling's solution strongly and was readily decomposed by alkali, chlorine ions being liberated.

5-*Keto*-1-p-*toluenesulphonyl*-2-*acetylpyrrolidine*.—The chloroacetyl derivative (5 g.), palladised calcium carbonate (5 g.), and pyridine (25 c.c.) were shaken in an atmosphere of hydrogen; after 2—2½ hours the absorption of the gas had ceased at a total uptake of 500—600 c.c. (*ca.* 1·5 mols.). The solution was filtered, and concentrated in a vacuum, and the crystalline residue recrystallised from chloroform–petroleum (yield, 85%); it formed needles from ethyl acetate–petroleum, m. p. 135·5°, $[\alpha]_{5461}$ − 4·5° (*c* = 2·5 in dioxan) (Found: N, 4·9; S, 11·7. $C_{13}H_{15}O_4NS$ requires N, 5·0; S, 11·4%). The *compound* reduced Fehling's solution. It could be brominated as follows: Bromine (1·1 equivs.) was added in small portions to the methyl ketone in chloroform. After starting with reluctance, the reaction proceeded vigorously. The solution was shaken with aqueous bisulphite, dried, and concentrated: the *bromo*-derivative was recrystallised from glacial acetic acid (65% yield), forming plates, m. p. 153·5°. The compound reduced Fehling's solution and was readily decomposed by alkali with liberation of bromine ions (Found: C, 43·3; H, 3·8; N, 3·85; Br, 22·2. $C_{13}H_{14}O_4NBrS$ requires C, 43·3; H, 3·9; N, 3·9; Br, 22·2%).

α-*Toluenesulphonamido*-δ-*ketohexoic Acid*.—To 5-keto-1-*p*-toluenesulphonyl-2-acetylpyrrolidine (6·7 g.) in dioxan (15 c.c.) was added N-sodium hydroxide (23·8 c.c.) and the solution was heated on the water-bath for 15 minutes. The solvent was removed in a vacuum, and the residue dissolved in water and extracted with chloroform. The product was obtained from the aqueous layer by acidification, extraction into chloroform, and removal of the solvent. Yield of recrystallised material, 60%; it formed plates from ethyl acetate, m. p. 138° (Found: N, 4·5; S, 10·6; equiv., 297. $C_{13}H_{17}O_5NS$ requires N, 4·7; S, 10·7%; equiv., 299). The *compound* reduced Fehling's solution: it was stable to acids and alkalis, being recovered unchanged both after treatment with 2N-potassium hydroxide for 2 hours and after refluxing with concentrated hydrochloric acid for 2 hours. The compound could be brominated in chloroform solution by the addition of bromine (1·1 equivs.) in small portions. The mixture had to be warmed to start the reaction, which then proceeded readily. The *bromo*-derivative was deposited as the reaction proceeded. Yield, 65%; it formed needles from ethyl acetate–benzene, m. p. 148·5° (decomp.). The compound reduced Fehling's solution, and readily liberated bromine ions on treatment with alkali (Found: N, 3·7; S, 8·4; Br, 20·9. $C_{13}H_{16}O_5NBrS$ requires N, 3·7; S, 8·45; Br, 21·2%).

Oxidation of α-Toluenesulphonamido-δ-ketohexoic Acid to dl-N-p-*Toluenesulphonylglutamic Acid.*—The keto-acid (0·5 g.) was added to a chilled mixture of 2N-sodium hydroxide (8·3 c.c.) and bromine (0·275 c.c.). The mixture was cooled for 10 minutes, kept at room temperature for 45 minutes, and finally warmed to 40—50° for an hour. The bromoform formed was removed by extraction with chloroform : the aqueous layer was then acidified, and the product extracted into ethyl acetate; removal of the solvent gave crude dl-p-*toluenesulphonylglutamic acid* in 75% yield. It formed prisms from ethyl acetate, m. p. 172·5°, which were optically inactive (Found : C, 48·3; H, 5·2; S, 10·6; N, 4·65; equiv. by titration, 148. $C_{12}H_{15}O_6NS$ requires C, 47·8; H, 5·0; S, 10·6; N, 4·65%; equiv., 150·5).

Synthesis of dl-p-*Toluenesulphonylglutamic Acid.*—*dl*-Glutamic acid monohydrate (0·495 g.), 2N-sodium hydroxide (4·5 c.c.), and *p*-toluenesulphonyl chloride (0·57 g.) were shaken and warmed till a clear solution was obtained. On acidification and cooling, the product separated in 50% yield. A further crop could be obtained from the mother-liquor. The acid formed prisms from ethyl acetate, m. p. 172°; a mixed m. p. determination showed identity with the compound obtained as above (Found : N, 4·5%; equiv. by titration, 150).

