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# Central Nervous System Active Compounds. II* The Synthesis of Some 4-, 5-, 6- and 7-Substituted Caprolactams

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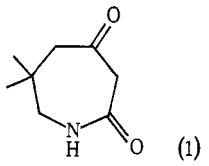
*Abstract*

The synthesis of caprolactam derivatives substituted at C4, C5, C6 and C7 with alkyl, aryl, acyl and hetero substituents is described. A variety of synthetic approaches to these compounds have been investigated and assessed, particularly for the synthesis of C4- and C6-substituted compounds. A significant number of the C4-, C6- and C7-substituted compounds prepared show central nervous system activity, ranging from convulsants to depressants depending on the position and nature of the substituent group.

As part of our aim to synthesize new compounds active in the central nervous system we have been investigating the activity of a variety of caprolactam (hexahydroazepin-2-one)† derivatives. In Part I of this series[1] we reported the synthesis of caprolactam derivatives substituted at N1, C2 and C3. In this paper we describe our work on the synthesis of compounds with substituents at C4, C5, C6 and C7.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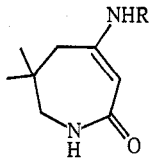
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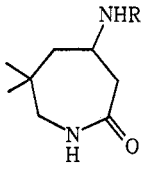

(3)

## Substitution at C4

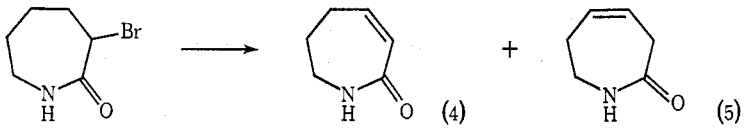
Caprolactams substituted at C4 are not generally accessible. The Beckmann[2,3] or Schmidt rearrangement of 3-alkylcyclohexanones gives mixtures of 4- and 6-alkylcaprolactams which are difficult to separate and pure compounds have been prepared by total synthesis.[4] We have, therefore, investigated alternative general methods for their synthesis. The 4-keto caprolactam (1), derived[5] from dimedone,

* Part I, *Aust. J. Chem.*, 1976, **29**, 2651.
† See footnote on p. 2652.

[1] Duong, T., Prager, R. H., Ward, A. D., and Kerr, D. I. B., *Aust. J. Chem.*, 1976, **29**, 2651.
[2] Ungnade, H. F., and McLaren, A. D., *J. Org. Chem.*, 1945, **10**, 29.
[3] Overberger, C. G., and Jabloner, H., *J. Am. Chem. Soc.*, 1963, **85**, 3431.
[4] Cefelin, P., Labsky, J., and Sebenda, J., *Collect. Czech. Chem. Commun.*, 1968, **33**, 270.
[5] Tamura, Y., Kita, Y., and Terashima, M., *Chem. Pharm. Bull.*, 1971, **19**, 529.

did not undergo addition reactions with organometallic reagents and treatment with Grignard reagents or organolithium compounds resulted only in formation of the enolate. However, (1) did react smoothly with amines to give the enamines (2). When an electron-withdrawing group was present on the aryl ring of these compounds (2; R = aryl) they showed a considerable sensitivity to moisture and were readily hydrolysed to (1). This water-sensitivity would clearly preclude their physiological use and, as a consequence, the corresponding dihydro derivatives (3) were prepared by catalytic reduction. These products (3) generally showed quite strong depressant activity and the effect of the type of substituent on the benzene ring on the central nervous system activity is currently being investigated.

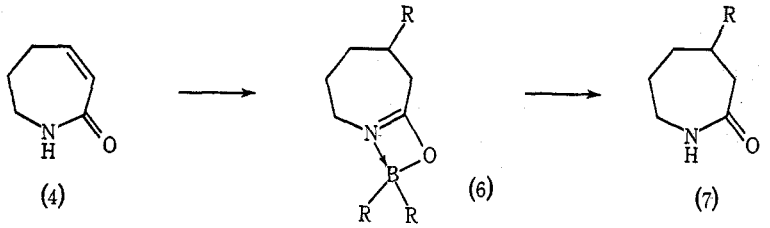
Two other methods were investigated for the synthesis of 4-substituted caprolactams. Brown[6] has described the conjugate addition of organoboranes to α,β-unsaturated ketones and lithium dialkylcuprates have similarly been added to both α,β-unsaturated ketones and esters.[7–10] It was of interest, therefore, to examine the possibility of conjugate addition to the unsaturated caprolactam (4), particularly since similar reactions with α,β-unsaturated amides do not appear to have been reported previously.[7] However, the required unsaturated caprolactams are not readily available. The Beckmann rearrangement of (*Z*)-cyclohexenone oxime gives (4) in poor yield; the (*E*) isomer yielded no lactam products.[11] However, a subsequent publication[12] provides results in conflict with these observations. The dehydrobromination of 3-bromocaprolactam gives a mixture[13] of (4) and (5) but ring contraction and other unidentified by-products have also been formed under some conditions.[14]




When the mixture of (4) and (5) was treated with lithium dibutylcuprate only low yields of products of conjugate addition could be obtained and with butylmagnesium bromide in the presence of cuprous chloride no addition at all occurred, nor did the use of the corresponding *N*-methyl derivative lead to higher yields of the desired products.

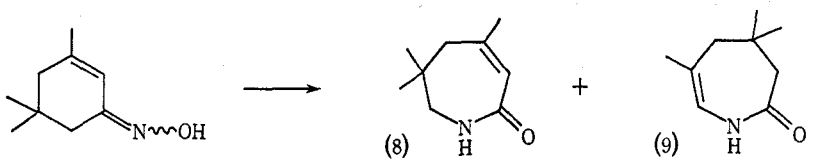
However, treatment of (4) and (5) with triethyl- or tributyl-borane in the presence of air resulted in the formation of the stable addition products (6) which could be converted into (7) by alkaline hydrogen peroxide although they were resistant to both acidic and alkaline workup. This method is thus of potential synthetic value and the scope of the reaction is being investigated.

[6] Brown, H. C., and Kabalka, G. W., *J. Am. Chem. Soc.*, 1970, **92**, 712, 714.
[7] Posner, G. H., *Org. React.*, 1972, **19**, 1.
[8] Posner, G. H., and Brunelle, D. J., *J. Chem. Soc., Chem. Commun.*, 1973, 907.
[9] Coates, R. M., and Sandefur, L. O., *J. Org. Chem.*, 1974, **39**, 275.
[10] Casey, C. P., and Marten, D. F., *Tetrahedron Lett.*, 1974, 925.
[11] Donat, F. J., and Nelson, A. L., *J. Org. Chem.*, 1957, **22**, 1107.
[12] Strizhakov, O. D., Zilberman, E. N., and Svetozarskii, S. V., *Zh. Obshch. Khim.*, 1965, **35**, 628 (*Chem. Abstr.*, 1965, **63**, 5535a).
[13] Reimschuessel, H. K., Sibilia, J. P., and Pascale, J. V., *J. Org. Chem.*, 1969, **34**, 959.
[14] Francis, W. C., Thornton, J. R., Werner, J. C., and Hopkins, T. R., *J. Am. Chem. Soc.*, 1958, **80**, 6238.



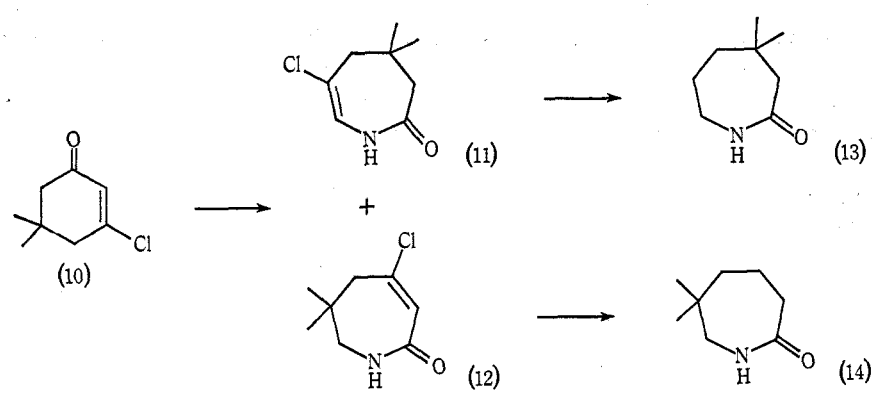
(4) (6) (7)

