892. *The Schmidt Reaction with Aromatic Ketones*

By D. Evans and I. M. Lockhart

The action of hydrazoic acid on some methoxy-derivatives of 1-tetralone and acetophenone is examined and compared with the results obtained in similar reactions with chromanones. The results are discussed in relation to the mechanism of the reaction.

Several groups of workers [1] have discussed the mechanism of the Schmidt reaction with ketones and have concluded that electronic effects can compete with steric effects in determining the products obtained from an unsymmetrical ketone. Uyeo [2] has reported utilising the electronic effects of substituents in the Schmidt reaction in synthetic work on the Amaryllidaceae alkaloids. From previous work on the behaviour of 4-chromanones in the Schmidt reaction,[3] we concluded that the mechanisms postulated were inadequate to predict the outcome of the Schmidt reaction on such a ketone and the present work was carried out in an effort to clarify the situation.

The results obtained from the Schmidt reaction on various ketones are summarised in the Table.

It has been confirmed that 1-tetralone (III) gives the 1-benzazepin-2-one (IV) on treatment with sodium azide in concentrated sulphuric acid. 6-Methoxy-1-tetralone (V), in which electronic effects are similar to those in 4-chromanone, gave the 2-benzazepin-1-one (VI) as the principal product. Both the Schmidt reaction and Beckmann rearrangement went in a similar manner using polyphosphoric acid, but the use of sulphuric acid in the latter afforded a sulphonated product.

Striking differences were noted in the ease of hydrolysis of the different benzazepinones. As determined by change in ultraviolet spectra, hydrolysis of the amide bond of the 1-benzazepin-2-one (IV) in 2N-hydrochloric acid at room temperature was more than 90% complete after 48 hr. although it was possible to isolate the benzazepinone from an acidic Schmidt reaction mixture without difficulty. In contrast, at least 80% of the 2-benzazepin-1-one (VI) was unchanged after three weeks in 2N-hydrochloric acid at room temperature. These results parallel those previously found with the benzoxazepinones.[3]

Acetophenone gives acetanilide in the Schmidt reaction; [4] we have found that *p*-methoxyacetophenone (VIII) gave a mixture of *p*-methoxyacetanilide (80%) (IX) and *p*-methoxy-*N*-methylbenzamide (20%) (X). In the Beckmann rearrangement it was necessary to use a temperature of 120° and *p*-hydroxyaniline was formed. Results with *o*-methoxyacetophenone were not as clear-cut; the Schmidt reaction gave a mixture of products but the Beckmann rearrangement led to the formation of *o*-methoxyacetanilide.

The present results and those with 4-chromanones [3] suggest that an aromatic-alicyclic ketone having an ether link *ortho* or *para* to the carbonyl group gives a benzamide derivative as the major product with hydrazoic acid rather than the acetanilide type of compound which is obtained when no such ether link is present.

Other substituents can reverse the effect of ether links in the ketone. Treatment of 3-dimethylaminomethyl-4-chromanone (XI) with sodium azide in concentrated sulphuric acid afforded the 1,5-benzoxazepinone (XII) in 70% yield. The structure of this product was confirmed by acid hydrolysis of the amide and identification of the resulting amino-acid by analysis, titration, and spectral evidence, while reduction of the benzoxazepinone

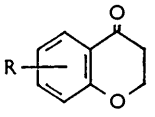
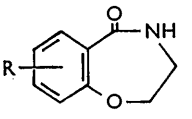
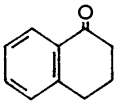
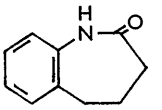
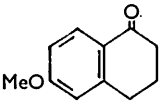
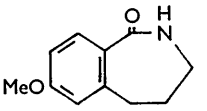
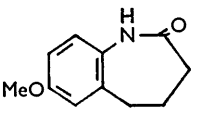
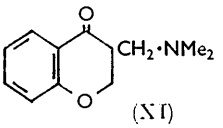
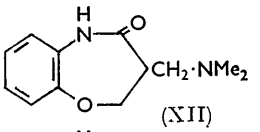
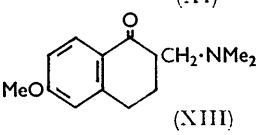
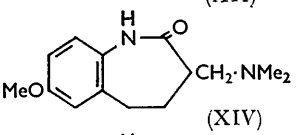
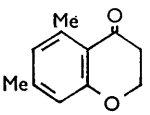
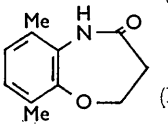
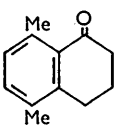
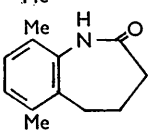
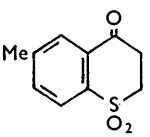
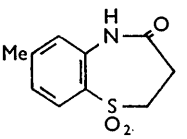
[1] *E.g.*, (*a*) H. J. Schmid, A. Hunger, and K. Hoffmann, *Helv. Chim. Acta*, 1956, **39**, 607; (*b*) C. L. Arcus, M. M. Coombs, and J. V. Evans, *J.*, 1956, 1498; (*c*) P. A. S. Smith and E. P. Antoniades, *Tetrahedron*, 1960, **9**, 210; (*d*) J. Mirek, *Bull. Acad. polon. Sci., Ser. Sci. chim.*, 1962, **10**, 421.

