Synthesis of 2,4-Diazabicyclo[3.3.0]octane-3,7-diones and 3-Thioxo-2,4-diazabicyclo[3.3.0]octan-7-one by an Intramolecular Michael-type Reaction. Stability of 2,4-Diaza-, 4-Oxa-2-aza-, and 4-Thia-2-aza-bicyclo-[3.3.0]octane-3,7-diones

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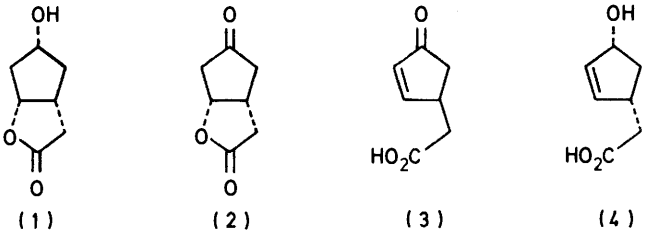
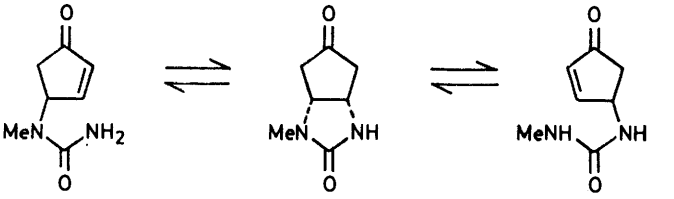
Novel 2,4-diazabicyclo[3.3.0]octane-3,7-diones (10) have been prepared by an intramolecular Michael-type cyclisation. The analogous 3-thioxo-2,4-diazabicyclo[3.3.0]octan-7-one system (20) is obtained by base-catalysed *retro*-Michael reaction of the less stable 3-arylimino-2-thia-4-azabicyclo[3.3.0]octan-7-one isomer (19). The 2-aza-4-oxabicyclo[3.3.0]octane-3,7-dione system (17) is shown to be very unstable to base, fragmenting *via* the carbamic acid to give carbon dioxide and a 4-*N*-substituted cyclopent-2-enone (11). The relative stability to base of these bicyclic systems is correlated with their structure.

THE synthesis of prostaglandins from [3.3.0]bicycles such as the Corey lactone is an established procedure.[1] In our studies on the synthesis of prostaglandin analogues, we prepared the recently reported [2] parent lactone (1) by the Corey route [3],† from bicyclo[2.2.1]hept-5-en-2-one [4] with the intention of oxidising it to the ketone (2) which is a potentially useful intermediate for the synthesis of bicyclic prostanoids. In the event, oxidation of (1) in acetone with chromic acid yielded the ring-opened ketone (3) as the only isolable pure product; the structure of (3) was confirmed by unambiguous synthesis from the previously obtained intermediate (4) by Jones oxidation. ^{1}H N.m.r. and i.r. studies of (3) indicated *ca.* 50% conversion into the bicyclic form (2) in acidified deuteriochloroform at 28 °C. In comparison, other workers have reported [5] that substituted analogues of (2), while quite labile (especially under basic conditions), are nevertheless isolable in crude form; moreover, these substituted bicyclic ketones are capable of undergoing nucleophilic addition at the ketonic carbonyl function with retention of the lactone system.



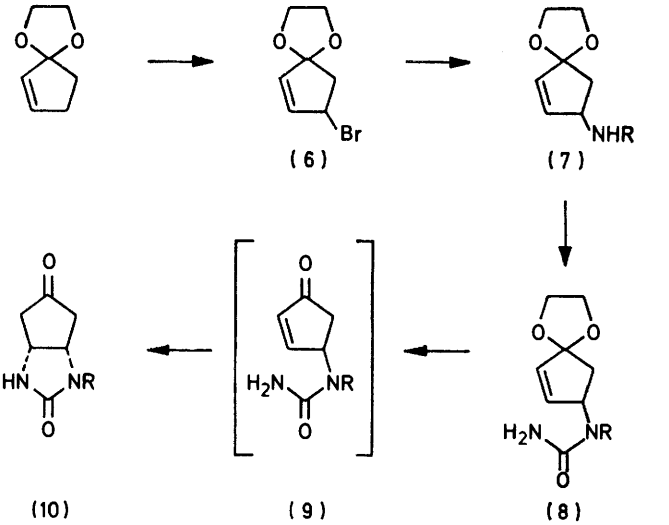
(1) (2) (3) (4)

It appeared to us that this 5-*exo*-*trig* [6] intramolecular Michael-type reaction could be exploited for the synthesis of other novel [3.3.0]heterobicyclic ketones which could be elaborated to a variety of prostaglandin analogues if they were sufficiently stable relative to their monocyclic isomers. Following the CNDO/2 approximation, ground-state energy calculations were performed; ‡ it was found that the bicyclic urea (5) should be *ca.* 4 kcal mol^{-1} more stable than the bicyclic lactone (2) relative to the respective monocyclic isomers. Accordingly, we set out to synthesise a suitable monocyclic urea containing a latent enone moiety which could be unmasked under mild conditions to give an internal donor–acceptor system which should cyclise.



