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Central Nervous System Active Compounds. XVI* Some Chemistry of 6-Oxo Caprolactams Derived from an Enamine Ring-Expansion Synthesis

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Abstract

Several 6-oxo caprolactam derivatives have been prepared by the ring-expansion of enaminopyrrolidones with dimethyl acetylenedicarboxylate. Other acetylenic systems did not react. The products exist in the enol form of the β-keto ester system are are very resistant towards hydrolysis. They react with hydrazine and phenylhydrazine to form pyrazolo[3,4-*c*]azepinones in low yield. Many of the caprolactams and their pyrazolo-fused derivatives show central nervous system activity of a depressant nature in mice.

Introduction

Recently we have been investigating the central nervous system activity of a variety of substituted caprolactam systems. Our studies[1] have shown that compounds with substituents at either C4 or C6, or both, have ,in general, the greatest activity. We have been able ot prepare[1–5] a wide variety of C4 substituted and some C4, C6 disubstituted derivatives but we have been unable to obtain suitable general methods that would enable a variety of C6 substituted caprolactams to be made. We have investigated in particular, methods that, in priciple, should lead to 6-oxo caprolactams. In this paper we report our studies on a ring-expansion reaction that forms this system.

The ring-expansion of enamines with acetylenic esters, particularly dimethyl acetylenedicarboxylate, has been known for some time.[6,7] However, the reaction has not often been applied to enamino lactams.[8] We thus chose to prepare enaminopyrrolidinones and to study their ring-expansion reactions with dimethyl acetylemedicarboxylate and related compounds.

* Part XV, *Aust. J. Chem.*, 1985, **38**, 931.

[1] Hutchison, G. I., Prager, R. H., and Ward, A. D., *Aust. J. Chem.*, 1980, **33**, 2477.
[2] Duong, T., Prager, R. H., Ward, A. D., and Kerr, D. I. B., *Aust. J. Chem.*, 1976, **29**, 2651.
[3] Duong, T., Prager, R. H., Tippett, J. M., Ward, A. D., and Kerr, D. I. B., *Aust. J. Chem.*, 1976, **29**, 2667.
[4] Mooney, B. A., Prager, R. H., and Ward, A. D., *Aust. J. Chem.*, 1980, **33**, 2717.
[5] Mooney, B. A., Prager, R. H., and Ward, A. D., *Aust. J. Chem.*, 1981, **34**, 2695.
[6] Cook, A. G., 'Enamines: Synthesis, Structure and Reactions' (Marcel Dekker: New York 1969).
[7] Hickmott, P. W., *Tetrahedron*, 1982, **38**, 3363.
[8] Haywood, D. J., and Reid, S. T., *J. Chem. Soc., Perkin Trans. 1*, 1977, 2457.

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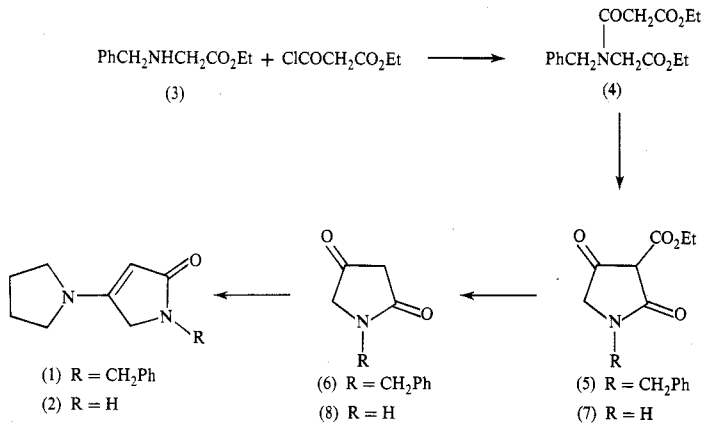
Results and Discussion

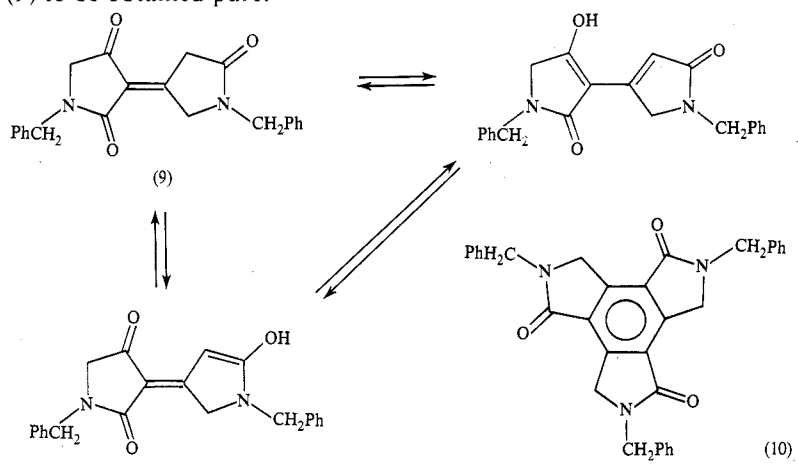
Sythesis of the Enamino Lactams

The *N*-benzyl lactam (1) was prepared by a literature procedure[9] (Scheme 1), which was improved if an added base or 2 equiv. of (3) were used in the formation of (4), and if the Dieckmann condensation of (4) was carried out under dry nitrogen The pyrrolidine-2,4-dione (6) was unstable and was used as soon as it had been prepared to form the enamine (1) which was also relatively unstable.



