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Dihydroindol-7(6*H*)-ones and 6,7-Dihydropyrrolo[2,3-*c*]azepine-4,8(1*H*,5*H*)-dione

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Abstract

3-Methylcyclohexenones may be converted into dihydroindol-7(6*H*)-ones by conversion of the epoxide into the 2-benzylamino-3-methylcyclohexenone, which reacts with dimethylformamide dimethyl acetal to give *N*-benzyldihydroindol-7(6*H*)-ones. The limitations of the process are discussed, as is the failure to convert the dihydroindol-7(6*H*)-ones into dihydropyrroloazepinediones by Beckmann or Schmidt rearrangements. An example of the latter compounds was made by a simple procedure from pyrrolecarboxylic acid.

Introduction

In a previous communication[1] we reported our investigation of the reaction of various 3-methylcyclohexenones with dimethylformamide dimethyl acetal (dmfdma). The ultimate aim was to develop a method to annelate a pyrrole ring to a cyclohexenone or a caprolactam in order to synthesize the pyrroloazepinedione (1), a possible natural product[2–6] or an artefact isolated from marine organisms.[7] In this communication we report a highly efficient synthesis of (1) based on more orthodox chemistry, and our limited success in the achievement of the synthetic goals, summarized retrosynthetically in Scheme 1.

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[2] Cimino, G., De Rosa, S., De Stefano, S., Mazzarella, L., Puliti, R., and Sodano, G., *Tetrahedron Lett.*, 1982, **23**, 767.
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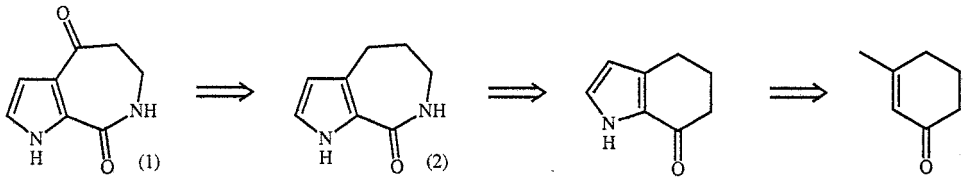
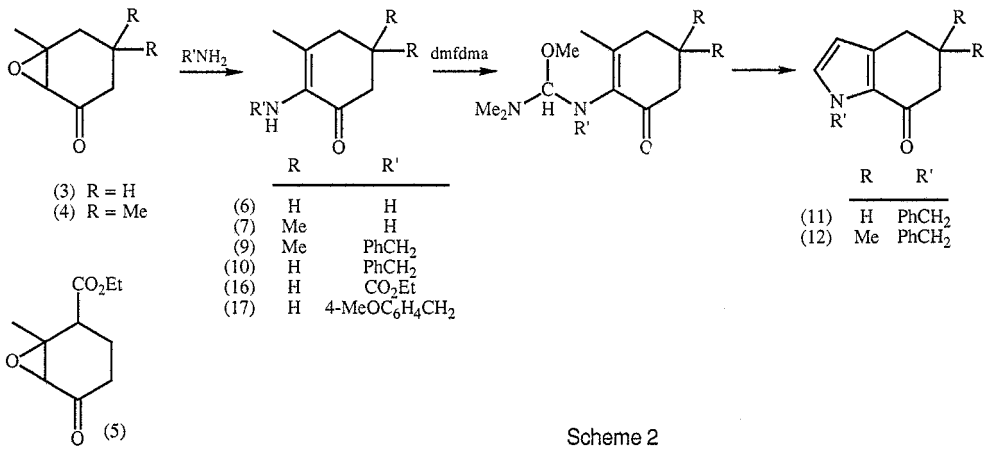


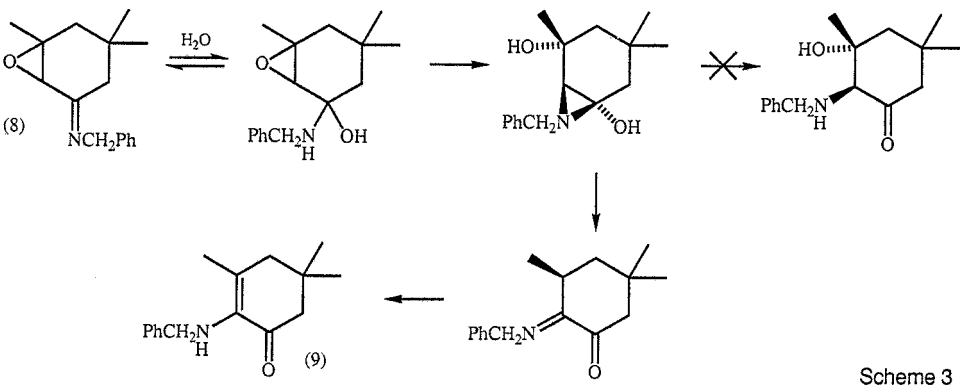
Scheme 1

Discussion

3-Methylcyclohexenone, isophorone and Hagemann's ester (ethyl 2-methyl-4-oxocyclohex-2-ene-1-carboxylate) were converted into the corresponding epoxides (3)–(5), and reacted with amines to give the enamines (6)–(10) and (17). The enamines were allowed to react with dmfdma in the hope of achieving a new pyrrole synthesis (Scheme 2).



Scheme 2



Scheme 3

The first step in the sequence was not straightforward, and required some study. Although (4) has been reported to react with ammonia to give (7),[8,9] reaction with benzylamine under standard conditions[9–12] gave instead the imine (8) at room temperature, which slowly gave the enamine (9) on heating. No reaction occurred in the absence of water, suggesting the pathway shown in Scheme 3. No evidence for the presence of the direct epoxide-opening product, the hydroxy amine, could be found, and, in view of evidence presented below in which the hydroxy amines could be dehydrated only with difficulty, we favour the pathway to (9) involving the imino ketone, as shown.