Another potential route to useful unsaturated caprolactams was through the Schmidt or Beckmann rearrangement of unsaturated cyclohexanones. As mentioned above there is some dispute about the products from the Beckmann rearrangement of cyclohexenone oximes; however, substituted cyclohexenone systems have been successfully rearranged. Thus both isomeric oximes of isophorone can be rearranged[15,16] to the corresponding caprolactams, (8) and (9); however, the Schmidt reaction gives only the conjugated caprolactam (8).[17] The high convulsant activity[18,19] of the lactams (8) and (9) and of their dihydro derivatives has made this substitution



(8) (9)

pattern a dominant factor in our investigation, hence its prominence in the work reported in this paper. The corresponding thiocaprolactams also have high convulsant activity.[1,19] The Schmidt reaction on the chloro derivative of dimedone (10) gives the lactams (11) and (12)[20] which are also useful intermediates for the synthesis of analogues of (8) and (9). Hydrogenation of the lactam (11) led to reductive removal of the chlorine to give 4,4-dimethylcaprolactam (13); similarly (12) gave (14) in high

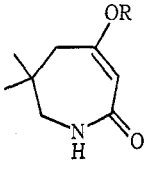


(10) (11) (12) (13) (14)

[15] Mazur, R. H., *J. Org. Chem.*, 1961, **26**, 1289.
[16] Montgomery, R. S., and Dougherty, G., *J. Org. Chem.*, 1952, **17**, 823.
[17] Koch, T. H., Geigel, M. A., and Tsai, C. C., *J. Org. Chem.*, 1973, **38**, 1090.
[18] 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.
[19] Prager, R. H., Breuker, E. L. M., Duong, T., Kerr, D. I. B., and Ward, A. D., unpublished data.
[20] Tamura, Y., and Kita, Y., *Chem. Pharm. Bull.*, 1971, **19**, 1735.

yield on reduction with platinum. The chloro lactams (11) and (12) are both convulsants with (12) being one of our most active compounds. This activity is retained in (14); however, (13) shows no activity at dose levels up to 200 mg/kg.[19]

The successful dehalogenation of halo ketones by silver-promoted zinc dust[21] in methanol or zinc dust and potassium iodide[22,23] suggested that this approach might prove useful for the reduction of (11) and (12). However, all attempts at reduction by these methods were unsuccessful. Treatment of (12) with 5% sodium amalgam gave no reduction; however, after 20 min at room temperature significant amounts of (15; R = Et) had formed and after 3 h a mixture of (15; R = Et) and the corresponding diethyl acetal was obtained. The use of tributylstannane as a reducing agent was also unsuccessful. In view of this inability to remove the chloride to provide a direct route to 4- or 6-substituted products we considered the possibility of replacing the chlorine by other functional groups. Thus treatment of (12) with sodium methoxide in methanol gave (15; R = Me) in good yield; this compound was also readily obtained by refluxing (1) in methanol–benzene. Hydrolysis of (15) with dilute hydrochloric acid gave (1) in high yield. Refluxing (12) with phosphorus pentasulphide in toluene gave the thio derivative (16) in good yield.

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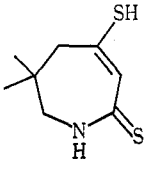
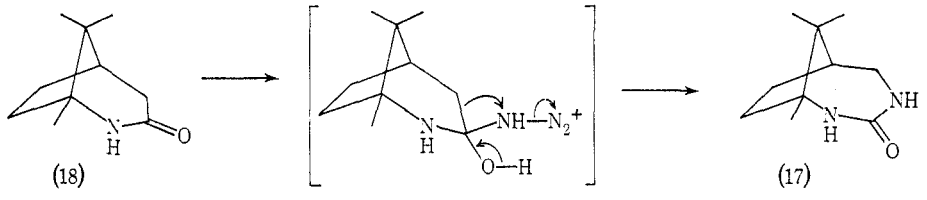



(16)

Three annelated caprolactams, which can be regarded as 4-substituted derivatives, were also prepared. Camphor, which does not form amide-type products through a Beckmann rearrangement of its oxime,[24,25] has been found to rearrange with hydrazoic acid, in polyphosphoric acid. The reaction proceeded very slowly and thin-layer chromatography of the mixture showed the presence of only one product (17), obtained in 34% yield, the structure of which is based on its spectral properties and microanalysis. We suggest that the initial product from the Schmidt reaction could be the expected amide (18) which rearranges further to give (17) as outlined in Scheme 1. However, we are unable to offer a convincing explanation for this



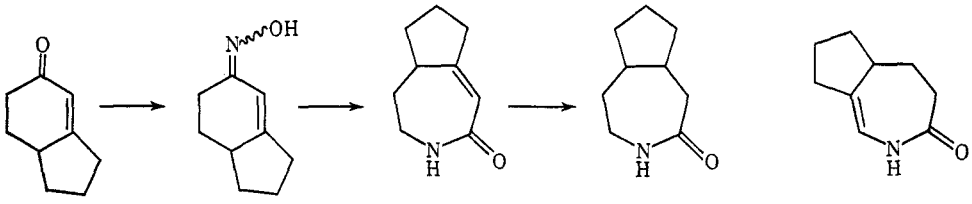

(18) (17)

Scheme 1

[21] Clark, R. D., and Heathcock, C. H., *J. Org. Chem.*, 1973, **38**, 3658.
[22] Crossley, A. W., and Renouf, N., *J. Chem. Soc.*, 1907, **91**, 63.
[23] Frank, R. L., and Hall, H. K., Jr, *J. Am. Chem. Soc.*, 1950, **72**, 1645.
[24] Leuckart, R., and Bach, E., *Ber. Dtsch. Chem. Ges.*, 1887, **20**, 104.
[25] Goldschmidt, H., *Ber. Dtsch. Chem. Ges.*, 1887, **20**, 483.

unusual pathway; usually amides react with hydrazoic acid to give tetrazoles.[26] For example, camphortetrazole, a powerful convulsant, requires the presence of a strong Lewis acid for its formation.[27]

The oximes (20), prepared from the ketone (19), were shown to be a mixture of (*Z*) and (*E*) isomers (3 : 2) by n.m.r. spectroscopy. Attempts to separate these two isomers by fractional crystallization or by column chromatography were unsuccessful. Reaction of the mixture with polyphosphoric acid at 130–135° afforded a single product (52%). N.m.r. and i.r. spectral data showed that this product is the conjugated system (21). This product was readily reduced to the saturated analogue (22). It is not clear whether the absence of the alternative rearrangement product (23) is due to the ready isomerization of the (*E*)-oxime to the (*Z*)-oxime under the reaction conditions or to the possibility that (23) does form but polymerizes under the reaction conditions.




(19) (20) (21) (22) (23)

**Substitution at C 5**

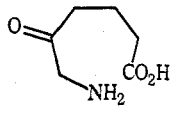
Derivatives of caprolactam substituted at C 5 are most readily available from rearrangement of 4-substituted cyclohexanones by the Beckmann[28] or the Schmidt[26] reaction. However, the 5-alkylcaprolactams obtained by this means proved to be inactive. Smythies[29] has published the details of a 'working model' for the γ-aminobutyric acid (Gaba) receptor site in the central nervous system. Although there is no experimental verification of this model it has proved to be useful in predicting or rationalizing the activity of some Gaba antagonists. Since our work has indicated[18] that many of our active caprolactams are antagonists of Gaba we have been interested in how well they 'fit' the model Gaba receptor. It is obvious from an inspection of the model that hydrophilic groups would be the most appropriate type of group at C 5 and that hydrophobic groups would cause unfavourable interactions. For this reason we prepared the 5-ethoxycarbonyl derivative and the benzoate of 5-hydroxycaprolactam but both compounds were inactive when injected intraperitoneally into mice.

