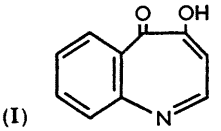
## 838. *Seven-membered Heterocyclic Systems. Part I. The Attempted Friedel–Crafts Cyclisation of γ-Arylsulphonamidobutyric Acids.*

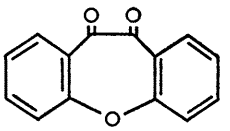
By JOHN T. BRAUNHOLTZ and FREDERICK G. MANN.

4 : 5 : 6 : 7-Tetrahydro-1-methyl-4-oxo-2 : 3-benzazepine (V; R = H, R′ = Me) has been prepared by a Dieckmann diester cyclisation. In this paper we describe attempts to establish an alternative synthesis of ketones of this type by Friedel–Crafts ring-closure of a variety of γ-arylsulphonamidobutyric acids; unexpected, and in certain cases rather complex, reactions occur with the formation of derivatives of *N*-phenylpyrrolid-2-one.

ALTHOUGH the synthesis and properties of non-benzenoid aromatic hydrocarbons and their derivatives have been widely studied in recent years, very few examples of analogous systems, such as the aza-azulenes,[1] in which one or more ·CH: groups are replaced by a heteroatom, have been reported. In particular, the azabenzotropolone (I) and its 7-ring isomers, are unknown, although two accounts of a synthesis of the related dibenzo-system containing oxygen (II) have recently appeared.[2,3]

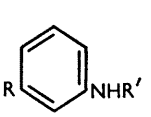



(I)

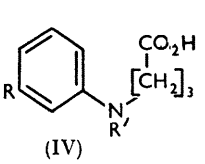



(II)

In an initial study of compounds of type (I), we have attempted to prepare substituted 4 : 5 : 6 : 7-tetrahydro-4-oxo-2 : 3-benzazepines (V) by the sequence of reactions described below (in which R′ = $SO_2Ph$ or $SO_2{\cdot}C_6H_4Me$, and R = H, Me, or OMe), as an alternative to the Dieckmann-type ring closure which Astill and Boekelheide[4] and we[5] have independently found to be effective in the preparation of the benzazepine (V; R = H, R′ = Me); the proposed conversion of the compound (V) into the azatropolone (I) would then be undertaken by a route analogous to that employed in the carbocyclic series by Cook *et al.*[6] The projected synthesis fails, however, at the cyclisation stage, the products of which are arylpyrrolid-2-ones, accompanied by arylsulphonyl chlorides or derivatives thereof.




(III)

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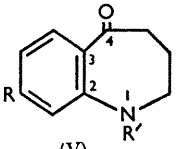



(V)

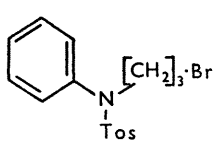
1-Bromo-3-cyanopropane[7] reacts readily, in aqueous ethanol containing one equivalent of sodium hydroxide, with the sulphonyl derivatives of aniline, *m*-toluidine and *m*-anisidine (III; R = H, Me or OMe, R′ = $SO_2Ph$ or $SO_2{\cdot}C_6H_4Me$) and of β-naphthylamine, but does not do so with the benzoyl derivative of *m*-anisidine (III; R = OMe, R′ = Bz).

The 3-(substituted amino)-1-cyanopropanes thus obtained undergo smooth alkaline hydrolysis, without loss of the sulphonyl groups, to the stable crystalline acids (IV; R = H, Me, or OMe, R′ = $SO_2Ph$ or $SO_2{\cdot}C_6H_4Me$) and their β-naphthyl analogues.

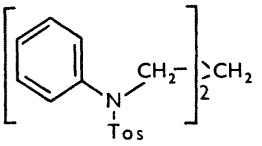
[1] Pauson, *Chem. Rev.*, 1955, **55**, 9.
[2] Mathys, Prelog, and Woodward, *Helv. Chim. Acta*, 1956, **39**, 1095.
[3] Rees, *Chem. and Ind.*, 1957, 76.
[4] Astill and Boekelheide, *J. Amer. Chem. Soc.*, 1955, **77**, 4079.
[5] Braunholtz and Mann, *Chem. and Ind.*, 1957, 266.
[6] Cook, Gibb, Raphael, and Somerville, *J.*, 1952, 603.
[7] Derick and Hess, *J. Amer. Chem. Soc.*, 1918, **40**, 537.

The corresponding 3-*m*-acetanisido-1-cyanopropane, prepared by a different route, is deacetylated under these conditions and yields the acid (IV; R = OMe, R′ = H).

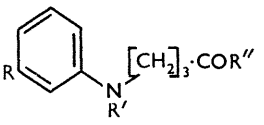
In an attempt to develop a better overall synthesis of the acids (IV), toluene-*p*-sulphonanilide (III; R = H, R′ = $SO_2$·$C_6H_4Me$) was treated in alkaline solution with trimethylene dibromide; the 1 : 3-disubstituted propanes (VI) and (VII; Tos = *p*-$SO_2$·$C_6H_4Me$) were obtained under a variety of conditions, but the yields of (VI) were too low to form the basis of an alternative route to the acids of type (IV). All attempts to prepare these acids by the reaction of amides (III; R = H, R′ = Bz, $SO_2Ph$, or $SO_2$·$C_6H_4Me$) with γ-bromobutyric acid or its ethyl ester in the presence of aqueous-alcoholic alkali failed.