[2] S. Uyeo, XIXth International Congress of Pure and Applied Chemistry. Congress Lectures, Butterworths, London, 1963, p. 269.

[3] D. Huckle, I. M. Lockhart, and M. Wright, *J.*, 1965, 1137.

[4] L. H. Briggs and G. C. De Ath, *J.*, 1937, 456.

Summary of results from the Schmidt reaction

Ketone	Product(s)
 (I)	 (II) (Ref. 3)
 (III)	 (IV)
 (V)	 (VI) + some  (VII)
p-MeO·C$_6$H$_4$·COMe (VIII)	*p*-MeO·C$_6$H$_4$·NHCOMe (IX) (80%) + *p*-MeO·C$_6$H$_4$·CONHMe (X) (20%)
 (XI)	 (XII)
 (XIII)	 (XIV)
 (XV)	 (XVI) in very poor yield
 (XVII)	 (XVIII)
 (XIX)	 (XX)

(XII) with lithium aluminium hydride afforded 2,3,4,5-tetrahydro-3-dimethylaminomethyl-1,5-benzoxazepine. No evidence of the alternative 1,4-benzoxazepinone was found. 3-Morpholinomethyl-4-chromanone behaved similarly to the 3-dimethylaminomethyl compound in the Schmidt reaction. 2-Dimethylaminomethyl-6-methoxy-1-tetralone (XIII) afforded the appropriate 1-benzazepin-2-one (XIV) in contrast with the 2-benzazepin-1-one (VI) from 6-methoxy-1-tetralone (V) itself.

Substituents in the *peri*-position to the carbonyl group of 4-chromanones could exert a profound effect. For example, under the conditions used, a 5% yield of the 1,5-benzoxazepin-4-one (XVI) was the best that could be obtained from 5,7-dimethylchroman-4-one (XV) in contrast with the formation of 1,4-benzoxazepin-5-one (II; R = H) from 4-chromanone (I; R = H) itself.[3] There was little effect in the 1-tetralone

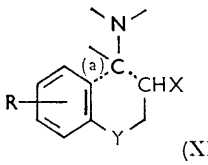
series where, with 5,8-dimethyl-1-tetralone (XVII), the Schmidt reaction afforded the 1-benzazepin-2-one (XVIII). The results with the *peri*-substituted 4-chromanones were probably indicative of the competing nature of steric and electronic effects with resultant very poor yields. However, in the *peri*-substituted 1-tetralones where electronic effects are much less, steric effects probably determined the outcome of the reaction.

No satisfactory product was obtained from 6-methyl-4-thiochromanone, but treatment of the corresponding sulphone (XIX) with sodium azide in concentrated sulphuric acid afforded the 1,5-benzothiazepin-4-one 1,1-dioxide (XX).

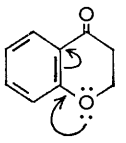
In discussing the mechanism of the Schmidt reaction for the aromatic-alicyclic ketones under consideration, it is suggested that the skeleton of the final intermediate which rearranges to give the amide might be represented by structure (XXI) where X = H or a basic side-chain, Y = CH_2, O, or SO_2, and R = H, Me, or MeO. Two amides are possible and in our work it cannot be said that one has been formed exclusively. Failure to isolate a second product may have been a consequence of its formation in low yield, its chemical nature, or because sensitivity to acid may have resulted in its complete destruction *in situ*.