**Substitution at C 6**

As is the case with 3- and 4-alkylated caprolactams no general synthesis of 6-alkylcaprolactams has been reported. Accordingly we investigated the possibility of a cyclization process affording the desired 6-substituted system. 6-Amino-5-

[26] Wolff, H., *Org. React.*, 1946, **3**, 307.
[27] Schmidt, K. F., U.S. Pat. 2,029,799 (*Chem. Abstr.*, 1936, **30**, 1950).
[28] Donaruma, L. G., and Heldt, W. Z., *Org. React.*, 1960, **11**, 1.
[29] Smythies, J. R., *Annu. Rev. Pharmacol.*, 1974, **14**, 9.

oxohexanoic acid (24)[30] appeared to be a suitable substrate for subsequent modification but this route has been frustrated by our inability to cyclize (24), under mild conditions, to the desired caprolactam (25). Battersby[31] and others have encountered similar difficulties in cyclizing 6-aminohexanoic acids. Although the desired cyclization has been achieved in other cases[31] with the corresponding ester we felt that under these rather forcing conditions intermolecular condensation involving the carbonyl group would dominate. Accordingly we turned our attention to efforts to hydrolyse the vinyl chloride system (11) that can be obtained from dimedone. To our surprise acidic or basic hydrolysis reactions have been unsuccessful; where reaction does occur ring-opened products are obtained. The vinyl chloride (11) was stable to diborane, even for extended periods, and reaction with sodium methoxide gave the acetal (26). Further work in this area is continuing but it is clear that this approach is not straightforward and is much less satisfactory as a general route than would at first appear.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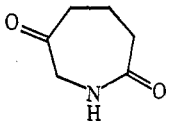
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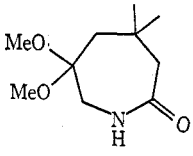
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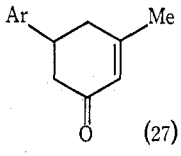
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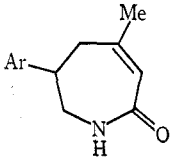
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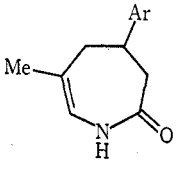

(29)

The work of Horning *et al.*[32] suggested a possible route to 6- and 4-arylcaprolactams. A series of aromatic aldehydes was condensed with ethyl acetoacetate to give the cyclohexenones (27). Contrary to the literature[16] the isomeric oximes of (27; Ar = Ph) could not be obtained in a pure state, as evidenced[33] by the n.m.r. spectra of the material produced from a variety of separation attempts. Accordingly (27) was treated with hydrazoic acid in polyphosphoric acid under carefully controlled conditions but only the conjugated caprolactam (28) could be isolated; again it is possible that the other rearrangement product (29), if it is formed, would be unstable under the reaction conditions and would be polymerized.

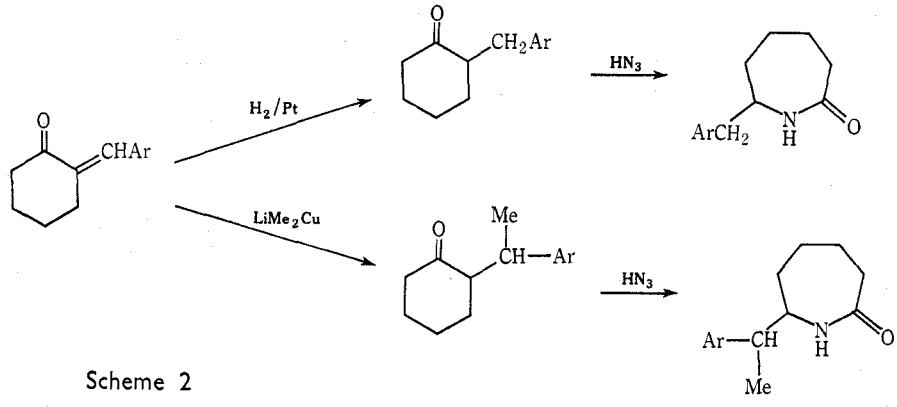
The caprolactam (28; Ar = Ph) has been described in the literature[16] as having m.p. 118° and u.v. absorption at 241 nm (ε 7250). The isomer (29), formed by a Beckmann rearrangement, is described[16] as having m.p. 146° and u.v. absorption at 211 nm (19000). The compound we isolated from the Schmidt reaction has m.p. 142–146°, $\lambda_{max}$ 218 nm (16000) and n.m.r. signals at $\delta$ 5·90 (broad singlet) due to the olefinic proton and a multiplet at 3·4 due to the groups $CH_2N$ and $CHC_6H_5$. The

[30] Lartillot, S., and Baron, C., *Bull. Soc. Chim. Fr.*, 1964, 783.
[31] Battersby, A. R., Beck, J. F., and McDonald, E., *J. Chem. Soc., Perkin Trans. 1*, 1974, 160, and references cited therein.
[32] Horning, E. C., Denekas, M. O., and Field, R. E., *J. Org. Chem.*, 1944, **9**, 547.
[33] Slomp, G., and Wechter, W. J., *Chem. Ind. (London)*, 1962, 41.

multiplet simplifies considerably on addition of $D_2O$ to the sample; this indicates that coupling to the NH proton is contributing to the observed multiplicity. The remaining high-field signals are readily attributable to the allylic methylene protons (2·62) and the allylic methyl (2·0). This n.m.r. spectrum is clearly much more compatible with (28; Ar = Ph) than with (29; Ar = Ph). Confirmation that (28; Ar = Ph) is indeed the correct structure for our product, and that the structures have been confused in the literature report, is provided by the u.v. data. α,β-Unsaturated amides of the type present in (28) would be expected[15,34] to have absorption at *c.* 218 nm whereas the enamide chromophore in (29) would be expected[15,35] to absorb at *c.* 240 nm.

**Substitution at C7**

The 7-substituted caprolactams are most conveniently obtained by the Beckmann[36] or, preferably, the Schmidt[37,38] rearrangement. Although the Schmidt reaction of 2-alkylcyclohexanones proceeds with migration of the more highly substituted bond, as expected,[39,40] the reaction with 2-phenylcyclohexanone was anomalous. When the oxime of 2-phenylcyclohexanone was treated with *p*-toluenesulphonyl chloride in pyridine the resultant Beckmann rearrangement led exclusively to 7-phenylcaprolactam, as reported.[36] However, the product from the treatment of 2-phenylcyclohexanone with hydrazoic acid depended on the solvent employed. Although it has been claimed[41] that only 7-phenylcaprolactam is formed by using hydrazoic acid in chloroform, we obtained a 2 : 1 mixture of the 3- and 7-phenylcaprolactams, readily separable by chromatography. In polyphosphoric acid the only lactam produced at 0–20° was the 3-phenyl isomer, with a mixture of the 3- and 7-isomers being obtained at 50°. Caprolactams with small alkyl groups at the 7-position (methyl, ethyl, propyl and isopropyl) have convulsant properties but larger alkyl




Scheme 2

[34] Mazur, R. H., *J. Am. Chem. Soc.*, 1959, **81**, 1454.
[35] Rosenkranz, G., Mancera, O., Sondheimer, F., and Djerassi, C., *J. Org. Chem.*, 1956, **21**, 520.
[36] Wenkert, E., and Barnett, B. F., *J. Am. Chem. Soc.*, 1966, **82**, 4671.
[37] Conley, R. T., *J. Org. Chem.*, 1958, **23**, 1330.
[38] Shechter, H., and Kirk, J. C., *J. Am. Chem. Soc.*, 1951, **73**, 3087.
[39] Smith, P. A. S., and Horwitz, J. P., *J. Am. Chem. Soc.*, 1950, **72**, 3718.
[40] Smith, P. A. S., and Ashby, B., *J. Am. Chem. Soc.*, 1950, **72**, 2503.
[41] Rosenmund, P., Sauer, D., and Trommer, W., *Chem. Ber.*, 1970, **103**, 496.

groups (butyl, phenyl, benzyl and cyclohexyl) lead to compounds with depressant properties.

The 7-benzyl systems were most conveniently prepared from the arylmethylene-cyclohexanones (Scheme 2). Reaction of cyclohexanone enamines with benzyl halides did not prove to be as satisfactory a method for the preparation of the 2-aryl-methylcyclohexanones. Conjugate addition of lithium dimethylcuprate to benzylidene-cyclohexanone proceeded smoothly and after Schmidt rearrangement a 1 : 1 mixture of diastereoisomers was obtained (Scheme 2).

Attempted nitration of 2-benzylcyclohexanone produced a complex mixture of products and selective reduction of 2-(*p*-nitrobenzylidene)cyclohexanone was unsuccessful. Thus catalytic and dissolving-metal reductions reduced the nitro group preferentially, and sodium borohydride, in ethyl acetate, reduced the carbonyl group only. The required 7-(*p*-nitrobenzyl)caprolactam was eventually prepared, in moderate yield, by nitration of 7-benzylcaprolactam. The effect of electron-withdrawing groups in increasing the depressant activity of 7-arylmethylcaprolactams is currently under investigation.