(VI)




(VII)




(VIII)

In view of the unusual results obtained in the cyclisation experiments described below, the ready conversion of the acids (IV; R = H or OMe, R′ = $SO_2$·$C_6H_4Me$) into their acid chlorides has been demonstrated by identification of the latter as the *p*-toluidides (VIII; R = H or OMe, R′ = $SO_2$·$C_6H_4Me$, R″ = NH·$C_6H_4Me$), which were in each case obtained in high yield.

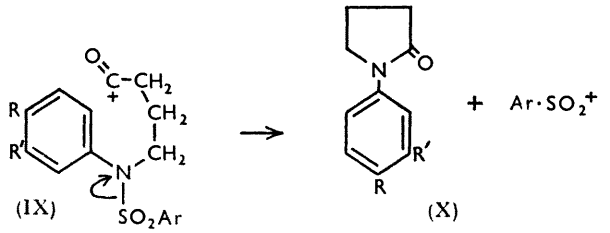
We have examined the Friedel–Crafts reactions of the chloride of the acid (IV; R = H, R′ = $SO_2$·$C_6H_4Me$) under a variety of conditions as an introduction to the detailed investigation of the products obtained in attempted cyclisations of γ-arylaminobutyric acids (IV) containing an activated aromatic nucleus. Our results, obtained with the above acid chloride, agree in several respects with those briefly described by Astill and Boekelheide,[4] who in attempting its cyclisation in benzene isolated phenyl *p*-tolyl sulphone and 1-phenylpyrrolid-2-one in approximately equal yields.

We find that γ-(toluene-*p*-sulphonanilido)butyryl chloride, when treated with aluminium chloride in benzene at room temperature, ultimately affords phenyl *p*-tolyl sulphone in *ca.* 50% yield. The remainder of the reaction product affords in very small yield the phenyl ketone (VIII; R = H, R′ = $SO_2$·$C_6H_4Me$, R″ = Ph) arising from the interaction of the chloride with the solvent. The ability of the chloride of the acid (IV; R = H, R′ = $SO_2$·$C_6H_4Me$) to form open-chain ketones is shown by its similar reaction with anisole, to give the ketone (VIII; R = H, R′ = $SO_2$·$C_6H_4Me$, R″ = $C_6H_4$·OMe) in *ca.* 15% yield. If a less reactive solvent (*e.g.*, carbon disulphide) or a less powerful catalyst (*e.g.*, stannic chloride) is used, toluene-*p*-sulphonyl chloride is isolated in rather low yield from the original reaction product.

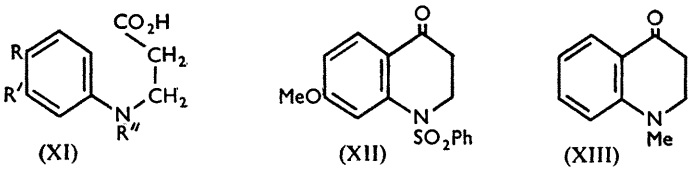
The ready cyclisation at room temperature of a wide variety of β-sulphonamidopropionic acids (XI) (see preceding paper) [8] shows that the sulphonamido-group is not inherently unstable under the above conditions, but that some other feature of the butyric acid (IV; R = H, R′ = $SO_2$·$C_6H_4Me$) is responsible for the unexpected course of the reaction. It is probable that a process represented as (IX ⟶ X), in which the carbonium ion attacks the nitrogen, with the expulsion of a sulphonyl ion, is favoured by the consequent formation of the stable pyrrolid-2-one ring rather than the desired seven-membered system. It is, however, noteworthy that phenyl *p*-tolyl sulphone has also been recorded by Johnson *et al.*[9] as a by-product from the cyclisation of the acid (XI; R = H, R′ = Cl, R″ = $SO_2$·$C_6H_4Me$) at room temperature; the other product isolated was the desired 7-chloro-1 : 2 : 3 : 4-tetrahydro-1-toluene-*p*-sulphonyl-4-oxoquinoline. It is unlikely in this case that a four-membered lactam analogous to (X) was formed. We

[8] Braunholtz and Mann, *J.*, 1957, preceding paper.
[9] Johnson, Woroch, and Buell, *J. Amer. Chem. Soc.*, 1949, **71**, 1901.

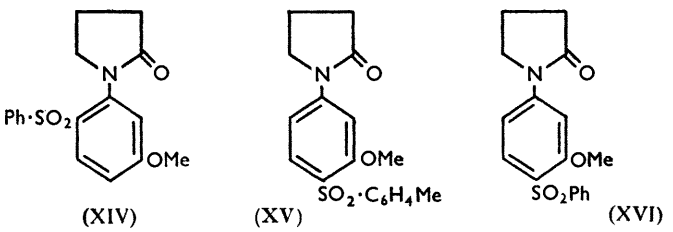
have now found that 1-benzenesulphonyl-1 : 2 : 3 : 4-tetrahydro-7-methoxy-4-oxoquinoline (XII) reacts with aluminium chloride in boiling benzene to give diphenyl sulphone in good yield, no other product being identified.




It was hoped that the desired cyclisation (IV ⟶ V) would be promoted, at the expense of pyrrolidone formation, by the use of substituted butyric acids containing activated aromatic nuclei. When, however, the acid (IV; R = Me, R′ = $SO_2Ph$), or the analogous compound derived from β-naphthylamine, was treated in benzene at room temperature with thionyl chloride followed by aluminium chloride, intractable tars were obtained.




