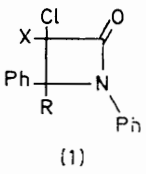
Syntheses of Heterocyclic Compounds. Part XXXIII.[1] Preparation and Reactions of 4-(2-Dialkylaminophenyl)azetidin-2-ones

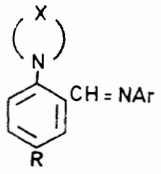
By **Robert L. Bentley** and **Hans Suschitzky,*** The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT, Lancashire

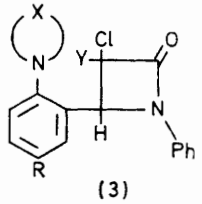
2-Dialkylaminobenzylideneanilines and various acid chlorides in presence of triethylamine were used to obtain the novel title compounds. Those β-lactams with an α-chloro-substituent underwent intramolecular cyclisation involving the dialkylamino-group with expulsion of the chlorine atom to give β-lactams bearing a fused indolinium system. Thermolysis of these fused β-lactams afforded various *N*-alkylindoles (with elimination of phenyl isocyanate). Aspects of stereochemistry, substituent effects, and alkaline or acidic hydrolysis of the fused β-lactams which lead to novel indole derivatives are described.

THE *in situ* generation of chloroketen was utilised recently [2] for the preparation of the β-lactam (1; R = Ph, X = H) from chloroacetyl chloride and a solution of diphenylmethyleneaniline and triethylamine in benzene at room temperature. Under similar conditions the 2-dialkylamino-5-nitrobenzylideneaniline (2; R = NO_2, X = $[CH_2]_5$, Ar = Ph) gave an intractable tarry [3] mixture, but the use of dichloroacetyl chloride furnished the azetidinone (3; R = NO_2, X = $[CH_2]_5$, Y = Cl) in 15% yield. We found, however, that when the reaction was carried out at 70 °C the yield of β-lactams (3a—d; R = NO_2, Y = Cl) was increased (50—80%). The dichloroacetyl chloride was slowly added as a dilute solution in benzene to the hot reaction mixture to keep the concentration of the intermediate dichloroketen to a minimum in order to retard polymerisation, particularly as an amine was present.[4] Monochloroacetyl chloride similarly gave fair yields of the appropriate 3-chloroazetidinones (3b—d; R = Y = H), but not (3a) and (3e) (*cf.* later). The formation of the β-lactams (3; R = H or NO_2, Y = H or Cl) is thus inhibited at room temperature but favoured at 70 °C. The inverse temperature effect was reported for the preparation of 3-chloro-1,4-diphenylazetidin-2-one (1; X = R = H) from benzylideneaniline, triethylamine, and chloroacetyl chloride, yielding 70% [2] of the β-lactam at room temperature and only 4% [5] at 70 °C. However, on repeating this reaction according to the reported method we obtained (contrary to the literature) only tar at room temperature, and a 60% yield in boiling benzene.



(1)



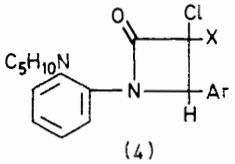


(3)

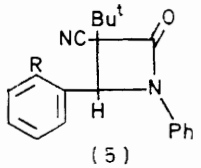
a; $[CH_2]_4$
b; $[CH_2]_5$
c; $[CH_2]_6$
d; $[CH_2]_2 \cdot O \cdot [CH_2]_2$
e; Me_2
f; Et_2

We prepared a number of dialkylaminophenylazetidin-2-ones from the Schiff's base (2) by using various acid chlorides as keten precursors (see Table 2 and Experimental section). Bromoacetyl bromide gave only intractable material with the Schiff's base (2; X = $[CH_2]_5$, R = H, Ar = Ph), which confirms the unsuitability of this keten precursor observed by others.[6] The dimethylamino-derivative (3e) was not isolable from the reaction in boiling benzene as it underwent a further reaction (see below). Cyano-t-butylketen,[7] which hitherto has not been made to react with anils, gave the α-cyano-α-t-butyl-β-lactams (5; R = $C_5H_{10}N$ or Me_2N) in good yield.

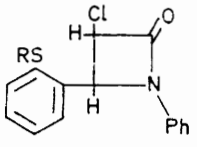
The thioethers (6; R = Ph or Bu^s) were also prepared, by an analogous method, in order to investigate the possibility of intramolecular interaction between the thiol group and the α-position of the β-lactam [*e.g.* (6) ⟶ (9)].



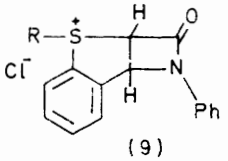
(4)



(5)



(6)



(9)

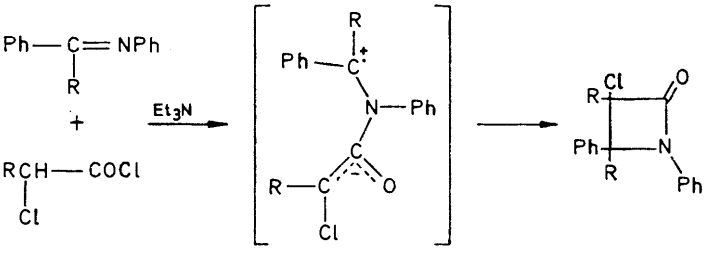
It has been established [5,6,8] that the coupling constant of vicinal protons in monocyclic β-lactams can be used to distinguish between *cis*- and *trans*-isomers ($J_{cis} > J_{trans}$). For instance Nelson [5] demonstrated that in 3-chloroazetidin-2-ones the coupling constant for the

[1] Part XXXII, S. S. Mathur and H. Suschitzky, *J.C.S. Perkin I*, 1975, 2479.
[2] F. Duran and L. Ghosez, *Tetrahedron Letters*, 1970, 245.
[3] J. S. Millership, Ph.D. Thesis, University of Salford, 1971.
[4] W. T. Brady and E. H. Hoff, jun., *J. Amer. Chem. Soc.*, 1968, **90**, 6256.
[5] D. A. Nelson, *Tetrahedron Letters*, 1971, 2543.
[6] A. K. Bose, C. S. Narayanan, and M. S. Manhas, *Chem. Comm.*, 1970, 975.
[7] H. W. Moore and W. Weyler, *J. Amer. Chem. Soc.*, 1970, **92**, 4132.
[8] A. Gomes and N. Jouille, *Chem. Comm.*, 1967, 935.

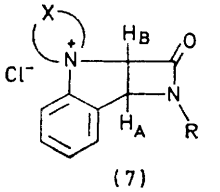
trans-isomer was *ca.* 2 and that for the *cis*-compound *ca.* 5 Hz. On this basis our dialkylaminophenyl β-lactams with vicinal protons (3; Y = H) were all assigned the *trans*-configuration as *J* was invariably *ca.* 2 Hz. No *cis*-isomers were detected. This is in keeping with reports [5] that the *trans*-3-chloroazetidin-2-one was the only isomer formed in the reaction of *o*-methoxybenzylideneaniline with chloroacetyl chloride. By contrast, the presence of an *ortho*-positioned, electron-withdrawing substituent on the *C*-aryl ring of the Schiff's base as in *N*-(*o*-nitrobenzylidene)-*p*-anisidine favoured formation of the *cis*-β-lactam, yielding a mixture in which the isomer ratio (*cis* : *trans*) was 50 : 50. Nelson's suggestion [5] that production of the *cis*-form in these cases is favoured at least partially by steric constraint is difficult to rationalise on the basis of these results. Moreover, greater steric strain in our 3-chloroazetidin-2-ones of type (3; Y = H) is indicated for the *cis*-isomer by molecular models. Some control on the *cis* : *trans* isomer ratio of β-lactams can be exerted in the reaction of azidoketen with anils by the mode of adding the keten precursor, azidoacetyl chloride.[9] However, this technique had no effect on the isomer formation of our dialkylamino-compounds (3; Y = H): the *trans*-isomer was invariably formed and not even traces of the *cis*-form were detected (n.m.r.). Epimerisation studies [6,10] also confirm that *trans*-isomers of 3-substituted 1,4-diphenylazetidin-2-ones are formed with greater ease.

The mechanism of the reaction between keten and Schiff's bases has been investigated by several workers.[8,11] All available evidence points to a two-step rather than a concerted pathway, involving an open-chain, dipolar intermediate as set out in Scheme 1.