In contrast to the slow reaction cited above, reaction of the epoxides with secondary amines such as morpholine[9,13] was much more rapid. Reaction of the enamines (10) and (9) with dmfdma at 150° proceeded as desired, to give the respective dihydroindolones (11) and (12) in 70% yield. The formation of *N*-unsubstituted derivatives by this methodology could not be realised directly. Firstly, isophorone epoxide (4) was extremely reluctant to react with ammonia, and no reaction occurred by any of the literature procedures.[9] Only when an emulsion of (4) in excess concentrated ammonia was sonicated did the desired enamine (7) form (19%), and (3), likewise, gave (6) in only 39% yield. Secondly, the unsubstituted enamines (6) and (7) reacted with dmfdma to give the amidine[1] (cf.[13]) which could not be induced to cyclize to the pyrrole under thermal, basic or acidic conditions. We had considered the 5-*endo*-trigonal ring closure (14) might prove unfavourable,[14,15] but were surprised at the reluctance of the 5-*exo*-trigonal process (15). It appears that considerable activation of the methyl groups may be necessary.[16] Synthetic equivalents of ammonia such as diallylamine[17] and hexamethyldisilazane[18] failed to react with the expoxide (4). The enamine (6) was converted into the carbamate (16), but subsequent reaction with dmfdma failed to show any evidence for the formation of a pyrrole ring.

Removal of the benzyl group in (11) could not be achieved by hydrogenolysis, a difficulty encountered in related systems,[19,20] and occurred only poorly on

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[13] Tobias, M. A., Strong, J. G., and Napier, R. P., *J. Org. Chem.*, 1970, **35**, 1709.

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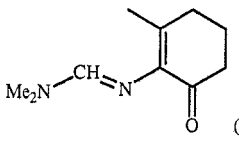
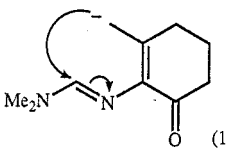
treatment with sodium in liquid ammonia.[21,22] Unfortunately, the incorporation of the more easily removable 4-methoxybenzyl group was not helpful, as the enamine (17) did not withstand the cyclization conditions with dmfdma.


(13)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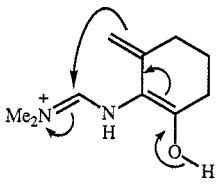
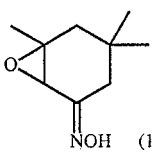
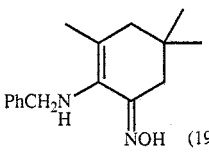

(15)

The synthesis of the dihydroindolones (11) and (12) had been our primary aim as it was expected that either the Beckmann or Schmidt rearrangements would occur selectively to give the acyl pyrrole (2) according to literature precedent with 2-acetylpyrrole[23] and 3-acylpyrroles.[24–27] The dihydroindolone (11) failed to undergo an efficient Beckmann or Schmidt reaction, the latter reaction leading to both rearrangement and debenzylation in the desired manner in mediocre yield (31%). The epoxy oxime (18) was reacted with benzylamine to give the hydroxyimino enamine (19) by ring opening of the epoxide, followed by dehydration of the *trans* amino alcohol by heating with lithium hydroxide. No pyrrole ring formation occurred with dmfdma presumably because of the reduced acidity of the methyl group. Finally, it was decided to attempt to annelate a caprolactam.


(18)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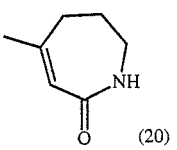
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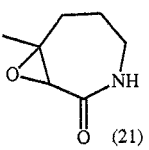
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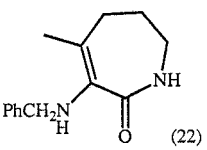
(22)

3-Methylcyclohexenone smoothly gave the desired caprolactam (20),[28] which could not be epoxidized with alkaline hydrogen peroxide[29] or *m*-chloroperoxybenzoic acid,[30] but the epoxide (21) was formed from the bromohydrin. The epoxide gave a mixture of epimeric amino alcohols on treatment with benzylamine, but this mixture was not cleanly dehydrated to the desired enamino lactam (22). A superior method involved conversion of

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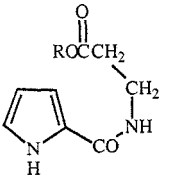
(20) into the *trans* bromohydrin and conversion of this into the *cis* amino alcohol with benzylamine in methanol. Dehydration to (22) was then achieved cleanly by heating with lithium hydroxide. As should be expected from the work above, reaction of (22) with dmfdma failed to give the desired pyrrole, presumably because of the poorer electron withdrawing properties of the amide group relative to ketone. Even the more reactive bis(dimethylamino)-t-butoxymethane[31] failed to form any pyrrolic material. The more straightforward and conventional route below was thus developed.

Pyrrole-2-carboxylic acid was conveniently coupled with the hydrochloride of ethyl 3-aminopropionate by *N,N'*-dicyclohexylcarbodiimide in the presence of triethylamine to yield the amide (23) in essentially quantitative yield. Use of the free amino ester led to lower yields (51%), accompanied by considerable acylurea. An alternative pathway, involving hydrolysis of *N*-(2-cyanoethyl)pyrrole-2-carboxamide, was less satisfactory. A number of attempts to cyclize the magnesium salt of (23) were unsuccessful,[32–34] as was the thermal cyclization.[35] The acid (24) cyclized only poorly in the presence of methanesulfonic acid[36] or polyphosphoric acid,[37] but addition of P_2O_5 to the polyphosphoric acid induced cyclization to the desired (1) in 85% yield. The overall yield of (1) from pyrrolecarboxylic acid was thus 80%. The structure of (1) was compared directly with an authentic sample, kindly given to us by Professor Schmitz.[7]



(23) R = Et
(24) R = H

Experimental

General details have been given in an earlier paper.[1]

