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Central Nervous System Active Compounds. I The Synthesis of Some Caprolactam Derivatives Substituted at N 1, C 2 and C 3

Thach Duong,[A] *Rolf H. Prager*,[A,B] *A. David Ward*[A,B] *and David I. B. Kerr*[C]

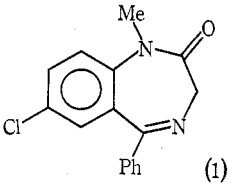
[A] Department of Organic Chemistry, University of Adelaide,
P.O. Box 498, Adelaide, S.A. 5001.
[B] Authors to whom correspondence should be addressed.
[C] Department of Human Physiology and Pharmacology, University of Adelaide,
P.O. Box 498, Adelaide, S.A. 5001.

Abstract

The synthesis of a number of caprolactam derivatives with alkyl, aryl and hetero atom substituents at N 1, C 2 and C 3 is described. Alkylation and arylation at C 3 by a variety of methods is discussed. Some of these compounds are powerful convulsing agents; a few are depressants.

Introduction

This work is part of a project aimed at finding new antagonists, or analogues, of the central nervous system transmitter, γ-aminobutyric acid (Gaba), which has been found to have a potent inhibitory action against epileptic seizures.[1,2] A number of



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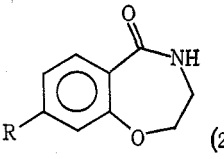

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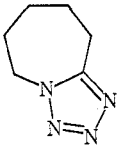

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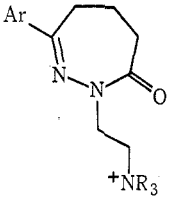

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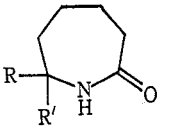


(5)

cyclic amides have been shown to be active on the central nervous system, particularly the seven-membered lactam system. Examples include diazepam[3] (Valium) (1) and the many related anticonvulsants and sedatives,[4] β-adrenergic blocking agents such

[1] Meldrum, B. S., *Int. Rev. Neurobiol.*, 1975, **17**, 1.
[2] Obata, K., *Int. Rev. Neurobiol.*, 1972, **15**, 167.
[3] Sternbach, L. H., *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 34.
[4] See, e.g. Ning, R. Y., Sternbach, L. H., Pool, W., and Randall, L. O., *J. Med. Chem.*, 1973, **16**, 879; Hester, J. B., Jr, and Rudjik, A. D., *J. Med. Chem.*, 1974, **17**, 293.

as (2),[5] convulsants such as metrazole (3),[6] analgesics (4)[7,8] and hypnotics (5).[9] A search of the literature for central nervous system activity in simple lactams reveals isolated examples, but no detailed examinations appear to have been made. Lien and coworkers[10,11] have shown that among cyclic lactams the greatest activity occurred with 2-azacyclononanone; however, they only examined four compounds. Because of its industrial importance in the synthesis of nylons caprolactam has been subjected to considerable pharmacological scrutiny. Polushkin[12] has reported hypertensive effects in dogs at low dosages but hypotension at larger doses. Goldblatt[13] has shown that caprolactam is an effective convulsant acting particularly on the cortex of the rhinencephalon.

To initiate a detailed study of the central nervous system activity of cyclic amides we chose to examine initially various caprolactam (hexahydroazepin-2-one)* derivatives, including those with ring and substituent unsaturation. Surprisingly, in view of the commercial importance of caprolactam, relatively few *C*-alkylated derivatives have been described and general methods of synthesis are not common. Our preliminary test results[14,15] on compounds that could be readily obtained indicated that derivatives with substituents at C3, C4, C6 and C7 and 4,6-disubstituted compounds were the more promising from a physiological point of view. This paper describes the synthesis and some reactions of *N*-substituted caprolactams and compounds with substituents at C2 and C3. In Part II we will discuss the preparation of derivatives with substituents at C4, C5, C6 and C7.

Results and Discussion

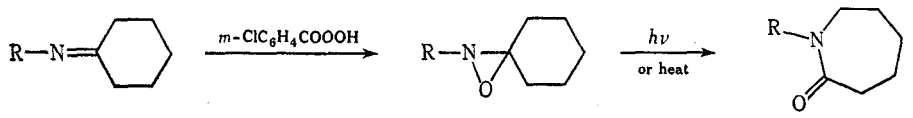
(*a*) *Substitution on Nitrogen*

Caprolactam can be alkylated on nitrogen or oxygen by alkyl sulphates in benzene;[16] however, reaction with an alkyl halide or sulphate in the presence of sodium hydride generally leads to *N*-alkylation.[17] *N*-Alkyl derivatives have also been prepared by the reaction of caprolactams with epoxides,[18] acetylenes,[18] aldehydes,[16] by the use of the Mannich reaction[19] and by the thermal rearrangement of allyl

* Caprolactam is the widely used trivial name for hexahydroazepin-2-one. We have found it more convenient to use the trivial name in the Introduction and Discussion sections; systematic names will be given under Experimental.

[5] Shtacher, G., Erez, M., and Cohen, S., *J. Med. Chem.*, 1973, **16**, 516.
[6] Childress, S. J., and Gluckman, M. I., *J. Pharm. Sci.*, 1964, **53**, 577.
[7] Koening, J. J., and Wermuth, C. G., *Tetrahedron Lett.*, 1973, 603.
[8] Wermuth, C. G., and Koening, J. J., *Angew. Chem., Int. Ed. Engl.*, 1962, **11**, 152.
[9] Nedenskov, P., Taub, W., and Ginsburg, D., *Acta Chem. Scand.*, 1958, **12**, 1405.
[10] Lien, E. J., Lien, L. L., and Tong, G. L., *J. Med. Chem.*, 1971, **14**, 846.
[11] Elison, C., Lien, E. J., Zinger, A. P., Hussain, M., Tong, G. L., and Golden, M., *J. Pharm. Sci.*, 1971, **60**, 1058.
[12] Polushkin, B. V., *Farmakol. Toksikol. (Moscow)*, 1964, **27**, 234 (*Chem. Abstr.*, 1964, **61**, 12506e).
[13] Goldblatt, M. W., Farquharson, M. E., Bennett, G., and Askew, B. M., *Br. J. Ind. Med.*, 1954, **11**, 1.
[14] Kerr, D. I. B., Dennis, B. J., Breuker, E. L. M., Prager, R. H., Ward, A. D., and Duong, T., *Brain Res.*, 1976, **110**, 413.
[15] Prager, R. H., Breuker, E. L. M., Duong, T., Kerr, D. I. B., and Ward, A. D., unpublished data.
[16] Benson, R. E., and Cairns, T. L., *J. Am. Chem. Soc.*, 1948, **70**, 2115.
[17] Marvel, C. S., and Moyer, W. W., Jr, *J. Org. Chem.*, 1957, **22**, 1065.
[18] Ziegenbein, W., and Franke, W., *Chem. Ber.*, 1957, **90**, 2291.
[19] Meyer, H. R., *Kunstst.-Plast. (Solothurn, Switz.)*, 1956, **3**, 160 (*Chem. Abstr.*, 1958, **52**, 11781e).

lactim ethers.[20] *N*-Arylcaprolactams have been prepared by the thermal rearrangement of nitrones.[21]

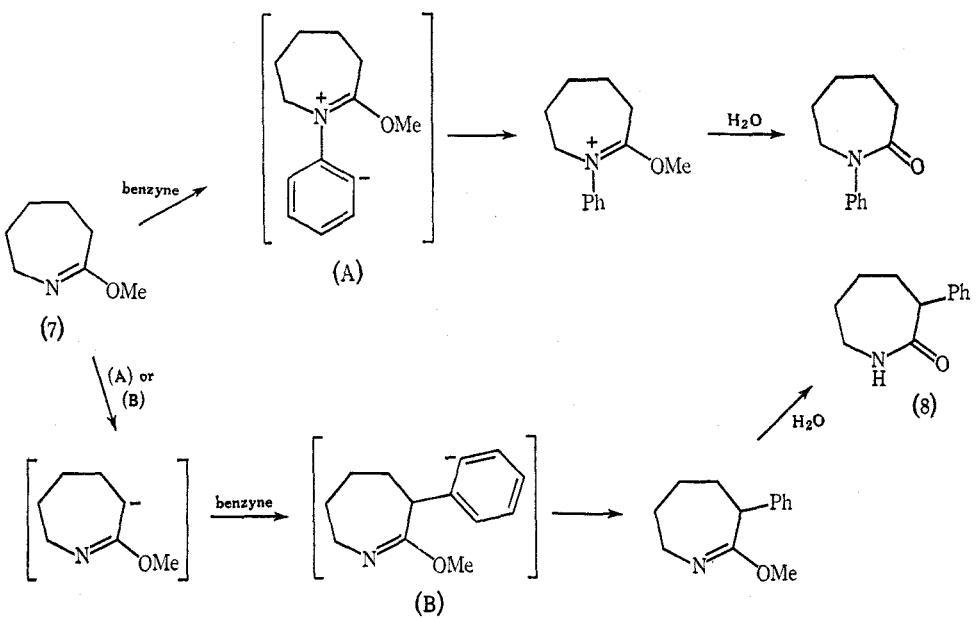


(6)