The outcome of the reaction with acetophenone, 1-tetralones (without a methoxy-substituent), and 4-thiochromanone 1,1-dioxide can be explained by steric effects in an azide intermediate.[1] However, the striking difference in the behaviour of 4-chromanone from that of 1-tetralone requires a more specific explanation of the role of electronic effects in the Schmidt reaction than has hitherto been given.

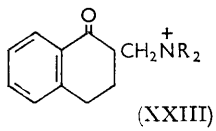
The present work suggests that an ether linkage *ortho*- or *para*- to the carbonyl group markedly increases the tendency to form a benzamide rather than a product related to acetanilide. Furthermore, Schmid *et al.*[1a] reported that the Schmidt reaction on a Mannich base of 1-tetralone gave the benzamide product. In these cases, there may be an increase in electron density of bond (a) (formula XXI) as a result of electromeric shifts as in formula (XXII) or by direct electronic attraction by the positively charged nitrogen in acid solution as in formula (XXIII). This might be considered as a distortion of the aromatic electron cloud towards the carbonyl group.



(XXI)



(XXII)



(XXIII)

Most of the results reported in this Paper can be explained if such an electronic effect leads to the formation of a benzamide product, while in its absence, the acetanilide-type of product is obtained, possibly determined by steric effects alone. The formation of benzamide-type products by the Schmidt reaction on a methoxyindanone,[2] 4,5,6,7-tetrahydro-4-oxothianaphthene,[5] and 1,2-dihydro-3*H*-pyrido[3,2,1-*kl*]phenothiazin-3-one [6] conforms to such an idea.

Apparently anomalous results have been obtained from the Schmidt reaction on the Mannich base of 4-chromanone [*e.g.*, compound (XI)] and of 6-methoxy-1-tetralone (XIII). These compounds each contain two groupings which might be expected to lead to a benzamide product. The predominance of the acetanilide-type of product may indicate that the effects of the ether link and the basic group interact or neutralise each other, either intramolecularly or intermolecularly, so that these electronic effects no longer play a significant role. Schmid *et al.*[1a] found that 5,6-dimethoxy-2-piperidinoethylindan-1-one yields the corresponding isocarbostyril. This appears to be anomalous but the extended side-chain may prevent interaction with or neutralisation of the effects of the ether links.

[5] S. Nishimura, M. Nakamura, M. Suzuki, and E. Imoto, *J. Chem. Soc. Japan*, 1962, **83**, 343 (*Chem. Abs.*, 1963, **59**, 3862).

[6] T. Ichii, *J. Pharm. Soc. Japan*, 1962, **82**, 999 (*Chem. Abs.*, 1963, **58**, 5666).

Similarities between the mechanism of the Schmidt reaction and the Beckmann rearrangement have been referred to frequently.[1b-d] Our evidence indicates that both reactions lead to the same product although the Beckmann rearrangement has been reported not to go where the Schmidt reaction has succeeded.[5] It has been shown that the action of lithium aluminium hydride on 4-chromanone oxime gives a significant amount of 2,3,4,5-tetrahydro-1,5-benzoxazepine,[7] presumably through a Beckmann-type rearrangement followed by reduction of the amide. We have confirmed this work which apparently conflicts with the results in a normal Beckmann rearrangement under acid conditions;[3] this suggests that the medium is important in determining the outcome of such a reaction. Zagorevskii and Dudykina [7a] also showed that the Beckmann rearrangement on thiochromanone oxime in polyphosphoric acid afforded the appropriate 1,5-benzothiazepin-4-one.

Finally, the effects of substituents are not as pronounced in the acetophenones as in the 1-tetralones and 4-chromanones and it may be that the fused-ring system plays an important part in the results discussed.

In the course of this work some *N*-substituted 1-benzazepin-2-ones were prepared by the reaction of the appropriate halide with the benzazepinone in the presence of sodamide. Reduction with lithium aluminium hydride afforded the appropriate benzazepines. Dihydrocarbostyril was prepared by the Schmidt reaction on indanone. The *N*-substituted derivatives of dihydrocarbostyril and of oxindole were prepared in a similar way to that used for the corresponding benzazepinones; these compounds were prepared to examine the effect of ring size in biological tests.