(5)

The very labile allylic bromide (6), prepared by bromination of cyclopenten-3-one ethylene acetal,[7] was treated with benzylamine to give the amine (7; R = CH_2Ph) (Scheme 1). Treatment of the amine



(10) (9) (8)

SCHEME 1

with cyanic acid gave the desired urea (8; R = CH_2Ph) which on deprotection gave the anticipated bicyclic urea (10; R = CH_2Ph) in quantitative yield; a similar reaction sequence led to (10; R = n-C_8H_{17}). These

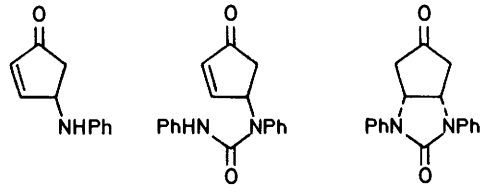
† The route to (1) described in ref. 2 *via* nortricyclanone was investigated by us at an early stage and found to be less efficient than the modified Corey synthesis described herein.

‡ The calculations were performed by Dr. J. G. Vinter of these Laboratories.

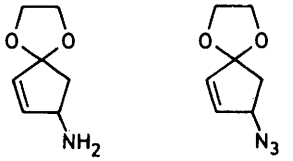
novel bicycles are quite stable; their monocyclic isomers were not detected on exposure to a variety of bases and acids. The ring-junction stereochemistry of (10) was assigned as *cis* from a study of molecular models which indicated that the alternative *trans* isomer would be excessively strained and thus unstable; the intense i.r. absorption at 1 700—1 705 cm^{-1}, indicative of an unstrained five-membered cyclic urea,[8] supports this assignment.

Under neutral conditions, a monocyclic system analogous to (9) could be isolated; treatment of (11) (described below) with phenyl isocyanate gave the monocyclic urea (12) in quantitative yield. In chloroform at 28 °C, (12) was surprisingly stable; however, on addition of triethylamine or on shaking the solution with a trace of concentrated hydrochloric acid rapid cyclisation occurred; even in the absence of any catalyst, dissolution in warm dimethyl sulphoxide induced complete and irreversible cyclisation giving the *cis*-fused bicyclic urea (13).

Attempts were made to prepare the primary amine (14) for conversion into the parent 2,4-diazabicyclo-[3.3.0]octane-3,7-dione. Reaction of the bromide (6) with ammonia in tetrahydrofuran gave only polymeric material, and attempted debenzylation of (7; R = CH_2Ph) with sodium and liquid ammonia led mainly to recovery of starting material and products of olefinic-bond reduction. The azide (15) was obtained from (6) in moderate yield by phase-transfer-catalysed reaction with sodium azide, but reduction of (15) with lithium aluminium hydride [9] or lithium borohydride failed to give the required amine (14). Lindlar reduction [10] gave very low and inconsistent yields of (14), the azide group being reduced slowly relative to the olefinic bond; insufficient material was obtained for conversion into the parent bicycle.

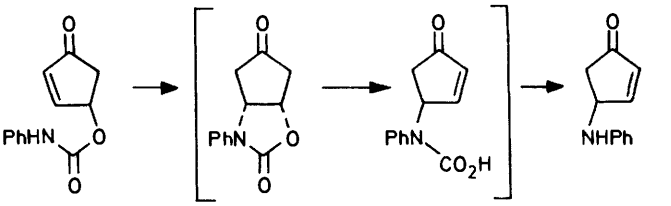


(11) (12) (13)



(14) (15)

In an investigation of the analogous oxazolidine bicyclic system, reaction of 4-hydroxycyclopent-2-enone [11] with phenyl isocyanate have the monocyclic urethane (16); treatment of the latter with a catalytic amount of triethylamine to (16) in chloroform led to a slow evolution of carbon dioxide with formation of the stable amino-ketone (11) in 96% yield. A likely mechanism is shown in Scheme 2; alternatively the loss of carbon dioxide with formation of the olefinic bond may be concerted, so providing a considerable driving-force for the reaction.