## Experimental

General experimental details have been described previously.[1]

*Schmidt Reaction on 3-Methylcyclohexanone*

A variety of conditions for the Schmidt reaction on 3-methylcyclohexanone were tried but all gave, by n.m.r., a mixture of 4- and 6-methylhexahydroazepin-2-one. Attempts to adequately separate these isomers by preparative t.l.c. or by preparative g.l.c. all proved unsuccessful.

*6,6-Dimethylhexahydroazepine-2,4-dione (1)*

A solution of dimedone (42·0 g) and hydroxylamine hydrochloride (20·8 g) in methanol (250 ml) was refluxed for 3 h. The methanol was removed and the crude hydrochloride was dissolved in methylene chloride and washed with dilute potassium carbonate. The dried ($MgSO_4$) extract was concentrated in vacuum to give a crude product (33·0 g) which was chromatographed on alumina (250 g). Elution with benzene (300 ml) gave a mixture of (*Z*) and (*E*) isomers in the ratio 6 : 1. Pure (*Z*)-*oxime* (3·0 g, 7%) was obtained by crystallization from light petroleum, m.p. 106–107° (Found: C, 64·2; H, 9·0; N, 8·2. $C_9H_{15}NO_2$ requires C, 63·9; H, 8·9; N, 8·3%). $\nu_{max}$ 3200, 3050, 1640, 1620 $cm^{-1}$. N.m.r. $\delta$ 8·67, br, OH, removed with $D_2O$; 6·05, s, CH=C; 3·70, s, $OCH_3$; 2·08, 4H, $2CH_2$; 1·01, s, $C(CH_3)_2$.

Elution with benzene–ethyl acetate (9 : 1) gave a 1 : 1 mixture of oximes as a brown oil (23·0 g, 55%), b.p. 90–100°/0·05 mm (lit.[5] 104–110°/0·07 mm).

The mixture of oximes was treated with polyphosphoric acid according to the procedure of Tamura *et al.*[5] to afford the lactam (1) in 75% yield, m.p. 146–147° (lit.[5] 145·5–146·5°).

*Attempted Reaction of (1) with Ethylmagnesium Bromide*

A solution of excess ethylmagnesium bromide in tetrahydrofuran was added to the keto lactam (1) and the mixture was kept at either 0° or 20° for 24 h. Starting material was recovered quantitatively, in both cases, after the usual workup.

*Reaction of (1) with Amines*

The amine (1 mmol) was dissolved in anhydrous chloroform or benzene (10 ml) and the keto lactam (1) (1 mmol) was added. The solution was refluxed for 24 h by using a Dean–Stark water separator. After cooling, the precipitated product (2) was collected and recrystallized from ethyl acetate. The following individual compounds were prepared in this manner.

*4-Benzylamino-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepin-2-one* (93%), m.p. 206–207° (Found: C, 73·5; H, 8·1; N, 11·1. $C_{15}H_{20}N_2O$ requires C, 73·7; H, 8·2; N, 11·5%).

*6,6-Dimethyl-4-phenylamino-2,5,6,7-tetrahydro-1H-azepin-2-one* (76%), m.p. 232° (Found: C, 73·3; H, 7·8; N, 12·3. $C_{14}H_{18}N_2O$ requires C, 73·0; H, 7·9; N, 12·2%).

*6,6-Dimethyl-4-(2′-methylphenylamino)-2,5,6,7-tetrahydro-1H-azepin-2-one* (80%), m.p. 227–228° (Found: C, 73·9; H, 8·3; N, 11·6. $C_{15}H_{20}N_2O$ requires C, 73·7; H, 8·2; N, 11·5%).

*4-[2′-(3″,4″-Dimethoxyphenyl)ethylamino]-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepin-2-one* (60%), m.p. 174–175° (Found: C, 68·0; H, 8·2; N, 8·6. $C_{18}H_{26}N_2O_3$ requires C, 67·9; H, 8·2; N, 8·8%).

*6,6-Dimethyl-4-(3′-nitrophenylamino)-2,5,6,7-tetrahydro-1H-azepin-2-one* (58%), m.p. 228–230° (Found: C, 61·1; H, 6·2; N, 15·4. $C_{14}H_{17}N_3O_3$ requires C, 61·1; H, 6·2; N, 15·3%).

*6,6-Dimethyl-4-(4′-nitrophenylamino)-2,5,6,7-tetrahydro-1H-azepin-2-one* (55%), m.p. 242–243° (Found: C, 60·8; H, 6·1; N, 15·4. $C_{14}H_{17}N_3O_3$ requires C, 61·1; H, 6·2; N, 15·3%).

*Reduction of the Enamino Lactams (2)*

(i) Lactam (2; R = Ph) (0·220 g) in ethanol (20 ml) was hydrogenated over platinum at room temperature and at atmospheric pressure overnight. Recrystallization of the crude product, obtained after removal of the catalyst and evaporation of the solvent, from ethyl acetate gave *6,6-dimethyl-4-phenylaminohexahydroazepin-2-one* (3; R = Ph) (0·195 g, 88%), m.p. 214–215° (Found: C, 72·3; H, 8·5; N, 11·9. $C_{14}H_{20}N_2O$ requires C, 72·4; H, 8·7; N, 12·1%). $\nu_{max}$ 3350, 3240, 1660, 1605 $cm^{-1}$.

(ii) In a similar fashion reduction of (2; R = 2-$MeC_6H_4$) gave, after recrystallization from ethyl acetate, *6,6-dimethyl-4-(2′-methylphenylamino)hexahydroazepin-2-one* (3; R = 2-$MeC_6H_4$) (83%), m.p. 174–175° (Found: C, 72·8; H, 8·9; N, 11·6. $C_{15}H_{22}N_2O$ requires C, 73·1; H, 9·0; N, 11·4%). $\nu_{max}$ 3200, 3050, 1660, 1606 $cm^{-1}$.

*Reaction of Keto Lactam (1) with Methanol*

The keto lactam (1) (0·50 g), methanol (10 ml) and *p*-toluenesulphonic acid (0·05 g) were heated together under nitrogen in benzene (20 ml) in a Dean–Stark apparatus. After 12 h the reaction mixture was washed with brine, sodium bicarbonate; it was then dried and evaporated. Recrystallization of the crude product from light petroleum gave *4-methoxy-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepin-2-one* (15; R = Me) (0·25 g, 56%), m.p. 148–149° (Found: C, 63·9; H, 9·0; N, 7·7. $C_9H_{15}NO_2$ requires C, 63·9; H, 8·9; N, 8·3%). $\nu_{max}$ 3150, 1660, 1602 $cm^{-1}$. N.m.r. ($CDCl_3$) $\delta$ 7·50, br, NH; 5·02, d, *J* 2Hz, $CH_3OC{=}CH$; 3·07, s, $OCH_3$; 2·97, d, *J* 7 Hz, $CH_2NH$; 2·23, s, $(CH_3)_2CCH_2$; 1·00, s, $(CH_3)_2C$.

*4-Butylhexahydroazepin-2-one*

(i) To a stirred suspension of cuprous chloride (2·50 g) in dry tetrahydrofuran (15 ml) at 0°, under nitrogen, was added butyllithium (2·0 M, 10 ml). The mixture was stirred for 15 min at 0°, then a solution of (4) and (5) (0·8 g) in dry tetrahydrofuran (10 ml) was added over 20 min. After being stirred at 0° for 5 h the reaction mixture was poured into dilute hydrochloric acid (30 ml) with vigorous stirring. Concentrated ammonium hydroxide was slowly added until the solution became blue and clear. The layers were separated and the aqueous portion was extracted with ether. Removal of the solvent from the combined organic extracts gave an oily material (0·22 g) which still contained starting material, as shown by t.l.c. The crude product was separated by preparative t.l.c. on silica, with chloroform–ethanol (95 : 5) as the eluting solvent, giving *4-butylhexahydroazepin-2-one* as a colourless oil (0·15 g, 30%, based on the content of (4)), b.p. 118–119°/0·8 mm. $\nu_{max}$ 3300, 1660 $cm^{-1}$. N.m.r. $\delta$ 7·91, br, NH; 3·13, br, $CH_2NH$; 2·23, br, $CH_2CO$; 1·90–1·10, complex, 12H; 0·90, m, $CH_3$. Mass spectrum *m/e* 169 ($M^{+\cdot}$) ($C_{10}H_{19}NO$ requires $M^{+\cdot}$ 169) (18%), 112 ($M-C_4H_9$) (100), 84 ($M-C_4H_9-CO$) (70). The oil was redistilled under reduced pressure (115–120°/0·9 mm) in a bulb-to-bulb apparatus but failed to give a consistent analysis.