α′-Chloro-α p-*toluenesulphonamidoacetone.*—*p*-Toluenesulphonylglycyl chloride (Schönheimer, *Z. physiol. Chem.*, 1926, **154**, 203) in chloroform was treated with an excess of diazomethane in ethereal solution. The mixture was kept for 15 minutes in ice and 15 minutes at room temperature : it was then ice-cooled while hydrogen chloride was passed in. The solvent was removed in a vacuum, and the partly crystalline residue treated with a little ether, in which the required product was insoluble. It formed prisms from ethyl acetate, m. p. 142°. The *compound* reduced Fehling's solution; it was readily decomposed by alkali, chlorine ions being liberated (Found : N, 5·5; Cl, 13·8. $C_{10}H_{12}O_3NClS$ requires N, 5·35; Cl, 13·6%).

ω-p-*Toluenesulphonamidoacetophenone.*—The *potassium* salt of *p*-toluenesulphonamide was first prepared as follows. To the amide (2 g.) in hot alcohol (4 c.c.) was added potassium hydroxide (0·7 g. in 2·75 c.c. of 75% alcohol). On addition of acetone to the cool mixture the potassium salt separated in plates (yield, 75%) (Found : K, 18·9. $C_7H_8O_2NSK$ requires K, 18·7%). The product (1 g.), ω-bromoacetophenone (1 g.), and benzene (5 c.c.) were refluxed for 2 hours. The liquid was then twice extracted with dilute sulphuric acid, dried, and concentrated. The residual oil crystallised on cooling; it formed plates from aqueous alcohol, m. p. 116° (yield, 30%). The *compound* reduced Fehling's solution (Found : C, 62·6; H, 5·1; S, 11·2; N, 4·9. $C_{15}H_{15}O_3NS$ requires C, 62·3; H, 5·2; S, 11·1; N, 4·8%).

Reduction Experiments.—Zinc wool (12·5 g.) was amalgamated by keeping for 1 hour at room temperature under 5% aqueous mercuric chloride (250 c.c.). It was then collected and divided into two approximately equal parts; one was added to the substance under test (0·5 g.) and refluxed with concentrated hydrochloric acid (50 c.c.) for 1 hour. The rest of the zinc and more acid (25 c.c.) were then added, and the boiling continued for another hour. The solution was then concentrated in a vacuum, and the residual syrup dissolved in water and repeatedly extracted with ethyl acetate; the extracts, after being shaken twice with aqueous bicarbonate, were dried and concentrated. The *p*-toluenesulphonamide in all cases needed no further purification; it was identified by mixed m. p., and in the case of γ-*p*-toluenesulphonamido-δ-ketohexoic acid, by analysis (Found : N, 7·9. Calc. : N, 8·2%). The yields of *p*-toluenesulphonamide were as follows : γ-*p*-toluenesulphonamido-δ-ketohexoic acid, 77%; 1-*p*-toluenesulphonyl-2-chloroacetylpyrrolidine, 70%; α′-chloro-α-*p*-toluenesulphonamidoacetone, 78·5%; ω-*p*-toluenesulphonamidoacetophenone, 88·5%; *N*-*p*-toluenesulphonylglycine, 0; *N*-*p*-toluenesulphonylglutamic acid, 0; 1-*p*-toluenesulphonylpyrrolidine-2-carboxylic acid, 0.

5-*Keto*-1-p-*toluenesulphonylpyrrolidine*-2-*carboxyamide.*—Dry ammonia was led into a chloroform solution of the corresponding acid chloride, obtained as described in the preparation of the chloromethyl ketone. The precipitate was recrystallised from aqueous alcohol (50%). the *product* being well washed with water. Yield, 65%. It formed needles, m. p. 196° (Found : N, 9·8; S, 11·4. $C_{12}H_{14}O_4N_2S$ requires N, 9·9; S, 11·35%).

N-p-*Toluenesulphonyl*isoglutamine.—5-Keto-1-*p*-toluenesulphonylpyrrolidine-α-carboxyamide and N-sodium hydroxide (1 equiv.) were warmed on the water-bath for 5 minutes. On acidification and cooling, the required *product* separated in 90—95% yield; it formed needles from aqueous alcohol. The compound melted over a range from 158° to 170° possibly owing to cyclisation on heating; this m. p. remained unchanged through repeated recrystallisations (Found : N, 9·25; S, 10·8; equiv., 300. $C_{12}H_{16}O_5N_2S$ requires N, 9·3; S, 10·7%; equiv., 300).