(16) (17) (11)

SCHEME 2

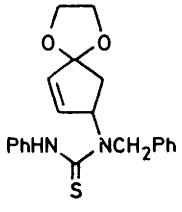
In contrast, treatment of (16) in tetrahydrofuran with acid gave a complex mixture which contained small amounts of (11), as identified by t.l.c.; very slow evolution of gas was observed. When (16) was exposed to hydrochloric acid in deuteriochloroform at 28 °C, proton resonances attributable to the expected bicycle (17) slowly appeared, reaching a maximum at 2 h (*ca.* 25% conversion) [$\delta(CDCl_3)$ 2.6—3.15 (m, 2 × $-CH_2-$), 4.55 (m, 1-methine), and 5.35 (m, 5-methine)], after which extensive decomposition occurred; nevertheless resonances attributable to the conjugate acid of (11) were also observable. Attempts to isolate (17) from the reaction mixture proved unsuccessful. 4-Hydroxycyclopent-2-enone did not react with alkyl isocyanates in the absence of base.[12] In the presence of an equivalent of triethylamine, reaction with n-octyl isocyanate [13] was extremely slow, even on heating, giving polymeric material.*

The study was extended to the preparation and cyclisation of thiourea analogues of system (5). Phenyl isothiocyanate reacted rapidly with (7; R = CH_2Ph) giving the protected thiourea (18); acid-catalysed deprotection of (18) initiated the expected cyclisation onto sulphur, giving the 4-aza-3-imino-2-thia[3.3.0]-bicycle (19) whose structure was confirmed by the presence of an intense i.r. absorption at 1 612 cm^{-1} assigned to the stretching mode of the imine bond; however, no indication of the proportions of *syn* : *anti* isomers in (19) was obtained. Traces of the isomeric thiourea (20; R = CH_2Ph) were also detected by t.l.c. In contrast, the *N*-phenylamine (11) reacted slowly with phenyl isothiocyanate, with triethylamine catalysis, to give the bicyclic thiourea (20; R = Ph) in moderate yield. Under these conditions, the isomeric 4-aza-2-thiabicycle was not formed. The dependence of the cyclisation mode on the reaction conditions was revealed by the observation that treatment of (19) with triethylamine in dimethyl sulphoxide (60 °C, $t_{\frac{1}{2}}$ *ca.* 2 min) or chloroform (28 °C, $t_{\frac{1}{2}}$ *ca.* 24 h) caused complete and irreversible rearrangement to the thiourea (20; R = CH_2Ph). The ^1H n.m.r. coupling between the ring-

* The anticipated product from the reaction of n-octyl isocyanate would be expected to be more basic than the *N*-phenylamine (11) and would therefore be likely to polymerise readily.[7]

junction methine protons was 8.2 Hz, confirming that the ring fusion was *cis*.[14]

It appears that the initial cyclisation occurs by attack of the soft sulphur atom on the soft carbon terminus of the enone system; attack by the harder nitrogen atom is very much slower. However, the system under study is unusual in having access to a facile base-catalysed rearrangement pathway to the isomeric thiourea which is therefore the product in the presence of triethylamine. Under the essentially non-equilibrium conditions of the experiments described, it is not possible to assign the relative thermodynamic stabilities of (19) and (20; R = CH_2Ph). However, when (19) was heated at 150 °C for 1 h it was transformed with only slight decomposition into a mixture of (19) (68%) and (20; R = CH_2Ph) (32%); when (20; R = CH_2Ph) was heated under the same conditions, (19) was not formed although some decomposition occurred. These results strongly indicate that the thiourea (20; R = CH_2Ph) is thermodynamically more stable than the isomeric imine (19).* This finding is consistent with results obtained from studies of the acyclic thioamide–thioimidate system [14] and dithiohydantoins and related heterocycles [15] which indicate the greater thermodynamic stability of the thioamide compared with the thioimidate moiety.



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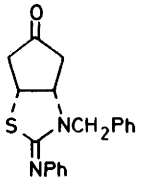

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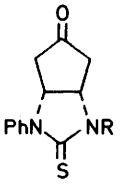
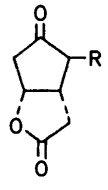
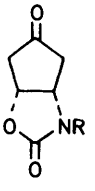


(20)

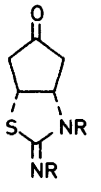
The relative stability to base of the five bicyclic systems studied is in the order (A) ≈ (B) ≪ (C) < (D) ≈ (E). This order is to be expected as the tendency



(A)



(B)



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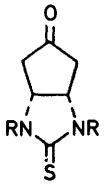
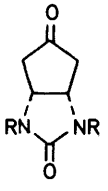


(D)



(E)

for the heterocyclic unit to behave as an intramolecular 'leaving-group' should decrease in proceeding from (A) to (E).