Scheme 1

Purification of the dione (6) by the literature procedure[9] was found to be unsatisfactory due to its propensity to self-condense in mildly basic conditions. Thus the crude dione (6), after dissolution in dilute sodium bicarbonate solution at room temperature, followed by filtration and acidification gave a product whose spectral data were not that expected for (6) and which was a complex mixture by t.l.c. The mass spectrum of this product showed peaks at 189, 360 and 513, corresponding to the molecular ions for the expected product as well as the self-condensation product (9, *E* and/or *Z*) from two molecules, and the product (10) derived from the self-condensation of three molecules of (6). Accurate mass measurements on these ions supported these structural assignments. Chromatography, followed by fractional crystallization allowed (9) to be obtained pure.

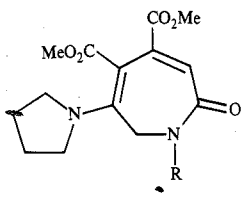


[9] Shamma, M., and Novak, L., *Collect. Czech. Chem. Commun.*, 1970, **35**, 3280.

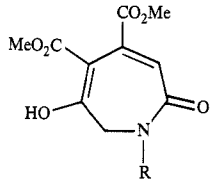
The corresponding unsubstituted lactam (2) was prepared by modifying the literature procedure[10] so that the coupling of ethyl hydrogen malonate and ethyl glycinate could be more conveniently carried out by using dicyclohexylcarbodiimide in aqueous acetonitrile. Both the keto ester (7) and the dione (8) were very insoluble in common organic solvents and were used without further purification. The enamine (2) was even less stable than its *N*-benzyl derivative (1).

Caprolactam Formation and Structure

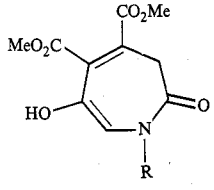
Both (1) and (2) condensed quite readily with dimethyl acetylenedicarboxylate enamino caprolactams (11) and (12) in 58% and 65% yield respectively. The *N*-benzyl system (1) did not condense with acetylenedicarboxylic acid, the (trimethylsilyl) ester of acetylenedicarboxylic acid, methyl propiolate and ethyl phenylpropiolate even under more forcing conditions. The lack of reaction in these latter cases reflects the much greater reactivity of dimethyl acetylenedicarboxylic compared to other acetylenic esters in this type of reaction, and the generally low reactivity of the enamino systems because of the electron-withdrawing amide group.



(11) R = CH_2Ph
(12) R = H



(13) R = CH_2Ph
(14) R = H



(15) R = CH_2Ph
(16) R = H

The enamino caprolactams (11) and (12) were hydrolysed readily in dilute acid to form the β-keto-ester systems whose spectral data showed that they were largely, if not entirely, in the enolic forms (13) and (14), and which also precluded the alternative structures (15) and (16). Thus the ^{13}C n.m.r. spectrum of (13) showed a signal at 101·2 ppm which could be assigned to C5 of the enolic system ; no signals were observed that would be consistant with this carbon being part of a non-enolic β-keto ester group. Only four signals were present above 100 ppm; all were in the region 47–53 ppm. Two of these signals are due to methoxyl carbons (*c.* 50 ppm) and the other two are the signals from methylene carbons attached to a nitrogen atom. In the alternative structure (15) a signal would be expected[11] in the region 30–37 ppm for a methylene carbon adjacent to an amide carbonyl.

The ultraviolet spectrum of (13) showed absorption maxima at 202, 256, 279, and 344 nm. These peaks were also present and were only slightly enhanced in alkaline solution, but when the spectrum was recorded in acidic solution only the peaks at 202 and 256 nm were observed. These data suggest that (13) is in the enolic form and that the peaks at 279 and 344 nm represent absorptions[12] due to some enolate ion being present at neutral pH.

[10] Lowe, G., and Yeung, H. W., *J. Chem. Soc., Perkin Trans. 1*, 1973, 2907.
[11] Johnson, L. F., and Jankowski, W. C., 'Carbon-13 N.M.R. Spectra' (John Wiley: New York 1972).
[12] Scott, A. I., 'Interpretation of the Ultraviolet Spectra of Natural Products' (Pergamon Press: Oxford 1964).

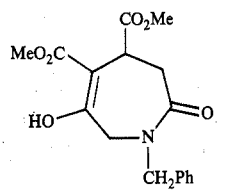
The proton n.m.r. spectrum of the enamine (11) showed broad resonances for the pyrrolidine protons and a quartet for the benzylic methylene protons. These signals indicate that restricted rotation, caused by non-bonded interactions of the pyrrolidine ring with the adjacent ester and benzyl systems, affects the signals of the pyrrolidine protons and makes the benzyl hydrogens non-equivalent.