Scheme 1

It appeared to us that an adaptation of the reported photochemical[22] or thermal[21] rearrangement of oxaziridines (Scheme 1) could be a useful general method for the synthesis of *N*-arylcaprolactams (6; R = Ar). However, the method gave only poor yields of *N*-phenyl- and *N*-*p*-chlorophenyl-caprolactam and failed to give any *N*-*p*-methoxyphenylcaprolactam. Because of the complex nature of the products obtained in these reactions it was felt that the method was not a suitable general route to these compounds.

A further method of *N*-arylation which proved to be of limited value because of the low yields obtained is the reaction of caprolactam derivatives with benzyne. However, the reaction is of mechanistic interest. Although caprolactam gave only very low yields of products, reaction of *O*-methylcaprolactim (7) with benzenediazonium-2-carboxylate at 70° led to a mixture of products from which *N*-phenylcaprolactam (15%) and 3-phenylcaprolactam (8) (10%) could be isolated. A plausible pathway for the reaction is suggested in Scheme 2.



Scheme 2

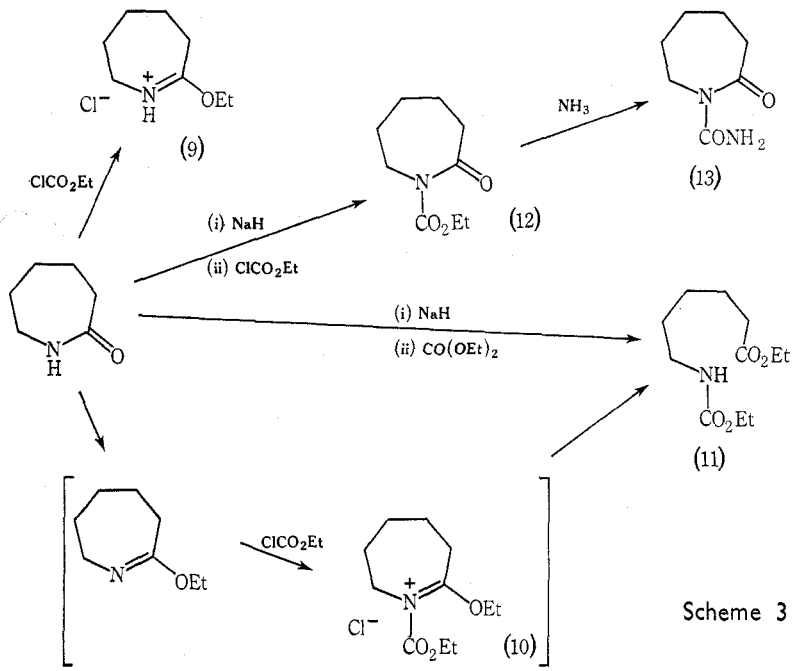
[20] Black, D. St.C., Eastwood, F. W., Okraglik, R., Poynton, A. J., Wade, A. M., and Walker, C. H., *Aust. J. Chem.*, 1972, **25**, 1483.

[21] Krimm, H., *Chem. Ber.*, 1958, **91**, 1057.

[22] Oliveros-Desherces, E., Riviere, M., Parello, J., and Lattes, A., *Tetrahedron Lett.*, 1975, 851; Reid, S. T., Tucker, J. N., and Wilcox, E. J., *J. Chem. Soc., Perkin Trans. 1*, 1974, 1359.

The 3-phenylcaprolactam (8) was identified by comparison with an authentic specimen prepared by the Schmidt rearrangement of 2-phenylcyclohexanone. The reaction is reported[23] to give only 7-phenylcaprolactam but on close examination the reaction was found to be very sensitive to the reaction conditions and can be made to proceed to give exclusively the 3-isomer.[24]

Since the testing program has shown[15] that *N*-alkylation or arylation leads to a marked decrease in convulsant activity, further investigation of potential routes to *N*-aryl derivatives was not made and the *N*-alkyl compounds (6) were prepared by conventional means. Furthermore the testing program has shown[15] that the activity is of short duration (typically 3–15 min). Since this could be due to rapid metabolism or excretion of the active compound, it was felt that an ethoxycarbonyl or an aminocarbonyl group attached to the ring nitrogen could produce a compound with more desirable characteristics from a drug point of view. The relatively slow hydrolysis of these substituents could maintain a constant supply of the parent caprolactam and the ethoxycarbonyl group in particular could confer lipid solubility, thereby increasing the concentration at the active site by facilitating passage through the blood–brain barrier.[25]



Scheme 3

Reaction of caprolactam with ethyl chloroformate leads to formation of the imino ether hydrochloride[26] (9) (Scheme 3). However, the sodium salt of caprolactam reacts in a different manner with ethyl chloroformate and provides the *N*-ethoxycarbonyl derivative (12) in good yield. It is important in this reaction to ensure that

[23] Rosenmund, P., Sauer, D., and Trommer, W., *Chem. Ber.*, 1970, **103**, 496.
[24] Duong, T., Prager, R. H., Tippett, J. M., Ward, A. D., and Kerr, D. I. B., *Aust. J. Chem.*, 1976, **29**, 2667.
[25] Edstrom, R., *Int. Rev. Neurobiol.*, 1964, **7**, 153.
[26] Brown, D. J., and Ienaga, K., *Aust. J. Chem.*, 1975, **28**, 119.

the sodium salt has completely formed before the ethyl chloroformate is added since caprolactam reacts much more readily with the reagent than does the sodium salt. The lactim ether thus produced reacts further with the reagent to yield, after workup, the ring-opened product (11) presumably via the salt (10) (Scheme 3). The sodium salt of caprolactam forms only the ring-opened product (11) when treated with diethyl carbonate. The *N*-ethoxycarbonyl derivative (12) is readily converted into the urea (13); however, the urethanes (e.g. (12)) were less active as convulsants than the parent lactam and (13) showed depressant properties.

(*b*) *Substitution at C2*

Because of the reported higher biological activities of thiolactams compared to the corresponding lactams[10,11] many of the caprolactams were converted into their thio derivatives by reaction with phosphorus pentasulphide. The caprolactams could be converted into the corresponding lactim ethers by treatment with methyl sulphate in benzene (this method generally gave the *N*-alkylcaprolactam as a by-product), with ethyl chloroformate (see above) or with methyl fluorosulphonate. This last method was the most convenient methylation procedure.

The thiocaprolactams were frequently powerful and extremely rapid-acting convulsants. The lactim ethers have not yet been subjected to a full physiological testing program; however, preliminary results indicate that they are not more active than the parent caprolactam.