EXPERIMENTAL

N.m.r. spectra were recorded on a Bruker WP-80 80 MHz or a Bruker HFX-90 90 MHz instrument operating in the pulse Fourier-transform mode. I.r. spectra were recorded on a Perkin-Elmer 297 or a Perkin-Elmer 580 instrument. Electron-impact mass spectra were recorded on an A.E.I. MS 902 instrument. Melting-points were obtained in capillary-tubes. Merck Kieselgel 60 silica was used for column chromatography; anhydrous sodium sulphate was used as the drying agent unless otherwise stated.

cis-2-(4-*Hydroxycyclopent-2-enyl*)*acetic Acid* (4).—Aqueous hydrogen peroxide (30%; 26.5 ml) was added over 1 h to a cooled, vigorously stirred mixture of bicyclo[2.2.1]hept-5-en-2-one (15.90 g) in ether (63 ml) and sodium hydroxide (7.05 g) in water (60 ml), maintaining the temperature at 10—25 °C. After a further 1½ h at that temperature, the aqueous layer was separated, washed once with ether, acidified to pH 1, then extracted with ethyl acetate (8 × 50 ml). Removal of the solvent and recrystallisation of the residue gave the *acid* (4) as large prisms (9.46 g, 52%), m.p. 84—86 °C (from ether) (Found: C, 58.7; H, 7.05%; $C_7H_{10}O_3$ requires C, 59.15; H, 7.04%), δ($CDCl_3$) 1.40 (1 H, dt, J_1 14, $J_2 = J_3 = 4.5$ Hz, *cis*-5-H), 2.2—3.2 (4 H, m, 2-CH_2, 1-H, *trans*-5-H), 4.84 (1 H, m, 4-H), 5.90br (2 H, s, 2- and 3-H), and 6.3br (2 H, −OH and $-CO_2H$), $\nu_{max.}$ (KBr) 3 430, 3 200—2 500, 1 710, 1 615w (C=C), 1 395, 1 200, 1 078, 1 005, and 780 cm^{-1}. Unchanged bicyclo[2.2.1]hept-5-en-2-one (2.0 g) was recovered from the ether extract.

1β,5β,7α-7-*Hydroxy*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (1).—A solution of the *cis*-acid (4) (2.00 g) and sodium hydroxide (1.54 g) in water (30 ml) was adjusted to pH 7 with solid carbon dioxide then added dropwise with stirring to a cooled (0 °C) solution of iodine (9.83 g) and potassium iodide (6.84 g) in water (10 ml). After 24 h at 0 °C, the solution was treated with slurry of sodium sulphite (5.35 g) and sodium carbonate (2.14 g) in water (16 ml) and the product was extracted into chloroform. After drying, removal of the solvent gave 1β,5β,7α,8β-7-hydroxy-8-iodo-2-oxabicyclo-[3.3.0]octan-3-one as a white solid (3.60 g, 95%), m.p. 120—121° (decomp.), δ($CDCl_3$) 1.90 (1 H, m, 6-H), 2.5—3.5 (5 H, m, 4-CH_2, 5- and 6-H, −OH), 4.39br (1 H, s, 8-H), 4.55 (1 H, m, 7-H), and 5.32 (1 H, d, m, *J* 7 Hz, 1-H). Without further purification, this *iodolactone* (1.34 g) in dry tetrahydrofuran (10 ml) and dry benzene (5 ml) was treated dropwise with stirring with tri-n-butyltin hydride (2.62 g) in dry tetrahydrofuran (27 ml) under dry nitrogen. After 30 min at room temperature, the solvent was removed and the residual oil was partitioned between water (25 ml) and n-hexane (25 ml) and stirred overnight. The aqueous layer was separated, extracted with two small portions of n-hexane, then saturated with sodium chloride and continuously extracted with ethyl acetate for 36 h. After removal of solvent, the residue was recrystallised from chloroform–ether giving the lactone (1) as plates (590 mg, 83%), m.p. 82—83 °C (lit.,[2] 76—77 °C) (Found: C, 58.95; H, 7.05. Calc. for $C_7H_{10}O_3$: C, 59.15; H, 7.05%), δ($CDCl_3$) 1.8—3.2 (9 H, m), 4.45 (1 H, m, 7-H), and 5.09 (1 H, t, *J* 6 Hz, 1-H), $\nu_{max.}$ (KBr) 3 410, 2 965, 2 930, 2 898, 1 735, 1 215, and 1 095 cm^{-1}.