Reactions of the Caprolactams

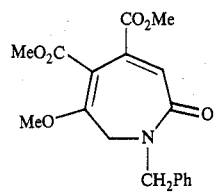
The *N*-benzyl caprolactam (13) proved to be remarkably stable to a variety of hydrolysis conditions. It was unaffected by being heated in aqueous acetonitrile for 5 days or after standing in dilute potassium hydroxide solution for 26 days. Heating (13) in dimethyl sulfoxide, containing a little water and with or without added salts,[13] gave a complex mixture as indicated by t.l.c. and whose n.m.r. spectrum indicated that substantial decomposition of the molecule had occurred. Heating (13) in aqueous methanolic potassium hydroxide gave a mixture of products, the majority of which still contained two methyl ester signals in their n.m.r. spectra. Acidic hydrolsis conditions were also unsuccessful. Treatment of (13) with dilute hydrochloric acid solution at room temperature for 4 days returned starting material (75%) and a small amount of another impure, and relatively unstable, product whose spectral properties were consistent with structure (15) and which gave a positive ferric chloride test. More vigorous acidic hydrolysis conditions produced a more complex reaction mixture but still failed to cause significant ester hydrolysis and appeared to form more of (15).

Trimethylsilyl iodide, which is believed to cause ester hydrolysis by *O*-alkyl cleavage rather than *O*-acyl cleavage,[14] reacted with (13) to give a mixture of products including some starting material. A major product was the reduced compound (17) which could not be obtained crystalline. These trimethylsilyl iodide reactions proved very difficult to reproduce and generally formed complex reaction products.

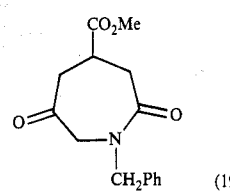
The methyl ether (18) of (13), prepared with diazomethane, was also subjected to hydrolysis conditions. Trimethylsilyl iodide gave three products, two of which were the demethylated material (13) and the reduction product (17). The final product appeared to have structure (19) form its spectral data and because it gave a positive test with Brady's reagent and a negative test with ferric chloride. Unfortunately this



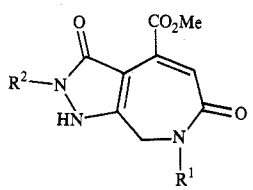
(17)



(18)



(19)



	R^1	R^2
(20)	H	H
(21)	H	Ph
(22)	CH_2Ph	H
(23)	CH_2Ph	Ph

[13] Krapcho, A. P., *Synthesis*, 1982, 805 and 893.
[14] Jung, M. E., and Lyster, M. A., *J. Am. Chem. Soc.*, 1977, **99**, 968.

result could not be reproduced when trimethylsilyl iodide, prepared by a variety of routes,[15] was used instead of the original commercial material.

Methanolic base converted the ether (18) into the enol (13) and a complex mixture of acidic material from which no pure components could be isolated. Neither the enol (13) nor the enamine (11) formed any *C*-methylated material when treated with excess methyl iodide. The enol (13) was stable towards sodium borohydride.

β-Keto ester systems can be converted readily into a variety of heterocyclic derivatives by reaction with reagents such as hydrazine, hydroxylamine, etc. It was thus of interest to establish whether (13) and (14) would condense with reagents of this type to form bicyclic products. Both (13) and (14) reacted with hydrazine [to form (20) and (22)] and with phenylhydrazine [to form (21) and (23)] all in low yield. No condensation products could be isolated from similar reactions by using hydroxylamine. The structures (21) and (23) are only tentatively assigned since there is no definitive proof for the position of the phenyl group in the pyrazole ring.

Physiological Activity

Some of the caprolactam derivatives obtained from this work were subjected to a preliminary testing for central nervous system activity. Compounds (11)–(14), (17), (18) and (20)–(23) all showed central nervous system activity that caused some loss of muscle control and decreased the activity of mice when tested, at levels below 100 mg/kg, as described previously.[1] The secondary amides, e.g. (12) and (14) were, in general, slightly more active than their *N*-benzyl derivatives but this may reflect the greater water solubility of these less substituted systems.

Experimental

Infrared spectra were determined on a Jasco IRA-1 infrared spectrophotometer as Nujol mulls for solids, and films for liquids; ultraviolet spectra on a Pye–Unicam SP8-100 spectrometer and nuclear magnetic resonance spectra on a Jeol PMX-60 spectrometer or a Bruker WP-80 spectrometer in deuterochloroform at 35° unless otherwise stated. Mass spectra were recorded on an AE1 MS-30 mass spectrometer at 70 eV. Unless reference to their preparation is given, all reagents were purified commercially available compounds (Aldrich).