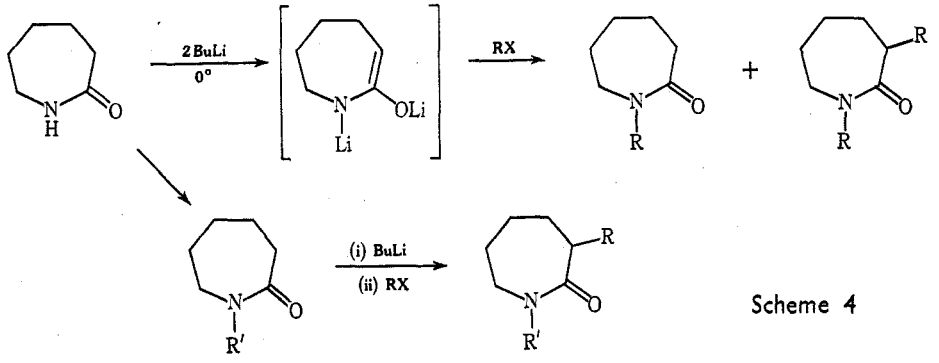
(*c*) *Substitution at C3*

Very few derivatives of caprolactam substituted at C3 have been prepared. The Schmidt[27] and Beckmann[28,29] reactions on 2-alkylcyclohexanones sometimes give mixtures containing 3-alkylcaprolactams in low yields and reference compounds have generally been prepared by indirect routes.[29] Dianions of acyclic amides have been selectively alkylated on carbon[30–32] but the reaction does not appear to have been examined with lactams. Our attempts to selectively *C*-alkylate caprolactam by forming the dianion and treating it with one equivalent of an alkyl halide have been unsuccessful, the products being the 1,3-dialkyl and the 1-alkyl derivatives with the return of some starting material (Scheme 4). This approach is of relevance for the alkylation of *N*-alkylcaprolactams (Scheme 4) but we have not pursued this aspect since the *N*-alkylcaprolactams are much less physiologically active than the unsubstituted system.[15]

Brown[33] has reported that the reaction of 2-bromocyclohexanone with trialkylboranes gives 2-alkylcyclohexanones and this reaction has recently been extended by Prager and Reece.[34] It seemed possible that alkylation of amides could similarly

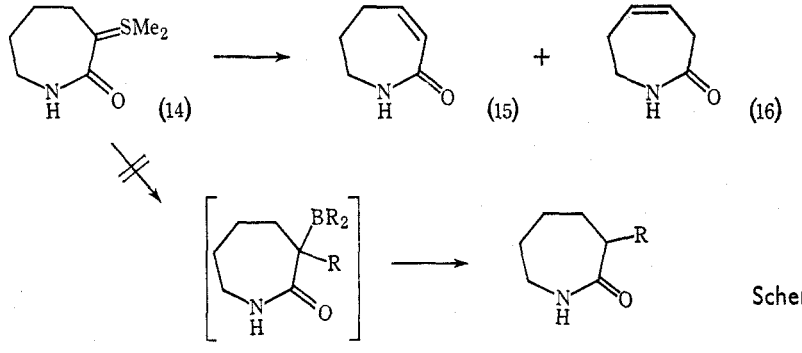
[27] Conley, R. T., *J. Org. Chem.*, 1958, **23**, 1330; Schechter, H., and Kirk, J. C., *J. Am. Chem. Soc.*, 1951, **73**, 3087.
[28] Donaruma, L. G., and Heldt, W. Z., *Org. React.*, 1960, **11**, 1.
[29] Cefelin, P., Frydrychova, A., Labsky, J., Schmidt, P., and Sebenda, J., *Collect. Czech. Chem. Commun.*, 1967, **32**, 2787.
[30] Wu, A., and Snieckus, V., *Tetrahedron Lett.*, 1975, 2057.
[31] Colwell, W. T., Gamamoto, K., Christie, P., and Henry, P. W., *Synth. Commun.*, 1972, **2**, 109.
[32] Durst, T., Van Den Elzen, R., and Legault, R., *Can. J. Chem.*, 1974, **52**, 3206.
[33] Brown, H. C., Rogic, M. M., and Rathke, M. W., *J. Am. Chem. Soc.*, 1968, **90**, 6218.
[34] Prager, R. H., and Reece, P. A., *Aust. J. Chem.*, 1975, **28**, 1775.

be achieved but neither 3-bromocaprolactam nor 3-bromo-1-methylcaprolactam were alkylated by triethylborane in the presence of potassium t-butoxide. The major product of this reaction arose from a reductive debromination process, which frequently leads to a by-product in the reaction of bromo ketones.[34]



Scheme 4

Tufariello[35] has reported that the *C*-alkylation of acyclic amides can be achieved by treating a sulphonium ylid with organoboranes. In our hands the caprolactam ylid (14) yielded only the elimination products (15) and (16) under these conditions (Scheme 5). It is interesting to note that both (15) and (16) are produced when caprolactams with suitable substituents at the 3-position undergo elimination; the formation of both isomers presumably reflects the equilibrium between the two unsaturated caprolactams.[36]

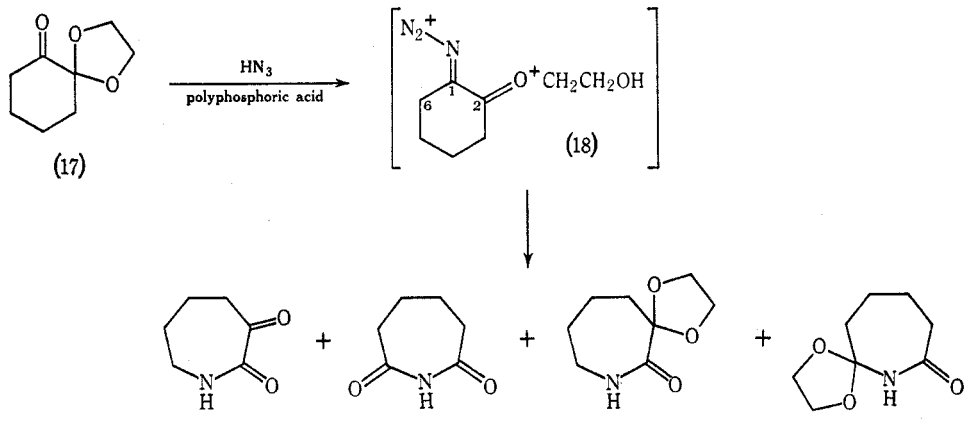


Scheme 5

We hoped to find a method for the Beckmann or Schmidt rearrangement of cyclohexane-1,2-dione that might lead to 3-oxocaprolactam (previously prepared[37] in poor yield), which could, in turn, prove to be a useful intermediate for the preparation of 3-substituted caprolactams. Unfortunately all attempts at the Beckmann rearrangement led to decomposition or the return of starting material and the Schmidt reaction led, through a fragmentation process, to 4-cyanopentanoic acid. Similar fragmentations have been observed with related compounds.[38] We therefore considered that the Schmidt reaction on the monoacetal (17) of cyclohexane-

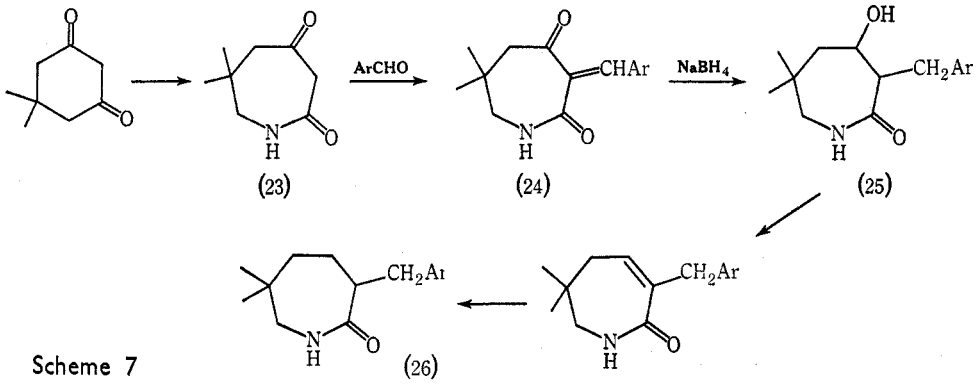
[35] Tufariello, J. J., Lee, L. T. C., and Wojtkowski, P., *J. Am. Chem. Soc.*, 1967, **89**, 6804.
[36] Reimschuessel, H. K., *J. Org. Chem.*, 1973, **38**, 169.
[37] Murakami, M., and Fukumoto, T., Jap. Pat. 3,111 (1963) (*Chem. Abstr.*, 1963, **59**, 11273b).
[38] Ohno, M., and Terasawa, I., *J. Am. Chem. Soc.*, 1966, **88**, 5683, and references cited therein.

1,2-dione might lead to more useful products, on the grounds that the intermediate could have a structure similar to (18) and would prefer to migrate the more electron-rich 1,6-bond rather than the 1,2-bond which might be preferred on steric grounds. In the event the reaction proceeded in only moderate yield to give a mixture which, from spectral data, consisted of essentially equal proportions of the four possible products (19)–(22) (Scheme 6).