* The isomer of (19) in which the two nitrogen substituents are reversed is a possible product of equilibration of (20; R = CH_2Ph) or (19); this isomer was not detected in these experiments.

2-(4-*Oxocyclopent*-2-*enyl*)*acetic Acid* (3).—(a) *From* (1). A solution of the lactone (1) (3.00 g) in acetone (30 ml) was stirred at 5 °C and chromium trioxide (1.50 g) in water (4.50 ml) containing concentrated sulphuric acid (1.28 ml) was added dropwise. The resulting suspension was stirred for 2 h at 5 °C and then for 2 h at room temperature, then diluted with water (10 ml). The supernatant liquid was decanted from the insoluble chromium salts, extracted with ethyl acetate, and the extract was washed once with brine and then dried. Removal of the solvent gave a yellow syrup (2.7 g) which deposited 2-(4-*oxocyclopent*-2-*enyl*)*acetic acid* (3) as prisms (430 mg, 15%), m.p. 101—102 °C (from acetone) (Found: C, 60.05; H, 6.0. $C_7H_8O_3$ requires C, 60.0; H, 5.7%), δ($CDCl_3$) 2.07 (1 H, dd, J_1 2.6, J_2 18.5 Hz, *cis*-5-H), 2.5—2.9 (3 H, m, *trans*-5-H, CH_2CO_2H), 3.40 (1 H, m, 1-H), 6.24 (1 H, dd, J_1 1.9, J_2 5.8 Hz, 3-H), 7.68 (1 H, dd, J_1 2.6, J_2 5.8 Hz, 2-H), and 10.38br (1 H, s, CO_2H), $\nu_{max.}$ (KBr) 3 250—2 600, 1 730, 1 690sh, 1 650, 1 580, 1 405, 1 170, and 800 cm^{-1}.

Examination of the mother-liquor (^1H n.m.r.) revealed the presence of *ca.* 60% of (3) and *ca.* 40% of the bicyclic isomer (2), δ($CDCl_3$) 5.20 (m, 1-methine) together with unidentified material.

(b) *From* (4). The acid (4) (3.00 g) was oxidised as in (a) to give crystalline (3) (1.50 g, 50%), identical (mixed t.l.c., mixed m.p., and n.m.r. and i.r. spectra) with the product obtained in (a).

Interconversion of the Acid (3) *and the Dione* (2).—(a) ^1H *N.m.r. studies*. A sample of (3) in deuteriochloroform was treated with *ca.* 10% of trifluoroacetic acid and examined periodically over 3 days, during which time a multiplet, δ *ca.* 5.30, due to (2), appeared with a proportionate decrease in the intensity of the olefinic resonances of (3); changes of a less simple nature occurred in the region δ 2.5—3.2. The final conversion (3) ⟶ (2) was *ca.* 35%.

(b) *I.r. studies*. Samples of (3) in chloroform (*ca.* 35 mg ml^{-1}) were treated with methanesulphonic acid at 25 °C and the conversion was followed by observing the appearance of absorptions at *ca.* 1 780 (lactone C=O) and 1 750 cm^{-1} (ketone C=O) and comparison with the coincident CO_2H and ketonic absorption of (3) at *ca.* 1 720 cm^{-1}. The highest conversion (*ca.* 50%) was obtained at 1 h with 1% acid as catalyst.

5-*Bromo*-3,3-*ethylenedioxycyclopentene* (6).—Cyclopenten-3-one ethylene acetal was brominated by the method of DePuy and co-workers [7] and the product was used without further purification. In order to obtain consistent yields, it was found necessary that all free bromine be removed from the *N*-bromosuccinimide by recrystallisation from benzene immediately prior to use; the bromination reaction, once started, proceeded rapidly and subsequent heating of the mixture as described [7] resulted only in rapid decomposition of the bromide (6).