Ethyl N-(*Ethoxycarbonylacetyl*)*benzylaminoacetate* (*4*)

Ethyl chloroformylacetate (prepared from the corresponding acid with thionyl chloride) (11·7 g, 78 mmol) in dry benzene (120 ml) was added over a period of 10 min to a stirred solution of ethyl benzylaminoacetate (30·0 g, 155 mmol) in dry benzene, cooled to 10°. The resulting mixture was stirred at room temperature for 24 h. The mixture was filtered, and the filtrate washed with 10% sodium bicarbonate solution (4 × 15 ml), and then dilute hydrochloric acid (3 × 10 ml). The organic phase was dried and the solvent removed to give the diester (4) (22·6 g, 96%) as an orange oil. ν_{max} 1740, 1650 cm^{-1}. N.m.r. δ 7·30, s, 5H, ArH; 4·67, s, $ArCH_2$; 3·9–4·5, m, 6H, $COCH_2CO$, OCH_2CH_3; 3·53, s, NCH_2CO_2; 1·27, t, 6H, CH_3.

Ethyl 1-Benzyl-2,4-dioxopyrrolidine-3-carboxylate (*5*)

To a stirred solution of sodium ethoxide [prepared from sodium (1 g) in benzene/ethanol azeotrope (760/40 ml)] under nitrogen was added diester (4) (24·0 g). The mixture was refluxed for 6 h and the resulting yellow solid was collected, dissolved in 10% sodium bicarbonate solution (80 ml),

[15] Jung, M. E., and Lyster, M. A., *J. Org. Chem.*, 1977, **42**, 3761; Jung, M. E., and Blumenkopf, T. A., *Tetrahedron Lett.*, 1978, 3657; Olah, G. A., Narang, S. C., Gupta, B. G. B., and Malhotra, R., *J. Org. Chem.*, 1979, **44**, 1247.

washed with benzene (1 × 30 ml) and then acidified with dilute sulfuric acid. The solid was filtered to give the lactam (5) (14·7 g, 72%) as a pale yellow powder, m.p. 122–124° (lit.[9] 128°).

1-Benzylpyrrolidine-2,4-dione (6)

The ester (5) (6·0 g, 23 mmol) in acetonitrile (170 ml, containing water 1 ml) was refluxed for 2·5 h, and then evaporated to dryness to give a dark orange oil[9] (4·2 g, 95%). ν_{max} 1770, 1600–1720 (br) cm^{-1}. N.m.r. δ 7·34, s, 5H, ArH; 4·63, s, $ArCH_2$; 3·73, s, $COCH_2N$; 3·10, s, $COCH_2CO$.

1-Benzyl-4-(pyrrolidin-1′-yl)-3-pyrrolin-2-one (1)

The ester (5) (6·0 g, 23 mmol) in acetonitrile (170 ml) containing water (1 ml) was refluxed for 2·5 h. Removal of the solvent under reduced pressure gave an oil which was redissolved in acetonitrile (200 ml) containing pyrrolidine (3·2 g, 46 mmol) and the mixture was refluxed under nitrogen for 1·5 h. Removal of the solvent gave a brown solid which was crystallized from dry benzene to yield the enamine (1) as light brown crystals (88%), m.p. 126–130°. Recrystallization from benzene afforded colourless needles, m.p. 128–131°. ν_{max} 1655, 1615 cm^{-1}. N.m.r. δ 7·25, s, Ar; 4·60, s, C=CH, $ArCH_2$; 3·70, s, $C{=}CCH_2N$; 3·15, m, CH_2N; 1·95, m, CH_2. Mass spectrum *m/e* 242 (M, 100%).

Reaction of (6) *with Base*

The oily lactam (6) was dissolved in dilute sodium bicarbonate solution at room temperature, filtered and then acidified with dilute hydrochloric acid to give a pale yellow solid, m.p. 187–198°, which was a complex mixture as shown by t.l.c. This material was fractionated on silica and the main fraction was repeatedly recrystallized from methanol to yield *1-benzyl-4-hydroxy-3-(1′-benzyl-5′-oxo-3′-pyrrolin-3′-yl)-3-pyrrolin-2-one* (9) m.p. 211·5–213·5° (Found: C, 73·4; H, 5·6. $C_{22}H_{20}N_2O_3$ requires C, 73·4; H, 5·8%). ν_{max} 1680, 1665, 1560 (br) cm^{-1}. N.m.r. δ ($CDCl_3$/CD_3SOCD_3) 7·11, s, ArH; 6·33, s, =C–H; 4·49, s, CH_2; 4·43, s, CH_2; 4·15, s, CH_2; 3·77, s, CH_2. Mass spectrum *m/e* 360 (M, 100%).

The mass spectrum of the yellow solid showed peaks at 189·0792 (calculated for $C_{11}H_{11}NO_2$, 189·0790); 360·1476 (calculated for $C_{22}H_{20}N_2O_3$, 360·1474) and 513·2048 (calculated for $C_{33}H_{27}N_3O_3$, 513·2052).

