809. *Pyrroles and Related Compounds. Part VII.*[1] *A Synthesis of Pyrroles from Esters of Toluene*-p-*sulphonylglycine*

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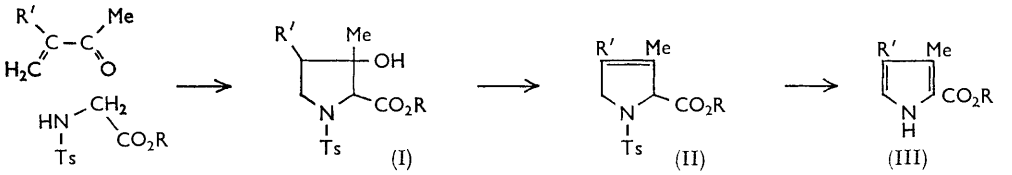
Esters of substituted pyrrole-2-carboxylic acids can be prepared from the esters of toluene-*p*-sulphonylglycine in three steps; (1) base-catalysed addition of an αβ-unsaturated ketone, (2) dehydration to a Δ^3-pyrroline (II), (3) introduction of a second double bond by elimination of toluene-*p*-sulphinic acid as an alkali-metal salt.

During our researches in porphyrin synthesis there appeared to be a need for esters of pyrrole-2-carboxylic acid bearing substituents at positions 3 and 4 but unsubstituted at position 5. Such compounds [*e.g.*, (III)] are not directly accessible by Knorrs' method, and instead they are usually prepared from the corresponding 5-methylpyrroles by trichlorination, hydrolysis, and decarboxylation.[2a] The last step, frequently so easy with pyrroles, is rendered difficult by the electron-withdrawing power of the 2-alkoxycarbonyl substituent. Consequently we sought an alternative, direct route and discovered the one described below.[3] Meanwhile our main synthetic work has taken different courses [4] in which pyrroles of type (III) are not intermediates, and therefore the time spent on this new synthesis of pyrroles has been limited. The method is probably general, but further development would be warranted if extensive use of it were foreseen.



Ts = toluene-*p*-sulphonyl

Toluene-*p*-sulphonylglycine was chosen as a starting material because the tosyl group would facilitate initial alkylation of the nitrogen and, at a later stage, it would dehydrogenate the ring while departing as toluene-*p*-sulphinate, as in the Bamford–Stevens reaction.[5] Methyl vinyl ketone, in excess, reacted slowly but smoothly with the ethyl ester of toluene-*p*-sulphonylglycine with the aid of potassium t-butoxide. The product (I; R = Et, R′ = H) was an oil, which for preparative purposes was used directly in the next stage of synthesis. However, it did crystallise and one of the stereoisomers could be purified. This carbinol (I) was cleanly dehydrated by phosphoryl chloride in cold pyridine to the crystalline Δ^3-pyrroline (II; R = Et, R′ = H), the structure of which was evident from the nuclear

[1] Part VI, A. Hayes, A. H. Jackson, J. M. Judge, and G. W. Kenner, preceding Paper.
[2] H. Fischer and H. Orth, "Die Chemie des Pyrrols," Akademische Verlag, Leipzig, 1934, Vol. I, (*a*) p. 241, (*b*) p. 238.
[3] A. H. Jackson, G. W. Kenner, and W. G. Terry, *Tetrahedron Letters*, 1962, 921.
[4] A. H. Jackson, G. W. Kenner, G. McGillivray, and G. S. Sach, *J. Amer. Chem. Soc.*, 1965, **87**, 676.
[5] W. R. Bamford and T. S. Stevens, *J.*, 1952, 4735.

magnetic resonance spectrum. Examination of molecular models shows that two steric factors operate against production of the conjugated Δ^2-pyrroline. The more important is proximity of the 1-tosyl and 2-ethoxycarbonyl substituents when they eclipse, but there is also less ring-strain in the Δ^3-structure. An analogous preference in the course of Dieckmann cyclisations to enolates of the pyrroline series has been reported recently.[6] The tosyl group was expelled in the final stage of synthesis and therefore this step was not sterically hindered. Cold sodium ethoxide rapidly eliminated sodium toluene-*p*-sulphinate, as in the unsubstituted dehydroproline case.[7] Presumably the proton is detached from position 2, activated by the ethoxycarbonyl group, and then tautomeric shift gives the pyrrole (III; R = Et. R′ = H); there is clear precedent of easy elimination from an α-toluene-*p*-sulphonamido-ketone.[8]

The t-butyl and benzyl esters (III; R = Bu^t or CH_2Ph, R′ = H) were prepared in the same way, using potassium t-butoxide in the final step. This was more satisfactory than benzyloxide in the latter instance, and the risk of ester interchange is not serious. The 3,4-dimethylpyrroles (III; R = Et or CH_2Ph, R′ = Me) were also prepared from isopropenyl methyl ketone without difficulty.