Experimental

Schmidt Reaction Methods.—Method A. Sodium azide (1·3 moles) was added portionwise to a stirred ice-cold solution of the ketone (1 mole) in four times its weight of concentrated sulphuric acid. The mixture was stirred for about 16 hr., poured on to crushed ice, the solution basified with 10N-sodium hydroxide (if the product was basic) and the product isolated with ether or light petroleum (b. p. 60—80°).

Method B. Sodium azide (1·3 moles) was added portionwise to a stirred solution of the ketone (1 mole) in polyphosphoric acid (equivalent to ten times the weight of the reaction mixture). The mixture was heated at 50° for 7½ hr. and poured into water. The solid which separated was recrystallised from an appropriate solvent.

Product from the Schmidt Reaction.—On 1-tetralones. Schmidt reactions on 1-tetralone and on 6-methoxy-1-tetralone [8] were carried out by the method of Briggs and De Ath.[4] The latter compound afforded prisms, m. p. 115—116° (from ethanol), which were shown to be predominantly 2,3,4,5-tetrahydro-7-methoxy-1*H*-2-benzazepin-1-one probably mixed with some of the corresponding 1-benzazepin-2-one (Found: C, 68·8; H, 7·0; N, 7·2. Calc. for $C_{11}H_{13}NO_2$: C, 69·1; H, 6·9; N, 7·3%). The same product was obtained from 6-methoxy-1-tetralone by method B.

2-Dimethylaminomethyl-6-methoxy-1-tetralone hydrochloride [9] (6·1 g.) treated by method A afforded 1,3,4,5-*tetrahydro*-7-*methoxy*-3-*dimethylaminomethyl*-2H-1-*benzazepin*-2-*one* (3·6 g.) as prisms, m. p. 143—144° (from ethyl acetate) (Found: C, 68·0; H, 8·2; N, 11·7. $C_{14}H_{20}N_2O_2$ requires C, 67·7; H, 8·1; N, 11·3%).

A similar reaction on 5,8-dimethyl-1-tetralone [10] (7·0 g.) gave 1,3,4,5-tetrahydro-6,9-dimethyl-2*H*-1-benzazepin-2-one (1·3 g.) as plates, m. p. 156—157°, from methanol–light petroleum (b. p. 60—80°) (lit.,[11] m. p. 158—160°), together with unchanged starting material (3·5 g.).

On acetophenones. By the method of Briggs and De Ath [4] *p*-methoxyacetophenone (11·4 g.)

[7] (*a*) V. A. Zagorevskii and N. V. Dudykina, *J. Gen. Chem.* (*U.S.S.R.*), 1963, **33**, 317; (*b*) A. Campbell, private communication.

[8] G. Stork, *J. Amer. Chem. Soc.*, 1947, **69**, 576.

[9] J. Lee, A. Ziering, L. Berger, and S. D. Heinemann, *Jubilee Vol., Emil. Barell*, 1946, 264 (*Chem. Abs.*, 1947, **41**, 6246).

[10] E. de B. Barnett and F. G. Sanders, *J.*, 1933, 434.

[11] G. Schroeter (with A. Gluschke, S. Götzky, J. Huang, G. Irmisch, E. Laves, O. Schrader, and G. Stier), *Ber.*, 1930, **63**, 1308.

afforded white prisms (5·6 g.), m. p. 114—116°, from benzene. Acid hydrolysis (see below) indicated that the product was a mixture of *p*-methoxyacetanilide (80%) and *N*-methyl-*p*-methoxybenzamide (20%). Method B gave the same product but in rather better yield. Under similar conditions *o*-methoxyacetophenone yielded a brown gum which was split into three unidentified fractions by distillation *in vacuo*.