Ethyl N-(*Ethoxycarbonylacetyl*)*aminoacetate*

Dicyclohexylcarbodiimide (6·19 g, 30 mmol) was added to a cooled, stirred solution of glycine ethyl ester hydrochloride (4·19 g, 30 mmol) and potassium ethyl malonate (5·10 g, 30 mmol) in acetonitrile/water (70 : 20 ml), and the mixture was stirred for a further 2 h. The precipitate was filtered and washed thoroughly with dichloromethane. The combined filtrates were evaporated, and the residue was crystallized from acetone/light petroleum, to yield the ester (5·34 g, 82%), m.p. 70–72° (lit.[10] 71·5–72°). ν_{max} 3280, 1740, 1730, 1640 cm^{-1}. N.m.r. δ 7·7, br, NH; 4·3, q, 4H, OCH_2CH_3; 4·1, d, CH_2N; 3·4, s, $COCH_2CO$; 1·3, 6H, t, CH_3.

4-(Pyrrolidin-1′-yl)-3-pyrrolin-2-one (2)

Methyl 2,4-dioxopyrrolidine-3-carboxylate[10] (2·53 g, 16·1 mmol) was refluxed in acetonitrile (1 l) for 2 h. Molecular sieves and pyrrolidine (2·30 g, 32·4 mmol) were then added, and the mixture was refluxed for a further 6·5 h. The solvent was evaporated and the residue extracted with hot chloroform. Evaporation of the extract and careful crystallization from chloroform/light petroleum afforded the enamine (2) (2·01 g, 82%) which decomposes on standing, m.p. 218·5–220°. ν_{max} 3200, 1655, 1605 cm^{-1}. N.m.r. δ 6·0, br, NH; 4·6, s, CH=C; 4·0, s, CH_2NH; 3·3, m, 4H, CH_2N; 2·0, m, 4H, CH_2CH_2N. Mass spectrum *m/e* 152 (M, 100%).

*Dimethyl 1-Benzyl-6-(pyrrolidin-1′-yl)-2-oxo-2,7-dihydro-1*H*-azepine-4,5-dicarboxylate* (11)

A mixture of the enamine (1) (4·40 g, 18·2 mmol) and dimethyl acetylenedicarboxylate (2·58 g, 18·2 mmol) in dry benzene (350 ml) was refluxed under nitrogen for 6 h. On cooling to room temperature, a yellow solid appeared and was collected (2·02 g, 29%), m.p. 236–237°. Concentration of the mother liquor gave a brown solid which, on crystallization from ethyl acetate, afforded pale yellow needles (2·0 g, 29%), m.p. 235–236·5°. The combined material was recrystallized from

chloroform/light petroleum to give the diester (11), m.p. 238–238·5°, which strongly retained solvent of crystallization. ν_{max} 1720, 1700, 1620 cm^{-1}. N.m.r. δ 7·50, m, Ar; 6·75, s, C=CH; 4·8, dd, *J* 18 Hz, $ArCH_2$; 4·10, br, CH_2N; 3·80, s, CO_2Me; 3·65, s, CO_2Me; 2·7–3·5, br, 4H, CH_2N; 1·1–1·9, br, 4H, CH_2. Mass spectrum *m/e* 384 (M).

*Dimethyl 1-Benzyl-6-hydroxy-2-oxo-2,7-dihydro-1*H*-azepine-4,5-dicarboxylate (13)*

(A) Dilute hydrochloric acid (16 ml) was added to a solution of the enamino caprolactam (11) (540 mg, 1·41 mmol) in methanol/chloroform (100 : 20 ml). The mixture was allowed to stand at room temperature for 1·5 h, after which it was diluted with water and extracted with chloroform. The organic phase was dried and evaporated to yield a white solid (457 mg, 98%). The material was recrystallized from chloroform/light petroleum to give *azepinedicarboxylate* (13) as colourless crystals, m.p. 119·5–121° (Found: C, 61·5; H, 5·1. $C_{17}N_{17}NO_6$ requires C, 61·6; H, 5·2%). ν_{max} 1740, 1640, 1620 cm^{-1}. N.m.r. δ 12·55, br, C=C–OH; 7·32, s, Ar; 6·92, s, C=CH; 4·70, s, $ArCH_2$; 3·85, 8H, s, CO_2Me, CH_2N. Mass spectrum *m/e* 331 (M). λ_{max} (EtOH) 202 (20230), 256 (7880), 279 (9500) and 344 (4930) nm. In ethanol plus one drop of concentrated sulfuric acid: λ_{max} 202, 256 nm.