Preparation of Enamines from the Corresponding Substituted Epoxycyclohexanones

(i) A solution of isophorone epoxide (1·00 g, 6·5 mmol) and benzylamine (0·8 ml, 7·8 mmol) in propan-1-ol (1·5 ml) and water (0·5 ml) was heated at reflux under a nitrogen atmosphere. Aliquots of the solution were withdrawn, the solvent removed under vacuum and the residue examined by ^{1}H n.m.r. spectroscopy. After 5 min reflux, quantitative conversion into the imine had occurred. An analytical sample was prepared by bulb-to-bulb distillation of a portion of the crude residue to give *N-benzyl-2,3-epoxy-3,5,5-trimethylcyclohexanone imine* as a colourless oil, b.p. 121–122°/0·3 mm (Found: C, 78·7; H, 8·6. $C_{16}H_{21}NO$ requires C, 79·0; H, 8·7%). ν_{max} (film) 1660, 1600, 1490, 740 cm^{-1}. N.m.r. δ 0·85, 0·97, 2×s, 6H,

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CMe_2; 1·35, s, 3H, **Me**CHO; 1·68, s, 1·85, s, 2·10, s, 2·20, s, 4H, CH_2; 3·30, s, 1H, CHO; 4·50, s, 2H, CH_2N; 7·18, s, 5H, ArH. Mass spectrum *m/z* 243 (M).

The conversion of imine into the enamine (9) was conveniently followed by using ^1H n.m.r. spectroscopy by observing the resonances of the benzylic methylene protons at δ 4·50 and 3·94 for the imine and enamine respectively. After 4·5 h reflux no further increase in the amount of enamine was evident. Removal of the solvents gave a red oil which was subjected to column chromatography on alumina. Elution with dichloromethane gave a fraction containing mainly the enamine contaminated with a small amount of the imine. Fractional distillation under reduced pressure gave *2-phenylmethylamino-3,5,5-trimethylcyclohex-2-en-1-one* (9) (0·79 g, 50%) as a pale yellow viscous oil, b.p. (block temp.) 109°/0·01 mm (Found: C, 80·9; H, 7·7%; $M^{+\bullet}$, 243·1620. $C_{17}H_{19}NO$ requires C, 80·6; H, 7·6%; $M^{+\bullet}$, 243.1623). ν_{max} (film) 3060, 3030, 1650, 1600, 1495 cm^{-1}. N.m.r. δ 0·87, s, 6H, CMe_2; 1·92, s, 2H, CH_2CO; 2·20, br s, 5H, MeC=C overlapping with CH_2C=C; 3·95, s, 2H, CH_2N; 7·13, s, 5H, ArH.

The following compounds were prepared in a similar manner, although the intermediate imines were not isolated.

(ii) *3-Methyl-2-phenylmethylaminocyclohex-2-en-1-one (10).* 2,3-Epoxy-3-methylcyclohexanone (3) was prepared from 3-methylcyclohex-2-en-1-one by using the procedure described by Yamazaki *et al.*[38] for the preparation of 2,3-epoxy-3-methylcyclopentanone. Distillation under reduced pressure gave the product in 87% yield, b.p. 83°/14 mm (lit.[39] 85°/15 mm). The title compound was prepared from 2,3-epoxy-3-methylcyclohexanone in methanol/water and refluxing for 4 h. Chromatography as in (i) followed by fractional distillation gave (10) as a pale yellow *oil* (70%), b.p. 101°/0·01 mm (Found: C, 78·3; H, 7·8; N, 6·7. $C_{14}H_{17}NO$ requires C, 78·1; H, 8·0; N, 6·5%). ν_{max} 3350, 1760, 1640, 1600 cm^{-1}. N.m.r. δ 1·92, s, 3H, MeC=C overlapping with m, 2H, C**H**$_2CH_2CO$; 2·33, m, CH_2C=C overlapping with CH_2CO; 3·93, s, 2H, CH_2N; 7·15, s, 3H, ArH. Mass spectrum *m/z* 215 (M).

(iii) *Ethyl 2-methyl-4-oxo-3-phenylmethylaminocyclohex-2-ene-1-carboxylate* was prepared from ethyl 2,3-epoxy-2-methyl-4-oxocyclohexane-1-carboxylate[40] (5) in methanol/water and refluxing the solution for 18 h. Column chromatography on alumina gave, after elution with dichloromethane/ethyl acetate, the title compound as an orange oil (87%). Distillation of a small portion of this material gave the *ester* as a pale orange oil,* b.p. (block temp.) 130°/0·03 mm (Found: $M^{+\bullet}$, 287.1531. $C_{17}H_{21}NO_3$ requires $M^{+\bullet}$, 287·1521). ν_{max} (film) 3350, 1730, 1670, 1635 cm^{-1}. N.m.r. δ 1·23, t, *J* 7 Hz, OCH_2**Me**; 1·87–2·63, m, 4H, CH_2CH_2CO overlapping with 1·97, br s, MeC=C; 3·27, br t, 1H, C**H**CO_2Et; 4·12, q, *J* 7 Hz, O**C**H_2Me overlapping with 3·98, s, 2H, CH_2N; 7·15, s, 5H, ArH.

(iv) *2-(4-Methoxyphenylmethyl)amino-3-methylcyclohex-2-en-1-one* (17) was prepared from 2,3-epoxy-3-methylcyclohexanone and 4-methoxybenzylamine in methanol/water at 70° for 5 h. Removal of the solvent and fractional distillation of the black residue gave (17) as a pale yellow oil (65%), b.p. 132°/0·004 mm (Found: C, 73·5; H, 7.9. $C_{15}H_{19}NO_2$ requires C, 73·4; H, 7·8%). ν_{max} (film) 3325, 1660, 1630, 1610, 1500 cm^{-1}. N.m.r. δ 1·93, s, 3H, MeC=C overlapping with 1·87, m, 2H, *H*5; 2·20–2·53, m, 4H, CH_2CO and CH_2C=C; 3·73, s, 3H, OMe; 3·87, s, 2H, CH_2N; 4·5, br s, NH; 6·93, d, *J* 8 Hz, 2H; 6·98, d, *J* 8 Hz, 2H.