The Friedel–Crafts treatment (in benzene at room temperature), when applied to the *m*-anisidine derivatives (IV; R = OMe, R′ = $SO_2Ph$ and $SO_2{\cdot}C_6H_4Me$), gave as the most readily isolated and purified products (yields *ca.* 12%) two closely similar crystalline compounds, [A], $C_{17}H_{17}O_4NS$, m. p. 200°, and [B], $C_{18}H_{19}O_4NS$, m. p. 222°, respectively. These substances have been isolated repeatedly and under the wide range of conditions summarised in Table 2 (p. 4181). In certain cases the use of benzene as solvent led to the isolation of diphenyl or phenyl *p*-tolyl sulphone; alumina chromatography of a benzene solution of the reaction product from a cyclisation in chlorobenzene, after separation of compound [A], gave 1-*m*-methoxyphenylpyrrolid-2-one (X; R = H, R′ = OMe) in *ca.* 30% yield.



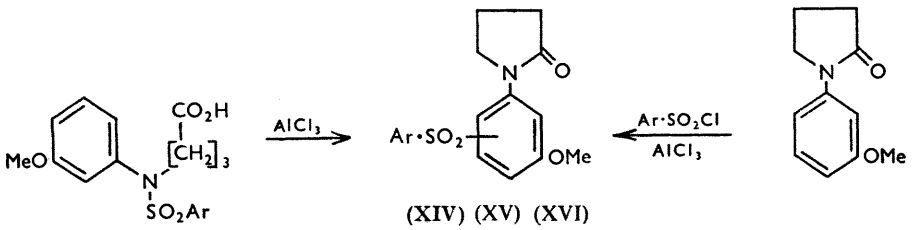

The following evidence shows that compounds [A] and [B] are 1-(2-benzenesulphonyl-5-methoxyphenyl)pyrrolid-2-one (XIV) and 1-(3-methoxy-4-toluene-*p*-sulphonylphenyl)-pyrrolid-2-one (XV) respectively; the migration of the arylsulphonyl group to the aromatic nucleus is a notable feature of these compounds, which are isomeric with the expected ketones.

(*a*) Synthetic experiments, suggested by the properties of (XIV) and (XV) summarised below (*b* and *c*), provide conclusive evidence for the structures assigned to these compounds.

When 1-*m*-methoxypyrrolid-2-one (X; R = H, R′ = OMe) is treated (in benzene at room temperature) with toluene-*p*-sulphonyl chloride in the presence of aluminium chloride, a moderate yield is obtained of a compound identical with (XV). When benzenesulphonyl

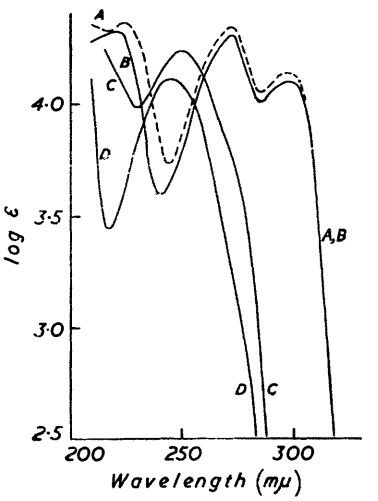
chloride is similarly used, a new compound, $C_{17}H_{17}O_4NS$, m. p. 223°, is obtained; this is isomeric with (XIV), which it closely resembles, and is assigned the structure (XVI) analogous to that of the toluene-*p*-sulphonyl compound. The two paths leading to substances (XIV), (XV), and (XVI) may therefore be summarised in the annexed scheme.

The positional assignment of the arylsulphonyl group in the compounds (XIV), (XV), and (XVI) involves a distinction between three possible isomers; one of these, in which this group is in the *ortho*-position to both methoxyl and nitrogen, is unlikely on steric grounds. The infrared spectra of the three compounds confirm, however, that the aromatic substitution is of the 1 : 2 : 4-type; this is characterised by strong absorption bands at 835 cm.$^{-1}$ (XIV), 840 cm.$^{-1}$ (XV), and 837 cm.$^{-1}$ (XVI), distinct in the case of (XV) from another strong band, at 814 cm.$^{-1}$, assigned to the $SO_2{\cdot}C_6H_4Me$ radical.




(XIV) (XV) (XVI)

There is a striking similarity (see Figure) between the ultraviolet spectra of 1-phenylpyrrolid-2-one and that of the Friedel–Crafts product derived from (IV; R = OMe, R′ = $SO_2Ph$); on the other hand, the sole product obtainable in the toluene-*p*-sulphonyl




*Ultraviolet absorption spectra of ethanolic solutions of:*
(*A*) 1-(3-*Methoxy*-4-*toluene*-p-*sulphonyl*)- (XV),
(*B*) 1-(4-*Benzenesulphonyl*-3-*methoxy*)- (XVI), *and*
(*C*) 1-(2-*Benzenesulphonyl*-5-*methoxy*)-*phenylpyrrolid*-2-*one* (XIV), *and*
(*D*) 1-*Phenylpyrrolid*-2-*one*.

series is related very closely spectroscopically (and presumably structurally) to that obtained from the reaction between 1-*m*-methoxyphenylpyrrolid-2-one and benzenesulphonyl chloride. This confirms the structures (XV) and (XVI) assigned to the latter pyrrolid-2-ones, the spectra of which are of the more complex type, with long wavelength absorption in the 300 mμ region; steric hindrance to coplanarity in the compound (XIV) is reflected in its ultraviolet spectrum, which is of a simple type and has no absorption maximum beyond 250 mμ.