We have also investigated the use of αβ-unsaturated aldehydes in these reactions. Our attempts to prepare ethyl pyrrole-2-carboxylate from acrolein were frustrated at the first stage owing to polymerisation. However, crotonaldehyde condensed with toluene-*p*-sulphonylglycine ethyl ester satisfactorily, and the intermediate oily pyrrolidine was converted into an oily pyrroline and thence into ethyl 5-methylpyrrole-2-carboxylate; the overall yield was small.

The chief limitation to general, large-scale use of the synthesis is availability of more complex αβ-unsaturated ketones. An obvious alternative is the Mannich base or its quaternary salt,[9] and indeed the derivative of acetone yielded the carbinol (I; R = Et, R′ = H). In almost all our experiments there was a twofold excess of unsaturated ketone or Mannich base because smaller proportions gave less satisfactory results. However, a good yield of the pyrrolidine (I; R = Et, R′ = H) was obtained from only 1 mole of the Mannich base by extending the reaction time to 14 days. It should be remarked that increasing the concentration of potassium t-butoxide, in order to accelerate cyclisations, reduces the yield of pyrrolidine. In our earlier work [3] dehydration was achieved by phosphorus pentoxide in boiling benzene and elimination of toluene-*p*-sulphinate by sodium hydride, but these reagents were superseded by phosphoryl chloride in pyridine and sodium alkoxides, respectively.

Experimental

Toluene-p-*sulphonylglycine Benzyl Ester*.—Toluene-*p*-sulphonylglycine (229 g.) was heated in benzene (2·5 l.) and benzyl alcohol (170 g.) with toluene-*p*-sulphonic acid (10 g.) under a Dean–Stark head. After 3 hr. no more water was produced and the solvents were removed under reduced pressure. The semi-solid residue was recrystallised from benzene–light petroleum (b. p. 60—80°) to give the required benzyl ester (290 g., 95%) as plates, m. p. 82° (lit.,[10] 82—84°).

Toluene-p-*sulphonylglycine t-Butyl Ester*.—Concentrated sulphuric acid (8 ml.) was added to a solution of toluene-*p*-sulphonylglycine (38·0 g.) in dry tetrahydrofuran (130 ml.) and methylene chloride (90 ml.), and a slow stream of isobutene was passed through the mixture for 4·5 hr. The reaction mixture was then neutralised by washing with excess of dilute aqueous sodium carbonate. The alkaline washings were back-extracted with methylene chloride, and the combined organic layers were washed with water and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the residual oil was crystallised from ethyl acetate–light petroleum (b. p. 60—80°) and gave the required *t-butyl ester* (34·0 g., 71%), m. p. 102—103° (with softening at 94—96°) (Found: C, 54·8; H, 6·6; N, 4·8. $C_{13}H_{19}NO_4S$ requires C, 54·7; H, 6·7; N, 4·9%).

[6] J. Blake, C. D. Willson, and H. Rapoport, *J. Amer. Chem. Soc.*, 1964, **86**, 5293.
[7] A. V. Robertson, J. E. Francis, and B. Witkop, *J. Amer. Chem. Soc.*, 1962, **84**, 1709.
[8] W. Paterson and G. R. Proctor, *Proc. Chem. Soc.*, 1961, 248.
[9] E. C. du Feu, F. J. McQuillin, and R. Robinson, *J.*, 1937, 53.
[10] E. Taschner and C. Wasielewski, *Annalen*, 1961, **640**, 139.