(ii) Butylmagnesium bromide was prepared from magnesium (1·20 g) and butyl bromide (6·75 g) in dry tetrahydrofuran (100 ml) in the usual way. The Grignard reagent was cooled to 0° and cuprous chloride was added to produce a bluish-green colour. The mixture of (4) and (5) (2·50 g) was then added, but no visible reaction was observed. Workup after 48 h at 0° gave a quantitative recovery of starting material.

(iii) Air (*c.* 1 ml/min) was drawn over a stirred solution of the lactams (4) and (5) (0·1 g) and tributylborane (2 mmol) in tetrahydrofuran (5 ml) containing water (50 $\mu$l) for 6 h. The mixture was worked up by oxidizing any residual organoborane with alkaline hydrogen peroxide at 0° for 30 min, and extraction then gave a colourless oil (0·085 g, 57%), the infrared and n.m.r. spectra of which were very similar to those obtained in (i). Once again distillation of material recovered after preparative t.l.c. failed to give a sample with satisfactory analyses.

*Reaction of (4) with Triethylborane*

When the lactam mixture (4) and (5) (0·1 g) was treated with a solution of triethylborane (2 mmol) in tetrahydrofuran (10 ml) as described above and the mixture was worked up by addition of only dilute sodium hydroxide, extraction gave a viscous oil (0·15 g, quantitative) which was pure by g.l.c. analysis. The mass spectrum had $M^{+\cdot}$ at *m/e* 208 and the n.m.r. spectrum was also consistent with structure (6). N.m.r. ($CDCl_3$) $\delta$ 3·40, br, $CH_2N$; 2·5–1·2, br, 12H; 0·70, t, *J* 7·5 Hz, 9H, $CH_2CH_3$. Attempted distillation of this material led to extensive decomposition.

*Reduction of 4-Chloro-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepin-2-one (12)*

(i) Reduction of (12) (0·20 g) in ethanol (20 ml) in the presence of platinum (0·1 g) at atmospheric pressure was complete within 4 h. Distillation (110°/0·07 mm) gave *6,6-dimethylhexahydroazepin-2-one* (14) (0·155 g, 95%) which solidified on standing, m.p. 100–101° (Found: C, 68·2; H, 10·8; N, 9·5. $C_8H_{15}NO$ requires C, 68·0; H, 10·7; N, 9·9%). $\nu_{max}$ 3180, 1660 $cm^{-1}$. N.m.r. $\delta$ 8·00, br, NH; 2·95, br, $CH_2N$; 2·30, br, $CH_2CO$; 1·60, m, 6H; 1·00, s, $C(CH_3)_2$.

(ii) The chloro lactam (12) (0·2 g) was dissolved in ethanol (5 ml) and stirred with 5% sodium amalgam (2 g). Aliquots were taken periodically for n.m.r. analysis. After 20 min the product was essentially a 1 : 1 mixture of (12) and the enol ether (15; R = Et), but after 3 h significant amounts (30%) of the diethyl acetal of (1) were evident. All resonances were ascribable to one or other of these compounds. In particular the vinyl proton of (12) resonated at $\delta$ 6·25, that of the enol ether at 5·02, and the acetal O–$CH_2$ signals at 4·15 were well separated from those of the enol ether at 3·81.

*Reaction of (12) with Sodium Alkoxides*

(i) Sodium (0·05 g) was dissolved in methanol (20 ml); the chloro lactam (12) (0·33 g) was added and the mixture was refluxed for 48 h. The methanol was removed, chloroform was added to the residue and the precipitated sodium chloride was removed by filtration. Evaporation of the chloroform gave a quantitative yield of crude product which was recrystallized from light petroleum to give (15; R = Me) (0·25 g, 74%), identical to the sample obtained above.

(ii) Substitution of ethanol for methanol in the above procedure gave (15; R = Et) (90%), m.p. 112–113°, identical with an authentic specimen.[1]

*Hydrolysis of (15) to Keto Lactam (1)*

Compound (15; R = Me) (0·05 g) in dilute hydrochloric acid (10 ml) was stirred at room temperature overnight and then at 60° for 30 min. The reaction mixture was neutralized with dilute sodium carbonate solution and extracted with chloroform. The extracts were dried, concentrated and the residue was crystallized from benzene–ether to give (1) (0·035 g, 73%).

*Reaction of (12) with Phosphorus Pentasulphide*

The lactam (12) (0·70 g), phosphorus pentasulphide (2·0 g) and toluene (25 ml) were refluxed overnight. Workup of the reaction mixture as described in Part I gave a brown solid (0·60 g, 79%). Recrystallization from ethyl acetate gave *4-mercapto-6,6-dimethyl-2,5,6,7-tetrahydro-1H-azepine-2-thione* as orange-yellow needles, m.p. 187–188° (Found: C, 51·4; H, 6·7; N, 7·7. $C_8H_{13}NS_2$ requires C, 51·4; H, 7·0; N, 7·5%). $\nu_{max}$ 3170, 1585, 1120 $cm^{-1}$. Mass spectrum *m/e* 187 ($M^{+\cdot}$) ($C_8H_{13}NS_2$ requires $M^{+\cdot}$ 187).

*The Schmidt Reaction on Camphor*

To a mixture of camphor (7·6 g) in polyphosphoric acid (160 g) at 20° was added sodium azide (4·0 g) in small portions over 90 min with gentle agitation. The mixture was then kept at 60–64° for 48 h. Workup of the reaction mixture in the usual way gave a crude product which was recrystallized from light petroleum to yield *1,9,9-trimethyl-2,4-diazabicyclo[4,2,1]nonan-3-one* (17) (2·90 g, 34%), m.p. 180–182° (Found: C, 66·0; H, 10·0; N, 15·7. $C_{10}H_{18}N_2O$ requires C, 65·9; H, 10·0; N, 15·4%). $\nu_{max}$ 3300, 3170, 1660 $cm^{-1}$. Mass spectrum *m/e* 182 ($M^{+\cdot}$).

*Beckmann Rearrangement of the Oximes (20)*

Redistilled ketone[42] (19) (4·08 g) was added to a mixture of hydroxylamine hydrochloride (2·0 g), sodium hydroxide (20%, 6·5 ml), water (13 ml) and ethanol (30 ml). The mixture was refluxed for 3 h and allowed to stand overnight at room temperature. Most of the ethanol was removed by evaporation in vacuum and the residue was extracted with ether (3 × 20 ml) and the combined extracts were dried and concentrated to give a gummy product (3·5 g, 84%). The n.m.r. spectrum indicated that the product was a mixture of oximes; attempted separation of this mixture by recrystallization was unsuccessful. N.m.r. $\delta$ 9·00, br, NOH (removed with $D_2O$); 6·70, br, olefinic hydrogen of (*Z*)-oxime; 5·95, br, olefinic hydrogen of (*E*)-oxime.[33] The crude mixture of oximes (0·30 g) was heated and stirred in polyphosphoric acid (3 ml) for 20 min at 130–135°. The cooled mixture was poured into water (100 ml) and extracted with chloroform (4 × 20 ml). The combined extracts were dried ($K_2CO_3$) and evaporated to give a brown solid which was recrystallized from light petroleum to yield *4-azabicyclo[5,3,0]dec-1-en-2-one* (21) (0·15 g, 50%), m.p. 120–121° (Found: C, 71·4; H, 8·5; N, 9·0. $C_9H_{13}NO$ requires C, 71·6; H, 8·7; N, 9·3%). $\nu_{max}$ 3180, 3120, 1660, 1610 $cm^{-1}$. N.m.r. $\delta$ 8·30, br, NH; 5·70, s, CH=C; 3·30, m, $CH_2N$.

*Hydrogenation of (21)*

Lactam (21) (0·05 g) in ethanol (10 ml) was hydrogenated over platinum at room temperature and at atmospheric pressure for 4 h. The usual workup of the reaction gave *4-azabicyclo[5,3,0]decan-3-one* (22) after crystallization from light petroleum, m.p. 95–95·5° (Found: C, 70·2; H, 9·7; N, 8·9. $C_9H_{15}NO$ requires C, 70·5; H, 9·9; N, 9·1%). N.m.r. $\delta$ 8·13, br, NH; 3·18, br, $CH_2N$.