The detailed course of the reactions whereby the acids (IV; R = OMe, R′ = $SO_2Ph$ and $SO_2{\cdot}C_6H_4Me$) give rise to the pyrrolidones (XIV) and (XV) respectively is not certain, nor is it known why these two compounds are of different types. It would, however, be expected that both the direct sulphonylation reactions of 1-*m*-methoxyphenylpyrrolid-2-one lead to substitution in the least hindered position of the aromatic nucleus.

Confirmatory evidence, obtained in the initial studies of (XIV) and (XV), may be summarised as follows:

(*b*) The two Friedel–Crafts products do not react with hydrazine or 2 : 4-dinitrophenylhydrazine, and the arylsulphonyl group is not removed by vigorous treatment with acid. We found however that the oxoquinolines, *e.g.*, (XII), of structure analogous to (V), behave normally in both respects; furthermore, 4 : 5 : 6 : 7-tetrahydro-1-methyl-4-oxo-2 : 3-benzazepine (V; R = H, R′ = Me), in which interaction between the amine and the carbonyl groups (with consequent reduction of ketonic properties) would be greater than in (V; R = OMe, R′ = $SO_2Ar$), has recently been shown also to possess ketonic properties.[5]

(*c*) Infrared evidence confirms the presence of the carbonyl group in the two products; the positions of the absorption maxima (1699 and 1703 cm.$^{-1}$) are compared in Table 1 with those of several related compounds, both cyclic amino-ketones (six- and seven-membered rings) and 1-substituted pyrrolid-2-ones. In the tetrahydro-4-oxoquinoline series (see preceding paper [8]) the 1-methyl compound (XIII) has approximately the same carbonyl absorption frequency as (XII); the conjugation of nitrogen with carbonyl which exists in the former amino-ketone is greatly reduced in the sulphonylated compound, but the nuclear methoxyl group in (XII) exerts a compensating influence on the carbonyl absorption frequency. It would, therefore, be predicted that the $\nu_{CO}$ values for the two new "cyclisation" products, if they had the amino-ketone structures (V; R = OMe, R′ = $SO_2Ph$ or $SO_2{\cdot}C_6H_4Me$), would be approximately equal to that observed for (V; R = H, R′ = Me), *i.e.*, 1665 cm.$^{-1}$. On the other hand, the observed frequencies are compatible with the allotted pyrrolid-2-one structures (XIV) and (XV).

TABLE 1. *Infrared absorption, in the region* 1650—1710 *cm.*$^{-1}$, *of cyclic amino-ketones and* 1-*arylpyrrolid*-2-*ones, determined with solid samples in Nujol mull* (*unless otherwise stated*).

| Amino-ketones | $\nu_{CO}$ (cm.$^{-1}$) | Pyrrolid-2-ones | $\nu_{CO}$ (cm.$^{-1}$) |
|---|---|---|---|
| (XII) | 1675 | (XIV) | 1699 |
| (XIII) | 1677 | (XV) | 1703 |
| (V; R = H, R′ = Me) * | 1665 | (XVI) | 1700 |
| | | (X; R = R′ = H) | 1672 |
| | | (X; R = Me, R′ = H) | 1683 |
| | | (X; R = H, R′ = OMe) | 1683 |

* Liquid film.

In view of the results discussed above, the attempted direct Friedel–Crafts cyclisations of the substituted γ-arylaminobutyric acids (IV) have been abandoned. Their success would clearly be dependent on the use of an acyl group R′ in (IV) which is not susceptible to displacement in the reaction of the acid chloride with aluminium chloride. The successful synthesis of ketones of type (V) by other routes will be described later.

## EXPERIMENTAL

*Preparation of* 1-*Bromo*-3-*cyanopropane*.—1-Bromo-3-cyanopropane was prepared by the method of Derick and Hess,[7] modified only in the use of commercial methanol without additional drying; the bromo-cyanide, b. p. 91—94°/14 mm., was obtained in 28% yield.

The benzenesulphonyl and toluene-*p*-sulphonyl derivatives of the appropriate arylamines were prepared by the usual Schotten–Baumann method. N-*Benzoyl*-m-*anisidine* was obtained as colourless crystals, m. p. 111° from ethanol (Found: N, 6·3. $C_{14}H_{13}O_2N$ requires N, 6·15%): Grammaticakis [10] gives m. p. 112° without analytical figures.

*Reaction of Toluene*-p-*sulphonanilide with* 1 : 3-*Dibromopropane*.—The sulphonanilide (5 g.) in ethanol (15 c.c.)–water (5 c.c.) containing sodium hydroxide (0·8 g.) was added to 1 : 3-dibromopropane (4 g.) in hot ethanol (10 c.c.). The mixture was heated under reflux for 3 hr., then diluted with water (50 c.c.). The precipitated heavy oil on fractional crystallisation from methanol ultimately gave the less soluble 1 : 3-*di*(*toluene*-p-*sulphonanilido*)*propane* (VII) (2·5 g., 46%), m. p. 135° (Found: C, 65·3; H, 5·8; N, 5·45. $C_{29}H_{30}O_4N_2S_2$ requires C, 65·3; H, 5·65; N, 5·3%) and the more soluble 1-*bromo*-3-(*toluene*-p-*sulphonanilido*)*propane* (VI) (1 g.,

[10] Grammaticakis, *Bull. Soc. chim. France*, 1951, 220.

14%), m. p. 66° after recrystallisation from aqueous methanol (Found: C, 52·5; H, 5·0; N, 3·85. $C_{16}H_{18}O_2NSBr$ requires C, 52·2; H, 4·95; N, 3·8%). The latter compound gave a strongly positive Beilstein test. Variation of the reaction conditions did not increase the yield of (VI).