On 4-chromanones. 3-Dimethylaminomethyl-4-chromanone hydrochloride [12] (17·8 g.) was treated by method A and afforded 2,3-*dihydro*-3-*dimethylaminomethyl*-1,5-*benzoxazepin*-4(5H)-*one* (10·7 g.) as white needles, m. p. 76·5°, from light petroleum (b. p. 60—80°) (Found: C, 65·2; H, 7·7; N, 12·8. $C_{12}H_{16}N_2O_2$ requires C, 65·4; H, 7·3; N, 12·7%). The benzoxazepinone gave a *hydrochloride* as needles, m. p. 229—230°, from ethanol (Found: C, 55·85; H, 6·8; N, 10·5. $C_{12}H_{17}ClN_2O_2$ requires C, 56·1; H, 6·7; N, 10·9%). A similar exeriment with 3-morpholinomethyl-4-chromanone hydrochloride [13] (8 g.) afforded 2,3-*dihydro*-3-*morpholinomethyl*-1,5-*benzoxazepin*-4(5H)-*one* (1·5 g.) as prisms, m. p. 121—122°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 64·45; H, 7·0; N, 11·0. $C_{14}H_{18}N_2O_3$ requires C, 64·1; H, 6·9; N, 10·7%). The benzoxazepinone gave a *hydrochloride* of m. p. 249—251° as rods from ethanol (Found: C, 56·65; H, 6·9; N, 9·6. $C_{14}H_{19}ClN_2O_3$ requires C, 56·3; H, 6·4; N, 9·4%). Submission of 5,7-dimethyl-4-chromanone (20 g.) to the Schmidt reaction using method A afforded 2,3-*dihydro*-6,8-*dimethyl*-1,5-*benzoxazepin*-4(5H)-*one* (1·1 g.) as prisms, m. p. 123—125°, from light petroleum (b. p. 60—80°) (Found: C, 69·2; H, 6·7; N, 7·5. $C_{11}H_{13}NO_2$ requires C, 69·1; H, 6·85; N, 7·3%). In two other similar experiments no benzoxazepinone was isolated.

A similar experiment with 5,7,8-trimethylchroman-4-one (20 g.) afforded 2,3-*dihydro*-6,8,9-*trimethyl*-1,5-*benzoxazepin*-4(5H)-*one* (700 mg.) as needles, m. p. 178—180°, from light petroleum (b. p. 60—80°) (Found: C, 70·3; H, 7·15; N, 7·1. $C_{12}H_{15}NO_2$ requires C, 70·2; H, 7·4; N, 6·8%).

On 6-methyl-4-thiochromanone 1,1-dioxide. 6-Methyl-4-thiochromanone 1,1-dioxide (14 g.) was treated by method A and afforded 2,3-*dihydro*-7-*methyl*-1,5-*benzothiazepin*-4(5H)-*one* 1,1-*dioxide* (6·7 g.) as white needles, m. p. 244—245°, from ethyl acetate (Found: C, 53·1; H, 5·15; N, 6·3. $C_{10}H_{11}NO_3S$ requires C, 53·3; H, 4·9; N, 6·2%).

Beckmann Rearrangements.—On 1-tetralones. (*a*) 6-Methoxy-1-tetralone oxime (2·3 g.) and concentrated sulphuric acid (4 ml.) were stirred at 40° for 1½ hr. and left overnight at room temperature. The mixture was poured into ice-cold water (50 ml.) and extracted with ether. Unchanged oxime (1·2 g.) was isolated from the ether extracts whilst the aqueous phase afforded white rods (1·1 g.), m. p. 149—151° (decomp.), from methanol–ether (Found: C, 43·5; H, 6·1; N, nil; S, 10·4%) which was believed to be a nuclear-sulphonated product.

(*b*) 6-Methoxy-1-tetralone oxime (2·0 g.) and polyphosphoric acid (30 ml.) were stirred at 120—130° for 10 min., and the mixture was poured into water (200 ml.). Chloroform extraction afforded a product which was predominantly 2,3,4,5-tetrahydro-7-methoxy-1*H*-2-benzazepin-1-one as prisms, m. p. 117—118°, from benzene–light petroleum (b. p. 60—80°).

On acetophenones. By a method similar to that described in (*a*) above, *o*-methoxyacetophenone oxime (3·0 g.) gave *o*-methoxyacetanilide (1·3 g.) as rods, m. p. 84—86°, from aqueous ethanol (lit.,[14] m. p. 84°). Under the same conditions, *p*-methoxyacetophenone oxime did not react but reaction at 120° (internal) for 15 min. afforded *p*-hydroxyaniline hydrosulphate (31%), as rods, which decomposed above 310° (Found: C, 34·8; H, 4·4; N, 6·9. Calc. for $C_6H_9NO_5S$: C, 34·8; H, 4·4; N, 6·8%).