(v) *2-Morpholino-3,5,5-trimethylcyclohex-2-en-1-one.* A solution of isophorone epoxide (1·00 g, 13·0 mmol) and morpholine (1·17 g, 13·0 mmol) in methanol (10 ml) and water (3 ml) was heated at 80° overnight. Removal of the solvent and distillation of the crude residue gave *2-morpholino-3,5,5-trimethylcyclohex-2-en-1-one* as a colourless oil (2·61 g, 90%), b.p. (block temp.) 90°/0·09 mm (Found: C, 69·5; H, 9·6%; $M^{+\bullet}$, 223·1577. $C_{13}H_{21}NO_2$ requires C, 69·9; H, 9·5%; $M^{+\bullet}$, 223·1572). ν_{max} (CH_2Cl_2) 3050, 1660, 1520, 1270 cm^{-1}. N.m.r. δ 1·00, s, 6H, CMe_2; 1·98, s, 2H, CH_2CO; 2·2, s, 5H, MeC=C and CH_2C=C; 2·83, br t, 4H, 2×CH_2N; 3·63, br t, 4H, 2×CH_2O.

* Some decomposition resulted on distillation.

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Cyclization of Enamines to Dihydroindol-7(6H)-ones

(i) A mixture of 2-phenylmethylamino-3,5,5-trimethylcyclohex-2-en-1-one (9) (500 mg, 2·06 mmol) and dimethylformamide dimethyl acetal (500 μl, 3·77 mmol) was heated at 150° overnight under a nitrogen atmosphere. A further amount (500 μl) of the acetal was added and the dark red mixture heated again overnight. Removal of the unreacted acetal and volatile material under vacuum gave a red oil which was chromatographed on alumina. Elution with dichloromethane gave the crude product (12) as a viscous orange oil* (365 mg, 70%). Bulb-to-bulb distillation of a small portion gave *5,5,-dimethyl-1-phenylmethyl-4,5-dihydroindol-7(6H)-one* (12) as a pale yellow viscous oil, b.p. 141–142°/0·25 mm (Found: $M^{+\bullet}$, 253·1467. $C_{17}H_{19}NO$ requires $M^{+\bullet}$, 253·1467). ν_{max} (film) 3075, 3025, 1640, 1500, 1595 cm^{-1}. N.m.r. δ 1·05, s, 6H, CMe_2; 2·30, s, 2H, H6; 2·58, s, 2H, H4; 5·43, s, 2H, CH_2N; 5·92, d, *J* 2 Hz, H3; 6·73, d, *J* 2 Hz, H2; 7·10, s, 5H, ArH.

(ii) *1-Phenylmethyl-4,5-dihydroindol-7(6H)-one* (11) was prepared from the corresponding enamine (10) by the procedure described in (i) except that the mixture was refluxed for only 3 h after the second addition of dimethylformamide dimethyl acetal. Removal of the unreacted acetal and volatiles under vacuum gave a dark red oil which was chromatographed on alumina. Elution with dichloromethane/ethyl acetate gave *1-phenylmethyl-4,5-dihydroindol-7(6H)-one* (11) (80%) which was distilled to give a pale orange viscous oil, b.p. 86–88°/0·005 mm (Found: C, 79·7; H, 6·3%; $M^{+\bullet}$, 225·1149. $C_{15}H_{15}NO$ requires C, 80·0; H, 6·7%; $M^{+\bullet}$, 225·1154). ν_{max} (film) 1650, 1600, 1550, 1500 cm^{-1}. N.m.r. δ 1·97, m, 2H, H5; 2·35, m, 2H, H4; 2·67, m, 2H, CH_2CO; 5·45, s, 2H, CH_2N; 5·92, d, *J* 2·5 Hz, H3; 6·68, d, *J* 2·5 Hz, H2; 7·12, s, 5H, ArH.

(iii) A complex mixture resulted when ethyl 2-methyl-4-oxo-3-phenylmethylaminocyclohex-2-ene-1-carboxylate (5) and dimethylformamide dimethyl acetal (2 equiv.) were heated at 160° for 2 h. The acetal and volatile material were removed under vacuum and the residue examined by ^1H n.m.r. spectroscopy. No resonances which could be ascribed to the cyclized material were present.

(iv) Attempted reaction of 2-(4-methoxyphenylmethyl)amino-3-methylcyclohex-2-en-1-one (17) with dimethylformamide dimethyl acetal (2 equiv.) at 160° for 2 h led to decomposition.

Preparation of 2-Amino-3,5,5-trimethylcyclohex-2-en-1-one (7)

A suspension of isophorone epoxide (5·00 g, 32·5 mmol) in aqueous ammonia (110 ml, sp. gr. 0·88) was subjected to ultrasound in a sonicator for 6 h at 35–40°. The solution was acidified with 10% hydrochloric acid and then extracted with dichloromethane. Removal of the solvent gave a pale brown oil which was shown to be the starting epoxide (2·62 g, 52%). The aqueous solution was basified with sodium carbonate and extracted with dichloromethane (4×50 ml). Removal of the solvent gave the crude amino compound as a light brown oil (950 mg, 19%). The product was purified by column chromatography on alumina with ether as the eluting solvent. Recrystallization form ether/pentane gave *2-amino-3,5,5-trimethylcyclohex-2-en-1-one* (7) as off-white plates, m.p. 66·5–75° (dec.) (Found: C, 70·3; H, 9·8. $C_9H_{15}NO$ requires C, 70·6; H, 9·9%). N.m.r. δ 1·00, s, 6H, CMe_2; 1·78, s, 2H, CH_2CO; 2·25, s, 3H, MeC=C overlapping with 2·20, m, 2H, CH_2C=C; 3·33, br s, NH_2. Mass spectrum *m/z* 153 (M).