Action of Hypobromite on 5-*Keto*-1-p-*toluenesulphonylpyrrolidine*-2-*carboxyamide.*—(a) The amide (1·14 g.) was added to a chilled mixture of bromine (0·655 g., 2 equivs.) and 2N-potassium hydroxide (10 c.c.). Oily droplets of bromoform separated in the first few minutes. The

mixture was warmed at 50° for 2 hours. After cooling and addition of N-hydrobromic acid (8·0 c.c.) *p*-toluenesulphonamide was precipitated in 35% yield, and identified by mixed m. p. On addition of a further 4·0 c.c. of acid, *p*-toluenesulphonyl*iso*glutamine separated in 50% yield (Found : N, 9·4%; equiv., 297). Properties and m. p. were identical with those of the compound prepared as above.

(b) The amide (2·75 g.), bromine (6 equivs.), and 2N-potassium hydroxide (44·5 c.c.) were allowed to react as above. On acidification *p*-toluenesulphonamide (1·125 g.) was deposited : on concentration of the mother-liquor a further crop was obtained, bringing the total yield to 80%. The aqueous mother-liquor was subjected to continuous ether extraction for 6 hours. The extract contained a little tarry material from which no crystalline substance could be isolated. Finally the material was warmed with acetyl chloride for 15 minutes, and then heated strongly : no sublimate of succinic anhydride was observed.

Conversion of N-p-*Toluenesulphonyl*iso*glutamine into* N-*Carbobenzyloxy*iso*glutamine.*—To the amide (4·1 g.) in liquid ammonia (70 c.c.) cooled with acetone and solid carbon dioxide, sodium (*ca.* 1·5 g.) was added in small pieces till a permanent blue colour was obtained. The ammonia was then allowed to boil off, the last traces being removed from the residual solid by powdering and desiccation in a vacuum. The solid was dissolved in water, and the solution extracted with ethyl acetate and concentrated to low bulk in a vacuum : it was then acidified to p_H 5 and again extracted with ethyl acetate. Magnesium oxide (0·75 g.) was added to the aqueous layer, followed by benzyl chloroformate (2·3 g.) in ether (10 c.c.) in small portions with cooling and shaking. The mixture was shaken for 1·5 hours at room temperature, the magnesia filtered off, and the aqueous layer separated and extracted with ether : on acidification the product separated in 65% yield. After crystallisation from 50% aqueous methyl alcohol, it had m. p. 174·5°. A mixed m. p. determination showed its identity with *N*-carbobenzyloxy*iso*glutamine prepared from carbobenzyloxyglutamic anhydride (Bergmann and Zervas, *Ber.*, 1932, **65**, 1192) (Found : N, 10·1. Calc. for $C_{13}H_{16}O_5N_2$: N, 10·0%).

N-p-*Toluenesulphonylaspartic Anhydride.*—*p*-Toluenesulphonylaspartic acid (Freudenberg and Noë, *Ber.*, 1925, **58**, 2399) was refluxed with 10 parts of acetyl chloride till a clear solution was obtained (10—15 mins.) : the residue on removal of solvent crystallised readily. Yield, 80%. It formed prisms from ethyl acetate–petroleum, m. p. 148° (Found : C, 48·8; H, 4·1; S, 11·7; N, 5·3. $C_{11}H_{11}O_5NS$ requires C, 49·0; H, 4·1; S, 11·9; N, 5·2%). The *compound* did not react with phosphorus pentachloride on long standing under dry ether.

α(?)-*Methyl* N-p-*Toluenesulphonylaspartate.*—The anhydride was treated with sodium methoxide (1 equiv.) in methyl-alcoholic solution at room temperature for 1 hour. The solvent was removed in a vacuum, the residue dissolved in water, and the solution extracted with ethyl acetate. The product was obtained from the aqueous layer by acidification, extraction into ethyl acetate, and removal of the latter. It formed needles from ethyl acetate–petroleum, m. p. 96°. Yield, 50% + a further crop from the mother-liquor (Found : N, 4·7. $C_{12}H_{15}O_2NS$ requires N, 4·65%). The *compound* could be recrystallised from water, in which it gave a solution markedly acid to litmus. The nature of the compound was confirmed by its behaviour on titration with N/70-alkali. It would be expected to neutralise one equivalent instantaneously, and a second by slow hydrolysis of the ester group. A drifting end-point was in fact observed after 1 equiv. had been added; a further 1·5 equivs. were added, and the solution was heated on the water-bath for 5 minutes, and then back-titrated against hydrochloric acid (Found : equiv., 152. Calc., 150·5).

The α-configuration is provisionally assumed for this compound by analogy with the α-esters obtained by similar reactions from carbobenzyloxy-glutamic and -aspartic anhydrides.

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