(B) A mixture of the enamino caprolactam (11) (150 mg, 0·39 mmol) and dilute hydrochloric acid (8 ml) in methanol/chloroform (30 : 6 ml) was allowed to stand at room temperature for 4 days, after which it was diluted with water and extracted with chloroform. The organic phase was dried and evaporated under vacuum to yield a yellow residue (140 mg). This oil was further partitioned into chloroform-soluble and -insoluble fractions. The chloroform-soluble fraction gave a yellow oil (104 mg, 75%) on solvent evaporation which possessed a ^1H n.m.r. spectrum identical to that of (13). The chloroform-insoluble fraction gave a yellow solid (30 mg, 21%) which gave an orange colour with ferric chloride and possessed a similar n.m.r. spectrum (CD_3SOCD_3) to that of (13) in the same solvent, the only difference being that the vinylic proton resonance appeared 0·9 ppm further upfield for the minor product (15), m.p. 275°. ν_{max} 3420 (br), 1740, 1720, 1680, 1625 cm^{-1}. The mass spectrum showed small peaks at *m/e* 331 and 345. This material could not be further purified.

*Dimethyl 2-Oxo-6-(pyrrolidin-1′-yl)-2,7-dihydro-1*H*-azepine-4,5-dicarboxylate (12)*

Dimethyl acetylenedicarboxylate (1·1 g, 7·7 mmol) in dry benzene (120 ml) was added to the enamine (2) (1·1 g, 7·2 mmol) and the mixture was refluxed under nitrogen for 5·5 h. The solvent was evaporated and the residue crystallized from benzene to give the enamino caprolactam (12) (1·39 g, 65%), m.p. 234–236° (Found: C, 57·1; H, 6·2. $C_{14}H_{18}N_2O_5$ requires C, 57·1; H, 6·2%). ν_{max} 3200, 1725, 1655 cm^{-1}. N.m.r. δ 8·6, br, NH; 6·5, s, CH=C; 4·0, s, CH_2NH; 3·8, s, CO_2Me; 3·6, s, CO_2Me; 3·3, br, CH_2N; 2·0, br, CH_2CH_2N. Mass spectrum *m/e* 294 (M, 100%).

*Dimethyl 6-Hydroxy-2-oxo-2,7-dihydro-1*H*-azepine-4,5-dicarboxylate (14)*

Dilute hydrochloric acid (25 ml) was added to a solution of the enamine (12) (1·06 g, 3·60 mmol) in methanol (250 ml); after 30 min the solution was diluted with water, and the solution extracted with chloroform. The extract was evaporated under vacuum, and the residue crystallized from chloroform/light petroleum affording the caprolactam (14) (583 mg, 67%), m.p. 167–170° (Found: C, 49·8; H, 4·6. $C_{10}H_{11}NO_6$ requires C, 49·8; H, 4·6). ν_{max} 3200, 1725, 1655, 1610 cm^{-1}. N.m.r. δ 12·8, br, OH; 7·7, br, NH; 6·7, s, CH=C; 3·8, m, 8H, CH_2N, CO_2Me. Mass spectrum *m/e* 241 (M).

Reaction of the Caprolactam (13) with Trimethylsilyl Iodide

To a stirred solution of the caprolactam (13) (123 mg, 0·37 mmol) in dry chloroform (5 ml) under nitrogen was added trimethylsilyl iodide (Aldrich, 300 mg, 1·5 mmol). The mixture was heated under reflux for 58 h, after which it was cooled to 5° and diluted with water (3 ml). Removal of the solvent under vacuum gave a brown residue which was dissolved in chloroform (40 ml), and washed with 10% sodium thiosulfate solution (10 ml), and water (10 ml). The organic phase was dried and the solvent removed. Preparative t.l.c. of the resulting colourless oil (111 mg) gave three fractions. The lowest R_F material (14 mg) was the caprolactam (13). T.l.c. of this material showed only one spot which coloured red when sprayed with a methanolic ferric chloride solution. The

highest R_F band gave spectral data consistent with *dimethyl 1-benzyl-6-hydroxy-2-oxo-2,3,4,7-tetrahydro-1H-azepine-4,5-dicarboxylate* (17), which was isolated as a colourless oil (46 mg, 41%) (Found: $M^{+\bullet}$ 333·1211. $C_{17}H_{19}NO_6$ requires 333·1212). ν_{max} ($CHCl_3$) 1740, 1665 cm^{-1}. N.m.r. δ 7·27, s, 5H, ArH; 3·67–5·10, m, 10H, $ArCH_2$, CH_2N, CO_2CH_3; 2·72–3·12, m, $CHCO_2$, CH_2CON.

The intermediate R_F band gave only a trace amount of organic material (<2 mg). The mass spectrum showed a relatively intense peak at *m/e* 275 indicating the presence of the reduced and decarboxylated compound (19). However, peaks at *m/e* 331 and 333 showed that separation of this band from others was incomplete.