Ethyl 3-*Hydroxy*-3-*methyl*-1-*toluene*-p-*sulphonylpyrrolidine*-2-*carboxylate*.—(*a*) From methyl vinyl ketone. Toluene-*p*-sulphonylglycine ethyl ester (85·7 g.) in t-butyl alcohol (80 ml.) and dry ether (1·2 l.) was added to a solution of potassium (0·93 g.) in t-butyl alcohol (500 ml.). Methyl vinyl ketone (70 g.) was then added dropwise and the mixture stirred for 3 days at room temperature. After removal of the solvent, the residual oil was taken up in ether and water. The ethereal layer was washed with dilute hydrochloric acid and water, and dried ($MgSO_4$). Evaporation of the ether gave the required pyrrolidine (88·0 g., 80%) as an oil, which slowly crystallised on standing for several weeks, but could be used directly for conversion into the corresponding pyrroline. In preliminary experiments the oily pyrrolidine (8·0 g.) was heated in boiling benzene (60 ml.) over phosphorus pentoxide (2 g.) for 30 min. After filtration and evaporation of the solvent the residual solid was recrystallised from benzene–light petroleum (b. p. 60—80°) and gave the *pyrrolidine* (5·9 g.) as chunky prisms, m. p. 106—108° (Found: C, 55·0; H, 6·4; N, 4·1. $C_{15}H_{21}NO_5S$ requires C, 55·0; H, 6·5; N, 4·3%).

(*b*) *Using a Mannich base.* Toluene-*p*-sulphonylglycine ethyl ester (2·0 g.) in dry tetrahydrofuran (10 ml.) and t-butyl alcohol (15 ml.) was mixed with a solution of potassium (0·015 g.) in t-butyl alcohol (12 ml.) and treated with 4-diethylaminobutan-2-one (3·3 g., 3 moles). The mixture was stirred for 2 days and then worked up as described in (*a*) above, giving the crude pyrrolidine (1·94 g., 87%) as prisms, m. p. 92—97° (from benzene). This material had an infrared spectrum identical with that of the product prepared as in (*a*), and gave an equally good yield of the Δ^3-pyrroline on dehydration. If only one mole of Mannich base was used in the condensation, the reaction required 14 days for completion.

Ethyl 3-*Methyl*-1-*toluene*-p-*sulphonyl*-Δ^3-*pyrroline*-2-*carboxylate*.—The foregoing oily pyrrolidine (1·45 g.) in dry pyridine (10 ml.) was treated with freshly distilled phosphoryl chloride (1·2 ml.) and kept at room temperature for 18 hr. The mixture was poured on to ice, and the resulting precipitate was collected and crystallised from aqueous ethanol to give the *pyrroline* (1·06 g., 78%) as needles, m. p. 123—125° (Found: C, 58·2; H, 6·2; N, 4·5. $C_{15}H_{19}NO_4S$ requires C, 58·2; H, 6·2; N, 4·5%), p.m.r. spectrum ($CDCl_3$): 2-$CO_2{\cdot}CH_2{\cdot}CH_3$, 5·82, 8·76; 2-*H*, 5·3; 3-CH_3, 8·34; 4-*H*, 4·59; 5-CH_2, 5·90; *N*-toluene-*p*-sulphonyl-CH_3, 7·62; aromatic *H*, AB quartet (J = 8 c./sec.) 2·68, 2·29 τ.

Ethyl 3-*Methylpyrrole*-2-*carboxylate*.—The foregoing pyrroline (6·23 g.) was dissolved in 1M-sodium ethoxide in ethanol (150 ml.) by stirring at room temperature. A crystalline precipitate (sodium toluene-*p*-sulphinate) began to form within 20 min., and stirring was continued for a further 2½ hr. The precipitate was filtered off, and the filtrate concentrated under reduced pressure at 35°. The residue was extracted several times with ether, and the extracts were washed with ice-cold water, dried ($MgSO_4$), and evaporated to dryness. The residue was recrystallised from light petroleum (b. p. 40—60°) to give ethyl 3-methylpyrrole-2-carboxylate (2·5 g., 81%) as needles, m. p. 56—58° (lit.,[11] 56°) (Found: C, 62·6; H, 7·3; N, 9·1. Calc. for $C_8H_{11}NO_2$: C, 62·7; H, 7·2; N, 9·1%).