Confirmation of the Structure of Products from the Schmidt and Beckmann Reactions.—Determinations of which of the alternative products had been obtained from these reactions were made by acid hydrolysis of the amide and examination of the products as previously described.[3] The product from the Schmidt reaction on 6-methoxy-1-tetralone (200 mg.) afforded an almost colourless gum (186 mg.); physicochemical measurements were consistent with the material being a mixture of 2-(3-aminopropyl)-4-methoxybenzoic acid hydrochloride and 2-amino-5-methoxyphenylbutyric acid hydrochloride, the former comprising at least 60% of the product (Found: C, 53·7; H, 6·6; N, 6·1. Calc. for $C_{11}H_{16}ClNO_3$: C, 53·9; H, 6·5; N, 5·7%). Only a gum was obtained on hydrolysis of 3-dimethylaminomethyl-1,3,4,5-tetrahydro-7-methoxy-2*H*-1-benzazepin-2-one, but titration of the product [pK_a ~4·3, ~5·9;

[12] P. F. Wiley, *J. Amer. Chem. Soc.*, 1951, **73**, 4205.
[13] R. H. Harradence, G. K. Hughes, and F. Lions, *J. Proc. Roy. Soc. New South Wales*, 1939, **72**, 273.
[14] F. Herold, *Ber.*, 1882, **15**, 1684.

~9·6 (in 50% ethanol)] was consistent with the structure assigned to the benzazepinone. 2-*Amino*-3,6-*dimethylphenylbutyric acid hydrochloride* was obtained as rods, m. p. 190—192°, from methanol–ether (Found: C, 58·85; H, 7·7; N, 6·0. $C_{12}H_{18}ClNO_2$ requires C, 59·1; H, 7·4; N, 5·7%), from the hydrolysis of 1,3,4,5-tetrahydro-6,9-dimethyl-2*H*-1-benzazepin-2-one.

o-*Amino*-α-*dimethylaminomethylphenoxypropionic acid dihydrochloride* was obtained as needles, m. p. 73°, from ethanol–ether (Found: C, 40·95; H, 7·5; N, 7·7. $C_{12}H_{20}Cl_2N_2O_3,2\frac{1}{2}H_2O$ requires C, 40·5; H, 7·1; N, 7·9%) on hydrolysis of 3-dimethylaminomethyl-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one. Hydrolysis of 6,8-dimethyl-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one afforded 2-*amino*-3,5-*dimethylphenoxypropionic acid hydrochloride* as prisms, m. p. 210—211°, from ethanol–ether (Found: C, 52·9; H, 6·5; N, 5·6. $C_{11}H_{16}ClNO_3,\frac{1}{2}H_2O$ requires C, 52·7; H, 6·65; N, 5·6%), and 2-*amino*-3,5,6-*trimethylphenoxypropionic acid hydrochloride* was obtained as prisms, m. p. 200°, from ethanol–ether (Found: C, 55·2; H, 7·35; N, 5·7. $C_{12}H_{18}ClNO_3$ requires C, 55·4; H, 7·0; N, 5·4%) from the corresponding 6,8,9-trimethylbenzoxazepinone.

Hydrolysis of 2,3-dihydro-7-methyl-1,5-benzothiazepin-4(5*H*)-one 1,1-dioxide afforded β-(2-*amino*-4-*tolylsulphonyl*)*propionic acid* as rods, m. p. 143—144° from water (Found: C, 49·75; H, 5·9; N, 5·9; S, 13·0. $C_{10}H_{13}NO_4S$ requires C, 49·4; H, 5·4; N, 5·8; S, 13·3%).

5,7-*Dimethylchroman*-4-*one*.—Cyanoethylation [15] of 3,5-xylen-1-ol (61 g.) afforded 3,5-*dimethylphenoxypropionitrile* (67 g.) as needles, m. p. 76—76·5°, from light petroleum (b. p. 60—80°) (Found: C, 75·35; H, 7·3; N, 7·6. $C_{11}H_{13}NO$ requires C, 75·4; H, 7·5; N, 8·0%). Cyclisation of the nitrile (67 g.) with polyphosphoric acid [16] at 165—175° afforded 5,7-*dimethylchroman*-4-*one* (41 g.) as prisms, m. p. 36—37°, from light petroleum (b. p. 60—80°) (Found: C, 75·25; H, 6·7. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·9%).