Attempted Cyclization of Amidine (13)

The amidine[1] (13) (100 mg, 0·56 mmol) was dissolved in polyphosphoric acid (10 ml) and the mixture heated at 125° for 3 h under a nitrogen atmosphere. Water (10 ml) was added, the mixture neutralized with solid sodium carbonate and the aqueous solution extracted with ethyl acetate. Removal of the solvent gave a brown oil (30 mg) identical to the starting material by n.m.r. and t.l.c. analysis. Similarly, the amidine (13) was not converted into the pyrrole by heating at 160° for 20 h, or by reaction with sodium hydride at 60° for 6 h.

* This compound was air-sensitive and a satisfactory microanalysis could not be obtained.

Attempted Heteroannelation of Enamine (6)

(i) The enamine (6) (100 mg, 0·8 mmol) was dissolved in trimethyl orthoformate (2 ml) containing 1 drop of acetic acid, and the solution was heated at reflux overnight under a nitrogen atmosphere. Removal of the unreacted orthoformate by rotary evaporation gave a brown oil. ^{1}H n.m.r. spectroscopy showed it to be largely unchanged starting material. No reaction occurred with bis(dimethylamino)-t-butoxymethane and potassium t-butoxide at 35° over two weeks.

(ii) 2-Amino-3-methylcyclohex-2-en-1-one (6) (100 mg, 0·8 mmol) was dissolved in chloroform (2 ml) and ethyl chloroformate (100 mg, 0·92 mmol) added dropwise. The mixture was stirred at room temperature for 10 min and then washed with saturated sodium bicarbonate solution (1 ml). The organic phase was separated, dried, filtered and the solvent removed to give *ethyl N-(2-methyl-6-oxocyclohex-1-enyl)carbamate* (16) as a pale brown oil (116 mg, 90%). The oil could not be induced to crystallize (Found: $M^{+\bullet}$, 197·1052. $C_{10}H_{15}NO_3$ requires $M^{+\bullet}$, 197·1052). ν_{max} ($CDCl_3$) 1710, 1665, 1640 cm^{-1}. N.m.r. δ 1·27, t, J 7 Hz, 3H; 1·7–2·27, m, 4H, CH_2CH_2CO overlapping with 1·97, s, 3H, MeC=C; 2·50, br t, 2H, CH_2C=C; 2·90, br s, NH; 4·13, q, J 7 Hz, 2H, C**H**$_2$Me.

The carbamate (100 mg, 0·51 mmol) was heated with dimethylformamide dimethyl acetal (200 μl, 0·91 mmol) at 160° for 6 h. Removal of the volatile material under reduced pressure left a brown oil. Examination of the oil by ^{1}H n.m.r. spectroscopy showed it to be a mixture of methyl and ethyl carbamates but no resonances which could be attributed to the cyclized material were present.

Attempted Debenzylation of 1-Phenylmethyl-4,5-dihydroindol-7(6H)-one (11)

Attempted hydrogenolysis of (11) in the presence of palladium on carbon gave only unchanged starting material. 1-Phenylmethyl-4,5-dihydroindol-7(6*H*)-one (11) (100 mg, 0·44 mmol) in ether (2 ml) was added to a solution of sodium (61 mg, 2·65 mmol) in liquid ammonia (7 ml). The mixture was stirred for 5 min and then quenched with saturated ammonium chloride solution. The organic phase was separated, the aqueous solution extracted with dichloromethane and the combined organic extracts were concentrated under vacuum to give a brown oil (70 mg). The residue was examined by ^{1}H n.m.r. spectroscopy which showed that only a small amount of the benzyl compound remained (δ 5·42). Chromatography on alumina gave, after elution with dichloromethane, the starting material (30 mg). Further elution with ethyl acetate gave a brown solid (30 mg) which darkened extremely rapidly and decomposed upon attempted recrystallization from dichloromethane/light petroleum. T.l.c. and n.m.r. analysis of the solid showed it to consist largely of a component containing no benzyl substituent and exhibiting two resonances in the ^{1}H n.m.r. spectrum (both multiplets) corresponding to the aromatic pyrrole protons of dihydroindol-7(6*H*)-one[41] (δ 6·10 and 7·05).

Attempted Schmidt Reaction on (12)

The ketone (12) (500 mg, 1·98 mmol) and sodium azide (257 mg, 3·45 mmol) were dissolved in polyphosphoric acid (10 ml) and heated at 120° for 3·5 h. Addition of ice, basification, and extraction with tetrahydrofuran gave a brown oil (300 mg). Column chromatography on alumina gave, after elution with ethyl acetate/dichloromethane (1 : 5), the starting ketone (50 mg, 10%). Further elution with ethyl acetate/dichloromethane (2 : 3) gave a brown oil (100 mg) which was identified as *5,5-dimethyl-4,5-dihydroindol-7(6H)-one* (31%). This oil, which could not be induced to crystallize, has spectral data consistent with its suggested structure (Found: $M^{+\bullet}$, 163·0741. $C_{10}H_{13}NO$ requires $M^{+\bullet}$, 163·0746). N.m.r. (D_2O exch.) δ 1·08, s, 6H, CMe_2; 2·33, s, 2H, H4; 2·62, s, 2H, H6; 6·02, d, J 2·5 Hz, H3; 7·00, d, J 2·5 Hz, H2.

Further elution with ethyl acetate gave a dark brown oil (100 mg) which was a complex mixture by t.l.c. and n.m.r. analysis.

[41] Kakushima, M., Hamel, P., Frenette, R., and Rokach, J., *J. Org. Chem.*, 1983, **48**, 3214.