5-*Benzylamino*-3,3-*ethylenedioxycyclopentene* (7; R = CH_2Ph).—The bromide (6) [from cyclopenten-3-one ethylene acetal (12.50 g)] in dry toluene (125 ml) was added dropwise over 10 min to a stirred solution of dry benzylamine (21.60 g, 2 mol. equiv.) in dry toluene (150 ml) at −25 °C. The yellow solution was stirred overnight at 5 °C, then at 40 °C for 3½ h, then cooled and the precipitated benzylamine hydrobromide filtered off. Removal of the solvent and dissolution of the residue in ether gave a second crop of benzylamine hydrobromide. After filtration and evaporation, the residual red-orange syrup was subjected to column chromatography on silica; elution with 25 : 1 v/v ethyl acetate–ethanol gave the enamine (7; R = CH_2Ph) as an orange oil (9.10 g, 40%). A small sample was distilled, giving a colourless oil, b.p. 102—104 °C at 0.05 mmHg, δ($CDCl_3$) 1.43br (1 H, s, NH), 1.83 (1 H, dd, J_1 5, J_2 14 Hz, *cis*-4-H), 2.43 (1 H, dd, J_1 7, J_2 14 Hz, *trans*-4-H), 3.80 (2 H, s, CH_2Ph), 3.93 (4 H, s, acetal CH_2), 3.75—3.95 (1 H, m, 5-H), 5.80 (1 H, dd, J_1 2, J_2 6 Hz, olefinic), 6.15 (1 H, dd, J_1 2.5, J_2 6 Hz, olefinic), and 7.31br (5 H, s, ArH), $\nu_{max.}$ (film) 3 305, 3 060, 3 030, 2 980, 2 960, 2 880, 1 605, 1 495, 1 455, 1 368, 1 108, 740, and 700 cm^{-1}. The *hydrochloride*, prepared by exchange with methylamine hydrochloride, had m.p. 175—176 °C (decomp.) (from chloroform–ether) (Found: C, 62.7; H, 6.95; N, 5.15. $C_{14}H_{18}ClNO_2$ requires C, 62.8; H, 6.7; N, 5.2%).

4,4-*Ethylenedioxycyclopent*-2-*enyl*(*octyl*)*ammonium Bromide* (7; R = n-C_8H_{17}, HBr).—3-Bromo-5,5-ethylenedioxycyclopentene (6) [from cyclopenten-3-one ethylene acetal (8.56 g)] in dry carbon tetrachloride (56 ml) was added dropwise to a stirred solution of dry n-octylamine (10.40 g, 2 mol. equiv.) in carbon tetrachloride (80 ml) at 0 °C. The yellow solution was stirred at room temperature for 18 h and the solvent was removed *in vacuo* to give a residual red oil which was purified by column chromatography on silica; elution with 9 : 1 v/v chloroform–ethanol, followed by recrystallisation from ether–chloroform gave the *hydrobromide* as creamy white lustrous plates (4.9 g, 22%), m.p. 158—159 °C (decomp.) (Found: C, 53.85; H, 8.2; N, 3.9. $C_{15}H_{28}BrNO_2$ requires C, 53.9; H, 8.4; N, 4.2%). The free base was a pale orange oil, δ($CDCl_3$) 0.87br (3 H, t, CH_3), 1.1—1.6 (13 H, m, chain −CH_2 and −NH), 1.78 (1 H, dd, J_1 5, J_2 14 Hz, *cis*-5-H), 2.46 (1 H, dd, J_1 7, J_2 14 Hz, *trans*-5-H), 2.64br (2 H, t, NCH_2), 3.7—4.0 (1 H, m, 1-H), 3.97 (4 H, s, acetal-CH_2), 5.80 (1 H, dd, J_1 2, J_2 6 Hz, olefinic), and 6.18 (1 H, dd, J_1 2.5, J_2 6 Hz, olefinic).

N-*Benzyl*-N-(4,4-*ethylenedioxycyclopent*-2-*enyl*)*urea* (8; R = CH_2Ph).—The enamine (7; R = CH_2Ph) (693 mg, 3 mmol) in ethanol (6.0 ml) was treated with a solution of potassium cyanate (360 mg, 4.5 mmol) in water (4.5 ml) followed by 1N-hydrochloric acid (3.0 ml) and the solution was set aside at room temperature for 18 h. The product was liberated by dilution with water and extracted into chloroform. The extract was dried and the solvent was removed to give a residue which was purified by column chromatography on silica; elution with 9 : 1 v/v methanol–ether gave the *urea* (8; R = CH_2Ph) as a pale yellow glass (800 mg, 95%), δ($CDCl_3$) 1.90 (1 H, dd, J_1 5, J_2 14 Hz, *cis*-5-H), 2.55 (1 H, dd, J_1 8, J_2 14 Hz, *trans*-5-H), 3.92 (4 H, s, acetal CH_2), 4.34 (2 H, s, CH_2Ph), 4.5br (2 H, s, NH_2), 5.47 (1 H, m, 1-H), 5.87 (2 H, m, olefinic), and 7.29br (5 H, s, ArH), $\nu_{max.}$ (film) 3 500—3 300, 1 655 (urea C=O), and 1 595 cm^{-1}.