*5-Alkylhexahydroazepin-2-ones*

The following compounds were prepared by the general procedure described by Conley:[37] 5-methylhexahydroazepin-2-one (90%), m.p. 40–41° (lit.[2] 41–42°); 5-ethylhexahydroazepin-2-one (90%), m.p. 55–56° (lit.[43] 56–57°); 5-isopropylhexahydroazepin-2-one (85%), m.p. 84–85° (lit.[43] 84°); 5-t-butylhexahydroazepin-2-one (87%), m.p. 152–154° (lit.[43] 156–157°); *5,5-dimethylhexahydroazepin-2-one* (92%), m.p. 88° (Found: C, 67·9; H, 10·6; N, 9·8. $C_8H_{15}NO$ requires C, 68·0; H, 10·7; N, 9·9%).

*Ethyl 7-Oxohexahydroazepine-3-carboxylate*

The literature[44] procedure for the preparation of triethyl 4-oxocyclohexane-1,1,3-tricarboxylate was followed but the product was clearly different to that described in the literature and a combination of n.m.r. and mass spectral data suggested that the product was a 1 : 1 mixture of diethyl 4-oxocyclohexane-1,3-dicarboxylate and 3-ethoxycarbonyl-4-oxocyclohexanecarboxylic acid. The product was esterified by dissolving the crude material in ethanol containing a little conc. sulphuric acid at 20° for 12 h. Distillation of the product gave *diethyl 4-oxocyclohexane-1,3-dicarboxylate*, b.p. 134/1·5 mm (Found: C, 59·8; H, 7·8. $C_{12}H_{18}O_5$ requires C, 59·5; H, 7·5%). N.m.r. ($CDCl_3$) $\delta$ 4·2, two quartets, *J* 7 Hz, 4H; 2·6–1·8, 8H; 1·25, t, *J* 7 Hz, 6H. $\nu_{max}$ 1720, 1650 $cm^{-1}$. Mass spectrum *m/e* 242 ($M^{+\cdot}$, 10%).

[42] Stork, G., Brizzolara, A., Landesman, H., Szmuszkovicz, J., and Terrell, R., *J. Am. Chem. Soc.*, 1963, **85**, 207.
[43] Schaffer, A., Kaufold, R., and Ziegenbein, W., *Chem. Ber.*, 1955, **88**, 1906.
[44] Artico, M., Guiliano, R., and Lattanzi, F., *Ann. Chim. (Rome)*, 1963, **53**, 1811 (*Chem. Abstr.*, 1964, **60**, 11910g).

The crude mixture of esters and acids obtained above was hydrolysed to 4-oxocyclohexanecarboxylic acid as described.[42] The product had properties identical to those described by Hardegger *et al.*[45] The acid was esterified with ethanol–sulphuric acid and the product converted into the lactam in the usual way. *Ethyl 7-oxohexahydroazepine-3-carboxylate* (58%) was purified by distillation, b.p. 160–165°/0·6 mm (Found: C, 58·2; H, 7·9; N, 7·4. $C_9H_{15}NO_3$ requires C, 58·4; H, 8·2; N, 7·6%). $\nu_{max}$ 3400, 1715, 1660 $cm^{-1}$. N.m.r. ($CDCl_3$) $\delta$ 7·55, br, NH; 4·18, t, $J$ 7 Hz, $CH_2O$; 3·30, br, $CH_2N$; 2·50, br, 3H; 1·95, br, 4H; 1·26, t, $J$ 7 Hz, 3H.

*Benzyl 7-Oxohexahydroazepine-3-carboxylate*

Benzyl 4-oxocyclohexanecarboxylate was prepared by the method of Jones *et al.*[46] and converted into the lactam in the usual way. *Benzyl 7-oxohexahydroazepine-3-carboxylate* (95%), m.p. 128–131°, was purified by crystallization from chloroform–light petroleum (Found: C, 66·7; H, 6·5. $C_{13}H_{15}NO_3$ requires C, 66·9; H, 6·5%). $\nu_{max}$ 3180, 1705, 1655 $cm^{-1}$. N.m.r. ($CDCl_3$) $\delta$ 8·05, dd, $J$ 2, 7 Hz, 2H; 7·50, m, 3H; 6·90, br, NH; 5·35, q, $J$ 5 Hz, 1H; 3·35, m, $CH_2N$; 2·65, $CH_2CO$; 2·10, m, 4H.

*6,6-Dimethylhexahydroazepin-2-one (14) from Keto Lactam (1)*

The method was adapted from that used by Fieser.[47] A mixture of keto lactam (1) (0·70 g) and ethane-1,2-dithiol (0·5 ml) in a test tube at 0° was treated with boron trifluoride etherate (0·5 ml) and the mixture was homogenized with a stirring rod. The mixture became warm and soon set to a white solid. After 10 min methanol (10 ml) was added, the mixture was stirred well and cooled and the solid collected and washed with a little cold methanol. Recrystallization from ethyl acetate afforded the *thioacetal* of (1) (0·80 g, 77%), m.p. 229–230° (Found: C, 52·1; H, 7·4; N, 5·9. $C_{10}H_{17}NOS_2$ requires C, 51·9; H, 7·4; N, 6·1%). $\nu_{max}$ 3200, 3080, 1670 $cm^{-1}$. N.m.r. ($CDCl_3$) $\delta$ 6·70, br, NH; 3·40, s, $S(CH_2)_2S$; 3·10, s, $CH_2CO$; 3·06, d, $J$ 7 Hz, $CH_2N$; 2·30, s, $CH_2C(CH_3)_2$; 1·04, s, $C(CH_3)_2$.

The thioacetal (0·10 g) was refluxed with Raney nickel in ethanol overnight. The solution was filtered and the nickel washed thoroughly with ethanol and then with ether. Evaporation of the solvents gave a solid which on recrystallization from light petroleum gave 6,6-dimethylhexahydroazepin-2-one, identical with the sample obtained from the reduction of (12).

*6,6-Dimethoxy-4,4-dimethylhexahydroazepin-2-one (26)*

Sodium (0·06 g) was dissolved in methanol (10 ml); the chloro lactam (11) (0·172 g) was added and the mixture was refluxed overnight. The methanol was removed and chloroform added to the residue. The mixture was filtered, the chloroform was evaporated from the filtrate and the residue was recrystallized from n-hexane at −70° to give the *lactam* (26), m.p. 70° (Found: C, 59·6; H, 9·6; N, 6·8. $C_{10}H_{19}NO_3$ requires C, 59·7; H, 9·5; N, 7·0%). $\nu_{max}$ 3160, 3040, 1660 $cm^{-1}$. N.m.r. $\delta$ 6·50, br, NH; 4·03, br, $CH_2N$; 3·35, s, $OCH_3$; 1·95, s, $CH_2CO$; 1·40, m, 2H; 1·00, s, $C(CH_3)_2$.

*Reduction of 6-Chloro-4,4-dimethyl-2,3,4,5-tetrahydro-1H-azepin-2-one (11)*

(i) The lactam (11) (0·10 g) in ethanol (15 ml) was hydrogenated over platinum at room temperature and at atmospheric pressure for 4 h. The usual workup gave, after recrystallization from light petroleum, *4,4-dimethylhexahydroazepin-2-one* (13) (0·075 g, 90%), m.p. 103–104° (Found: C, 68·1; H, 10·7; N, 10·0. $C_8H_{15}NO$ requires C, 68·0; H, 10·7; N, 9·9%). $\nu_{max}$ 3180, 3080, 1660 $cm^{-1}$. N.m.r. $\delta$ 6·90, br, NH; 3·20, br, $CH_2N$; 2·42, br, $CH_2CO$; 1·67, m, 4H; 1·02, s, $C(CH_3)_2$.

(ii) Zinc dust (2·0 g) was stirred for 4 min with dilute hydrochloric acid (10 ml). The supernatant liquid was decanted and the zinc was washed with acetone (2 × 20 ml) and ether (10 ml). Lactam (11) (0·30 g) in methanol (15 ml) and potassium iodide (0·25 g) in methanol (10 ml) were added and the mixture was stirred overnight. The reaction mixture was then filtered and the filtrate evaporated. The residue was partitioned between dilute hydrochloric acid (20 ml) and ether (50 ml) and the ether

[45] Hardegger, E., Plattner, P. A., and Black, F., *Helv. Chim. Acta*, 1944, **27**, 793.
[46] Jones, E. R. H., and Sondheimer, F., *J. Chem. Soc.*, 1949, 615.
[47] Fieser, L. F., *J. Am. Chem. Soc.*, 1954, **76**, 1945.

layer was dried and evaporated to yield a solid (0·28 g) that was identical in all respects to the starting material.