The 4-(*o*-dialkylaminophenyl)azetidin-2-ones (3) were prepared to investigate the possibility of interaction between the tertiary amino-group and the β-lactam ring. We have shown that such a tertiary amino-effect [12] in *o*-substituted dialkylanilines can give rise to intramolecular cyclisation, which in the present case would lead to novel fused β-lactams. Such a ring closure occurred simply on heating the piperidino-lactam (3; R = Y = H, X = $[CH_2]_5$) under reflux in ethanol, producing the fused indolinium–β-lactam (7; R = Ph, X = $[CH_2]_5$) as a white, water-soluble, crystalline solid. The structural assignment is supported by elemental analysis, by an i.r. band at 1 760 cm^{-1} (C : O) and by its ^1H n.m.r. spectrum. The latter spectrum was similar to the parent compound (3b; R = Y = H) except for a significant downfield shift, especially of signals due to the α- and β-methylene protons in the piperidine ring, by *ca.* 1.1 and 0.5 p.p.m., respectively owing to deshielding by the quaternary nitrogen. Moreover, the coupling between the vicinal protons H_A and H_B was 5 Hz, whereas that in the starting material (3) was 1.5 Hz, indicating a change from *trans*- to *cis*-conformation during the internuclear cyclisation. Such an inversion of configuration is consistent with substitution at C-3 of the azetidinone ring. The importance of the relative positions of the interacting sites is emphasized by the fact that the ' reverse ' *trans*-β-lactams (4; Ar = Ph, *p*-$NO_2C_6H_4$, or *p*-$MeOC_6H_4$, X = H) were unchanged after being heated in boiling ethanol for 2 days. Solvent polarity affected the rate of internal salt formation. Whereas in boiling benzene the β-lactam (3b; R = Y = H) was stable indefinitely, it was converted into (7) in refluxing ethanol or acetonitrile within 1 h and in dimethyl sulphoxide at room temperature over 2 days. Addition of a small amount of water to its solution in boiling ethanol, methanol, or acetonitrile increased the rate of intramolecular displacement considerably. This at first sight appears unexpected but it may be rationalised on the basis that an uncharged reactant is converted into a charged product [(3) ⟶ (7)]. Analogous conversions were observed with the β-lactams (3c and d) to give the indolinium compounds (7;



SCHEME 1



(7)

R = Ph, X = $[CH_2]_6$ or $[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$), and also with the appropriate 1-alkyl-substituted lactams to give the fused ring structures (7; X = $[CH_2]_5$, R = C_6H_{11}, Bu^n, or $PhCH_2$) as viscous oils. We have already mentioned that neither the 2-pyrrolidino- nor the 2-dimethylaminobenzylideneaniline (2; R = H, Ar = Ph, X = $[CH_2]_4$ or Me_2) gave the expected β-lactam when treated with

[9] A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, 1967, **23**, 4769.

[10] J. L. Luche, H. B. Kagan, R. Parthasarathy, G. Tsoucaris, C. de Rango, and C. Zelwer, *Tetrahedron*, 1968, **24**, 1275.

[11] H. B. Kagan and J. L. Luche, *Tetrahedron Letters*, 1968, 3093; R. Huisgen, B. Davis, and M. Morikawa, *Angew. Chem. Internat. Edn.*, 1968, **7**, 826.

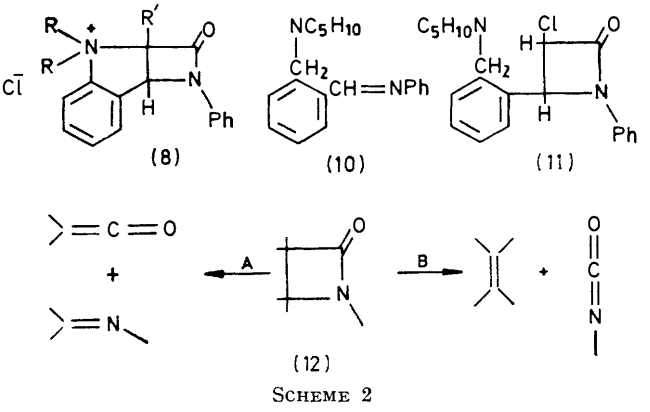
[12] O. Meth-Cohn and H. Suschitzky, *Adv. Heterocyclic Chem.*, 1972, **14**, 211.

chloroacetyl chloride. Instead, the fused β-lactams (7; R = Ph, X = $[CH_2]_4$ or Me_2) were formed directly, *via* the now unstable intermediate (3; Y = H, R, and X as before), possibly because of the greater nucleophilicity of these two dialkylamino-groups. The ^1H n.m.r. spectrum of the quaternary dimethyl compound (7; R = Ph, X = Me_3) shows the methyl groups as two separated three-proton singlets (at τ 5.7 and 5.9) because of their different environments in the fused structure. By contrast the *p*-nitro-substituted lactam (3; R = NO_2, Y = H) was unchanged after 2 days in boiling ethanol, owing to the reduced nucleophilicity of the piperidino-nitrogen atom. However, intramolecular substitution could be engendered at higher temperature (see below) Neither could the 3,3-dichloroazetidin-2-ones (3; R = H, Y = Cl, X = $[CH_2]_5$ or Me_2) be made to undergo internuclear cyclisation to give an indolinium system in boiling solvents (ethanol, dimethylformamide, or dimethyl sulphoxide). This lack of reactivity may be attributed at least in part to the electronic repulsion between the chlorine atom and the lone pair on the tertiary amino-nitrogen, which prevents attack on C-3 of the azetidinone ring. Not surprisingly, the nitro-derivatives (3a—d; R = NO_2, Y = Cl) too could not be made to cyclise. Substitution of a methyl group at C-3 of the azetidinone ring (3b—d; R = H, Y = Me) also prevented internal cyclisation, even on prolonged boiling in ethanol, except in the case of the dimethylamino-derivative (3e; R = H, Y = Me) which gave a 45% yield of the fused β-lactam (8; R = R′ = Me). Failure of these compounds to give the fused lactam except in the case of the more flexible dimethylamino-group is accounted for by steric overcrowding in an S_N2-type transition state. By contrast the phenyl-substituted lactams (3a—c; Y = Ph) were readily converted into the corresponding fused ring systems (8; R′ = Ph, RR = $[CH_2]_{4-6}$) in boiling ethanol. The increased reactivity of these α-phenyl β-lactams as compared to that of the α-methyl derivatives could be due to a change in the mechanism from an S_N2 to an S_N1 type.

No internal cyclisation was achieved with the cyano-t-butyl-lactam (5; R = $C_5H_{10}N$ or Me_2N), even on prolonged heating in high boiling aprotic dipolar solvents, probably owing to steric hindrance. Similarly, the thio-substituents in (6; R = Ph or Bu^s) did not give a sulphonium salt (9) even in refluxing solvents. Some decomposition occurred slowly, which may have been due to the instability of positively charged sulphur compounds.

Several workers have investigated nucleophilic reactions of α-halogeno-β-lactams, 6-halogenopenams [13] and 7-chlorocephems,[14] and found the halogen atom to be inert or only slightly reactive. It was suggested by Manhas and Bose [15] that this lack of reactivity may be due to excessive ring strain on the halogen-bearing atom in an S_N2 reaction. The azide ion was found to be only moderately successful in replacing the chlorine atom in a *trans*-α-chloro-β-lactam in hot dimethyl sulphoxide [16] after 24 h. We,[17] as well as other workers,[18] have found the preparation of α-azido-β-lactams by the displacement method generally unproductive. Against this background, the halogen reactivity in our α-chloro-β-lactam (3) towards the dialkylamino-nitrogen is remarkable, and may be attributed to the stereochemical and thermodynamic advantages associated with intramolecular reactions.

The β-lactams described so far are fused to a five-membered ring; it was of interest to explore the scope of the method by attempting fusion to a six-membered ring. The Schiff's base (10) needed for the preparation of the β-lactam (11) was obtained from aniline and the parent aldehyde, which was best made by reaction of n-butyl-lithium with *N*-benzylpiperidine followed by treatment of the intermediate *ortho*-lithio-compound with dimethylformamide. Treatment with chloroacetyl, dichloroacetyl, or 3-chloropropionyl chloride under various conditions in attempts to bring about lactam formation invariably yielded tars.

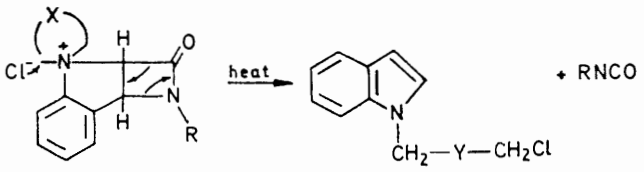


SCHEME 2

Two types of cleavage (Scheme 2, A and B) are observed to occur with β-lactams under electron impact [19] as well as by thermolysis.[20,21] Bicyclic β-lactams [22] are thermolysed usually at a lower temperature than monocyclic ones. We investigated the thermal stability of the fused azetidinones (7) prompted by the fragmentation patterns of their mass spectra. The highest mass peak of (7; X = $[CH_2]_5$, R = Ph) is at *m/e* = 221, consistent with loss of PhNCO from the molecular ion (M^+ 340). A similar elimination occurred on heating (7; X and R as above) in boiling xylene. The presence of phenyl isocyanate in the reaction mixture was confirmed by

[13] D. Hauser and H. P. Sigg, *Helv. Chim. Acta*, 1967, **50**, 1327.
[14] K. R. Henery-Logan and J. V. Rodricks, *J. Amer. Chem. Soc.*, 1963, **85**, 3524.
[15] M. S. Manhas and A. K. Bose, ' beta-Lactams, Natural and Synthetic, Part 1,' Interscience, New York, 1971, p. 96.
[16] M. D. Bachi and O. Goldberg, *J.C.S. Perkin I*, 1972, 2332.
[17] D. Johnson and H. Suschitzky, unpublished results.
[18] B. G. Chatterjee, V. V. Rao, and P. N. Moza, *Tetrahedron*, 1967, **23**, 499.
[19] M. Fischer, *Chem. Ber.*, 1968, **101**, 2669.
[20] H. Staudinger, *Ber.*, 1911, **44**, 521.
[21] L. A. Paquette, M. J. Wyvratt, and G. R. Allen, *J. Amer. Chem. Soc.*, 1970, **92**, 1763.
[22] R. D. G. Cooper and F. L. José, *J. Amer. Chem. Soc.*, 1970, **92**, 2575.