N-(4,4-*Ethylenedioxycyclopent*-2-*enyl*)-N-*octylurea* (8; R = n-C_8H_{17}).—Prepared from the hydrobromide (7; R = n-C_8H_{17}, HBr) as in the preceding example with the exception that no added acid was required, the *urea* (8; R = n-C_8H_{17}) was obtained as a glass (97%), δ($CDCl_3$) 0.94br (3 H, t, CH_3), 1.2—1.9 (12 H, m, chain-CH_2), 1,89 (1 H, dd, J_1 5, J_2 15 Hz, *cis*-5-H), 2.51 (1 H, dd, J_1 8, J_2 15 Hz. *trans*-5-H), 3.07 (2 H, m, NCH_2), 3.95 (2 H, s, acetal CH_2), 4.56br (2 H, s, NH_2), 5.18 (1 H, m, 1-H), and 5.90 (2 H, m, olefinic), $\nu_{max.}$ (film) 3 500—3 300, 1 650 (urea C=O), and 1 595 cm^{-1}.

2-*Benzyl*-2,4-*diaza*-cis-*bicyclo*[3.3.0]*octane*-3,7-*dione* (10; R = CH_2Ph).—The urea (8; R = CH_2Ph) (640 mg, 2.33

mmol) in tetrahydrofuran (9.4 ml) was treated with 2N-hydrochloric acid (9.4 ml). After 1 h at room temperature, the solution was diluted with water and the product extracted into chloroform. The extract was dried and the solvent was evaporated off to give a white solid which was recrystallised from ether–chloroform to give the *bicyclic urea* (10; R = CH_2Ph) as prisms (530 mg, 98%), m.p. 135—136 °C (Found: C, 67.9; H, 5.95; N, 12.25. $C_{13}H_{14}N_2O_2$ requires C, 67.85; H, 6.1; N, 12.15%), δ($CDCl_3$) 2.2—2.7 (4 H, m, 6- and 8-CH_2), 4.02 (1 H, d, *J* 15 Hz, *H*CHPh), 4.0—4.6 (2 H, m, 1- and 5-H), 4.76 (1 H, d, *J* 15 Hz, HC*H*Ph), 5.94br (1 H, s, NH), and 7.29br (5 H, s, ArH), $\nu_{max.}$ (KBr) 3 210, 3 090, 2 905, 1 735 (ketone C=O), 1 705 (urea C=O), 1 600, 1 580, 1 490, 1 460, 1 450, 1 360, 1 245, 755, and 700 cm^{-1}.

2-*Octyl*-2,4-*diaza*-cis-*bicyclo*[3.3.0]*octane*-3,7-*dione* (10; R = n-C_8H_{17}).—The bicycle (10; R = n-C_8H_{17}), prepared from the urea (8; R = n-C_8H_{17}) as in the previous experiment, was obtained in 75% yield as fluffy *needles*, m.p. 54—56 °C (from ether–hexane) (Found: C, 66.5; H, 9.35; N, 10.85. $C_{14}H_{24}N_2O_2$ requires C, 66.65; H, 9.5; N, 11.1%), δ($CDCl_3$) 0.91br (3 H, t, CH_3), 1.0—1.7 (12 H, m, chain-CH_2), 2.4—2.6 (4 H, m, 6- and 8-CH_2), 2.85 (1 H, m, *H*CH–N), 3.35 (1 H, m, HC*H*–N), 4.2—4.5 (2 H, m, 1- and 5-H), and 6.02br (1 H, s, –NH), $\nu_{max.}$ (KBr) 3 270, 2 920, 2 860, 1 740 (ketone C=O), 1 695 (urea C=O), 1 460, 1 398, 1 340, 1 245, and 762 cm^{-1}.