Treatment of (13) with Diazomethane

Excess diazomethane in ether (25 ml) was added to a solution of the caprolactam (203 mg) in tetrahydrofuran (15 ml). The mixture was allowed to stand at room temperature for 1 h, after which it was quenched by the dropwise addition of dilute acetic acid. The solvent was removed under vacuum and the residue was dissolved in chloroform, washed with water (2 × 10 ml), dried and concentrated to give *dimethyl 1-benzyl-6-methoxy-2-oxo-2,7-dihydro-1H-azepine-4,5-dicarboxylate* (18) (193 mg, 92%) as colourless crystals from methanol, m.p. 128–129° (Found: C, 62·7; H, 5·6. $C_{18}H_{19}NO_6$ requires C, 62·6; H, 5·6%). ν_{max} ($CHCl_3$) 1740, 1730, 1640, 1610 cm^{-1}. N.m.r. δ 7·22, s, 5H, ArH; 7·05, s, C=CH; 4·68, s, $ArCH_2$; 3·80, s, CH_2N; 3·43–3·75, 3s, 9H, CO_2CH_3, CH_3OC=C. Mass spectrum *m/e* 345 (M).

Reaction of the Methyl Ether (18) with Trimethylsilyl Iodide

The methyl ether (18) (103 mg, 0·3 mmol) was treated with trimethylsilyl iodide (240 mg, 1·2 mmol) in an identical manner to that described above for (13). A similar workup procedure gave a colourless oil (80 mg). Preparative t.l.c. of this material, with ethyl acetate, gave three fractions. The lowest R_F fraction (9 mg, 11%) was the enolic caprolactam (13). T.l.c. and n.m.r. data indicated that the highest band consisted of the reduction product (17) (19 mg, 24%). The central fraction gave *methyl 1-benzyl-2,6-dioxo-2,3,4,5,6,7-hexahydro-1H-azepine-4-carboxylate* (19) (20 mg, 25%) as a colourless oil (Found: $M^{+\bullet}$ 275·1171. $C_{15}H_{17}NO_4$ requires 275·1158). ν_{max} ($CHCl_3$) 1740, 1730, 1670 cm^{-1}. N.m.r. δ 7·30, s, 5H, ArH; 4·63, s, $ArCH_2$; 3·87, s, CH_2N; 3·73, s, CO_2CH_3; 2·60–3·33, m, CH_2CO, CH_2CON, $CHCO_2$. This material was found to be homogeneous by t.l.c. and did not colour red when sprayed with methanolic ferric chloride solution. Addition of a few drops of an acidic solution of 2,4-dinitrophenylhydrazine in ethanol (Brady's Reagent) to a solution of (19) in chloroform gave a yellow precipitate.

Reaction of (18) with Potassium Hydroxide

A mixture of the caprolactam (18) (120 mg, 0·35 mmol) and potassium hydroxide (97 mg, 1·73 mmol) in aqueous methanol (15 ml) was stirred at room temperature for 8 h, after which no starting material remained. The reaction mixture was adjusted to pH 4 with dilute hydrochloric acid and the solvent removed. Extraction of the residue with ethyl acetate and evaporation of the solvent gave a colourless oil (90 mg). The caprolactam (13) (20%) could be identified (n.m.r.; t.l.c.) in the chloroform-soluble portion of this oil.

Reactions of the Caprolactams (11) and (13) with Hydrogen Iodide

The caprolactams, (11) or (13), dissolved in an organic solvent, were treated with hydrogen iodide or hydriodic acid. In all cases complex, intractable products were obtained. These results suggest that hydrogen iodide, which could be present in the trimethylsilyl iodide reactions, is not involved in the formation of the observed products.

Attempted Ring Expansions of the Enamine (1)

(A) A mixture of the enamine (49 mg, 0·2 mmol) and acetylenedicarboxylic acid (23 mg, 0·2 mmol) in acetonitrile (20 ml) was refluxed for 48 h under nitrogen. The reaction mixture was evaporated under vacuum to give a brown solid (71 mg) which consisted of the acid and unchanged enamine (t.l.c.; n.m.r.).

(B) (i) A mixture of the enamine (73 mg, 0·3 mmol) and methyl propiolate (26 mg, 0·31 mmol) in benzene (30 ml) was refluxed for 20 h under nitrogen. T.l.c. of the reaction mixture indicated that no reaction had occurred. A catalytic amount of boron trifluoride etherate was added to the reaction mixture and heating was continued for a further 40 h. T.l.c. showed that little reaction had taken place and the solvent was removed. The residue was dissolved in chloroform (20 ml), briefly washed with water (1 × 10 ml), dried and evaporated under vacuum to give an orange oil (89 mg) which consisted of unchanged enamine (n.m.r.).

(ii) A mixture of methyl propiolate (15 mg, 0·18 mmol) and enamine (40 mg, 0·17 mmol) in methanol (20 ml) was refluxed for 60 h under nitrogen. T.l.c. and n.m.r. indicated that the mixture consisted almost entirely of starting materials.

(iii) A mixture of the enamine (170 mg, 0·7 mmol) and methyl propiolate (65 mg, 0·8 mmol) in benzene (10 ml) was heated at 100° in a sealed tube for 48 h. The reaction mixture was concentrated to give a dark brown solid (175 mg) which was shown to consist entirely of the starting enamine (t.l.c.; n.m.r.).