5,7,8-*Trimethylchroman*-4-*one*.—Cyanoethylation [15] of 2,3,5-trimethylphenol (68 g.) afforded 2,3,5-*trimethylphenoxypropionitrile* (81 g.) as needles, m. p. 69—70°, from light petroleum (b. p. 60—80°) (Found: C, 76·1; H, 7·8; N, 7·4. $C_{12}H_{15}NO$ requires C, 76·15; H, 8·0; N, 7·4%). Cyclisation of the nitrile (81 g.) with polyphosphoric acid [16] at 180° afforded 5,7,8-trimethylchroman-4-one (60 g.) as prisms, m. p. 38—39°, from light petroleum (b. p. 40—60°) (Found: C, 75·9; H, 7·6. Calc. for $C_{12}H_{14}O_2$: C, 75·8; H, 7·4%). Dann *et al.*[17] record b. p. 100—120°/2 mm., giving a waxy solid on cooling, for this compound.

3-*Dimethylaminomethyl*-2,3,4,5-*tetrahydro*-1,5-*benzoxazepine Hydrochloride*.—3-Dimethylaminomethyl-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one hydrochloride (6 g.) was dissolved in N-sodium hydroxide and extracted into benzene (200 ml.). The dried benzene solution was slowly added to a well-stirred suspension of lithium aluminium hydride (2·5 g.) in anhydrous ether (200 ml.). The mixture was refluxed for 2 hr., cooled, wet ether (20 ml.), water (50 ml.), and 2N-sodium hydroxide (12·5 ml.) cautiously added, and the whole refluxed for a further 2 hr. The mixture was filtered hot, and the organic phase from the filtrate dried ($MgSO_4$), and evaporated. Distillation *in vacuo* afforded the *benzoxazepine* (1·8 g.) as a colourless liquid, b. p. 123—126°/0·7 mm. (m. p. 25°) (Found: C, 69·8; H, 8·5. $C_{12}H_{18}N_2O$ requires C, 69·9; H, 8·8%). Addition of ethereal hydrogen chloride to the benzoxazepine in ether afforded a microcrystalline *hydrochloride* (1·8 g.) of ill-defined m. p. (decomposition and sublimation up to 215°) (Found: C, 48·6; H, 7·6; N, 9·4. $C_{12}H_{20}Cl_2N_2O,H_2O$ requires C, 48·5; H, 7·5; N, 9·4%).

N-*Substituted* 1-*Benzazepin*-2-*ones*.—The benzazepinone (0·05 mole) was added to a suspension of sodamide (2·05 g., 0·053 mole) in dry dioxan (75 ml.); the mixture was stirred under reflux until evolution of ammonia ceased. The appropriate halide (0·053 mole) was added and heating continued for 5 hr. The cooled solution was evaporated under reduced pressure and the residue purified by standard procedures. The following *N*-substituted benzazepinones were prepared by this method: 1-(2-*morpholinoethyl*)-1,3,4,5-*tetrahydro*-2H-1-*benzazepin*-2-*one* (64%) with b. p. 178—180°/0·9 mm. (Found: C, 69·5; H, 8·2; N, 9·9. $C_{16}H_{22}N_2O_2$ requires C, 70·0; H, 8·1; N, 10·2%), which afforded a *maleate* as plates, m. p. 146—147° (Found: C, 61·4; H, 6·7; N, 7·2. $C_{20}H_{26}N_2O_6$ requires C, 61·5; H, 6·7; N, 7·2%) and an *oxalate* as prisms, m. p. 218—220° (decomp.) (Found: C, 59·6; H, 6·7; N, 7·8. $C_{18}H_{24}N_2O_6$ requires C, 59·3; H, 6·6; N, 7·7%); 1,3,4,5-*tetrahydro*-1-(2-*piperidinoethyl*-2H-1-*benzazepin*-2-*one* (51%) with b. p. 156—158°/0·6 mm. (Found: C, 74·6; H, 8·9. $C_{17}H_{24}N_2O$ requires C, 75·0; H, 8·9%)

[15] G. B. Bachman and H. A. Levine, *J. Amer. Chem. Soc.*, 1948, **70**, 599.
[16] U.S.P. 2,792,407.
[17] O. Dann, G. Volz, and O. Huber, *Annalen*, 1954, **587**, 16.