Benzyl 3-*Methylpyrrole*-2-*carboxylate*.—Toluene-*p*-sulphonylglycine benzyl ester (80·0 g.) in t-butyl alcohol (80 ml.) and dry ether (1·2 l.) was added to a solution of potassium (0·7 g.) in t-butyl alcohol (350 ml.). The mixture was stirred while methyl vinyl ketone (50 g.) was added dropwise. After 3 days the product was worked up as in the case of the ethyl analogue, and benzyl 3-hydroxy-3-methyl-1-toluene-*p*-sulphonylpyrrolidine-2-carboxylate (110 g., 88%) isolated as an oil, which could not be crystallised but was characterised by the similarity of its i.r. spectrum to that of the analogous ethyl ester and by dehydration to the corresponding Δ^3-pyrroline. This pyrrolidine was also obtained in good yield by the use of the Mannich base 4-diethylaminobutan-2-one in place of methyl vinyl ketone.

The oily pyrrolidine (17 g.) in dry pyridine (100 ml.) was treated with phosphoryl chloride (12 ml.) and kept at room temperature for 18 hr. The mixture was poured on to ice and extracted with ether in the usual way. The benzyl 3-methyl-Δ^3-pyrroline-2-carboxylate (13·0 g., 80%) was isolated as an oil which could not be crystallised even after careful chromatography.

This pyrroline (10 g.) was dissolved in 1N-sodium benzyloxide (35 ml.) and the solution left at 20° for 20 hr. After removal of the benzyl alcohol by distillation at 100°/1·5 mm. the residue was extracted with chloroform, and the extracts were washed with water, dried ($MgSO_4$), and evaporated to dryness. The residual brown oil was chromatographed on alumina (Grade III) in light petroleum (b. p. 60—80°), and the appropriate eluates gave the desired *pyrrole benzyl ester* (1·2 g., 21%) as needles, m. p. 89—90° [from light petroleum (b. p. 40—60°)] (Found:

[11] H. Fischer and O. Wiedemann, *Z. physiol. Chem.*, 1926, **155**, 58.

C, 72·5; H, 6·2; N, 6·6. $C_{13}H_{13}NO_2$ requires C, 72·5; H, 6·1; N, 6·5%). Mr. J. Wass has since found that potassium t-butoxide in t-butyl alcohol (in place of sodium benzyloxide) gives better results, and he has obtained a 44% overall yield from toluene-*p*-sulphonylglycine benzyl ester.

t-Butyl 3-*Methylpyrrole*-2-*carboxylate*.—This compound was prepared from toluene-*p*-sulphonylglycine t-butyl ester (19·0 g.) and methyl vinyl ketone (15·0 g.) in the same manner as described above for the corresponding benzyl ester. The intermediate pyrrolidine and pyrroline were both oils, and the final stage was effected by 1N-sodium ethoxide in ethanol in 1 hr. The required *pyrrole* was obtained in 46% overall yield, and crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 99—100° (Found: C, 66·3; H, 8·5; N, 7·8. $C_{10}H_{15}NO_2$ requires C, 66·3; H, 8·3; N, 7·7%).

Ethyl 3-*Hydroxy*-3,4-*dimethyl*-1-*toluene*-p-*sulphonylpyrrolidine*-2-*carboxylate*.—Toluene-*p*-sulphonylglycine ethyl ester (42·8 g.) in dry ether (500 ml.) was added to a solution of potassium (0·55 g.) in t-butyl alcohol (300 ml.). Isopropenyl methyl ketone (34·0 g.) was added dropwise to the stirred solution. Stirring was continued for 8 days at room temperature, and the product was then obtained in the same manner as the 3-methyl analogue except that chloroform was used for the extraction instead of ether. The *dimethylpyrrolidine* (52 g., 90%) was obtained as an oil which crystallised slowly on standing for 2 days, and on recrystallisation from benzene–light petroleum (b. p. 60—80°) it formed prisms m. p. 125—128° (Found: C, 56·4; H, 6·8; N, 4·1. $C_{16}H_{23}NO_5S$ requires C, 56·3; H, 6·8; N, 4·1%). This product could also be prepared from the Mannich base, 3-methyl-4-dimethylaminobutan-2-one, instead of isopropenyl methyl ketone.