Scheme 6

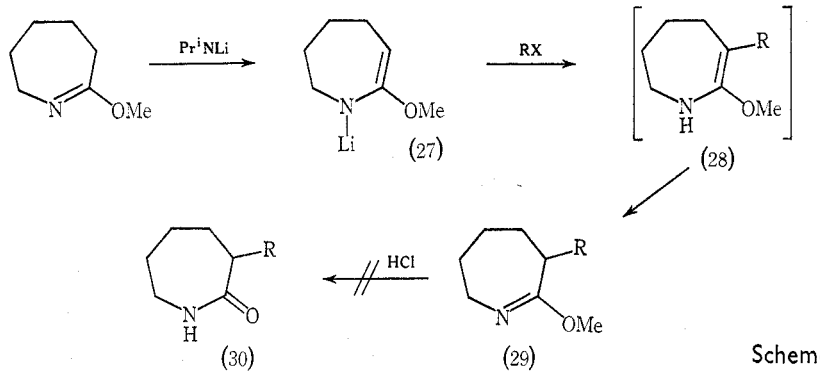
Since dihydroresorcinols have been successfully converted into caprolactams, both by the Beckmann[39] and Schmidt[40,41] rearrangements, it seemed worthwhile to attempt to exploit this reaction for the synthesis of 3-substituted caprolactams (Scheme 7). The keto amide (23) reacts readily with aromatic aldehydes to form the benzylidene derivative (24); however, reaction of these products with sodium borohydride caused reduction of the double bond as well as the ketone group and none of the allylic alcohol could be isolated. These products (25) should be readily dehydrated and reduced and would provide an alternative, albeit rather lengthy, route to some 3-alkylcaprolactams (26) (Scheme 7).



Scheme 7

[39] Tamura, Y., Kita, Y., and Terashima, M., *Chem. Pharm. Bull.*, 1971, **19**, 529.
[40] Tamura, Y., and Kita, Y., *Chem. Pharm. Bull.*, 1971, **19**, 1735.
[41] Tamura, Y., Yoshimura, Y., and Kita, Y., *Chem. Pharm. Bull.*, 1971, **19**, 1068.

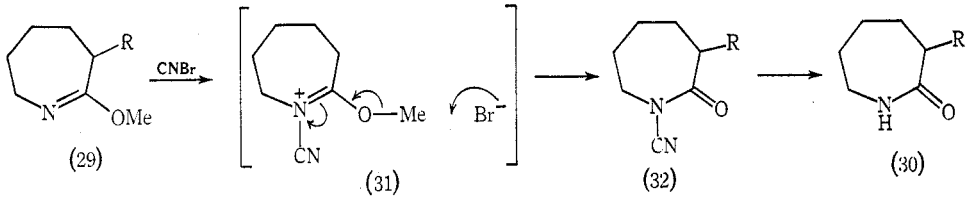
We have been able to extend the recently published procedure[42,43] for the alkylation of lactim ethers to the caprolactam area and this method has resulted in the synthesis of some 3-alkylcaprolactams and their corresponding lactim ethers (Scheme 8). An unresolved feature of this reaction is the nature of the product formed in the alkylation of the lithio intermediate (27). Acidification of the reaction mixture with the weak acid ammonium chloride gave the lactim ether (29) in high yield. However, (29) did not form (30) on treatment with mineral acid but instead a dark polymeric material was obtained. The lactim ether could not be efficiently hydrolysed to (30) with aqueous base. Direct acidification of the alkylation reaction mixture with mineral acid gives the lactam (30) in poor yield. These results suggest that (29) is not present in the mixture at the end of the alkylation procedure; possibly (28) reacts with mineral acid to form both (29) and (30), the former polymerizing.



(27) (28) (30) (29)

Scheme 8

We thus sought alternative means of hydrolysing the lactim ethers to caprolactams. One approach, which relies on the higher basicity of the lactim ethers, was to treat (29) with cyanogen bromide in an endeavour to form (31) which we hoped would react *in situ* to form the *N*-cyanocaprolactam (32) (Scheme 9). We expected that the cyano group could be reductively removed to yield the desired caprolactam. In the event the reaction of *O*-methylcaprolactim (29; R = H) with cyanogen bromide gave a mixture which included some *N*-cyanocaprolactam (32; R = H). Reduction, either with zinc and acetic acid or by catalytic hydrogenation, of the fraction containing (32) cleanly converted it into caprolactam; however, the relatively low yield of (32) and the complexity of the reaction mixture indicate that this would not be a satisfactory general method.



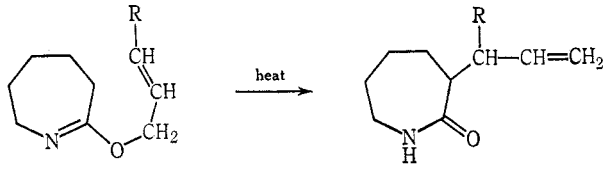
(29) (31) (32) (30)

Scheme 9

The required hydrolysis of the caprolactim ethers has however been achieved by adsorbing them on alumina overnight, followed by elution of the caprolactam

[42] Trost, B. M., and Kunz, R. A., *J. Org. Chem.*, 1974, **39**, 2476.
[43] Trost, B. M., and Kunz, R. A., *J. Am. Chem. Soc.*, 1975, **97**, 7152.

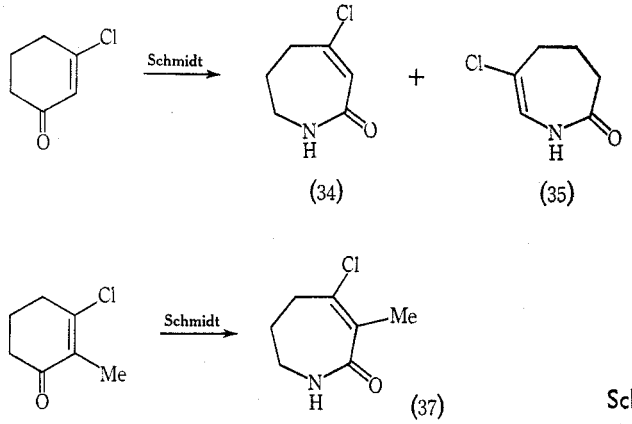
derivative with ethyl acetate. At this stage this approach provides the most direct and generally applicable route to 3-alkylcaprolactams (30).



(33) Scheme 10

An alternative approach (Scheme 10) to this system involves a Claisen rearrangement of the alkyl imidate derivative (33) and proceeds in good overall yield[20] but this method is rather restrictive in the present context.

The keto amide (23) is potentially a useful intermediate for the synthesis of 3-alkylcaprolactam derivatives since base-catalysed alkylation at C 3 is facilitated by the functional groups present. However, the general use of this type of reaction is limited by the fact that although alkylation with methyl iodide gives a good yield of the 3-methyl derivative, alkylation with other alkyl halides is complicated by the ambident nature of the anion and considerable amounts of *O*-alkylation products are formed.



(34) (35) (37) Scheme 11

Similar difficulties restrict an approach (Scheme 11) based on the Schmidt or Beckmann rearrangement of 3-chloro-2-alkylcyclohex-2-en-1-one. It has been reported[40] that the Schmidt reaction on 3-chlorocyclohex-2-en-1-one forms approximately equal quantities of the two possible rearrangement products (34) and (35). However, in a similar reaction on 3-chloro-2-methylcyclohex-2-en-1-one (36) only one product (37) could be isolated. Its structure was confirmed by reduction to 3-methylcaprolactam. The applicability of this route for the synthesis of 3-alkylcaprolactams is limited by the ambident alkylation problem referred to above.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were determined on a Perkin–Elmer 337 or a Unicam SP200 infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian T60 spectrometer in carbon tetrachloride, unless otherwise stated, with tetramethylsilane as an internal reference. Mass spectra were recorded with a Hitachi Perkin–Elmer RMU-6D double-focusing mass spectrometer operating

at 70 eV. Gas–liquid chromatography was performed on Autoprep 700 and 705 or Pye 104 instruments, nitrogen being used as carrier gas. Light petroleum refers to the fraction of b.p. 50–65°. Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

General Method for N-*Alkylation*

A mixture of hexahydroazepin-2-one (1 mmol), sodium hydride (1·2 mmol) and dry benzene (15 ml) was stirred at 20° under nitrogen until hydrogen evolution ceased (*c.* 4 h). A solution of alkyl halide (2 mmol) in benzene (5 ml) was added over 20 min and the mixture stirred for 3 h. The mixture was washed with water, dried, and the solvent evaporated. The following products were prepared in this manner.