*Preparation of γ-Arylaminobutyric Acids.*—(i) *γ-Benzenesulphonanilidobutyric acid* (IV; R = H, R′ = $SO_2Ph$). A solution of benzenesulphonanilide (4·6 g.) and 1-bromo-3-cyanopropane in ethanol (15 c.c.)–water (3 c.c.) containing sodium hydroxide (1 g.) was heated under reflux for 4½ hr. It was then concentrated and diluted with water (25 c.c.), depositing the crystalline 1-(*benzenesulphonanilido*)-3-*cyanopropane*, m. p. 81° from aqueous ethanol (5·5 g., 93%) (Found: C, 63·6; H, 5·35; N, 9·35. $C_{16}H_{16}O_2N_2S$ requires C, 63·9; H, 5·1; N, 9·5%).

The nitrile was readily hydrolysed when heated under reflux (4½ hr.) in ethanol (20 c.c.)–water (6 c.c.) containing potassium hydroxide (6 g.). When the mixture was acidified with concentrated hydrochloric acid, a heavy oil separated and soon solidified. Recrystallisation from aqueous ethanol gave the *acid* (IV; R = H, R′ = $SO_2Ph$), m. p. 104° (5 g., 86%) (Found: C, 60·7; H, 5·25; N, 4·55. $C_{16}H_{17}O_4NS$ requires C, 60·3; H, 5·35; N, 4·4%).

(ii) *Other (closely related) γ-butyronitriles and γ-butyric acids.* The following nitriles and acids were similarly prepared; 1-*cyano*-3-(*toluene*-p-*sulphonanilido*)*propane*, m. p. 102—104° from ethanol (Found: C, 64·5; H, 5·65; N, 8·9. $C_{17}H_{18}O_2N_2S$ requires C, 64·9; H, 5·75; N, 8·9%); 1-(*N*-benzenesulphonyl-*m*-toluidino)-3-cyanopropane, an oil; 1-*cyano*-3-(N-*toluene*-p-*sulphonyl*-m-*toluidino*)*propane*, m. p. 80° from aqueous ethanol (Found: C, 65·4; H, 5·9; N, 8·55. $C_{18}H_{20}O_2N_2S$ requires C, 65·7; H, 6·15; N, 8·55%): 1-(*N*-benzenesulphonyl-*m*-anisidino)-3-cyanopropane, an oil; 1-*cyano*-3-(N-*toluene*-p-*sulphonyl*-m-*anisidino*)*propane*, m. p. 93° from ethanol (Found: C, 62·8; H, 6·1; N, 8·4. $C_{18}H_{20}O_3N_2S$ requires C, 62·8; H, 6·0; N, 8·15%); 1-(*N*-benzenesulphonyl-β-naphthylamino)-3-cyanopropane and its *N*-toluene-*p*-sulphonyl-analogue, viscous syrups. *m*-Benzanisidide did not react with 1-bromo-3-cyanopropane under the conditions described above.

Hydrolysis of the nitriles by potassium hydroxide in aqueous ethanol under reflux gave the following *butyric acids*: γ-(Toluene-*p*-sulphonanilido)- (IV; R = H, R′ = $SO_2{\cdot}C_6H_4Me$), m. p. 164—165° from aqueous ethanol (lit.,[4] 165°) (Found: C, 61·3; H, 6·0; N, 4·5. Calc. for $C_{17}H_{19}O_4NS$: C, 61·3; H, 5·75; N, 4·2%): γ-(N-*benzenesulphonyl*-m-*toluidino*)- (IV; R = Me, R′ = $SO_2Ph$), m. p. 134° from aqueous ethanol (Found: C, 61·3; H, 5·4; N, 4·3. $C_{17}H_{19}O_4NS$ requires C, 61·3; H, 5·75; N, 4·2%); γ-(N-*toluene*-p-*sulphonyl*-m-*toluidino*)- (IV; R = Me, R′ = $SO_2{\cdot}C_6H_4Me$), m. p. 115° from aqueous ethanol (Found: C, 61·9; H, 5·9; N, 4·15. $C_{18}H_{21}O_4NS$ requires C, 62·2; H, 6·1; N, 4·05); γ-(N-*benzenesulphonyl*-m-*anisidino*)- (IV; R = OMe, R′ = $SO_2Ph$), m. p. 112° from benzene (Found: C, 58·6; H, 5·7; N, 4·0. $C_{17}H_{19}O_5NS$ requires C, 58·5; H, 5·5; N, 4·0%); γ-(N-*toluene*-p-*sulphonyl*-m-*anisidino*)- (IV; R = OMe, R′ = $SO_2{\cdot}C_6H_4Me$), m. p. 86—87° (from benzene–*cyclo*hexane) (Found: C, 59·9; H, 5·8; N, 3·9. $C_{18}H_{21}O_5NS$ requires C, 59·5; H, 5·8; N, 3·85%); γ-(N-*benzenesulphonyl*-β-*naphthylamino*)-, m. p. 175° from ethanol (Found: C, 64·8; H, 4·85; N, 4·0. $C_{20}H_{19}O_4NS$ requires C, 65·0; H, 5·2; N, 3·8); γ-(N-*toluene*-p-*sulphonyl*-β-*naphthylamino*)-, m. p. 142° from aqueous ethanol followed by benzene (Found: C, 65·5; H, 5·7; N, 3·95. $C_{21}H_{21}O_4NS$ requires C, 65·7; H, 5·5; N, 3·65%).