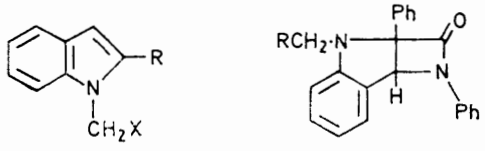
trapping with aniline to give diphenylurea. The other product no longer showed the typical lactam carbonyl i.r. band at 1 760 cm^{-1}. On the basis of its elemental analysis and spectral data [M^+ — PhNCO and isomer pattern corresponding to 1 Cl; n.m.r. bands at τ 2.8 (4 aromatic H), 2.85 and 3.6 (d, 1 aromatic H each), 6.2 and 6.8 (each t, 2H), and 8.6 (6 H)] the compound was found to be 1-(5-chloropentyl)indole (13; Y = $[CH_2]_3$), formed as set out in Scheme 3 in 95% yield. The



(7) (13)

SCHEME 3

comparative ease and high yield of these thermal conversions involving a retro-cycloaddition with loss of PhNCO as well as ring-opening of one of the spiran rings by nucleophilic attack of the chloride ion on the activated α-methylene group is ascribable to the strain of the system and the formation of stable products. The indole (14) could also be made directly from the monocyclic lactam (3b; R = Y = H) in boiling xylene in similar yield, *via* the fused ring intermediate (7), since



(14) (15)

the 3,3-dichloro-compounds (3; R = H, Y = Cl), which are stable in boiling xylene or bis-(2-methoxyethyl) ether, do not form fused β-lactams (see above).

Similarly, the fused β-lactams (7; X = $[CH_2]_4$, $[CH_2]_6$, or $[CH_2]_2$·O·$[CH_2]_2$) gave the novel *N*-alkylindoles (13; Y = $[CH_2]_2$, $[CH_2]_4$, or CH_2·O·CH_2) in refluxing xylene in excellent yield, and the dimethyl compound (7; X = Me_2) was converted quantitatively into *N*-methylindole by loss of phenyl isocyanate and presumably methyl chloride.

Even the nitro-substituted β-lactam (3b; R = NO_2, Y = H) fragmented on prolonged boiling in xylene (3 days) into *N*-(1-chloropentyl)-5-nitroindole in low yield, although the intermediate fused β-lactam could not be isolated as it was obviously unstable at the temperature necessary for its formation. The 3-chloro-3-methylazetidinones (3a—d; R = H, Y = Me) were stable in both xylene and bis-(2-methoxyethyl) ether but slowly decomposed into tars in boiling ethylene glycol. By contrast the dimethylamino-derivative (3e; R = H, Y = Me) gave a small yield of 1,2-dimethylindole when heated at 200 °C for 1 h. It is significant that this is the only 3-methyl derivative which could be converted into the corresponding fused β-lactam (8; R = R′ = Me) (see above). As expected the 3-cyano-3-t-butylazetidinones (5) were stable in boiling solvents even at 200 °C. Only concentrated sulphuric acid at 100 °C produced a reaction, converting the nitrile into an amide without affecting the lactam ring.

The 3-chloro-3-phenylazetidinones (3; R = H, Y = Ph) were far more ready to cyclise intramolecularly than other 3,3-disubstituted derivatives. Thus the 3-chloro-3-phenylazetidinones (3a—d; R = H, Y = Ph) were converted quantitatively into the corresponding 1-(ω-chloroalkyl)-2-phenylindoles (14; R = Ph, X = $[CH_2]_3$-Cl, $[CH_2]_4Cl$, and CH_2·O·$[CH_2]_2Cl$) in boiling xylene. In addition some of the 3-chloro-3-phenylazetidinones (3; R = H, Y = Ph) differed in their behaviour from the 3-chloro-analogues (3; R = Y = H). The dimethylamino-compound (3e; R = H, Y = Ph) was obtained from the appropriate Schiff's base and α-chlorophenylacetyl chloride in the presence of triethylamine only at room temperature in benzene. In boiling benzene the above reactants unexpectedly produced the uncharged fused β-lactam (15; R = H), presumably formed by way of the quaternary salt (8; R′ = Ph, R = Me) with loss of methyl chloride. Attempts to produce the salt (8; R′ = Ph, R = Me) from the dimethylamino-β-lactam failed, in contrast to the behaviour of the dimethylamino-α-lactam (3e; R = Y = H) as described above. The uncharged fused β-lactam (15; R = H) proved unstable; it was quickly and quantitatively converted in hot ethanol and slowly in boiling benzene into 1-methyl-2-phenylindole (14; X = H, R = Ph) with elimination of phenyl isocyanate. Analogous reactions were achieved with the 3-chloro-3-phenyl analogues (3a—c; R = H, Y = Ph) by a careful choice of conditions (see Experimental section), according to the sequence set out in Scheme 4, often quantitatively in some of the steps. In the case of the morpholino-derivative (3d; R = H, Y = Ph) it was not possible to produce the salt (7; R = Ph, X = $[CH_2]_2$·O·$[CH_2]_2$) or the indolo-β-lactam (15; R = CH_2·O·$[CH_2]_2Cl$), as the starting material (3d) was either not affected by the hot solvent (ethanol) or directly converted to the 2-phenylindole (14; X = CH_2·O·$[CH_2]_2Cl$, R = Ph). The nonconformity of this derivative (3d) could be due to the reduced nucleophilicity of the morpholino-nitrogen atom as compared with those of the other amines.[23] It thus appears that formation of the fused β-lactam (7) occurs at higher temperature when the products intermediate in the chain of events leading to (14) (see Scheme 4) are unstable.

(3a—c and e; R = H, Y = Ph) ⟶
(8; R¹ = Ph, RR = $[CH_2]_{4-6}$) ⟶
(15; R = H, or $[CH_2]_{3-5}Cl$) ⟶ (14; R = Ph, X as R in 15)

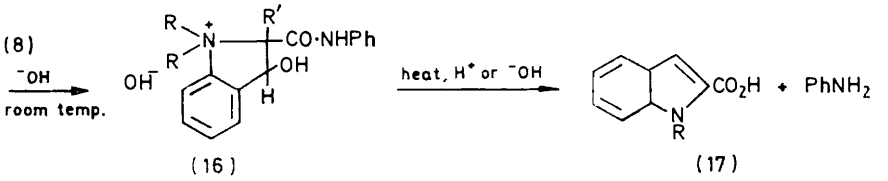
SCHEME 4

It is not clear why in the non-phenylated β-lactams (3; R = Y = H), the analogue to the indolo-β-lactam

[23] H. Suhr, *Annalen*, 1965, **687**, 175; 1965, **689**, 111; A. J. Gordon and R. A. Ford, 'The Chemist's Companion, A Handbook of Practical Data,' Wiley, New York, 1972, p. 59.

(15) was not isolable but easily lost phenyl isocyanate to give the *N*-alkylindole (13). It can only be concluded that the presence of the phenyl group (*a*) facilitates nucleophilic fission of the polymethylene ring in (8), possibly by 'steric squeezing', and (*b*) stabilises the indolo-lactam (15).

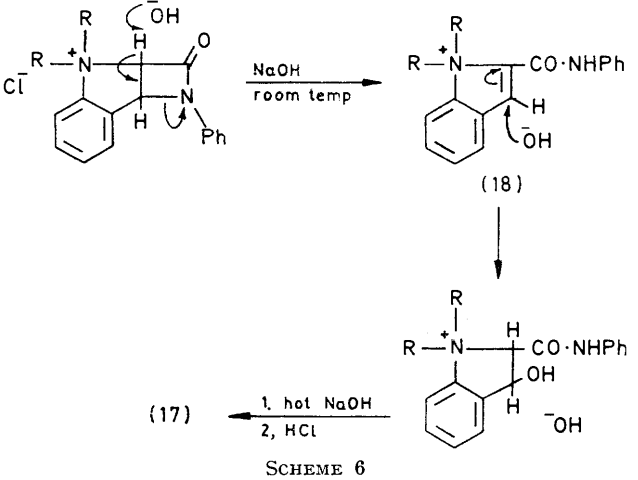
It is well established that fusion of the β-lactam ring, particularly to a five-membered ring, make it susceptible to hydrolysis.[24] The substituents present on the β-lactam ring may also affect both the rate and mode of hydrolysis.[15,25] It was, therefore, of interest to investigate the influence of ring fusion as well as of the substituent pattern on the hydrolytic behaviour of our novel β-lactams.