Preparation of 2,3-Epoxycyclohexanone Oximes

(i) 2,3-Epoxy-3,5,5-trimethylcyclohexanone oxime (18) was prepared in 95% yield as a mixture of *E* and *Z* isomers according to the method of Corey *et al.*[42] The oily product was of sufficient purity to be used directly in the subsequent reactions (Found: C, 63·7; H, 8·8%; $M^{+\bullet}$, 169·1099. $C_9H_{15}NO_2$ requires C, 63·9; H, 8·9%; $M^{+\bullet}$, 169·1102). ^1H n.m.r. δ 0·87, 0·95, 2×s, CMe_2; 1·38, s, 3H, MeCO; 1·62–2·80, complex, 4H, H3 and H5; 3·32, s, and 4·08, s, 1H, CHO; 8·58, br s, OH.

(ii) 2,3-Epoxy-3-methylcyclohexanone oxime was prepared by adding 2,3-epoxy-3-methylcyclohexanone (3) (1·00 g, 7·94 mmol) to a solution of hydroxylamine hydrochloride (552 mg, 7·94 mmol) and sodium bicarbonate (667 mg, 7·94 mmol) in water (50 ml) and stirring the mixture vigorously for 20 min. Extraction with ether (3×25 ml) and removal of the solvent gave the oxime in 90% yield as a colourless viscous oil (mixture of *E* and *Z* isomers) (Found: $M^{+\bullet}$, 141·0785. $C_7H_{11}NO_2$ requires $M^{+\bullet}$, 141·0790). ν_{max} (film) 3300 (broad), 1640 (weak) cm^{-1}.

3-Hydroxy-2-phenylmethylamino-3,5,5-trimethylcyclohexanone Oxime

Isophorone epoxide oxime (3·70 g, 21·9 mmol) and benzylamine (2·34 g, 21·9 mmol) were dissolved in methanol (25 ml) and the solution heated at reflux for 6 h. The methanol was removed under vacuum to give a pale yellow oil. Ether was then added and the precipitate which formed was removed by filtration. Spectral data of the crystalline solid suggested that it was a mixture of *E* and *Z* isomers of *2-hydroxy-3-phenylmethylamino-3,5,5-trimethylcyclohexanone oxime* (1·00 g, 17%), m.p. 155–159° (Found: C, 69·8; H, 8·6%; $M^{+\bullet}$+1, 277·1905. $C_{16}H_{24}N_2O_2$ requires C, 69·5; H, 8·8%. $C_{16}H_{25}N_2O_2$ requires 277·1916). ν_{max} 3450, 3360, 3310, 1650 (weak) cm^{-1}. N.m.r. [$CDCl_3$/$(CD_3)_2SO$] δ 0·97, 1·05, 2×s, CMe_2; 1·17, s, MeCN; 1·60, s, 2H, H4; 2·35, q, *J* 13 Hz, 2H, H6; 3·00 and 3·33, 2×s, 1H, C**H**OH; 3·62, d, *J* 12 Hz, 1H; 3·78, d, *J* 12 Hz, 1H, CH_2N; 7·18, s, 5H, ArH; 9·94, br s, OH. The mother liquor gave upon distillation *3-hydroxy-2-phenylmethylamino-3,5,5-trimethylcyclohexanone oxime* (4·50 g, 74%) as a colourless oil (mixture of *E* and *Z* isomers), b.p. 158°/0·01 mm which crystallized on standing, m.p. 148–158° (Found: C, 69·6; H, 8·9%; $M^{+\bullet}-OH$, 259·1805. $C_{16}H_{24}N_2O_2$ requires C, 69·5; H, 8·8%. $C_{16}H_{23}N_2O$ requires 259·1810). ν_{max} 3350, 3000–2500 (broad), 1650 (weak), 1600, 1500 cm^{-1}. N.m.r. δ 0·93, 1·02, 2×s, 6H, CMe_2; 1·22, s, 3H, MeCO; 1·48, s, 1·63, s, 1·85, s, 2·72, s, 4H, H4 and H6; 2·92, s, 1H, CHN; 3·75, br s, 2H, CH_2N; 7·15, s, 5H, ArH. ^{13}C n.m.r. δ 157·3, C1; 139·9, 128·4, 127·2, ArC; 74·2, s, C3; 65·7, d, C2; 53·6, t, CH_2Ar; 49·3, t, C6; 36·3, 33·4, 31·5, 29·4, 28·1, 3×Me, C4 and C5.

3-Hydroxy-3-methyl-2-phenylmethylaminocyclohexanone Oxime

The title compound was prepared in 90% yield as described above. Distillation of a portion of the crude reaction mixture yielded a colourless liquid, b.p. (block temp.) 170°/0·06 mm which crystallized on standing. Recrystallization from ethyl acetate/light petroleum gave *3-hydroxy-3-methyl-2-phenylmethylaminocyclohexanone oxime* as colourless needles, m.p. 140–170° (Found: C, 67·9; H, 8·0. $C_{14}H_{20}N_2O_2$ requires C, 67·7; H, 8·1%). ν_{max} 3300, 1645 (weak), 1600, 1490 (weak) cm^{-1}. ^1H n.m.r. δ (*E* and *Z* isomers) 1·18, s, 3H, MeCO; 1·62, m, 4H, H4 and H5; 2·07–2·70, m, 2H, H6; 2·96, br s, 1H, C**H**OH; 3·68, br s, 2H, CH_2N; 7·15, s, 5H, ArH. Mass spectrum *m/z* 249 (M+1), 231 ($M-H_2O$).

2-Phenylmethylamino-3,5,5-trimethylcyclohex-2-en-1-one (19)

An intimate mixture of finely powdered lithium hydroxide (100 mg, 4·18 mmol) and the oxime of the 3-hydroxy compound above (200 mg, 0·72 mmol) was heated slowly under vacuum in a bulb-to-bulb apparatus until the product began to distil. The *title compound* (125 mg, 67%) was thus obtained as a viscous yellow oil, b.p. (block temp.) 145°/0·03 mm (Found: C, 71·1; H, 8·3%; $M^{+\bullet}$+1, 259·1813. $C_{16}H_{22}N_2O$ requires C 74·4; H, 8·6%. $C_{16}H_{23}N_2O$ requires 259·1810). ν_{max} (film) 3500–2500, 1650, 1615, 1590 cm^{-1}. N.m.r. δ 0·97, br s, 6H, CMe_2; 2·12, m, 5H, MeC=C and H4; 2·63, s, 2·97, s, 2H, H6 (*E* and *Z* isomers); 3·85, s, 2H, CH_2N; 7·32, s, 5H, ArH; 7·73, br s, NH and OH.