(iii) *Use of γ-bromobutyric ester.* A number of unsuccessful attempts were made (cf. Clemo and Perkin,[11] Elderfield *et al.*[12]) to bring about reaction between toluene-*p*-sulphonanilide or benzo-*m*-anisidide and ethyl γ-bromobutyrate in aqueous ethanol containing sodium hydroxide (either 2 mols. or a large excess). Unchanged amino-derivatives were recovered.

(iv) *Derivatives of acetyl*-m-*anisidine* (III; R = OMe, R′ = Ac). Acetyl-*m*-anisidine (16·5 g.) in xylene (75 c.c.) was heated at 130° with sodium wire (2·9 g.) for 1 hr.; hydrogen was evolved and a spongy white mass of the sodium derivative of acetyl-*m*-anisidine was formed. 1-Bromo-3-cyanopropane (20 g.) was added, and after a further 3 hours' heating the sodium bromide was filtered off and washed with ether, which was added to the xylene. Removal of the solvents left the impure 1-(acetyl-*m*-anisidino)-3-cyanopropane as a brown oil which partially decomposed on attempted distillation.

The nitrile could not be cyclised by the aluminium chloride–potassium chloride–sodium chloride melt method,[13] from which the starting material was not recovered.

[11] Clemo and Perkin, *J.*, 1924, **125**, 1608.
[12] Elderfield, Gensler, Bembry, Kremer, Brody, Hageman, and Head, *J. Amer. Chem. Soc.*, 1946, **68**, 1259.
[13] Allison, Braunholtz, and Mann, *J.*, 1954, 403.

Alkaline hydrolysis of the nitrile (3 g.) in boiling aqueous ethanol (10 c.c./20 c.c.) containing potassium hydroxide (5 g.) gave after 8 hr. crude γ-*m*-anisidinobutyric acid (IV; R = OMe, R′ = H) as a brown oil which was characterised by conversion into γ-(*N*-benzenesulphonyl-*m*-anisidino)butyric acid, m. p. 112°.

*Characterisation of Acid Chlorides.*—In view of anomalous results obtained in cyclisation reactions (below), simple derivatives of certain acid chlorides were prepared.

(i) γ-(*N*-Toluene-*p*-sulphonanilido)butyric acid (IV; R = H, R′ = $SO_2$·$C_6H_4Me$). The acid (0·5 g.) was converted by thionyl chloride in benzene into the syrupy acid chloride. *p*-Toluidine (0·35 g., 2 mols.) in dry benzene was added to the chloride (also in benzene), giving an immediate precipitate of the amine hydrochloride. The benzene layer when washed with water, dilute hydrochloric acid, and again with water, afforded the colourless γ-(N-*toluene*-p-*sulphonanilido*)*butyro*-p-*toluidide* (VIII; R = H, R′ = $SO_2$·$C_6H_4Me$, R″ = NH·$C_6H_4Me$) (0·55 g., 84%), m. p. 124° from benzene (Found: C, 68·5; H, 6·1; N, 6·85. $C_{24}H_{26}O_3N_2S$ requires C, 68·2; H, 6·2; N, 6·65%). Mixed m. p.s: with toluene-*p*-sulphonyl-*p*-toluidine, m. p. 95—110°; with phenyl *p*-tolyl sulphone, m. p. 95—120°.

(ii) γ-(*N*-Toluene-*p*-sulphonyl-*m*-anisidino)butyric acid (IV; R = OMe, R′ = $SO_2$·$C_6H_4Me$). The acid (0·5 g.) when treated as above gave *p*-toluidine hydrochloride (almost theoretical yield) and a syrup which eventually solidified and when recrystallised from benzene–*cyclo*hexane gave γ-(N-*toluene*-p-*sulphonyl*-m-*anisidino*)*butyro*-p-*toluidide* (VIII; R = OMe, R′ = $SO_2$·$C_6H_4Me$, R″ = NH·$C_6H_4Me$), m. p. 114—115° (Found: C, 66·3; H, 5·9; N, 6·5. $C_{25}H_{28}O_4N_2S$ requires C, 66·3; H, 6·2; N, 6·2%).

*Preparation of* 1-*Arylpyrrolid*-2-*ones.*—Authentic samples of three 1-arylpyrrolidones were prepared for comparative purposes: 1-Phenylpyrrolid-2-one (X; R = R′ = H) prepared by the action of polyphosphoric acid (100°, 1 hr.) on (IV; R = H, R′ = $SO_2$·$C_6H_4Me$) had m. p. 65—66° after crystallisation from ether–light petroleum (b. p. 40—60°) (Found: N, 8·7. Calc. for $C_{10}H_{11}ON$: N, 8·7%). Lit.,[4] m. p. 70—71°.

1-*p*-Tolylpyrrolid-2-one (X; R = Me, R′ = H) was obtained (43%) by the interaction of *p*-toluidine (10 g.) and γ-butyrolactone (10 g., 1·2 mols.) in a sealed vessel at 200° (12 hr.), the product crystallising when the reaction mixture was cooled. Recrystallisation from light petroleum (b. p. 60—80°) containing a few drops of ethanol gave the pyrrolid-2-one in needles, m. p. 87·5° (Found: C, 75·7; H, 7·65; N, 7·7. Calc. for $C_{11}H_{13}ON$: C, 75·4; H, 7·5; N, 8·0%). Lit.,[14] m. p. 88·5°. An attempt to prepare 1-*p*-nitrophenylpyrrolid-2-one in this way was unsuccessful, *p*-nitroaniline being the only crystalline material recovered.