SCHEME 5

Addition of dilute aqueous sodium hydroxide to an aqueous solution of the quaternary β-lactam (8; R = Me, R′ = H) produced within minutes a precipitate. Its i.r. spectrum indicated cleavage of the lactam ring [bands at 1 640 (C:O) and 3 300 and 3 400 (NH and OH), and no band at 1 760 cm^{-1}]. Its ^1H n.m.r. spectrum confirmed that the quaternary nitrogen ring had been retained [separate bands at τ 6.21 and 6.5 (s, 2 Me) and complex bands at 2.45 and 3.15 (m, 4 H and 5 H, respectively, aromatic)] thereby confirming the conversion into the indolinium structure (16; R = Me, R′ = H). The hydrolysis product (16) gradually dissolved in hot aqueous 4M-hydroxide, and acidification gave *N*-methylindole-2-carboxylic acid (17; R = Me) and aniline. The changes are consistent with Scheme 5 (R = Me, R′ = H). At room temperature, cleavage of the N–C(4) bond of the lactam thus occurs to give the amide (16), which on boiling in sodium hydroxide loses aniline, water, and presumably methanol to give the 1,2-disubstituted indole (17). The following mechanism is suggested to account for the hydrolysis steps (Scheme 6): abstraction of the 3-proton of the azetidinone ring by base (facilitated by the vicinity of the quaternary nitrogen and the carbonyl group), followed by fission of the β-lactam to yield the intermediate (18), which as an αβ-unsaturated carbonyl compound suffers nucleophilic attack by ⁻OH at its β-carbon atom, assisted further by the quaternary structure. Support for the proposed mechanism is provided by resistance of (8; R = Me, R′ = H) to hydrolysis in boiling hydrochloric acid and by the inability of sodium hydroxide solution to effect any changes in the phenyl-substituted indolinium–β-lactam (8; RR = $[CH_2]_n$, R′ = Ph), which lacks the significant proton. Alkaline hydrolysis of the homologues (7; X = $[CH_2]_{4-6}$) proceeded in an analogous way yielding the corresponding amides (16; RR = $[CH_2]_{4-6}$, R′ = H). Unlike the dimethyl-substituted compound (16; R′ = H, R = Me) these amides did not readily undergo further hydrolysis in boiling sodium hydroxide solution. In preference, hydrolysis occurred at this stage with boiling aqueous 15% hydrochloric acid to give the corresponding *N*-(ω-chloroalkyl)indole-2-carboxylic acids (17; R = $[CH_2]_{4-6}Cl$). Boiling hydrochloric acid also effected hydrolysis of the dimethyl compound (16; R′ = H, R = Me). Prolonged heating of the amides (16; RR = $[CH_2]_{5-6}$, R′ = H) in 2M-sodium hydroxide solution gave a 50—60% yield of the corresponding *N*-(ω-hydroxyalkyl)indoles (17; R = $[CH_2]_{5-6}$·OH), whereas the pyrrolidino compound gave only intractable tars.

Finally, treatment of the monocyclic β-lactam (3; R = Y = H) in ethanolic sodium hydroxide under reflux gave *N*-(5-hydroxypentyl)indole-2-carboxylic acid (14; R = CO_2H, X = $[CH_2]_4$·OH), probably *via* the fused lactam (7; R = Ph, X = $[CH_2]_5$).



SCHEME 6

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 257 instrument for liquid films or Nujol mulls, ^1H n.m.r. spectra on a Varian A60A or EM360 instrument for solutions in deuteriochloroform unless stated otherwise, and mass spectra on an A.E.I. MS12 instrument. M.p.s were determined on a Buchi apparatus or a Kofler hot stage.

[24] R. H. Earle, D. T. Hurst, and M. Viney, *J. Chem. Soc.* (*C*), 1969, 2093.

[25] M. Perelman and S. A. Mizsak, *J. Amer. Chem. Soc.*, 1962, **84**, 4988; G. Opitz and J. Koch, *Angew. Chem. Internat. Edn.*, 1963, **2**, 152; A. K. Bose and I. Kugajevsky, *Tetrahedron*, 1967, **23**, 957.

(A) *Preparation of Aldehydes.*—2-Dialkylamino-5-nitrobenzaldehydes and 2-dialkylaminobenzaldehydes were made by published methods.[26-28]

2-(*Piperidinomethyl*)*benzaldehyde*. To an ice-cold solution of *N*-benzylpiperidine (8.75 g, 0.05 mol.) in sodium-dried ether (100 ml) was added n-butyl-lithium (30 ml of a solution in hexane containing 0.002 3 mol ml^{-1}, 0.069 mol). The mixture was stirred under nitrogen at 0 °C for 30 min and then allowed to warm to room temperature. The clear solution was stored at room temperature for 2 days then cooled in an ice-bath while a solution of dry *NN*-dimethylformamide (5.04 g, 0.069 mol) in dry ether (30 ml) was added dropwise over 30 min. The mixture was stirred at room temperature for 12 h, then poured onto ice, and the product was extracted with ether. The extract was washed with water (2 × 20 ml), dried ($MgSO_4$), evaporated, and distilled. The fraction of b.p. 140—150° at 1.5 mmHg was collected (7.5 g) and redistilled to give 2-(*piperidinomethyl*)*benzaldehyde*, b.p. 135° at 0.9 mmHg (5.3 g, 52%), $\nu_{max.}$ 1 700 cm^{-1} (C=O) (Found: C, 77.0; H, 8.3; N, 7.0. $C_{13}H_{17}NO$ requires C, 76.8; H, 8.4; N, 6.9%).

(B) *Preparation of Schiff's Bases.*—2-Dialkylamino-5-nitrobenzylideneanilines were prepared as reported.[3]

2-*Dialkylaminobenzylideneanilines*. To the appropriate freshly distilled 2-dialkylaminobenzaldehyde (0.10 mol) in benzene (50 ml) were added redistilled aniline (0.10 mol) and toluene-4-sulphonic acid (1 crystal). The solution was refluxed in a Dean–Stark apparatus until the theoretical amount of water had been collected, then cooled and filtered. The benzene was removed on a steam-bath *in vacuo*. 2-Piperidinobenzylideneaniline was obtained as a yellow solid, m.p. 53—54° [from light petroleum (b.p. 40—60°)]; the other Schiff's bases (Table 1) were liquids. 2-(*Phenylthio*)*benzylideneaniline* was prepared as above as a yellow oil (Found: C, 79.2; H, 5.0; N, 4.7. $C_{19}H_{15}NS$ requires C, 78.9; H, 5.2; N, 4.8%). 2-(*s-Butylthio*)*benzylideneaniline* was obtained by the same method (Found: C, 75.5; H, 6.9; N, 5.3. $C_{17}H_{19}NS$ requires C, 75.8; H, 7.1; N, 5.2%).

[26] K. Niewiadomski and H. Suschitzky, *J.C.S. Perkin I*, 1975, 1670.

(C) *Preparation of Monocyclic β-Lactams.—General method*. To a stirred solution of the appropriate Schiff's base (0.01 mol) and triethylamine (0.015 mol) in sodium-dried benzene (80 ml), maintained at reflux temperature, was added a solution of the appropriate acid chloride (0.01 mol) in dry benzene (50 ml), dropwise over 2 h. Stirring was then continued for an additional 15 min, and the solution allowed to cool. Triethylamine hydrochloride was removed by filtration and washed with benzene (20 ml). The combined filtrates were evaporated to give the crude β-lactam, which was purified by recrystallisation. If the reaction mixture was tarry the β-lactam was initially purified by filtration through a column of type H alumina (15 × 4 cm; eluted with benzene). The properties of the 4-(2-dialkylaminophenyl)azetidin-2-ones are given in Table 2.

trans-3-*Chloro*-4-*phenyl*-1-(2-*piperidinophenyl*)*azetidin*-2-*one*, white prisms from methanol (64%), had m.p. 154°, $\nu_{max.}$ 1 775 cm^{-1} (C=O) (Found: C, 70.1; H, 6.1; N, 8.2. $C_{20}H_{21}ClN_2O$ requires C, 70.5; H, 6.2; N, 8.2%). trans-3-*Chloro*-4-(4-*methoxyphenyl*)-1-(2-*piperidinophenyl*)*azetidin*-2-*one*, white plates from ethanol (72%), had m.p. 135—136°, $\nu_{max.}$ 1 780 cm^{-1} (C=O) (Found: C, 67.7; H, 6.3; N, 7.5. $C_{21}H_{23}ClN_2O_2$ requires C, 68.0; H, 6.3; N, 7.6%). trans-3-*Chloro*-4-(3-*nitrophenyl*)-1-(2-*piperidinophenyl*)*azetidin*-2-*one*, pale-yellow needles from ethanol–water (11%), had m.p. 131°, $\nu_{max.}$ 1 780 cm^{-1} (C=O) (Found: C, 62.3; H, 5.4; N, 10.9. $C_{20}H_{20}ClN_3O_3$ requires C, 62.3; H, 5.2; N, 10.9%). 3,3-*Dichloro*-4-(3-*nitrophenyl*)-1-(2-*piperidinophenyl*)*azetidin*-2-*one*, yellow prisms from 3 : 1 ethanol–ethyl acetate (60%), had m.p. 157—158°, $\nu_{max.}$ 1 795 cm^{-1} (C=O) (Found: C, 56.6; H, 4.4; N, 9.9. $C_{20}H_{19}Cl_2N_3O_3$ requires C, 57.1; H, 4.6; N, 10.0%). 3,3-*Dichloro*-4-(4-*nitrophenyl*)-1-(2-*piperidinophenyl*)*azetidin*-2-*one*, pale-yellow prisms from ethanol (43%), had m.p. 144—146°, $\nu_{max.}$ 1 790 cm^{-1} (C=O) (Found: C, 56.9; H, 4.4; N, 9.8. $C_{20}H_{19}Cl_2N_3O_3$ requires C, 57.1; H, 4.6; N, 10.0%). trans-3-*Chloro*-1-*phenyl*-4-(2-*phenylthiophenyl*)*azetidin*-2-*one* (6; R = Ph), prisms from chloroform (58%), had m.p. 98—100°, $\nu_{max.}$ 1 765 cm^{-1} (C=O) (Found: C, 68.7; H, 4.5; N, 4.0. $C_{21}H_{16}ClNOS$ requires C, 69.0; H, 4.4; N, 3.8%). trans-3-*Chloro*-1-*phenyl*-4-(2-*s-butylthiophenyl*)*azetidin*-2-*one*, pale yellow oil after chromatography on alumina with benzene eluant (52%), had $\nu_{max.}$ 1 770 cm^{-1} (C=O) (Found: C, 66.6; H, 6.2; N, 3.7. $C_{19}H_{20}ClNOS$ requires C, 66.0; H, 5.8; N, 4.1%).