N-Methylhexahydroazepin-2-one (6; R = Me) (90%), b.p. 100–102°/18 mm (lit.[16] 50–51°/4 mm).

N-Ethylhexahydroazepin-2-one (6; R = Et) (85%), b.p. 110–113°/8 mm (lit.[16] 97°/5 mm).

N-Butylhexahydroazepin-2-one (6; R = Bu) (92%), b.p. 80–82°/0·6 mm (lit.[19] 137–140°/17 mm).

N-*Isobutylhexahydroazepin-2-one* (6; R = Bu^i) (55%), b.p. 148–150°/25 mm (Found: C, 71·1; H, 11·6. $C_{10}H_{19}NO$ requires C, 71·0; H, 11·3%).

N-Benzylhexahydroazepin-2-one (6; R = CH_2Ph) (55%), m.p. 56–57° (lit.[22] 55–57°).

N-*Isopentylhexahydroazepin-2-one* (6; R = $CH_2CH_2CHMe_2$) (55%), b.p. 148–150°/18 mm (Found: C, 72·4; H, 11·1; N, 7·6. $C_{11}H_{21}NO$ requires C, 72·1; H, 11·5; N, 8·0%).

N-*Octylhexahydroazepin-2-one* (6; R = $(CH_2)_7Me$) (60%), b.p. 152–154°/2·5 mm (Found: C, 74·5; H, 12·1; N, 6·2. $C_{14}H_{27}NO$ requires C, 74·6; H, 12·1; N, 6·3%).

N-*Phenylhexahydroazepin-2-one* (*6*; *R* = *Ph*)

(i) To a solution of *N*-cyclohexylideneaniline (12·0 g) in chloroform (50 ml), *m*-chloroperoxybenzoic acid (14·0 g) in chloroform (200 ml) was added over a period of 30 min. The resulting mixture was stirred at room temperature for 20 h, and then filtered through an alumina column. The chloroform was removed and the residue taken up in cyclohexane and placed in a silica flask and exposed to sunlight for 2 days. The cyclohexane was then removed and the brown oil distilled giving *N*-phenylhexahydroazepin-2-one (6) as a colourless solid (4·0 g, 30%), m.p. 75° (lit.[21] 75°). N.m.r. ($CDCl_3$) δ 7·2, m, 5H, aromatic protons; 3·70, br, 2H, CH_2N; 2·50, br, 2H, CH_2CO; 1·70, br, 6H.

In the same way *N*-*p*-chlorophenylhexahydroazepin-2-one was prepared in 3% yield, m.p. 67° (lit.[21] 68–69°), but the method gave only dark resinous material in attempted preparations of *N*-*p*-methoxyphenylhexahydroazepin-2-one.

(ii) A mixture of *O*-methylcaprolactim[16] (0·40 g) and benzenediazonium-2-carboxylate[44] (3·0 g) in 1,2-dichloroethane (50 ml) was heated under reflux for 30 min after the mixture became homogeneous (5 min). After removal of the solvent the residue was chromatographed on alumina eluting with light petroleum–methylene chloride mixtures and finally ethyl acetate. Each fraction was examined by i.r. and n.m.r. spectroscopy. The early fractions were combined and rechromatographed to give *O*-methylcaprolactim and *N*-phenylhexahydroazepin-2-one. This mixture (0·15 g) was purified by preparative t.l.c. to give pure *N*-phenylhexahydroazepin-2-one (0·08 g, 15%), m.p. 74–75°. Preparative t.l.c. on later fractions from the column, on material that contained mainly caprolactam, allowed the separation of 3-phenylhexahydroazepin-2-one (0·065 g, 10%), m.p. 180–185°, identical with an authentic sample.[24]

(iii) A mixture of hexahydroazepin-2-one (2·0 g) and benzenediazonium-2-carboxylate (3·5 g) in 1,2-dichloroethane (30 ml) was heated until an homogeneous solution formed (5 min); it was then refluxed for 20 min. The solvent was removed and the dark residue was chromatographed on alumina. The early fractions eluted with light petroleum–methylene chloride mixtures contained *N*-phenylhexahydroazepin-2-one (0·3 g) by n.m.r. spectroscopy. Later fractions contained hexahydroazepin-2-one as well as a considerable amount of apparently polymeric material.

Ethyl 2-Oxohexahydroazepine-1-carboxylate (*12*)

Hexahydroazepin-2-one (1·13 g, 10 mmol) in benzene (80 ml) was stirred with excess sodium hydride (0·75 g, 30 mmol) at 20° until hydrogen evolution ceased (3 h). Ethyl chloroformate (1·2 ml, 12 mmol) was then slowly added and the mixture stirred for a further 2 h. The mixture was then

[44] Logullo, F. M., Seitz, A. H., and Friedman, L., *Org. Synth.*, 1973, Coll. Vol. V, 54.

washed with water, dried, and the product chromatographed on alumina. Elution with benzene gave the *urethane* (12) (0·75 g), b.p. 90°/0·2 mm (Found: C, 58·5; H, 8·1; N, 7·3. $C_9H_{15}NO_3$ requires C, 58·4; H, 8·3; N, 7·5%). ν_{max} 1718, 1665 cm^{-1}. N.m.r. ($CDCl_3$) δ 4·35, q, J 7 Hz, 2H; 3·90, br, 2H; 2·70, br, 2H; 1·75, br, 6H; 1·35, t, J 7 Hz, 3H.

*Ethyl 4,6,6-Trimethyl-2-oxo-2,5,6,7-tetrahydro-1*H*-azepine-1-carboxylate*

This *product*, b.p. 125°/0·05 mm, was obtained in 85% yield by the above procedure (Found: C, 73·8; H, 8·5; N, 6·2. $C_{12}H_{19}NO_3$ requires C, 74·0; H, 8·5; N, 6·2%). N.m.r. ($CDCl_3$) δ 5·90, q, J 1·5 Hz, 1H; 4·35, q, J 7 Hz, 2H; 3·55, s, 2H; 2·15, s, 2H; 2·02, q, J 1·5 Hz, 3H; 1·35, t, J 7 Hz, 3H; 1·00, s, 6H. M^+ 225 (50%).

2-Oxohexahydroazepine-1-carboxamide (13)

The urethane (12) (1·0 g) was dissolved in methanol (10 ml) and treated with liquid ammonia (5 ml) at 0° until the ammonia had evaporated. Addition of ether precipitated the urea (13) (0·8 g) which was recrystallized from acetone–light petroleum as colourless *needles*, m.p. 101° (Found: C, 53·5; H, 8·3. $C_7H_{12}N_2O_2$ requires C, 53·8; H, 7·8%). ν_{max} (Nujol) 3400, 3180, 1686, 1650 cm^{-1}. N.m.r. ($CDCl_3$) δ 5·55, br, 2H; 3·15, br t, 2H; 2·20, br, 2H; 1·50, br, 6H.

Ethyl 6-Ethoxycarbonylaminohexanoate (11)

(i) Hexahydroazepin-2-one (1·13 g, 10 mmol) was converted into its sodium salt as above, and treated with ethyl carbonate (1·35 ml, 11 mmol). The reaction mixture was worked up after 3 h at room temperature and alumina chromatography then gave *ethyl 6-ethoxycarbonylaminohexanoate* (1·2 g) as a colourless oil, b.p. 110–115/0·1 mm (Found: C, 57·4; H, 9·0; N, 6·2. $C_{11}H_{21}NO_4$ requires C, 57·1; H, 9·2; N, 6·1%). ν_{max} 3350, 1725, 1710 cm^{-1}. N.m.r. ($CDCl_3$) δ 5·5H, br, 1H; 4·15, q, J 7 Hz, 2H; 4·11, q, J 7 Hz, 2H; 3·18, br, 2H; 2·15, br, 2H; 1·50, br, 6H; 1·27, t, J 7 Hz, 3H; 1·23, t, J 7 Hz, 3H.