[42] Corey, E. J., Melvin, L. S., Jr, and Haslanger, M. F., *Tetrahedron Lett.*, 1975, 3117.

3-Methyl-2-phenylmethylaminocyclohex-2-en-1-one Oxime

The title compound was prepared by dehydration of the corresponding oxime as described above. The *enamino oxime* was obtained in 83% yield as a viscous yellow oil, b.p. 142°/0·015 mm (Found: $M^{+\bullet}$+1, 231·1489. $C_{14}H_{19}N_2O$ requires 231·1497). ν_{max} (CH_2Cl_2) 3500–2500, 2900, 1665 (broad), 1590, 1560 cm^{-1}. N.m.r. δ 2·10, s, 3H, MeC=C; 1·53–3·02, m, 6H, H4,5,6; 3·80, s, 3·85, s, 2H, CH_2N (*E* and *Z* isomers); 7·3, s, 5H, ArH; 7·70, br s, NH, OH.

3-Bromo-4-hydroxy-4-methyl-2,3,4,5,6,7-hexahydroazepin-2(1H)-one

4-Methyl-2,5,6,7-tetrahydroazepin-2(1*H*)-one[29] (20) (1·00 g, 8·00 mmol) was dissolved in water (50 ml) and *N*-bromosuccinimide (1·42 g, 8·00 mmol) was added to the vigorously stirred solution. The *N*-bromosuccinimide dissolved and the solution was stirred at room temperature for 30 min. The aqueous solution was concentrated under vacuum to a volume of approximately 5–10 ml and the product allowed to crystallize, affording the trans *bromohydrin* (1·0 g, 56%) as colourless needles. An analytical sample was prepared by recrystallization twice from acetone/light petroleum and had m.p. 181·5–184° (dec.) (sublimes 155°) (Found: C, 37·8; H, 5·3. $C_7H_{12}BrNO_2$ requires C, 37·8; H, 5·5%). ν_{max} 3275, 3225, 1650 cm^{-1}. N.m.r. δ 1·30, s, 3H, MeC; 1·48–2·26, m, 4H, H5 and H6; 3·18, m, 2H, CH_2N; 4·15, s, CHBr; 7·43, br s, NH; 10·77, br s, OH. Mass spectrum *m/z* 221, 223 (M).

*3,4-Epoxy-4-methyl-2,3,4,5,6,7-hexahydroazepin-2(1H)-one (21)**

The bromohydrin (1·0 g, 4·50 mmol) was dissolved in a solution of sodium hydroxide (200 mg, 5·00 mmol) in water (50 ml) and the mixture stirred at room temperature for 30 min. The solution was extracted with ether (3×20 ml) and the combined extracts dried, filtered and the solvent removed. Distillation under reduced pressure yielded (21) as a colourless oil (572 mg, 90%), b.p. 97°/0·001 mm (Found: C, 59·8; H, 7.9%; $M^{+\bullet}$, 141·0784. $C_7H_{11}NO_2$ requires C, 59·6; H, 7·6%; $M^{+\bullet}$, 141·0790). ν_{max} (film) 3250 (broad), 1660, 1180 cm^{-1}. ^1H n.m.r. δ 1·40, s, 3H, MeCO; 1·53–2·32, m, 4H, H5 and H6; 3·22, s, CHO; 3·28, m, 2H, CH_2N; 7·17, br s, NH.

4-Hydroxy-4-methyl-3-phenylmethylamino-2,3,4,5,6,7-hexahydroazepin-2(1H)-one

The bromohydrin (2·4 g, 10·8 mmol) and benzylamine (1·16 g, 10·8 mmol) were dissolved in water (25 ml) containing sodium bicarbonate (900 mg, 10·7 mmol) and the solution refluxed for 2 h. The mixture was then cooled and extracted with chloroform (3×15 ml). Removal of the solvent gave the cis *aminohydroxylactam* as a colourless solid (2·20 g, 82%). An analytical sample, prepared by bulb-to-bulb distillation (block temp. 135°/0·001 mm) yielded colourless needles, m.p. 141–53° (Found: C, 67·3; H, 8·4. $C_{14}H_{20}N_2O_2$ requires C, 67·7; H, 8·1%). ν_{max} (CH_2Cl_2) 3300 (broad), 1660, 1610 (weak), 1500 (weak) cm^{-1}. ^1H n.m.r. δ 0·97, s, 3H, **Me**COH; 1·47–2·28, m, 6H, H5,6,7; 3·23, m, 2H, CH_2N overlapping with 3·28, s, 1H, CHCO; 3·68, d, *J* 12 Hz, 1H, and 3·78, s, *J* 12 Hz, CH_2N; 6·53, br s, 1H, NH; 7·25, s, 5H, ArH.

4-Methyl-3-phenylmethylamino-2,4,6,7-tetrahydroazepin-2(1H)-one (22)

A mixture of the hydroxy amine (500 mg, 2·00 mmol) and anhydrous lithium hydroxide (50 mg, 2·08 mmol) was heated under reduced pressure in a bulb-to-bulb apparatus. The *enamine* (22) was obtained as an orange oil (80%), b.p. 125°/0·001 mm (Found: $M^{+\bullet}$, 230·1425. $C_{14}H_{18}N_2O$ requires 230·1419). ν_{max} (film) 3300 (broad), 1650, 1630, 1490 cm^{-1}. ^1H n.m.r. (80 MHz) δ 1·78, m, 2H, H6; 2·16, s, 3H, MeC=C; 2·45, m, 2H, CH_2C=C; 3·28, m, 3H, CH_2N and NH.