(D) *Intramolecular Cyclisation of* 3-*Chloro*-4-(2-*dialkylaminophenyl*)*azetidin*-2-*ones.*—(i) 2,2a,3,7b-*Tetrahydro*-3,3-*dimethyl*-2-*oxo*-1-*phenyl*-1H-*azeto*[3,2-b]*indolium chloride* (7; X = Me_2, R = Ph). *N*-(2-Dimethylaminobenzylidene)aniline (2.24 g) was treated with chloroacetyl chloride (1.1 g) and triethylamine (1.1 g) by the general method given above

[27] D. B. Mobbs, Ph.D. Thesis, University of Salford, 1967.

[28] G. V. Garner, D. B. Mobbs, H. Suschitzky, and J. S. Millership, *J. Chem. Soc.* (*C*), 1971, 3693.

TABLE 1

N-(2-Dialkylaminobenzylidene)anilines (2; Ar = Ph, R = H)

X	M^+	$\nu_{C=N}$/ cm^{-1}	Found (%) C	H	N	Formula	Required (%) C	H	N
NMe_2	224	1 630	80.0	7.1	12.5	$C_{15}H_{16}N_2$	80.3	7.2	12.5
NEt_2	252	1 635	81.2	7.8	11.0	$C_{17}H_{20}N_2$	80.9	8.0	11.1
$[CH_2]_4$	250	1 630	81.2	7.4	11.0	$C_{17}H_{18}N_2$	81.6	7.2	11.2
$[CH_2]_5$	264	1 635	81.4	7.8	10.6	$C_{18}H_{20}N_2$	81.8	7.6	10.6
$[CH_2]_6$	278	1 630	82.0	8.2	10.2	$C_{19}H_{22}N_2$	82.0	7.9	10.1
$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	266	1 630	77.0	7.0	10.3	$C_{17}H_{18}N_2O$	76.7	6.8	10.5

2-*Formylphenyl thioethers*. 2-Fluorobenzaldehyde (0.05 mol), the appropriate thiol (0.055 mol), propan-2-ol (40 ml), and potassium carbonate (0.055 mol) were stirred under reflux for 20 h, cooled, and poured into water (100 ml). The precipitated oil was extracted into chloroform and the extract washed with water (2 × 50 ml), dried ($MgSO_4$), and evaporated; the product was purified by distillation. 2-(*Phenylthio*)*benzaldehyde* (70%) had b.p. 161—163° at 0.7 mmHg, $\nu_{max.}$ 1 700 cm^{-1} (C=O) (Found: C, 73.2; H, 4.6. $C_{13}H_{10}OS$ requires C, 72.9; H, 4.7%). 2-(*s-Butylthio*)*benzaldehyde* (51%) had b.p. 110—112° at 0.2 mmHg, $\nu_{max.}$ 1 700 cm^{-1} (C=O) (Found: C, 67.8; H, 7.4. $C_{11}H_{14}OS$ requires C, 68.0; H, 7.3%).

for the preparation of monocyclic β-lactams. Removal of the benzene left an oil which partially crystallised on trituration with ethyl acetate. The title *compound* was filtered off and recrystallised from ethyl acetate containing a few drops of methanol (yield 1.5 g, 49%); m.p. 230° (Found: C, 64.4; H, 5.8; N, 8.6; $C_{17}H_{17}ClN_2O$, H_2O requires C, 64.0; H, 6.0; N, 8.8%); $\nu_{max.}$ 1 760 cm^{-1} (C=O); τ [$(CD_3)_2SO$] 1.80—2.85 (m, 8 aromatic H), 1.62 (q, 1 aromatic H), 3.64 (1 H, d) and 3.83 (1 H, d) (*J* 4.5 Hz), 5.98 (3 H, s), and 6.17 (3 H, s).

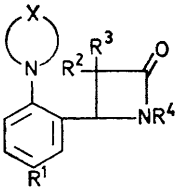
(ii) 2,2a,3,7b-*Tetrahydro*-2-*oxo*-1-*phenylspiro*-[1H-*azeto*[3,-2-b]*indolium*-3,1′-*pyrrolidinium*]*chloride* (7; X = $[CH_2]_4$, R = Ph). This *compound* was prepared from *N*-(2-pyrrolidinobenzylidene)aniline (2.5 g) as in (i); yield 1.4 g (41%); m.p. 172° (decomp.) (Found: C, 66.7; H, 5.8; N, 7.8. $C_{19}H_{19}ClN_2O,H_2O$ requires C, 66.2; H, 6.1; N, 8.1%); τ [$(CD_3)_2SO$] 2.10—2.95 (m, 8 aromatic H), 1.55 (q, 1 aromatic H), 3.35 (1 H, d) and 3.65 (1 H, d) (*J* 5.0 Hz), 5.20 (2 H, m), 5.73 (2 H, m), and 7.40br (4 H, s).

(iii) 2,2a,3,7b-*Tetrahydro*-2-*oxo*-1-*phenylspiro*-[1H-*azeto*[3,2-b]*indolium*-3,1′-*piperidinium*], -3,1′-*perhydroazepinium*], *and* -3,4′-*morpholinium*] (7; X = $[CH_2]_5$, $[CH_2]_6$, *or* $[CH_2]_2$·O·$[CH_2]_2$, R = Ph). The appropriate 3-chloro-4-(2-dialkylaminophenyl)-1-phenylazetidin-2-one (3b—d; Y = R = H) (0.01 mol) was heated under reflux in 95% ethanol (50 ml), the reaction being followed by t.l.c. When all the starting material had disappeared (1 h for X = $[CH_2]_5$, 3 h for X = $[CH_2]_6$, and 48 h for X = $[CH_2]_2$·O·$[CH_2]_2$) the reflux condenser was removed and the solution was boiled while ethyl acetate was added at such a rate that the volume remained approximately constant. When turbidity developed the addition was stopped and the solution was set aside to crystallise. The *piperidinium salt* (7; X = $[CH_2]_5$, R = Ph) (92%) had m.p. 183° (decomp.), $\nu_{max.}$ 1 760 cm^{-1} (C=O) (Found: C, 67.1; H, 6.2; N, 8.0. $C_{20}H_{21}ClN_2O$, H_2O requires C, 66.9; H, 6.5; N, 7.8%); τ [$(CD_3)_2SO$] (q, 1 aromatic H), 2.10—2.85 (m, 8 aromatic H), 3.27 (1 H, d) and 3.65 (1 H, d) (*J* 5.0 Hz), 5.60 (2 H, m), 6.10 (2 H, m), and 7.85br (6 H, s). The *perhydroazepinium salt* (7; X = $[CH_2]_6$, R = Ph) (78%) had m.p. 167° (decomp.), $\nu_{max.}$ 1 760 cm^{-1} (C=O) (Found: C, 68.0; H, 6.5; N, 7.7. $C_{21}H_{23}ClN_2O,H_2O$ requires C, 67.6; H, 6.8; N, 7.5%); τ [$(CD_3)_2SO$] 1.60 (1, 1 aromatic H), 1.84—2.85 (m, 8 aromatic H), 3.37 (1 H, d) and 3.63 (1 H, d) (*J* 4.5 Hz), 5.35 (2 H, m), 6.05 (2 H, m), and 7.90br (8 H, s). The *morpholinium salt* (7; X = $[CH_2]_2$·O·$[CH_2]_2$, R = Ph) (39%) had m.p. 188° (decomp.), $\nu_{max.}$ 1 760 cm^{-1} (C=O) (Found: C, 62.9; H, 6.1; N, 8.0. $C_{19}H_{19}ClN_2O_2$, H_2O requires C, 6.23; H, 5.9; N, 7.8%); τ [$(CD_3)_2SO$] 1.65 (q, 1 aromatic H), 1.75—2.50 (m, 8 aromatic H), 3.20 (1 H, d) and 3.45 (1 H, d) (*J* 5.0 Hz), 5.35br (4 H, d), and 6.05 (4 H, m).