(C) (i) A mixture of ethyl phenylpropiolate (74 mg, 0·42 mmol) and the enamine (83 mg, 0·34 mmol) in benzene (15 ml) was refluxed for 20 h under nitrogen. T.l.c. of the reaction mixture indicated that only starting materials were present. A catalytic amount of boron trifluoride etherate was added and the mixture was refluxed for a further 40 h. Workup gave only the starting materials (n.m.r.; t.l.c.).

(ii) By using similar reaction conditions to those described in (B)(ii), starting materials were recovered (t.l.c.).

(D) The bis(trimethylsilyl) ester of acetylenedicarboxylic acid and the enamine were refluxed for 36 h in xylene, under nitrogen. The solution darkened considerably during this time although t.l.c. indicated substantial amounts of starting material were still present at the end of this time. The solvent was removed, the residue was redissolved in dichloromethane and methanol and treated with dilute hydrochloric acid at room temperature overnight. Base extraction of the resulting material gave only a small amount of acidic material as a dark oil which proved intractable.

(E) The enamine and either methyl propiolate, ethyl phenylpropiolate or the bis(trimethylsilyl) ester of acetylenedicarboxylic acid[16] were exposed to sunlight for 3 days. At the end of this time t.l.c. indicated that substantial amounts of the enamine were still present in each case.

Preparation of Pyrazolo[3,4-c]azepines

A mixture of the hydrazine hydrochloride (2·0–2·5 equiv.), enol caprolactam (1·0 equiv.) and methanol (25 ml) was refluxed for 48 h, under nitrogen. The reaction mixture was worked up as described below.

(*a*) *Reaction between (14) and hydrazine dihydrochloride.*—The reaction mixture was evaporated under vacuum and the residue was washed with water and filtered to give *methyl 3,6-dioxo-1,2,3,6,7,8-hexahydropyrazolo[3,4-c]azepine-4-carboxylate* (20) (15%) as a yellow solid, m.p. 228–232° (Found: $M^{+\bullet}$ 223·0590. $C_9H_9N_3O_4$ requires 223·0593). ν_{max} 3160, 1698, 1690, 1635, 1560 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 6·34, s, C=CH; 4·53–6·16, br, 3H, NH; 3·94, s, CH_2N; 3·75, s, CO_2CH_3.

(*b*) *Reaction between (13) and hydrazine dihydrochloride.*—The reaction mixture was evaporated under vacuum and addition of warm chloroform to the residue, followed by filtration, removed unchanged hydrazine dihydrochloride. Upon cooling to room temperature, the chloroform solution afforded *methyl 7-benzyl-3,6-dioxo-1,2,3,6,7,8-hexahydropyrazolo[3,4-c]azepine-4-carboxylate* (22) (22%) as pale yellow crystals, m.p. 194–196°, after recrystallization from chloroform (Found: C, 60·7; H, 5·1; $M^{+\bullet}$ 313·1064. $C_{16}H_{15}N_3O_4$ requires C, 61·3; H, 4·8%; $M^{+\bullet}$ 313·1062). ν_{max} ($CHCl_3$) 3480, 1725, 1705, 1630 cm^{-1}. N.m.r. δ 7·25, s, 5H, ArH; 7·02, s, C=CH; 4·70, s, $ArCH_2$; 4·15, s, CH_2N; 3·95, s, CO_2CH_3.

(*c*) *Reaction between (14) and phenylhydrazine hydrochloride.*—The reaction mixture was stirred for a further 12 h at room temperature and the yellow precipitate was filtered to give *methyl 3,6-dioxo-2-phenyl-1,2,3,6,7,8-hexahydropyrazolo[3,4-c]azepine-4-carboxylate* (21) (12 mg, 5%), m.p. 248° (Found: $M^{+\bullet}$ 299·0909. $C_{15}H_{13}N_3O_4$ requires 299·0906). ν_{max} 3140w, 1735, 1635 cm^{-1}. The poor solubility of this material in the usual n.m.r. solvents did not enable the spectrum to be recorded.

[16] Hergott, H. H., and Simchen, G., *Synthesis*, 1980, 626.

(*d*) *Reaction between* (*13*) *and phenylhydrazine hydrochloride*.—The reaction mixture was stirred for a further 12 h at room temperature and the pale white precipitate was filtered to give *methyl 7-benzyl-3,6-dioxo-2-phenyl-1,2,3,6,7,8-hexahydropyrazolo*[*3,4*-c]*azepine-4-carboxylate* (23) (10%), m.p. 196–199° after recrystallization from methanol (Found: C, 67·8; H, 4·9; $M^{+\bullet}$ 389·1366. $C_{22}H_{19}N_3O_4$ requires C, 67·8; H, 4·9%; $M^{+\bullet}$ 389·1375). ν_{max} ($CHCl_3$) 3000–3160, 1695, 1630, 1620, 1600, 1575, 1500 cm^{-1}. N.m.r. δ 11·25, br, NH; 7·20–7·77, m, 10H, ArH; 7·00, s, C=CH; 4·70, s, $ArCH_2$; 4·12, s, CH_2N; 3·93, s, CO_2CH_3.

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