Ethyl 3-(Pyrrol-2′-ylcarbonylamino)propanoate (23)

Pyrrole-2-carboxylic acid (11·23 g, 0·10 mol), ethyl 3-aminopropanoate hydrochloride (15·5 g, 0·1 mol) and *N,N′*-dicyclohexylcarbodiimide (20·89 g, 0·1 mol) were mechanically

* 7-Methyl-8-oxa-3-azabicyclo[5.1.0]octan-2-one.

stirred in dichloromethane (400 ml) under nitrogen. Freshly distilled dry triethylamine (14 ml, 0·1 mol) was added to the solution, and the mixture stirred for 15 h. The precipitated dicyclohexylurea was collected by filtration, and washed with dichloromethane. The combined filtrate and washings were concentrated and passed through a short alumina column to remove a little more urea to give the *title compound* (20·0 g), a sample of which was recrystallized from benzene as colourless prisms, m.p. 180–181° (Found: C, 57·3; H, 6·8%; $M^{+\bullet}$, 210·1007. $C_{10}H_{14}N_2O_3$ requires C, 57·1; H, 6·7%; $M^{+\bullet}$, 210·1004). ν_{max} 3250(br), 1720, 1620, 1560, 1510 cm^{-1}. ^1H n.m.r. δ 1·23, t, J 7 Hz, 3H, Me; 2·55, t, J 6 Hz, 2H, CH_2CO; 3·62, q, J 6 Hz, 2H, CH_2N; 4·10, q, J 7 Hz, CH_2O; 6·10, t J 3 Hz, H4′; 6·55, m, 1H, H3′; 6·80, m, 1H, H5′; 10·36, br s, 2H, NH.

3-(Pyrrol-2′-ylcarbonylamino)propanoic Acid (24)

The ester above (20·0 g) was heated at 60–70° with a solution of sodium hydroxide (8·11 g) in water (100 ml) for 1 h. The cooled reaction mixture was filtered, extracted with ether and acidified at 0° to pH 4. Extraction with ethyl acetate (5×100 ml) gave a colourless oil which solidified on cooling (18·0 g, 99%), m.p. 149–150°. A sample was recrystallized from ethyl acetate/light petroleum, m.p. 150° (Found: C, 52·9; H, 5·3%; $M^{+\bullet}$, 182·0690. $C_8H_{10}N_2O_2$ requires C, 52·7; H, 5·5%; $M^{+\bullet}$, 182·0691). ν_{max} 3420, 3350, 3500–2500 (br), 1710, 1590 (br), 1540 cm^{-1}. ^1H n.m.r. ($CDCl_3/CD_3SOCD_3$) δ 2·55, t, 2H, C**H**$_2CO_2H$; 3·58, q, 2H, CH_2N; 6·05, m, H4′; 6·62, m, H3′; 7·32, br t, NHCO; 10·68, br s, NH; 14·00, br s, 1H, CO_2H.

N-(2-Cyanoethyl)pyrrole-2-carboxamide

The title compound was prepared as described for (23) from 3-aminopropionitrile and pyrrole-2-carboxylic acid in a mixture of acetonitrile and tetrahydrofuran. The crude product was purified by column chromatography on alumina with dichloromethane as the eluting solvent to give *N-(2′-cyanoethyl)pyrrole-2-carboxamide* as a pale yellow oil (90%) which crystallized on standing. An analytical sample was prepared by recrystallization first from ethyl acetate/light petroleum then ethyl acetate as pale yellow plates, m.p. 146–147° (Found: C, 58·8; H, 5·5. $C_8H_9N_3O$ requires C, 58·9; H, 5·6%). ν_{max} 3375, 3210 (broad), 2250, 1640, 1630, 1560, 1535 cm^{-1}. ^1H n.m.r. ($CDCl_3/CD_3SOCD_3$) δ 2·65, t, J 7 Hz, 2H; 3·62, q, J 7, 10 Hz, 2H; 6·20, m, 1H, H4; 6·80, m, 1H, H3 overlapping with 6·90, m, 1H, H5; 9·89, br s, 1H, NH. Mass spectrum m/z 163 (M).

6,7-Dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione (1)

The acid (14·45 g) was added to polyphosphoric acid (100 ml) to which *c.* 20 g diphosphorus pentoxide had been added, and the mixture mechanically stirred at 118–120° under nitrogen. After 30 min the homogeneous, dark brown solution was cooled and poured onto ice (1000 g). A little brown solid was removed by filtration and discarded; the solution was neutralized with sodium hydroxide and the precipitate collected. The filtrate was continuously extracted with ethyl acetate for 3 days, and the precipitated solids were extracted by Soxhlet extraction with acetone. The combined products (11·0 g, 85%) crystallized from ethanol as white plates m.p. 294–296°. The analytical sample was sublimed (140°/0·02 mm) (Found: C, 58·6; H, 4·9%; $M^{+\bullet}$, 164·0589. $C_8H_8N_2O_2$ requires C, 58·5; H, 4·9%; $M^{+\bullet}$, 164·0586). A mixed m.p. with an authentic sample (lit.[7] m.p. 275–277°) was undepressed, and the samples had identical R_F values and spectral data. ν_{max} ($CDCl_3$) 3425, 3275, 3075 (weak), 1650, 1640, 1560 cm^{-1}. ν_{max} (Nujol) 3235, 3080, 1675, 1640, 1555 cm^{-1}. ^1H n.m.r. ($CDCl_3/CD_3SOCD_3$) δ 2·75, m, 2H, CH_2CO; 3·50, m, 2H, CH_2N; 6·67, t, J 3 Hz, H3; 7·61, t, J 3 Hz, H2; 8·33, br t, NH; 12·17, br s, 1H, NHCO.

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