Repetition of this experiment but refluxing the reaction mixture for 2 days gave a similar result and only starting material could be obtained.

(iii) Treatment of the chloro compound (11) with silver-promoted zinc dust,[21] under literature conditions, yielded only starting material when the reaction was worked up.

(iv) To a solution of (11) (0·170 g) in dry benzene (20 ml) was added dropwise tributylstannane (0·30 g) with stirring under nitrogen over a period of 30 min and external cooling. After the addition had been completed the reaction mixture was stirred at room temperature overnight. The usual workup led only to recovery of (11).

(v) Diborane (4 mmol) generated in the usual way in diglyme (20 ml) was carried by a slow stream of nitrogen into a chilled, stirred solution of (11) (0·344 g, 2 mmol) in dry tetrahydrofuran (30 ml). The solution was stirred under nitrogen at room temperature overnight. Oxidative workup gave a gummy residue (0·30 g) whose infrared spectrum was almost identical to that of the starting material.

*Attempted Cyclization of (24)*

A mixture of the amino acid[30] (0·13 g) and *N,N'*-dicyclohexylcarbodiimide (0·26 g) in chloroform (15 ml) was stirred at room temperature overnight. Workup of the reaction mixture led only to recovery of the amino acid.

*Preparation of 5-Aryl-3-methylcyclohex-2-enones (27)*

(i) 3-Methyl-5-phenylcyclohex-2-enone was prepared in 56% yield by the method of Horning *et al.*,[32] b.p. 138–140°/1 mm (lit.[16] 160–164°/5 mm). Related compounds prepared in this manner are listed below.

*5-(4'-Methoxyphenyl)-3-methylcyclohex-2-enone* (42%), b.p. 200°/4 mm. The *2,4-dinitrophenylhydrazone* derivative of this compound had m.p. 197–200° (Found: C, 60·3; H, 5·1; N, 14·1. $C_{20}H_{20}N_4O_5$ requires C, 60·6; H, 5·1; N, 14·1%).

*5-(4'-Hydroxyphenyl)-3-methylcyclohex-2-enone* (40%), m.p. 106–108° (Found: C, 77·1; H, 7·0. $C_{13}H_{14}O_2$ requires C, 77·2; H, 7·0%).

*3-Methyl-5-(4'-nitrophenyl)cyclohex-2-enone* (66%), m.p. 133–136° (Found: C, 67·6; H, 5·7; N, 5·9. $C_{13}H_{13}NO_3$ requires C, 67·5; H, 5·7; N, 6·1%).

(ii) In the case of the *p*-nitrophenyl compound the decarboxylation step of the above procedure gave a complex mixture of products. 3-Methyl-5-phenylcyclohex-2-enone (1·1 g) was added to a stirred mixture of concentrated nitric acid (3 ml) and sulphuric acid (3 ml) at 0° at such a rate that the temperature did not exceed 10°. After an additional hour at 0° the reaction mixture was worked up in the usual way and the crude solid was recrystallized from ethanol to yield the ketone.

*Schmidt Reaction on 5-Aryl-3-methylcyclohex-2-enones (27)*

(i) Sodium azide (0·26 g, 4·0 mmol) was added to an ice-cold, stirred solution of the ketone (27; Ar = Ph) (0·3 g, 1·6 mmol) in polyphosphoric acid (9 g) and the mixture was stirred at 0° for 1·5 h, then at room temperature for 1·5 h and finally heated at 55° for 3·5 h. Water (30 ml) was added to the cooled mixture and the solution was extracted with dichloromethane (5 × 30 ml). Evaporation of the dried extracts yielded the crude amide which was purified by preparative t.l.c. on silica with ether as the developing solvent and then crystallized from chloroform–light petroleum to yield *4-methyl-6-phenyl-2,5,6,7-tetrahydro-1H-azepin-2-one* (28; Ar = Ph) (0·097 g, 30%), m.p. 142–146° (lit.[16] 118·3–118·7°, see Discussion: Substitution at C6). $\nu_{max}$ 1670, 1620 $cm^{-1}$. N.m.r. ($CDCl_3$) $\delta$ 7·3, s, 5H; 5·9, s, CH=C; 3·3–3·5, m, 3H, CH–$C_6H_5$, $CH_2N$; 2·5–2·7, m, $CH_2$; 2·0, s, $CH_3C$=C. Mass spectrum *m/e* 201 ($M^{+\cdot}$) ($C_{13}H_{15}NO$ requires $M^{+\cdot}$ 201).

(ii) Treatment of the ketone (27; Ar = *p*-$MeOC_6H_4$) with a fivefold excess of sodium azide as described above gave, after crystallization from ethyl acetate–light petroleum, *6-(4'-methoxyphenyl)-4-methyl-2,5,6,7-tetrahydro-1H-azepin-2-one* (28; Ar = *p*-$MeOC_6H_4$), m.p. 189–192° (Found: C, 72·5; H, 7·3; N, 6·3. $C_{14}H_{17}NO_2$ requires C, 72·7; H, 7·4; N, 6·1%). $\nu_{max}$ 1670, 1620 $cm^{-1}$. N.m.r. ($CDCl_3$) $\delta$ 7·2, d, *J* 9 Hz; 6·9, d, *J* 9 Hz, both aryl hydrogens; 5·9, s, CH=C; 3·8, s, $CH_3O$;

3·3–3·5, m, 3H, $CH_2N$, $CHC_6H_4$; 2·5–2·7, m, $CH_2$; 2·0, s, $CH_3C{=}C$. Mass spectrum *m/e* 231 ($M^{+\cdot}$) ($C_{14}H_{17}NO_2$ requires $M^{+\cdot}$ 231).

(iii) An attempted Schmidt reaction on the ketone (27; Ar = *p*-$HOC_6H_4$) by the method described above gave only a very small amount of chloroform-soluble product, which did not show any amide absorption in its infrared spectrum. Basification of the aqueous layer followed by continuous chloroform extraction did not yield any additional material.

When the *p*-acetoxyphenyl ketone was subjected to the same conditions a slow disappearance of starting material was observed by t.l.c. but again no amide products were produced.

(iv) Treatment of the ketone (27; Ar = *p*-$O_2NC_6H_4$) with excess hydrazoic acid as described above gave, after crystallization from ethyl acetate–light petroleum, *4-methyl-6-(4'-nitrophenyl)-2,5,6,7-tetrahydro-1H-azepin-2-one* (28; Ar = *p*-$O_2NC_6H_4$), m.p. 200–202° (Found: C, 63·2; H, 5·7; N, 11·1. $C_{13}H_{14}N_2O_3$ requires C, 63·4; H, 5·7; N, 11·4%). $\nu_{max}$ 1660, 1625 $cm^{-1}$. N.m.r. ($CDCl_3$) $\delta$ 8·35, d, *J* 9 Hz; 7·4, d, *J* 9 Hz, both aryl hydrogens; 5·9, s, CH=C; 3·4–3·7, m, $CH_2N$, $CHC_6H_4$; 2·5–2·7, m, $CH_2$; 2·0, s, $CH_3C{=}C$.

*Reaction of 2-Phenylcyclohexanone with Hydrazoic Acid*

(i) 2-Phenylcyclohexanone (5·0 g) was added slowly to polyphosphoric acid (100 g) stirred and cooled to 0°. Sodium azide (8 g) was then added in small portions and the stirring continued for a further 18 h at room temperature. The mixture was then poured onto ice, the solution was neutralized with sodium hydroxide and extracted with dichloromethane (5 × 30 ml). The product, obtained after removal of the solvent from the dried extracts, was shown to be at least a 10 : 1 mixture of 3- and 7-phenylhexahydroazepin-2-one by n.m.r. Chromatography of the product on alumina and elution with light petroleum gave an oil (1·5 g) which did not show any absorption in the carbonyl region of the infrared spectrum. Elution with ethyl acetate gave *3-phenylhexahydroazepin-2-one* (2·0 g) after recrystallization from ethyl acetate, m.p. 183–185° (Found: C, 76·2; H, 8·2; N, 7·4. $C_{12}H_{15}NO$ requires C, 76·1; H, 8·0; N, 7·4%). $\nu_{max}$ 3200, 1667 $cm^{-1}$. N.m.r. ($CDCl_3$) $\delta$ 7·30, s, 5H; 6·60, m, 1H; 3·78, m, 1H; 3·25, m, 2H; 1·90, m, 6H. Intermediate fractions from the column contained only unchanged ketone (0·7 g) and no fraction contained resonances at $\delta$ 4·5 ascribable to 7-phenylhexahydroazepin-2-one.