(ii) When less than 1 equiv. of sodium hydride was used to convert hexahydroazepin-2-one into its sodium salt, and 1·2 equiv. of ethyl chloroformate were added, the crude product obtained showed the properties of a mixture of the hexanoate (11) and the starting material. The latter could be removed by repeated extraction of an ethereal solution of the product with dilute HCl or, more conveniently, by chromatography on alumina. The product was thus resolved into approximately 40% of each component.

Reactions of Hexahydroazepin-2-ones with Methyl Fluorosulphonate

The lactam (1 mmol) in benzene (5 ml) was treated with methyl fluorosulphonate (1·2 mmol) dropwise at 20° and the mixture was kept at 20° for 1 h before workup, or 10 min in the case of the thiolactams. The mixture was then washed with cold potassium carbonate solution and water, dried and evaporated to give a colourless oil (quantitative) shown to be homogeneous by n.m.r. spectroscopy. Representative examples are listed below.

7-Methoxy-3,4,5,6-tetrahydro-2*H*-azepine (7) (90%), b.p. 100–102°/75 mm (lit.[16] 65–67°/24 mm).

*7-Methoxy-2-methyl-3,4,5,6-tetrahydro-2*H*-azepine* (95%), b.p. 110°/25 mm (Found: C, 68·2; H, 10·7; N, 9·6. $C_8H_{15}NO$ requires C, 68·0; H, 10·7; N, 9·9%).

*7-Methoxy-3,3,5-trimethyl-3,4-dihydro-2*H*-azepine* (90%), b.p. 40°/0·1 mm (Found: C, 71·7; H, 10·0; N, 8·4. $C_{10}H_{17}NO$ requires C, 71·8; H, 10·2; N, 8·4%).

*2-Methyl-7-methylthio-3,4,5,6-tetrahydro-2*H*-azepine* (85%), b.p. 45°/0·1 mm (Found: C, 61·1; H, 9·6; N, 9·0. $C_8H_{15}NS$ requires C, 61·1; H, 9·6; N, 8·9%).

General Method for the Preparation of N*-Alkylhexahydroazepine-2-thiones*

A mixture of the caprolactam (0·5 g), phosphorus pentasulphide (1·0 g) and toluene (15 ml) was refluxed for 3–5 h. The cooled reaction mixture was washed with water, which was back-extracted with chloroform. The combined organic phases were dried, evaporated and the residue was chromatographed on alumina. The following products were prepared in this manner.

N-*Isobutylhexahydroazepine-2-thione* (72%), b.p. 118–120°/0·01 mm (Found: C, 65·0; H, 10·4; N, 7·4. $C_{10}H_{19}NS$ requires C, 64·8; H, 10·3; N, 7·6%).

N-*Butylhexahydroazepine-2-thione* (72%), b.p. 110°/0·01 mm (Found: C, 64·6; H, 10·2; N, 7·8. $C_{10}H_{19}NS$ requires C, 64·8; H, 10·3; N, 7·6%).

N-*Isopentylhexahydroazepine-2-thione* (60%), b.p. 120°/0·01 mm (Found: C, 66·3; H, 10·6; N, 7·0. $C_{11}H_{21}NS$ requires C, 66·3; H, 10·6; N, 7·0%).

N-*Octylhexahydroazepine-2-thione* (85%), b.p. 110–112°/0·01 mm (Found: C, 69·6; H, 11·3; N, 5·7. $C_{14}H_{27}NS$ requires C, 69·7; H, 11·2; N, 5·8%).

1,3-Dimethylhexahydroazepin-2-one from Hexahydroazepin-2-one

A suspension of hexahydroazepin-2-one (1·13 g, 10 mmol) in freshly distilled tetrahydrofuran (20 ml) under nitrogen at 0° was treated during 10 min with butyllithium in hexane (10 ml, 2·0 M). The first equivalent of the reagent produced a voluminous white precipitate which dissolved on adding the second equivalent of butyllithium to afford a yellow solution. The mixture was stirred at 0° for 30 min, then a solution of methyl iodide (2·84 g) in tetrahydrofuran (10 ml) was added over 10 min. During the addition of this reagent a white precipitate formed. The reaction mixture was stirred at room temperature for a further hour, then hydrolysed by the addition of 3 M HCl. The organic layer was separated and the aqueous layer was extracted with ether (3 × 20 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed to afford a yellow-orange liquid in 42% yield. G.l.c. analysis of this liquid showed four products. The products were separated by preparative g.l.c. (Apiezon M 5%, 6 ft, 180°) and the major component was identified as 1,3-dimethylhexahydroazepin-2-one by comparison with an authentic sample. ν_{max} 1560 cm^{-1}. N.m.r. ($CDCl_3$) δ 3·40, m, CH_2N; 3·00, s, NCH_3; 2·60, br, CHCO; 2·00–1·30, complex, 6H, $(CH_2)_3$; 1·15, d, J 7 Hz, $CHCH_3$. Mass spectrum m/e 141, M^+; $C_8H_{15}NO$ requires 141. Two other components were identified as hexahydroazepin-2-one (trace) and *N*-methylhexahydroazepin-2-one.

Alkylation of N-*Methylhexahydroazepin-2-one*

N-Methylhexahydroazepin-2-one was treated with one equivalent of butyllithium at 0° and the anion was alkylated as described above. The 3-alkylated products formed in this manner are listed below.

N,*3-Dimethylhexahydroazepin-2-one* (34%), b.p. 96–97°/13 mm (Found: C, 68·0; H, 10·5; N, 9·9. $C_8H_{15}NO$ requires C, 68·0; H, 10·7; N, 9·9%).

3-Ethyl-N-methylhexahydroazepin-2-one (34%), b.p. 110–111°/28 mm (Found: C, 69·6; H, 10·9; N, 8·9. $C_9H_{17}NO$ requires C, 69·6; H, 11·0; N, 9·0%).

N-*Methyl-3-propylhexahydroazepin-2-one* (30%), b.p. 116–118°/23 mm (Found: C, 71·0; H, 11·3; N, 8·4. $C_{10}H_{19}NO$ requires C, 71·0; H, 11·3; N, 8·3%).

3-Butyl-N-*methylhexahydroazepin-2-one* (35%), b.p. 124°/23 mm (Found: C, 72·3; H, 11·3; N, 7·4. $C_{11}H_{21}NO$ requires C, 72·1; H, 11·5; N, 7·6%).

Reaction of 3-Bromohexahydroazepin-2-one with Triethylborane in the Presence of Potassium t-Butoxide

A suspension of 3-bromohexahydroazepin-2-one[45] (0·119 g) in anhydrous tetrahydrofuran (15 ml) under nitrogen at 0° was treated with triethylborane (2·2 ml, 0·9 M) in tetrahydrofuran followed by slow addition of potassium t-butoxide (3 ml, 0·25 M) in dry tetrahydrofuran. The reaction mixture was stirred at room temperature for 1 h. A solution of methyl iodide (0·213 g, 1·5 equiv.) in dry tetrahydrofuran (5 ml) was added over 10 min; the reaction mixture was stirred at room temperature overnight, added to water (15 ml) and then extracted with chloroform. Evaporation of the solvent gave a mixture of three products (0·08 g) which were separated by means of preparative thin-layer chromatography. 3-Bromo-1-methylhexahydroazepin-2-one (0·04 g) was identified by its n.m.r. spectrum. N.m.r. ($CDCl_3$) δ 4·70, br, 1H, CHBr; 3·40, m, 2H, CH_2NCH_3; 3·00, s, 3H, NCH_3; 2·40–1·50, complex, 6H, $(CH_2)_3$. 3-Bromohexahydroazepin-2-one and hexahydroazepin-2-one were identified by comparison with authentic specimens.

[45] Francis, W. C., Thornton, J. R., Werner, J. C., and Hopkins, T. R., *J. Am. Chem. Soc.*, 1958, **80**, 6238.