which afforded a *citrate* as prisms, from methanol–ether, m. p. 154—156° (Found: C, 59·1; H, 6·8; N, 5·7. $C_{23}H_{32}N_2O_8$ requires C, 59·5; H, 6·9; N, 6·0%); 1-(3-*dimethylaminopropyl*)-1,3,4,5-*tetrahydro*-2H-1-*benzazepin*-2-*one* (62%), b. p. 140—142°/0·4 mm., n_D^{21} 1·5436 (Found: C, 73·3; H, 8·7; N, 11·9. $C_{15}H_{22}N_2O$ requires C, 73·1; H, 9·0; N, 11·4%) which afforded a *citrate* as prisms, from methanol–ether, of m. p. 133—135° (Found: C, 57·1; H, 6·9; N, 6·4. $C_{21}H_{30}N_2O_8$ requires C, 57·5; H, 6·9; N, 6·4%); 1-*ethyl*-1,3,4,5-*tetrahydro*-2H-1-*benzazepin*-2-*one* (75%), b. p. 105—106°/0·5 mm., n_D^{20} 1·5567 (Found: C, 76·0; H, 7·9; N, 7·5. $C_{12}H_{15}NO$ requires C, 76·2; H, 8·0; N, 7·4%).

1-(2-*Morpholinoethyl*)*oxindole*.—Reaction of 2-oxindole and 2-morpholinoethyl chloride by a similar method afforded 1-(2-*morpholinoethyl*)*oxindole* (58%) with b. p. 178—180°/1·5 mm., n_D^{21} 1·5608 (Found: C, 68·6; H, 7·6; N, 11·7. $C_{14}H_{18}N_2O_2$ requires C, 68·3; H, 7·4; N, 11·4%). The *hydrochloride*, obtained as plates from methanol–ether, had m. p. 235—238° (decomp.) (Found: C, 59·9; H, 7·0; N, 10·0. $C_{14}H_{19}ClN_2O_2$ requires C, 59·5; H, 6·8; N, 9·9%).

1-(2-*Morpholinoethyl*)*hydrocarbostyril Hydrochloride*.—Dihydrocarbostyril [4] and 2-morpholinoethyl chloride similarly gave 1-(2-*morpholinoethyl*)*hydrocarbostyril* (52%), b. p. 159—162°/0·4 mm., n_D^{21} 1·5698 (Found: C, 68·8; H, 7·7; N, 11·3. $C_{15}H_{20}N_2O_2$ requires C, 69·2; H, 7·7; N, 10·8%). The *hydrochloride* was obtained as prisms, m. p. 213—215°, from methanol–ether (Found: C, 60·7; H, 7·3; N, 9·4. $C_{15}H_{21}ClN_2O_2$ requires C, 60·7; H, 7·1; N, 9·4%).

1-(2-*Morpholinoethyl*)-2,3,4,5-*tetrahydro*-1H-1-*benzazepine*.—1-(2-Morpholinoethyl)-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one (13 g.) in anhydrous ether (100 ml.) was added during 15 min. to a stirred suspension of lithium aluminium hydride (3·6 g.) in ether (200 ml.). The mixture was refluxed for 5 hr., cooled, decomposed by addition of damp ether (50 ml.) and water (50 ml.) and refluxed for a further 1 hr. The mixture was filtered and the ether solution washed with water and dried (Na_2SO_4). Distillation afforded the *benzazepine* (11·3 g.) as a colourless oil, b. p. 140—143°/0·4 mm., n_D^{22} 1·5530 (Found: C, 73·3; H, 9·2; N, 10·5. $C_{16}H_{24}N_2O$ requires C, 73·8; H, 9·3; N, 10·8%). The *dihydrochloride*, as rods from propan-2-ol–methanol, had m. p. 202—204° (Found: C, 57·8; H, 8·1; N, 8·2. $C_{16}H_{26}Cl_2N_2O$ requires C, 57·7; H, 7·9; N, 8·4%).

1-*Ethyl*-2,3,4,5-*tetrahydro*-1H-1-*benzazepine*.—1-Ethyl-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one (6·4 g.) was reduced with lithium aluminium hydride (2·6 g.) as described above. The *benzazepine* (4·9 g.) was obtained as a colourless oil, b. p. 89—90°/1·7 mm., n_D^{20} 1·5481 (Found: C, 81·9; H, 9·6; N, 8·3. $C_{12}H_{17}N$ requires C, 82·2; H, 9·8; N, 8·0%), which afforded a *hydrochloride* as prisms of m. p. 136—138° from methanol (Found: C, 68·2; H, 8·4; N, 6·8. $C_{12}H_{18}ClN$ requires C, 68·1; H, 8·6; N, 6·6%).

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