(ii) When the above reaction was repeated, adding the sodium azide at room temperature and then warming the reaction mixture to 55°, there was obtained a 30% yield of a product shown to be a 1 : 3 mixture of 7- and 3-phenylhexahydroazepin-2-one by n.m.r. spectroscopy and t.l.c.

(iii) Repetition of the literature procedure[41] gave a 60% yield of a yellow oil which was shown by n.m.r. spectroscopy to be a 1 : 2 mixture of 7- and 3-phenylhexahydroazepin-2-one.

*7-Cyclohexylhexahydroazepin-2-one*

2-Phenylcyclohexanol was hydrogenated, in the presence of platinum, in ethanol at 4 atm overnight and the crude product was oxidized with Jones reagent at 0°. The product, which contained a trace of 2-phenylcyclohexanone, was treated with sodium azide in polyphosphoric acid at room temperature overnight. The crude product (80%), obtained as outlined above, was purified by chromatography on alumina. Elution with light petroleum–dichloromethane (1 : 1) and recrystallization from ether gave *7-cyclohexylhexahydroazepin-2-one*, m.p. 139° (Found: C, 73·8; H, 10·7; N, 7·1. $C_{12}H_{21}NO$ requires C, 73·8; H, 10·8; N, 7·2%). N.m.r. ($CDCl_3$) $\delta$ 5·8, m, 1H; 3·20, m, 1H; 2·50, m, 2H; 2·2–1·2, m, 17H.

*7-Alkylhexahydroazepin-2-ones*

The method of preparation was adapted from that of Conley,[37] the 2-alkylcyclohexanone, polyphosphoric acid and sodium azide being used at 50°. The following compounds were prepared in this manner. In some cases the lactams were converted into the corresponding thiolactams by the usual procedure.[1]

7-Methylhexahydroazepin-2-one (96%), m.p. 88–89° (lit.[37] 90–91°); 7-ethylhexahydroazepin-2-one (95%), m.p. 91–92° (lit.[38] 91–92°); 7-propylhexahydroazepin-2-one (95%), m.p. 97–98°

(lit.[37] 97–98°); 7-butylhexahydroazepin-2-one (94%), m.p. 73–73·5° (lit.[48] 70°); 7-isopropyl-4-methylhexahydroazepin-2-one (98%), m.p. 120–121° (lit.[49] 119–120°).

*7-Methylhexahydroazepine-2-thione* (67%), m.p. 87–88° (Found: C, 58·8; H, 9·0; N, 9·1. $C_7H_{13}NS$ requires C, 58·7; H, 9·1; N, 9·8%).

*7-Propylhexahydroazepine-2-thione* (89%), m.p. 83–83·5° (Found: C, 63·3; H, 9·9; N, 8·0. $C_9H_{17}NS$ requires C, 63·1; H, 10·0; N, 8·2%).

*7-Isopropyl-4-methylhexahydroazepine-2-thione* (82%), m.p. 106–107° (Found: C, 65·2; H, 10·4; N, 7·6. $C_{10}H_{19}NS$ requires C, 64·8; H, 10·3; N, 7·6%).

*7-Arylmethylhexahydroazepin-2-ones*

These were prepared by the Schmidt rearrangement of the corresponding 2-arylmethylcyclohexanone,[50,51] the following procedure being used. Sodium azide (1·4 g, 21·5 mmol) was added to an ice-cold, stirred solution of the 2-arylmethylcyclohexanone (10·6 mmol) in polyphosphoric acid (60 g). The resulting mixture was stirred at 0° for 1·5 h and then stirring was continued at room temperature until the i.r. spectrum of an aliquot showed that the reaction was complete (*c.* 6 h). The reaction mixture was diluted with ice-water (400 ml) and the solution was extracted with dichloromethane (3 × 150 ml). The solvent was removed from the dried ($MgSO_4$) extracts to yield the crude amide which was recrystallized from ethyl acetate–light petroleum. The following compounds were prepared in this manner.

*7-Benzylhexahydroazepin-2-one* (49%), m.p. 157–160° (Found: C, 76·7; H, 8·3; N, 6·9. $C_{13}H_{17}NO$ requires C, 76·8; H, 8·4; N, 6·9%).

*7-(4′-Methoxybenzyl)hexahydroazepin-2-one* (40%), m.p. 153–155° (Found: C, 72·1; H, 8·4; N, 6·2. $C_{14}H_{19}NO_2$ requires C, 72·1; H, 8·2; N, 6·0%).

*7-(2′-Methoxybenzyl)hexahydroazepin-2-one* (42%), m.p. 120–122° (Found: C, 72·3; H, 8·2; N, 5·9. $C_{14}H_{19}NO_2$ requires C, 72·1; H, 8·2; N, 6·0%).

*7-(4′-Methylbenzyl)hexahydroazepin-2-one* (45%), m.p. 174–175° (Found: C, 77·5; H, 8·8; N, 6·5. $C_{14}H_{19}NO$ requires C, 77·4; H, 8·8; N, 6·5%).

*7-(1′-Phenylethyl)hexahydroazepin-2-one*

Methyllithium was added to a slurry of cuprous iodide (3·07 g, 16·1 mmol) in ether (40 ml) at 0° under nitrogen, until all the solid had dissolved. 2-Benzylidenecyclohexanone[52] (2·0 g, 10·8 mmol) in ether (20 ml) was then added dropwise over a period of 10 min and the mixture was stirred at 0° for an additional 30 min. The reaction mixture was poured into cold dilute nitric acid (300 ml) and extracted with ether (3 × 150 ml). The combined organic extracts were dried ($MgSO_4$), the solvent was removed and the residue was chromatographed on silica (60 g). Elution with ether–light petroleum (5 : 95) gave 2-(1′-phenylethyl)cyclohexanone as a light yellow oil; $\nu_{max}$ 1700 $cm^{-1}$. This ketone formed a crystalline *2,4-dinitrophenylhydrazone*, m.p. 207–210°, after recrystallization from dichloromethane–light petroleum (Found: C, 62·5; H, 5·7; N, 14·4. $C_{20}H_{22}N_4O_4$ requires C, 62·8; H, 5·8; N, 14·6%).

The ketone was treated with hydrazoic acid, by using the general procedure described above, to yield *7-(1′-phenylethyl)hexahydroazepin-2-one* (37%), m.p. 92–114°, after recrystallization from light petroleum (Found: C, 77·0; H, 8·7. $C_{14}H_{19}NO$ requires C, 77·4; H, 8·8%). The wide melting range and the multiplicity of signals in the n.m.r. indicate that the product was a mixture of diastereoisomers.

*7-(4′-Nitrobenzyl)hexahydroazepin-2-one*

7-Benzylhexahydroazepin-2-one (50 mg) was added to an ice-cold, stirred mixture of concentrated nitric acid (5 ml) and concentrated sulphuric acid (5 ml). After 10 min at 0° the reaction

[48] Holmquist, H. E., Rothrock, H. S., Theobald, C. W., and Englund, B. E., *J. Am. Chem. Soc.*, 1956, **78**, 5339.
[49] Wallach, O., *Justus Liebigs Ann. Chem.*, 1900, **312**, 171.
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[52] Wallach, O., *Ber. Dtsch. Chem. Ges.*, 1907, **40**, 70.

mixture was poured onto ice (50 g). Extraction with dichloromethane (3 × 20 ml) and evaporation of the dried ($MgSO_4$) extracts yielded a crude product which was recrystallized from ethyl acetate–light petroleum to give *7-(4'-nitrobenzyl)hexahydroazepin-2-one* (40%), m.p. 153–154° (Found: C, 63·3; H, 6·7; N, 11·4. $C_{13}H_{16}N_2O_3$ requires C, 62·9; H, 6·5; N, 11·3%). $\nu_{max}$ 1660 $cm^{-1}$. N.m.r. ($CDCl_3$) $\delta$ 8·3, d, *J* 8 Hz; 7·5, d, *J* 8 Hz, aromatic protons; 6·4, br, NH; 3·4–3·8, m, 1H; 2·8, d, *J* 7 Hz, $C_6H_4CH_2$–; 1·1–2·6, m, 8H.

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