A mixture of *m*-anisidine (15 g.) and γ-butyrolactone (13 g., 1·2 mols.) was heated at 220—230° under an air-condenser. After 3 hr. it was distilled, giving fractions (*a*) b. p. 85—110°/14 mm. (10 g.), mainly unchanged lactone, (*b*) b. p. 118—124°/14 mm. (11 g.), unchanged *m*-anisidine, and (*c*) b. p. 175—180°/3 mm. (2·5 g., 11%), which solidified and when recrystallised from ether–light petroleum (b. p. 40—60°) gave 1-m-*methoxyphenylpyrrolid*-2-*one* (X; R = H, R′ = OMe), m. p. 56° (Found: C, 69·0; H, 6·55; H, 7·45. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·85; N, 7·35%).

*Reaction of* 1-m-*Methoxypyrrolid*-2-*one with Acyl Chlorides.*—(i) *With benzenesulphonyl chloride.* The pyrrolidone (0·5 g.) in dry chlorobenzene (10 c.c.) was heated at 130° for 5 min. with the sulphonyl chloride (0·5 g., 1·1 mols.) and powdered aluminium chloride (0·5 g., 1·5 mols.); the mixture was cooled, shaken with slight excess of dilute aqueous sodium hydroxide, and extracted with benzene. This extract on evaporation yielded colourless crystals which, recrystallised from ethanol–acetone, gave 1-(4-*benzenesulphonyl*-3-*methoxy*)*phenylpyrrolid*-2-*one* (XVI), m. p. 223° (0·1 g., 12%) (Found: C, 61·3; H, 5·5; N, 4·35. $C_{17}H_{17}O_4NS$ requires C, 61·6; H, 5·2; N, 4·25%), mixed m. p. with the Friedel–Crafts product from γ-(*N*-benzenesulphonyl-*m*-anisidino)butyric acid, 175—185°.

(ii) *With toluene*-p-*sulphonyl chloride.* The pyrrolidone (0·5 g.), treated as above, but with toluene-*p*-sulphonyl chloride, afforded 1-(3-methoxy-4-toluene-*p*-sulphonyl)phenylpyrrolid-2-one (0·1 g., 12%), m. p. 222° (from ethanol–acetone), identical with the pyrrolid-2-one obtained from the attempted cyclisation.

*Attempted Cyclisation of the γ-Substituted Butyric Acids.*—(i) γ-*Toluene*-p-*sulphonanilido-butyric acid* (see also Astill and Boekelheide [4]). The acid (5 g.) was converted in the usual way into the chloride, which was treated in benzene with powdered aluminium chloride (5 g.) and set aside for 20 hr. The mixture was poured into a slight excess of aqueous sodium hydroxide

[14] Tafel and Stern, *Ber.*, 1900, **33**, 2235.

and extracted with benzene, which on evaporation yielded a brown syrup, which was dissolved in warm ethanol. A crystalline product was obtained, and on further recrystallisation from ethanol yielded phenyl *p*-tolyl sulphone (1·7 g., 50%), m. p. 125° (Found: C, 67·2; H, 5·0. Calc. for $C_{13}H_{12}O_2S$: C, 67·3; H, 5·15%) (lit.,[15] m. p. 127—127·5°. The original ethanolic mother-liquors when treated with 2 : 4-dinitrophenylhydrazine furnished in very small yield *γ-toluene-p-sulphonanilidobutyrophenone 2 : 4-dinitrophenylhydrazone*, orange-red platelets, m. p. 200—202° (insertion at 195°), after crystallisation from aqueous dioxan (Found: C, 60·3; H, 4·45; N, 12·5. $C_{29}H_{27}O_6N_5S$ requires C, 60·7; H, 4·75; N, 12·2%).

Small yields (15—25%) of free toluene-*p*-sulphonyl chloride, identified by m. p. and mixed m. p., were isolated when stannic chloride was employed in place of aluminium chloride, or when carbon disulphide replaced benzene.

In another experiment, anisole (2 g.) was added to a cyclisation mixture derived from the acid (5 g.) as described above. The deep purple mixture was set aside for 15 hr. and then worked up. The residue from the benzene extract had an odour of anisole, and did not crystallise. It was therefore treated in ethanol with 2 : 4-dinitrophenylhydrazine, giving *p-methoxyphenyl 3-N-toluene-p-sulphonanilidopropyl ketone 2 : 4-dinitrophenylhydrazone*, m. p. 226—228° (from dioxan) (Found: C, 59·8; H, 5·1; N, 11·8. $C_{30}H_{29}O_7N_5S$ requires C, 59·7; H, 4·85; N, 11·6%): 0·5 g., 13%.

(ii) *γ-(N-Benzenesulphonyl-m-toluidino)- and γ-(N-benzenesulphonyl-β-naphthylamino)-butyric acid.* Conversion of these acids into their chlorides, followed by treatment with aluminium chloride, gave ultimately dark tars from which no crystalline product could be isolated, although benzenesulphonyl chloride was in each case identified by its odour.

(iii) *γ-(N-Benzenesulphonyl-m-anisidino)butyric acid.* Many attempts to cyclise this acid are summarised in Table 2. In addition to other products, *1-(2-benzenesulphonyl-5-methoxyphenyl)pyrrolid-2-one* (XIV), m. p. 200°, colourless crystals from ethanol–acetone, was isolated in variable yield (usually 10—15%) (Found: C, 61·8; H, 5·0; N, 4·35%; *M*, in boiling acetone, 351. $C_{17}H_{17}O_4NS$ requires C, 61·6; H, 5·2; N, 4·25%; *M*, 332).