Ethyl 3,4-*Dimethyl*-1-*toluene*-p-*sulphonyl*-Δ^3-*pyrroline*-2-*carboxylate*.—The foregoing pyrrolidine (12·0 g.) was heated in boiling benzene (500 ml.) with phosphorus pentoxide (54 g.) for 1 hr. After filtration and evaporation of the solvent, the residual oil crystallised from ethyl acetate–light petroleum (b. p. 40—60°) and gave the Δ^3-*pyrroline* (5·7 g., 50%) as long needles, m. p. 112—113° (Found: C, 59·2; H, 6·5; N, 4·2. $C_{16}H_{21}NO_4S$ requires C, 59·4; H, 6·5; N, 4·3%), p.m.r. spectrum ($CDCl_3$): 2-$CO_2{\cdot}CH_2{\cdot}CH_3$, 5·81, 8·75; 2-*H*, 5·22; 3-CH_3 and 4-CH_3, 8·43; 5-CH_2, 5·99; *N*-toluene-*p*-sulphonyl-CH_3, 7·59; aromatic *H*, AB quartet (J = 8 c./sec.), 2·69 and 2·27 τ.

Ethyl 3,4-*Dimethylpyrrole*-2-*carboxylate*.—The Δ^3-pyrroline (0·8 g.) in 1N-sodium ethoxide (18 ml.) was kept at 20° for 2 hr. After work-up as in the previous examples, the *dimethylpyrrole* (0·34 g., 82%) crystallised from light petroleum (b. p. 40—60°) as small plates, m. p. 93—95° (Found: C, 64·7; H, 8·0; N, 8·6. $C_{19}H_{13}NO_2$ requires C, 64·7; H, 7·8; N, 8·4%).

Benzyl 3,4-*Dimethylpyrrole*-2-*carboxylate*.—Toluene-*p*-sulphonylglycine benzyl ester (40·0 g.) in dry tetrahydrofuran (100 ml.) and t-butyl alcohol (125 ml.) was added to a solution of potassium (0·5 g.) in t-butyl alcohol (250 ml.), and the mixture was treated with isopropenyl methyl ketone (33 g.) dropwise. The mixture was stirred for 6 days at 20°, filtered, and worked up as before to give benzyl 3,4-dimethyl-1-toluene-*p*-sulphonylpyrrolidine-2-carboxylate (35 g., 70%) as an oil.

The oily pyrrolidine (7·1 g.) in pyridine (15 ml.) was treated with phosphoryl chloride (5 ml.) and heated at 100° for 1·5 hr. The mixture was poured on to ice and extracted with ether, etc., in the usual way. The *benzyl* 3,4-*dimethyl*-Δ^3-*pyrroline*-2-*carboxylate* (4·7 g., 69%) crystallised from aqueous ethanol as plates, m. p. 100—101° (Found: C, 65·3; H, 6·0; N, 3·5. $C_{21}H_{23}NO_4S$ requires C, 65·4; H, 6·0; N, 3·6%), p.m.r. spectrum ($CDCl_3$): 2-$CO_2{\cdot}CH_2{\cdot}C_6H_5$, 4·71 and 2·64; 2-*H*, 5·10; 3-CH_3 and 4-CH_3, 8·44; 5-CH_2, 5·96; *N*-toluene-*p*-sulphonyl, -CH_3, 7·61, aromatic-*H*, AB quartet (J = 8 c./sec.), 2·69 and 2·27 τ.

The foregoing Δ^3-pyrroline (1·0 g.) was dissolved in 1N-potassium t-butoxide (10 ml.) and stirred at 20° for 1 hr. After removal of the solvent, the residue was extracted with ether. The extracts were washed with water, dried ($MgSO_4$), and evaporated to dryness. The residual *benzyl* 3,4-*dimethylpyrrole*-2-*carboxylate*. (0·45 g., 75%) crystallised from light petroleum as needles, m. p. 73—74° (Found: C, 73·3; H, 6·6; N, 6·3. $C_{14}H_{15}NO_2$ requires C, 73·3; H, 6·6; N, 6·1%).

Ethyl 5-*Methylpyrrole*-2-*carboxylate*.—This compound was prepared from toluene-*p*-sulphonylglycine ethyl ester and crotonaldehyde (by the same procedure as for the 3-methyl analogue) in 3% overall yield. The dehydration step gave only 36% of pyrroline, but the main loss occurred in the final elimination owing in part to the exceptional volatility and solubility of this pyrrole. No doubt the overall yield could be increased somewhat, but the synthesis is

certainly less efficient in this instance. The pyrrole crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 97—99° (lit.,[2b] m. p. 100°) (Found: C, 62·7; H, 7·3; N, 9·1. Calc. for $C_8H_{11}NO_2$: C, 62·7; H, 7·2; N, 9·1%).

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