(iv) 2,2a,3,7b-*Tetrahydro*-3,3,7b-*trimethyl*-2-*oxo*-1-*phenyl*-1H-*azeto*[3,2-b]*indolium chloride* (8; R = R′ = Me). 3-Chloro-4-(2-dimethylaminophenyl)-3-methyl-1-phenylazetidin-2-one (3e; R = H, Y = Me) (3.14 g) was heated under reflux in 95% ethanol (50 ml) for 1 week and the product was worked up as in (iii) to give the title *compound* (1.5 g, 45%) as pale-pink needles, m.p. 150° (decomp.) (Found:

TABLE 2

Properties of the 4-(2-dialkylaminophenyl)azetidin-2-ones



X	R^1	R^2	R^3	R^4	Yield (%)	M.p. (°C)	$\nu_{C=N}$/ cm^{-1}	Found (%) C	H	N	Formula	Required (%) C	H	N
$[CH_2]_4$	NO_2	Cl	Cl	Ph	75	225	1 785	55.8	4.3	10.2	$C_{19}H_{17}Cl_2N_3O_3$	56.2	4.2	10.3
$[CH_2]_5$	NO_2	Cl	Cl	Ph	85	209	1 790	56.9	4.4	9.7	$C_{20}H_{19}Cl_2N_3O_3$	57.1	4.6	10.0
$[CH_2]_6$	NO_2	Cl	Cl	Ph	49	172	1 790	58.2	5.0	9.8	$C_{21}H_{21}Cl_2N_3O_3$	58.1	4.9	9.7
$[CH_2]_2$·O·$[CH_2]_2$	NO_2	Cl	Cl	Ph	52	202	1 785	54.0	4.2	9.9	$C_{19}H_{17}Cl_2N_3O_4$	54.0	4.1	9.9
$[CH_2]_5$	H	Cl	H *	Ph	55	132	1 760	70.2	6.0	8.2	$C_{20}H_{21}ClN_2O$	70.5	6.2	8.2
$[CH_2]_6$	H	Cl	H *	Ph	52	106	1 765	70.9	6.5	7.8	$C_{21}H_{23}ClN_2O$	71.1	6.5	7.9
$[CH_2]_2$·O·$[CH_2]_2$	H	Cl	H *	Ph	25	168	1 760	66.3	5.3	8.2	$C_{19}H_{19}ClN_2O_2$	66.6	5.4	8.2
Me_2	H	Me	Cl	Ph	64	121—122	1 765	69.0	5.9	8.8	$C_{18}H_{19}ClN_2O$	68.7	6.1	8.9
$[CH_2]_4$	H	Me	Cl	Ph	61	178—180	1 760	70.1	6.0	8.3	$C_{20}H_{21}ClN_2O$	70.5	6.2	8.2
$[CH_2]_5$	H	Me	Cl	Ph	65	142—145	1 770	69.9	6.4	8.1	$C_{21}H_{23}ClN_2O$	71.1	6.5	7.9
$[CH_2]_6$	H	Me	Cl	Ph	54	140—141	1 760	71.9	6.6	7.6	$C_{22}H_{25}ClN_2O$	71.6	6.8	7.6
Me_2	H	Ph	Cl	Ph	10	124	1 760	73.1	5.5	7.5	$C_{23}H_{21}ClN_2O$	73.3	5.6	7.4
$[CH_2]_4$	H	Ph	Cl	Ph	63	135—137 †	1 765	74.4	5.3	7.1	$C_{25}H_{23}ClN_2O$	74.5	5.7	6.9
$[CH_2]_5$	H	Ph	Cl	Ph	75	144—147 †	1 760	75.2	6.0	6.6	$C_{20}H_{25}ClN_2O$	74.9	6.0	6.7
$[CH_2]_6$	H	Ph	Cl	Ph	32	148	1 770	75.4	6.0	6.2	$C_{27}H_{27}ClN_2O$	75.4	6.3	6.5
$[CH_2]_2$·O·$[CH_2]_2$	H	Ph	Cl	Ph	60	150—152 †	1 760	71.5	5.3	6.5	$C_{25}H_{23}ClN_2O_2$	71.7	5.5	6.7
$[CH_2]_5$	H	Cl	Cl	Ph	83	131	1 785	64.0	5.5	7.4	$C_{20}H_{20}Cl_2N_2O$	64.0	5.4	7.5
Me_2	H	Cl	Cl	Ph	65	121—122	1 780	60.8	4.9	8.2	$C_{17}H_{16}Cl_2N_2O$	60.9	4.8	8.3
$[CH_2]_5$	H	Me	H *	Ph	66	125—126	1 760	78.7	7.6	8.5	$C_{21}C_{24}N_2O$	78.7	7.5	8.7
$[CH_2]_5$	H	OPh	H *	Ph	75	172—173	1 750	78.3	6.4	6.8	$C_{26}H_{26}N_2O_2$	78.4	6.6	7.0
$[CH_2]_5$	H	Cl	H *	C_6H_{11}	24	89—90	1 775	69.0	7.9	8.0	$C_{20}H_{27}ClN_2O$	69.2	7.8	8.1
$[CH_2]_5$	H	Cl	H *	Bu^n	44	67—68	1 775	67.2	8.0	8.5	$C_{18}H_{25}ClN_2O$	67.4	7.8	8.7
$[CH_2]_5$	H	Cl	H *	CH_2Ph	66	122—123	1 770	71.0	6.4	7.8	$C_{21}H_{23}ClN_2O$	71.4	6.5	7.9
$[CH_2]_5$	H	CN	Bu^t	Ph	67	174—175	1 760	77.3	7.4	10.9	$C_{25}H_{29}N_3O$	77.5	7.5	10.9
Me_2	H	CN	Bu^t	Ph	68	196—197	1 760	75.8	7.0	12.0	$C_{22}H_{25}N_3O$	76.0	7.2	12.1

* *trans* by ^1H n.m.r. † Decomp.

C, 64.5; H, 6.2; N, 8.1. $C_{18}H_{19}ClN_2O$, requires C, 64.9; H, 6.4; N, 8.4%); τ [$(CD_3)_2SO$] 1.70 (1 H, q), 2.05—3.10 (m, 8 aromatic H), 4.05 (1 H, s), 6.08 (3 H, s), 6.25 (3 H, s), and 7.85 (3 H, s).

(E) *Preparation of* 1-*Alkylindoles*.—(i) 1-(ω-*Chloroalkyl*)-*indoles* (13). The appropriate 3-chloro-4-(2-dialkylaminophenyl)-1-phenylazetidin-2-one (3; R = Y = H) (1.0 g) or the appropriate fused azetidinone (7) (1.0 g) was heated in boiling xylene (20 ml) until all the starting material had disappeared (t.l.c.; 2—12 h). The solution was cooled and the xylene removed *in vacuo*. The residual oil was chromatographed on alumina with benzene as eluant. In each case the first fraction was 1-(ω-chloroalkyl)indole, which was purified by distillation (Kugelrohr); for details see Table 3. The ^1H n.m.r. spectra were in agreement with the assigned structures.

In one experiment 3-chloro-1-phenyl-4-(2-piperidinophenyl)azetidin-2-one (3b; R = H = Y) (1.0 g) was thermolysed as above and the xylene was distilled into a solution of aniline (0.5 g) in benzene (5 ml). On evaporation of the solvent, diphenylurea, m.p. 236—238° (lit.,[29] 238°) separated, identical [i.r. spectrum and mixed m.p. (236—237°)] with an authentic sample.

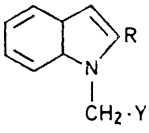
R = H, Y = Ph). The title compounds were prepared by the method given in (C), and purified by column chromatography on alumina [light petroleum (b.p. 60—80°) as eluant] followed by recrystallisation from the same solvent. For 3-chloro-4-(2-dimethylaminophenyl)-1,3-diphenylazetidin-2-one (3e; R = H, Y = Ph) the reaction was carried out at room temperature.

(ii) 2,2a,3,7b-*Tetrahydro*-2-*oxo*-1,7b-*diphenylspiro*-[1H-*azeto*[3,2-b]*indolium*-3-1′-*piperidinium*]*chloride* (8; R′ = Ph, RR = $[CH_2]_5$). 3-Chloro-1,3-diphenyl-4-(2-piperidinophenyl)azetidin-2-one (3b; Y = Ph, R = H) (1.0 g) was heated under reflux in 95% ethanol (20 ml) for 2 h. The solution was evaporated while ethyl acetate was added dropwise to keep the volume constant. When the mixture became cloudy the solution was set aside to crystallise. The *chloride* (0.9 g, 90%) had m.p. 155° (decomp.); $\nu_{max.}$ 1 760 cm^{-1} (C=O) (Found: C, 72.1; H, 5.9; N, 6.4. $C_{26}H_{25}ClN_2O,H_2O$ requires C, 71.8; H, 6.2; N, 6.4%).