Reaction of Sulphonium Ylid (14) with Triethylborane

A mixture of 3-bromohexahydroazepin-2-one (0·50 g) and dimethyl sulphide (1·50 g) in ethanol (10 ml) was heated in a sealed tube at 100° for 24 h. On cooling, the sulphonium salt crystallized as a colourless deliquescent solid, characterized only by its infrared spectrum (ν_{max} 1640 cm^{-1}). The sulphonium salt (0·50 g) was suspended in freshly distilled tetrahydrofuran (10 ml) and stirred with sodium hydride (0·20 g) at 20° until evolution of hydrogen ceased (2 h).[46] To the yellow suspension was added triethylborane (4·5 mmol) in tetrahydrofuran (3 ml) and the mixture was stirred for 4 h at 20°. The reaction was quenched by the addition of 3 M sodium hydroxide (5 ml) followed by 30% hydrogen peroxide (2 ml). After 3 h stirring at 20°, extraction with ether gave a colourless oil (0·70 g) which was chromatographed on alumina in benzene to remove the paraffin oil. The main fraction (0·30 g) was eluted with methylene chloride and appeared from its n.m.r. spectrum to be a mixture of the ylid and the elimination products, 2,3,6,7-tetrahydro-1*H*-azepin-2-one (15) and 2,5,6,7-tetrahydro-1*H*-azepin-2-one (16). Neither earlier nor later fractions indicated the presence of any alkylated material.

Schmidt Rearrangement of 1,4-Dioxaspiro[4,5]decan-6-one (17)

1,4-Dioxaspiro[4,5]decan-6-one (17) was prepared from cyclohexane-1,2-dione and ethylene glycol in dry benzene according to the literature procedure, b.p. 105–107°/10 mm (lit.[47] 115–116°/22 mm).

To a stirred solution of (17) (1·56 g) in polyphosphoric acid (45·0 g) sodium azide (0·68 g) was added in portions over a period of 40 min. The mixture was heated at 50–55° overnight with occasional shaking. It was then cooled and poured into a mixture of crushed ice and water (50 ml) and extracted with chloroform. The extract was dried and concentrated in vacuum giving a gummy residue (0·30 g). The crude product was chromatographed on alumina (25 g).

(i) Elution with benzene–ethyl acetate (9 : 1) gave (20) (0·03 g, 2·2%). N.m.r. ($CDCl_3$) δ 6·60, br, NH; 2·60–1·60, complex, 8H, 4(CH_2).

(ii) Elution with ethyl acetate gave (22) (0·03 g, 1·6%). N.m.r. ($CDCl_3$) δ 6·80, br, NH; 4·30, 2H; 3·80, 2H, $-OCH_2CH_2O-$; 2·60–1·80, complex, 8H.

(iii) Elution with ethyl acetate–methanol (9 : 1) gave (21) (0·03 g, 1·6%). N.m.r. ($CDCl_3$) δ 7·20, br, NH; 4·30, 2H, $-OCH_2CH_2O-$; 3·70, 2H, $-OCH_2CH_2O-$; 3·30, br, CH_2NH; 2·60–1·60, complex, 6H.

(iv) Elution with ethyl acetate–methanol (1 : 1) gave (19) (0·028, 2·0%). N.m.r. ($CDCl_3$) δ 6·80, br, NH; 3·50, br, CH_2NH; 2·80–1·80, complex, 6H.

3-Arylmethylene-6,6-dimethylhexahydroazepine-2,4-diones (24)

The aldehyde (1·0 g) was added to the keto lactam (23) (2 g) in conc. hydrochloric acid (60 ml) and the mixture was stirred at room temperature for 36 h. The solution was extracted with chloroform, the extracts were washed with water, dried and evaporated and the residue crystallized from ethanol. The following compounds were obtained in this manner.

3-Benzylidene-6,6-dimethylhexahydroazepine-2,4-dione (96%), m.p. 217–218° (Found: C, 72·2; H, 7·0; N, 5·5. $C_{15}H_{17}NO_2$ requires C, 74·0; H, 7·0; N, 5·8%).

*6,6-Dimethyl-3-*p*-nitrobenzylidenehexahydroazepine-2,4-dione* (52%), m.p. 193–194° (Found: C, 62·5; H, 5·6; N, 9·8. $C_{15}H_{16}N_2O_4$ requires C, 62·5; H, 5·6; N, 9·7%).

*3-*p*-Chlorobenzylidene-6,6-dimethylhexahydroazepine-2,4-dione* (54%), m.p. 189–190° (Found: C, 64·9; H, 5·8; N, 4·8. $C_{15}H_{16}ClNO_2$ requires C, 64·9; H, 5·8; N, 5·0%).

3-(3′,4′-Dimethoxybenzylidene)-6,6-dimethylhexahydroazepine-2,4-dione (61%), m.p. 187–188° (Found: C, 67·4; H, 6·9; N, 4·6. $C_{17}H_{21}NO_4$ requires C, 67·3; H, 7·0; N, 4·6%).

*6-Alkyl-7-methoxy-3,4,5,6-tetrahydro-2*H*-azepine (29) and 3-Alkylhexahydroazepin-2-one (30)*

The general method for the alkylation of (7) is as follows. Anhydrous tetrahydrofuran (20 ml) and diisopropylamine (2·00 g, 0·02 mol) were added to a dry flask purged with nitrogen and main-

[46] Ratts, K. W., and Yao, A. N., *J. Org. Chem.*, 1966, **31**, 1185.
[47] Jaeger, R. H., and Smith, H., *J. Chem. Soc.*, 1955, 160.

tained under a nitrogen atmosphere. After cooling the mixture to −5°, butyllithium in hexane solution (10 ml, 2·0 M) was added in a controlled manner to prevent the temperature from exceeding 0°. *O*-Methylcaprolactim (1·80 g, 0·015 mol) was added dropwise while maintaining the temperature of reaction below 0°. The reaction was stirred at 0° for another 3 h, and alkyl halide (2·0–2·5 equiv.) was added either neat or in tetrahydrofuran solution. The reaction was completed by stirring at room temperature for 5 h.

Isolation of the azepine (29).—Half of the reaction mixture was neutralized with saturated ammonium chloride and then extracted with portions of ether. The combined organic extracts were washed with water, dried and evaporated to give the following compounds.

*7-Methoxy-6-methyl-3,4,5,6-tetrahydro-2*H*-azepine* (68%), b.p. 60–62°/12 mm (Found: C, 67·7; H, 10·9; N, 10·3. $C_8H_{15}NO$ requires C, 68·0; H, 10·7; N, 9·9%).

*6-Ethyl-7-methoxy-3,4,5,6-tetrahydro-2*H*-azepine* (65%), b.p. 70–72/11 mm (Found: C, 69·4; H, 11·0; N, 9·4. $C_9H_{17}NO$ requires C, 69·6; H, 11·0; N, 9·0%).

*7-Methoxy-6-propyl-3,4,5,6-tetrahydro-2*H*-azepine* (70%), b.p. 89–90°/10 mm (Found: C, 71·1; H, 11·3; N, 8·0. $C_{10}H_{19}NO$ requires C, 71·0; H, 11·3; N, 8·3%).

Isolation of the azepin-2-one (30).—The remaining reaction mixture was neutralized with ice-cold 10% HCl and then extracted with three portions of ether. The combined organic layers were dried and the solvent was removed to afford (30) in moderate yield. Analytical samples were obtained by preparative g.l.c. (OV101 20%, 6 ft). Subsequently the hydrolysis procedure below was utilized. The following products were obtained: 3-methylhexahydroazepin-2-one, m.p. 92–93° (lit.[29] 94°); 3-ethylhexahydroazepin-2-one, m.p. 98–99° (lit.[48] 99–100°); and 3-propylhexahydroazepin-2-one, m.p. 79–80° (lit.[48] 80–81°).

Hydrolysis of the Methoxytetrahydroazepines (29)

The caprolactim ether (29) (100 mg) in light petroleum or benzene (2 ml) was applied to a dry column of alumina (50 g) and partly developed with benzene (10 ml). After 24 h elution with ethyl acetate yielded the caprolactam (60–80 mg). The method was applied successfully to (7), 7-ethoxy-3,4,5,6-tetrahydro-2*H*-azepine[16] (prepared by the method of Brown *et al.*[26]), 7-methoxy-2-methyl-3,4,5,6-tetrahydro-2*H*-azepine and 7-methoxy-3,3,5-trimethyl-3,4-dihydro-2*H*-azepine. Each lactam was identified by its n.m.r. and i.r. spectrum and m.p.