TABLE 2. *Summary of procedures giving the pyrrolid-2-one* (XIV) *from the acid* (IV; R = OMe, R′ = $SO_2Ph$).

| Method | Temp. | Time (hr.) | Yield (%) |
|---|---|---|---|
| (*a*) $SOCl_2$–$C_6H_6$; $AlCl_3$–$C_6H_6$ | Room | 15—112 | 5—10 |
| (*b*) $SOCl_2$–$C_6H_6$; $AlCl_3$–$C_6H_6$ | Reflux | ¼—4 | 7 |
| (*c*) $SOCl_2$–$C_6H_6$; $AlCl_3$–PhCl | 110—140° | 5—10 (min.) | 8—15 |
| (*d*) $SOCl_2$–$C_6H_6$; $SnCl_4$–$C_6H_6$ | Room | 48 | 3 |
| (*e*) $SOCl_2$–$C_6H_6$; $SnCl_4$–$C_6H_6$ | 50—60° | 3 | 3 |
| (*f*) $PCl_5$–$C_6H_6$; $AlCl_3$–$C_6H_6$ | Room | 36 | 10 |
| (*g*) $PCl_5$–$C_6H_6$; $SnCl_4$–$C_6H_6$ | Room | 15—20 | 15 |
| (*h*) $H_2SO_4$–$H_3PO_4$ | 165° | ½ | 5 |
| (*i*) Polyphosphoric acid | 115°; 150—160° | 2; ½ | 3 |

In a typical experiment [(*a*), Table 2], the acid (1 g.) was converted into the chloride with thionyl chloride (1 c.c.) in benzene, and volatile materials removed under reduced pressure. A cooled solution of the residual brown syrup in dry benzene (20 c.c.) was treated with powdered aluminium chloride (1 g.). The mixture effervesced and became dark; after 20 hr. at room temperature, it was extracted with a slight excess of cold 10% aqueous sodium hydroxide, and the benzene layer on evaporation left a dark brown gum. A warm ethanolic solution of this residue soon deposited the crystalline pyrrolid-2-one (XIV) (100 mg., 10%). No other crystalline products could be isolated from the ethanolic mother-liquors, which showed no ketonic properties but had the smell of benzenesulphonyl chloride.

This experiment, with the time of reaction extended to 40 hr., gave a slightly increased yield of (XIV), and when it was extended to 112 hr. a very small yield of ketonic material was also isolated from the ethanolic mother-liquors (as the 2 : 4-dinitrophenylhydrazone), having probably been formed by reaction of the acid chloride with benzene.

When a large-scale cyclisation (5 g. of acid in 40 c.c. of benzene) was attempted, the major crystalline product (*ca.* 50%) was diphenyl sulphone, m. p. 122—123° (lit.,[16] 124°) (Found: C, 66·6; H, 4·7. Calc. for $C_{10}H_{12}O_2S$: C, 66·1; H, 4·6%), separated with difficulty by fractional crystalline from the pyrrolidone (XIV).

[15] Beringer, Brierley, Drexler, Gindler, and Lumpkin, *J. Amer. Chem. Soc.*, 1953, **75**, 2711.
[16] Hinsberg, *Ber.*, 1910, **43**, 289.

Reactions in chlorobenzene [(*c*) Table 2] gave slightly improved yields of the pyrrolidone (XIV); a crystalline sulphone was not obtained, but chromatography (alumina) of a benzene extract of the products after removal of (XIV) gave 1-*m*-methoxyphenylpyrrolid-2-one (X; R = H, R′ = OMe) as the major eluate (benzene), followed (benzene–ethanol) by a small quantity of uncrystallisable black tar.

(iv) γ-(*Toluene*-p-*sulphonyl*-m-*anisidino*)*butyric acid*. Preparation of the acid chloride, and subsequent cyclisation attempts, were carried out under conditions corresponding to those in Table 2.

1-(3-*Methoxy*-4-*toluene*-p-*sulphonyl*)*phenylpyrrolid*-2-*one* (XV), m. p. 222° (from ethanol–acetone), was obtained in 5—10% yield (Found: C, 62·9; H, 5·45; N, 4·15. $C_{18}H_{19}O_4NS$ requires C, 62·6; H, 5·55; N, 4·05%). In a typical prolonged experiment (room temperature, 100 hr.) phenyl *p*-tolyl sulphone (30%) and the pyrrolidone (XV) (4%) were obtained.

*Chemical Properties of the Pyrrolid*-2-*ones* (XIV) *and* (XV).—(i) The pyrrolidones were soluble in warm concentrated hydrochloric acid; partial recrystallisation of the unchanged pyrrolidones occurred on cooling, followed by their complete separation on dilution with water. 70% Sulphuric acid (1 day at room temperature) or boiling acetic acid–hydrochloric acid [9] were also without effect; a solution of (XIV) in concentrated sulphuric acid slowly darkened and charred.

(ii) The pyrrolidones were partially soluble in a boiling 30% solution of potassium hydroxide in aqueous ethanol (1 : 1 v/v) but were precipitated unchanged when the solutions were cooled.

(iii) Attempted reductions by lithium aluminium hydride in boiling ether, or sodium in boiling ethanol or butan-1-ol, failed, possibly because of the insolubility of the pyrrolidones (XIV) and (XV).

We are greatly indebted to Dr. A. J. Tetlow, who investigated the preparation of acetyl-*m*-anisidine derivatives and also carried out preliminary experiments on the preparation and cyclisation of γ-(*N*-benzenesulphonyl-*m*-anisidino)butyric acid (IV; R = OMe, R′ = $SO_2Ph$).

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