2,2a,3,7b-*Tetrahydro*-2-*oxo*-1,7b-*diphenylspiro*-[1H-*azeto*-[3,2-b]*indolium*-3,1′-*perhydroazepinium*] *chloride* (8; R′ = Ph, RR = $[CH_2]_6$). 3-Chloro-4-(2-perhydroazepin-1-ylphenyl)-1,3-diphenylazetidin-2-one (3c; R = H, Y = Ph) (1.0 g) was heated in 95% ethanol for 12 h and the product

TABLE 3

1-(ω-Chloroalkyl)indoles



Y	R	Yield (%)	M^+	Found (%) C	H	N	Formula	Required (%) C	H	N
$[CH_2]_2$	H	90	207	69.6	6.7	7.0	$C_{12}H_{14}ClN$	69.4	6.8	6.8
$[CH_2]_3$	H	95	221	70.1	7.2	6.4	$C_{13}H_{16}ClN$	70.4	7.3	6.3
$[CH_2]_4$	H	91	235	71.5	7.7	6.1	$C_{14}H_{18}ClN$	71.3	7.7	5.9
$[CH_2{\cdot}O{\cdot}CH_2]$	H	94	223	64.1	6.5	6.4	$C_{12}H_{14}ClNO$	64.4	6.3	6.3
$[CH_2]_2$	Ph	91	283	76.2	6.3	4.8	$C_{18}H_{18}ClN$	76.2	6.4	4.9
$[CH_2]_3$	Ph	95	297	76.7	6.5	4.6	$C_{19}H_{20}ClN$	76.6	6.7	4.7
$[CH_2]_4$	Ph	90	311	76.9	6.9	4.5	$C_{20}H_{22}ClN$	77.1	7.1	4.5
$[CH_2{\cdot}O{\cdot}CH_2]$	Ph	85	299	72.2	6.2	4.8	$C_{18}H_{18}ClNO$	72.1	6.0	4.7

(ii) 1-*Methylindole*. Compound (7; X = Me_2, R = Ph) (2.8 g) was thermolysed in xylene (50 ml) as in (i). Column chromatography on alumina with benzene as eluant gave 1-methylindole (1.1 g, 85%), identical with an authentic sample.

(iii) 1-(5-*Chloropentyl*)-5-*nitroindole*. 3-Chloro-4-(5-nitro-2-piperidinophenyl)-1-phenylazetidin-2-one (3b; Y = H, R = NO_2) (2.8 g) was heated in boiling xylene (50 ml) for 3 days. The dark solution was cooled and the xylene distilled off *in vacuo*. The tarry residue was chromatographed on alumina with benzene as eluant to give as the first fraction the *indole* (0.8 g, 30%), m.p. 60—61° [from light petroleum (b.p. 60—80°)] (Found: C, 58.9; H, 5.4; N, 10.5. $C_{13}H_{15}ClN_2O_2$ requires C, 58.7; H, 5.6; N, 10.5%).

(iv) 1,2-*Dimethylindole*. 3-Chloro-4-(2-dimethylaminophenyl)-3-methyl-1-phenylazetidin-2-one (3e; Y = Me, R = H) (1.6 g) was heated at 200 °C in an oil-bath for 1 h. The dark tar was cooled and chromatographed on alumina (benzene eluant). The first band was the title compound, m.p. 54—55° (lit.,[29] 56°); yield 85 mg (8.7%).

(F) *Stepwise Reactions of* 3-*Chloro*-4-(2-*dialkylaminophenyl*)-1,3-*diphenylazetidin*-2-*ones* (*Scheme* 3).—(i) 3-*Chloro*-4-(2-*dialkylaminophenyl*)-1,3-*diphenylazetidin*-2-*ones* (3a—e; worked up as above. The *chloride* (0.65 g, 62%) had m.p. 157—160° (decomp.); $\nu_{max.}$ 1 765 cm^{-1} (C=O) (Found: C, 71.9; H, 6.2; N, 6.0. $C_{27}H_{27}ClN_2O,H_2O$ requires C, 72.2; H, 6.5; N, 6.2%).

(iii) 1,2a,3,7b-*Tetrahydro*-3-*methyl*-1,7b-*diphenylazeto*[3,2-b]*indol*-2-*one* (15; R = H). To a stirred solution of *N*-(2-dimethylaminobenzylidene)aniline (2.3 g) and triethylamine (1.5 g) in dry benzene (80 ml) maintained at reflux temperature, was added a solution of chloro(phenyl)acetyl chloride (1.9 g) in dry benzene (50 ml), dropwise, over 2 h. The solution was then cooled and triethylamine hydrochloride filtered off. The filtrate was concentrated *in vacuo* and the oily residue chromatographed on alumina with light petroleum (b.p. 60—80°) as eluant. The first fraction was recrystallised from ethyl acetate–petroleum (b.p. 60—80°) to give the title *compound* (1.6 g, 50%) as needles, m.p. 152—153°, $\nu_{max.}$ 1 735 cm^{-1} (C=O), *m/e* 326 (M^+) and 207 (100%, $M^+ - 119$); τ 2.20—3.20 (m, 14 aromatic H), 4.60 (1 H, s), and 7.00 (3 H, s) (Found: C, 80.8; H, 5.7; N, 8.6. $C_{22}H_{18}N_2O$ requires C, 80.9; H, 5.6; N, 8.6%).

3-(4-*Chlorobutyl*)-1,2a,3,7b-*tetrahydro*-1,7b-*diphenylazeto*-

[29] I. Heilbron and H. M. Bunbury, 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London.

[3,2-b]*indol*-2-*one* (15; R = $[CH_2]_3Cl$). 3-Chloro-1,3-diphenyl-4-(2-pyrrolidinophenyl)azetidin-2-one (3a; R = H, Y = Ph) (1.0 g) was dissolved in methanol (20 ml) and heated under reflux for 8 h. The solvent was removed *in vacuo*; purification of the residue from ethanol gave the *product* (0.75 g, 75%), m.p. 136°, $\nu_{max.}$ 1 740 cm^{-1} (C=O) (Found: C, 74.2; H, 5.7; N, 6.7. $C_{25}H_{23}ClN_2O$ requires C, 74.5; H, 5.7; N, 6.9%); τ 1.95—2.10 (m, 13 aromatic H), 3.45 (t, 1 aromatic H), 4.73 (1 H, s), 6.45—7.25 (4 H, m), and 8.05—8.50 (4 H, m).

3-(5-*Chloropentyl*)-1,2a,3,7b-*tetrahydro*-1,7b-*diphenylazeto*-[3,2-b]*indol*-2-*one* (15; R = $[CH_2]_4Cl$). Compound (8; R′ = Ph, RR = $[CH_2]_5$) (1.0 g) was dissolved in ethanol (20 ml) and the solution was distilled while toluene was added dropwise. When the internal temperature had reached 100 °C the still-head was replaced by a reflux condenser and the solution was heated under reflux for 30 min. The solution was cooled and the solvent removed *in vacuo*. The residue was triturated with petroleum (b.p. 60—80°) to give the *product* as needles (0.85 g, 85%), m.p. 109°, $\nu_{max.}$ 1 740 cm^{-1} (C=O), *m/e* 416 (M^+) (Found: C, 74.7; H, 5.9; N, 6.6. $C_{26}H_{25}ClN_2O$ requires C, 74.9; H, 6.0; N, 6.7%); τ 2.20—2.95 (m, 13 aromatic H), 3.28 (1 H, t), 4.60 (1 H, s), 6.35—6.95 (4 H, m), and 8.10—8.85 (6 H, m).

3-(6-*Chlorohexyl*)-1,2a,3,7b-*tetrahydro*-1,7b-*diphenylazeto*-[3,2-b]*indol*-2-*one* (15; R = $[CH_2]_5Cl$). This was prepared as for (15; R = $[CH_2]_4Cl$) from the β-lactam (8; R′ = Ph, RR = $[CH_2]_6$) as *needles* (0.81 g, 81%), m.p. 116°, $\nu_{max.}$ 1 740 cm^{-1} (C=O), *m/e* 430 (M^+) (Found: C, 75.5; H, 6.5. $C_{37}H_{27}ClN_2O$ requires C, 75.4; H, 6.3; N, 6.5%); ^1H n.m.r. spectrum as expected.

(iv) 1-*Alkyl*-2-*phenylindoles* (14; R = Ph). 1-*Methyl*-2-*phenylindole* (14; R = Ph, X = H). Compound (15; R = H) (1.0 g) was dissolved in ethanol (20 ml) and heated under reflux for 5 h. T.l.c. (alumina; benzene) showed two spots, one of which corresponded to ethyl phenylcarbamate. The solvent was removed *in vacuo* to give the indole (0.6 g, 94%), m.p. 99—100° (from aqueous ethanol) (lit.,[29] 100°).

1-(ω-*Chloroalkyl*)-2-*phenylindoles* (14; R = Ph, X = $[CH_2]_{3-5}Cl$ or $CH_2{\cdot}O{\cdot}[CH_2]_2Cl$). The appropriate 3-chloro-4-(2-dialkylaminophenyl)-1,3-diphenylazetidin-2-one (3a—d; R = H, Y = Ph) (1.0 g) was heated in xylene (20 ml) under reflux for 6 h. The solvent was removed *in vacuo* and the *indole* was purified by chromatography on alumina with benzene as eluant (Table 3). The indoles were also obtained by thermolysis of compounds (8; R′ = Ph, RR = $[CH_2]_5$ or $[CH_2]_6$) or (15; R = H or $[CH_2]_{3-5}Cl$) by the above method.