Reaction of (29; R = H) with Cyanogen Bromide

Very little reaction occurred in hexane at 70°/3 h or in dimethylformamide at 20°/12 h. In an n.m.r. tube the reaction was complete in deuterochloroform at 35° within an hour and the *O*-methyl signal shifted from δ 3·30 to three signals at 3·95, 3·70 and 3·65. On addition of water only two methoxyl signals (3·65, 3·60) were visible.

O-Methylcaprolactim (0·6 g) was refluxed with cyanogen bromide (1·0 g) in methylene chloride (15 ml) for 2 h. The n.m.r. spectrum of the crude product showed two methoxyl groups (δ 3·70, 3·65). The product was separated by preparative t.l.c. (CH_2Cl_2/light petroleum, 1 : 1) into two major fractions. The first (250 mg), b.p. 140°/0·1 mm, appeared from spectral data to be a mixture; ν_{max} 3280, 2250, 1727, 1665 cm^{-1}. The second fraction (230 mg) was a colourless oil and was by n.m.r. spectroscopy a 1 : 1 mixture of hexahydroazepin-2-one and 2-oxohexahydroazepine-1-carbonitrile; ν_{max} 3280, 2250, 1660 cm^{-1}. Hydrogenation of this material in ethanol–acetic acid with platinum gave, after workup, a product (200 mg) that was identical in all respects with hexahydroazepin-2-one.

General Procedure for the Alkylation of 6,6-Dimethylhexahydroazepine-2,4-dione (23)

To a solution of the keto lactam (23) (0·10 mol) and sodium methoxide (0·10 mol) in methanol (20 ml) was added the alkyl halide (0·20 mol) in portions, with stirring at room temperature. The reaction mixture was refluxed for 10 h and concentrated in vacuum. Chloroform was added to the residue and the precipitated sodium halide was removed. Evaporation of the chloroform yielded a crude product which was treated as described below.

[48] Fabrichnyi, B. P., Shalavina, I. F., and Goldfarb, Y. L., *Zh. Org. Khim.*, 1965, **1**, 1507 (*Chem. Abstr.*, 1966, **64**, 586c).

(i) *Alkylation with methyl iodide.*—*3,6,6-Trimethylhexahydroazepine-2,4-dione* (69%), m.p. 124–125°, was obtained when the crude product was recrystallized from light petroleum (Found: C, 64·0; H, 8·9; N, 8·3. $C_9H_{15}NO_2$ requires C, 63·9; H, 8·9; N, 8·3%). No trace of the *O*-methylated product could be detected by examination of the n.m.r. spectrum. ν_{max} 3280, 1708, 1670 cm^{-1}. N.m.r. ($CDCl_3$) δ 7·00, br, 1H, NH; 3·50, m, 2H, CH_2NH; 3·00, q, *J* 8 Hz, 1H, $CHCH_3$; 2·50, s, 2H, CH_2CO; 1·30, d, *J* 8 Hz, 3H, $CHCH_3$; 1·02–1·00, 6H, $C(CH_3)_2$.

(ii) *Alkylation with ethyl iodide.*—The combined yield was 60%. The two lactams were separated by preparative t.l.c. with chloroform–ethanol (95 : 5). *3-Ethyl-6,6-dimethylhexahydroazepine-2,4-dione* (35%) was recrystallized from ether–benzene, m.p. 132–133° (Found: C, 65·8; H, 9·3; N, 7·5. $C_{10}H_{17}NO_2$ requires C, 65·5; H, 9·3; N, 7·6%). ν_{max} 3200, 3080, 1708, 1675 cm^{-1}. N.m.r. ($CDCl_3$) δ 7·20, br, 1H, NH; 3·40, m, 2H, CH_2NH; 3·00, m, 1H, $CHCH_2$; 2·47, s, 2H, CH_2CO; 1·84, dq, *J* 7 Hz, 2H, $CHCH_2CH_3$; 1·02–1·00, 6H, $C(CH_3)_2$; 0·90, 3H, CH_2CH_3. *4-Ethoxy-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepin-2-one* (18%) was recrystallized from light petroleum, m.p. 112–113° (Found: C, 65·5; H, 9·1; N, 7·6. $C_{10}H_{17}NO_2$ requires C, 65·5; H, 9·3; N, 7·6%). ν_{max} 3180, 1650, 1610 cm^{-1}. N.m.r. δ 8·53, br, 1H, NH; 4·87, d, *J* 2 Hz, C=CH; 3·80, q, *J* 7 Hz, 2H, $-OCH_2CH_3$; 3·84, d, *J* 7 Hz, CH_2NH; 2·18, s, 2H, $CH_2C(CH_3)_2$; 1·35, t, *J* 7 Hz, 3H, OCH_2CH_3; 1·00, s, 6H, $C(CH_3)_2$.

(iii) *Alkylation with isopropyl bromide.*—The combined yield was 70%. The two lactams were separated as described in (ii). *3-Isopropyl-6,6-dimethylhexahydroazepine-2,4-dione* (30%) was recrystallized from light petroleum, m.p. 150–151° (Found: C, 66·7; H, 9·6; N, 7·0. $C_{11}H_{19}NO_2$ requires C, 67·0; H, 9·7; N, 7·1%). ν_{max} 3200, 3080, 1708, 1660 cm^{-1}. N.m.r. ($CDCl_3$) δ 6·70, br, 1H, NH; 3·34, m, 2H, CH_2NH; 2·95, m, 1H, $CHCH(CH_3)_2$; 2·45, s, 2H, CH_2CO; 1·65, br, 1H, $CH(CH_3)_2$; 1·00–0·90, complex, 12H. *4-Isopropoxy-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepin-2-one* (30%) was recrystallized from light petroleum, m.p. 124–125° (Found: C, 67·3; H, 9·7; N, 7·2. $C_{11}H_{19}NO_2$ requires C, 67·0; H, 9·7; N, 7·1%). ν_{max} 3180, 1650, 1610 cm^{-1}. N.m.r. ($CDCl_3$) δ 6·80, br, 1H, NH; 5·00, d, *J* 2 Hz, –C=CH; 4·30, q, *J* 7 Hz, 1H, $-OCHC(CH_3)_2$; 2·90, d, *J* 6 Hz, 2H, $-CH_2NH$; 2·20, s, 2H, $-CH_2C(CH_3)_2$; 1·30, d, *J* 7 Hz, 6H, $CH(CH_3)_2$; 1·00, s, 6H, $C(CH_3)_2$.

Schmidt Rearrangement of 3-Chloro-2-methylcyclohex-2-en-1-one (36)

To a stirred mixture of 3-chloro-2-methylcyclohex-2-en-1-one (1·0 g) and polyphosphoric acid (40·0 g) sodium azide (0·7 g) was added in small portions, over a period of 40 min. The mixture was then heated at 120° for 2 h with occasional shaking, cooled and poured into a mixture of crushed ice and water and extracted with chloroform. The extract was dried and concentrated in vacuum to give a white solid which was recrystallized from light petroleum affording *4-chloro-3-methyl-2,5,6,7-tetrahydro-1H-azepin-2-one* (37) as colourless needles (0·60 g, 54%), m.p. 105–106° (Found: C, 53·0; H, 6·2; N, 8·4. $C_7H_{10}ClNO$ requires C, 52·6; H, 6·3; N, 8·8%). N.m.r. ($CDCl_3$) δ 8·70, br, 1H, NH; 3·20, br, 2H, CH_2NH; 2·63, m, 2H, CH_2CCl; 2·00, complex, 5H, CH_3 and methylene protons. No trace of the isomeric 6-chloro-7-methyl-2,3,4,5-tetrahydro-1*H*-azepin-2-one could be detected by examination of the n.m.r. spectrum or by t.l.c.

3-Methylhexahydroazepin-2-one from the Reduction of (37)

The chloro lactam (37) (0·10 g) in ethanol (10 ml) was hydrogenated over platinum at room temperature and at atmospheric pressure overnight. The filtrate, after removal of catalyst by filtration, was evaporated to dryness to give a white solid which was recrystallized from light petroleum affording 3-methylhexahydroazepin-2-one as colourless needles (0·065 g, 81%), m.p. 92–93°. Its spectral data were identical in all respects with those of an authentic sample.

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