(G) *Hydrolysis of the Azetoindolium Chlorides* (7; R = Ph, X = Me_2 or $[CH_2]_{4-6}$).—(i) 1,1-*Dialkyl*-2-*benzamido*-3-*hydroxyindolinium hydroxides* (16); *general procedure*. The appropriate azetoindolium chloride (1.0 g) was dissolved in cold water (20 ml) and to the stirred solution was added 4M-sodium hydroxide (10 ml). The product precipitated within 1 min and the suspension was stirred for 15 min. The product was filtered off and recrystallised from methanol–ethyl acetate. 2-*Benzamido*-3-*hydroxy*-1,1-*dimethylindolinium hydroxide* (16; R = Me, R′ = H) was obtained as needles, m.p. 260° (80%) (Found: C, 68.3; H, 6.6; N, 9.2. $C_{17}H_{20}N_2O_3$ requires C, 68.0; H, 6.7; N, 9.3%); $\nu_{max.}$ 1 640 (C=O), 3 300 (NH), and 3 400 cm^{-1} (OH); τ (CD_3OD) 2.20—2.55 (m, 4 aromatic H), 2.60—3.35 (m, 5 aromatic H), 4.21 (1 H, d), 5.50 (1 H, d), 6.21 (3 H, s), and 6.52 (3 H, s).

2-*Benzamido*-3-*hydroxyspiro*[*indolinium*-1,1′-*pyrrolidinium*] *hydroxide* (16; RR = $[CH_2]_4$, R′ = H) (82%) had m.p. 230—235° (decomp.) (Found: C, 70.2; H, 7.0; N, 8.4. $C_{19}H_{22}N_2O_3$ requires C, 69.9; H, 6.8; N, 8.6%); $\nu_{max.}$ 1 640 (C=O), 3 300 (NH), and 3 400 cm^{-1} (OH); τ (CH_3OD) 2.35—2.60 (m, 4 aromatic H), 2.65—3.35 (m, 5 aromatic H), 4.10 (1 H, d), 5.10 (1 H, d), 5.75br (2 H, s), 6.10—6.40 (2 H, m), and 7.50—7.85 (4 H, m).

2-*Benzamido*-3-*hydroxyspiro*[*indolinium*-1,1′-*piperidinium*] *hydroxide* (16; RR = $[CH_2]_5$, R′ = H) (89%) had m.p. 220—225° (decomp.) (Found: C, 70.9; H, 7.2; N, 8.0. $C_{20}H_{24}N_2O_3$ requires C, 70.6; H, 7.1; N, 8.2%); $\nu_{max.}$ 1 635 (C=O), 3 300 (NH), and 3 400 cm^{-1} (OH); ^1H n.m.r. spectrum as expected.

2-*Benzamido*-3-*hydroxyspiro*[*indolinium*-1,1′-*perhydroazepinium*] *hydroxide* (16; RR = $[CH_2]_6$, R′ = H) was obtained as needles (83%), m.p. 223—228° (decomp.) (Found: C, 71.0; H, 7.6; N, 7.6. $C_{21}H_{26}N_2O_3$ requires C, 71.2; H, 7.4; N, 7.9%); $\nu_{max.}$ 1 640 (C=O), 3 300 (NH), and 3 400 cm^{-1} (OH); ^1H n.m.r. spectrum as expected.

(ii) N-*Alkylindole*-2-*carboxylic acids* (17). 1-Methylindole-2-carboxylic acid (17; R = Me) was obtained by alkaline hydrolysis of compound (16; R = Me, R′ = H) (1.0 g) in boiling 2N-sodium hydroxide (20 ml) for 4 h. The mixture was cooled and acidified with hydrochloric acid. The precipitated solid was filtered off, washed with water, air-dried, and recrystallised from petroleum (b.p. 80—100°) to give the acid (0.5 g, 88%), m.p. 215° (decomp.) [lit.,[30] 214° (decomp.)]. [Its methyl ester had m.p. 98° (lit.,[30] 97—98°).] The acidified filtrate was cooled to 0 °C, diazotised, and added to a cold alkaline solution of 2-naphthol to give 1-phenylazo-2-naphthol, identical with an authentic sample.[29] 1-Methylindole-2-carboxylic acid also was obtained (85%) by hydrolysis of (7; X = Me_2, R = Ph) with boiling 2M-sodium hydroxide.

When compound (16; R = Me, R′ = H) (1.0 g) was hydrolysed in 15% boiling hydrochloric acid (20 ml) for 1 h, the same acid was obtained (0.45 g, 79%).

1-(ω-*Chloroalkyl*)*indole*-2-*carboxylic acids*. The appropriate indolinium hydroxide (16; R′ = H, RR = $[CH_2]_{4-6}$) (1.0 g) was boiled in aqueous 15% hydrochloric acid for 30 min. The *product* was filtered off, washed with water, air-dried, and recrystallised from petroleum (b.p. 80—100°); for details see Table 4).

1-(ω-*Hydroxyalkyl*)*indole*-2-*carboxylic acids*; *general procedure*. The appropriate indolinium hydroxide (16; R′ = H, RR = $[CH_2]_{4-6}$) (1.0 g) was suspended in 2M-sodium hydroxide (20 ml) and heated on a steam-bath for 48 h. After cooling, the solution was decanted from a little starting material and acidified with concentrated hydrochloric acid. The product was extracted with chloroform and the extract was washed with water and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* gave the acid, which was purified from petroleum (b.p. 60—80°).

1-(5-*Hydroxypentyl*)*indole*-2-*carboxylic acid* (17; R = $[CH_2]_5{\cdot}OH$) (0.3 g, 50%) had m.p. 106—107° (Found: C, 67.9; H, 7.0; N, 5.7. $C_{14}H_{17}NO_3$ requires C, 68.0; H, 6.9; N, 5.7%); τ 2.15—3.10 (5 H, m), 5.43 (2 H, t), 6.50 (2 H, t), 8.00—8.95 (6 H, m), and 4.95 (2 H, s; removed on addition of D_2O).

1-(6-*Hydroxyhexyl*)*indole*-2-*carboxylic acid* (17; R = $[CH_2]_6{\cdot}OH$) (0.4 g, 60%) had m.p. 124—125° (Found: C, 68.8; H, 7.3; N, 5.2. $C_{15}H_{19}NO_3$ requires C, 69.1; H, 7.3; N, 5.4%); ^1H n.m.r. spectrum as expected.

1-(4-*Hydroxybutyl*)*indole*-2-*carboxylic acid* (17; R =

[30] P. Johnson, *J. Amer. Chem. Soc.*, 1945, **67**, 423.

$[CH_2]_4$·OH) could not be isolated after similar treatment of (8; R′ = H, RR = $[CH_2]_4$).

Attempted Acidic Hydrolysis of the Azetoindolium Chloride (8; R = Me, R′ = H).—The title compound (1.0 g) was heated in hydrochloric acid (10 ml) for 8 h. Evaporation to dryness *in vacuo* gave starting material only. When the heating period was extended to 3 days decomposition occurred.

Attempted Alkaline Hydrolysis of the Azetoindolium Chloride (8; RR = $[CH_2]_5$, R′ = Ph).—The title compound (1.0 g) was dissolved in water (20 ml) and 4M-sodium hydroxide (10 ml) was added. The solution was kept at ambient temperature for 2 h, after which a white solid had precipitated. This was filtered off and air dried (0.9 g). The ^{1}H n.m.r. spectrum was identical with that of the starting material but the i.r. spectrum showed strong absorption at 3 400—3 200 cm^{-1} (OH). Attempts to recrystallise this compound failed because of decomposition to a viscous oily mixture.

TABLE 4

1-(ω-Chloroalkyl)indole-2-carboxylic acids (17)

R	Yield (%)	M.p. (°C)	Found (%) C	H	N	Formula	Required (%) C	H	N	τ Values ($CDCl_3$) Aromatic H	Aliphatic H	CO_2H *
$[CH_2]_4Cl$	75	137—138	62.2	5.5	5.7	$C_{13}H_{14}ClNO_2$	62.0	5.6	5.6	2.15—2.78 (5 H, m)	5.40 (2 H, t) 6.40 (2 H, t) 8.15 (4 H, s, br)	—1.50 (1 H, s)
$[CH_2]_5Cl$	81	127—128	62.9	6.0	5.2	$C_{14}H_{16}ClNO_2$	63.3	6.1	5.3	2.10—2.90 (5 H, m)	5.35 (2 H, t) 6.44 (2 H, t) 8.19 (6 H, m)	—1.50 (1 H, s)
$[CH_2]_6Cl$	86	118—119	64.7	6.5	5.2	$C_{15}H_{18}ClNO_2$	64.5	6.5	5.0	2.05—2.95 (5 H, m)	5.38 (2 H, t) 6.45 (2 H, t) 8.05—8.85 (8 H, m)	—1.55 (1 H, s)

* Removed on addition of D_2O.

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