N-(4-*Oxocyclopent*-2-*enyl*)-NN′-*diphenylurea* (12).—Phenyl isocyanate (119 mg, 1 mmol) in dry tetrahydrofuran (2.0 ml) was treated with solid 4-anilinocyclopent-2-enone (11) (173 mg, 1 mmol) and the solution was set aside at room temperature for 18 h. The solvent was removed *in vacuo* leaving a buff crystalline residue, which was recrystallised from chloroform–hexane to give the *urea* (12) as buff prisms (200 mg, 67%), m.p. 134—135 °C (Found: C, 73.75; H, 5.55; N, 9.3. $C_{18}H_{16}N_2O_2$ requires C, 73.95; H, 5.5; N, 9.6%), δ($CDCl_3$) 2.26 (1 H, dd, J_1 3, J_2 18 Hz, *cis*-5-H), 2.80 (1 H, dd, J_1 6.5, J_2 18 Hz), 6.0 (2 H, m, 1-H and NH), 6.14 (1 H, dd, J_1 2.0, J_2 5.5 Hz, 3-H), 6.9—7.5 (10 H, m, ArH), and 7.60 (1 H, dd, J_1 2.0, J_2 5.5 Hz, 2-H), $\nu_{max.}$ (KBr) 3 400, 3 050, 2 940, 1 712, 1 663, 1 590, 1 520, 770, 740, and 705 cm^{-1}.

2,4-*Diphenyl*-2,4-*diaza*-cis-*bicyclo*[3.3.0]*octane*-3,7-*dione* (13).—The urea (12) (100 mg) in chloroform (2.0 ml) was treated with concentrated hydrochloric acid (0.1 ml) and the mixture was shaken at room temperature for 30 min. The solution was washed with water and the organic phase was separated, dried, and concentrated *in vacuo* to give a crystalline residue, which was recrystallised from chloroform–hexane yielding the *bicyclic urea* (13) as needles (100 mg, 100%), m.p. 171—173 °C (decomp.) (Found: C, 73.65; H, 5.55; N, 9.5. $C_{18}H_{16}N_2O_2$ requires C, 73.95; H, 5.5; N, 9.6%), δ($CDCl_3$) 2.3—2.9 (4 H, m, 6- and 8-CH_2), 4.80 (2 H, m, 1- and 5-H), and 6.9—7.5 (10 H, m, ArH), $\nu_{max.}$ (KBr) 3 055, 2 930, 1 740 (ketonic C=O), 1 700 (urea C=O), 1 600, 1 495, 1 405, 1 390, 750, 715, and 690 cm^{-1}.

Cyclisation of (12) by warming a 5% solution in dimethyl sulphoxide at 60 °C for 30 min also gave a quantitative yield of (13).

4,4-*Ethylenedioxycyclopent*-2-*enyl Azide* (15).—3-Bromo-5,5-ethylenedioxycyclopentene (6) [from cyclopenten-3-one ethylene acetal (2.50 g)] in carbon tetrachloride (30 ml) and sodium azide (3.9 g) in water (12 ml) were vigorously stirred for 19 h at room temperature in the presence of Adogen 464 * (0.60 g). The layers were separated and the aqueous phase was extracted with chloroform; the combined organic extract was dried, filtered, and the solvent was removed *in vacuo* at room temperature. The residue was purified by chromatography on silica, eluting with 3 : 2 v/v hexane–ether giving the *azide* (15) as an oil (1.80 g, 55%), m.p. 19—21 °C, b.p. 53.0—53.5 °C at 0.3 mmHg (Found: C, 49.65; H, 5.5; N, 24.0. $C_7H_9N_3O_2$ requires C, 50.3; H, 5.4; N, 25.15%), δ($CDCl_3$) 2.00 (1 H, dd, J_1 4, J_2 14 Hz, *cis*-5-H), 2.51 (1 H, dd, J_1 7, J_2 14 Hz, *trans*-5-H), 3.96 (4 H, s, acetal CH_2), 4.38 (1 H, m, 1-H), and 5.99 (2 H, m, olefinic) (double resonance on the olefinic signals caused the multiplet at δ 4.38 to collapse to a double doublet, J_1 4, J_2 7 Hz; the signals at δ 2.00 and 2.51 were unaffected), $\nu_{max.}$ (liquid) 3 060, 2 960, 2 885, 2 098 (azide), 1 475, 1 430, 1 365, 1 260, 1 090, 1 050, 1 025, 1 000, and 945 cm^{-1}.

5-*Amino*-3,3-*ethylenedioxycyclopentene* (14).—The azide (15) (433 mg) in ethanol (24 ml) was treated with Lindlar catalyst [9] (160 mg) and quinoline (32 mg) and the mixture was stirred vigorously under hydrogen at 1 atm at room temperature for 4.5 h. The filtered (Celite) solution furnished a yellow gum which was chromatographed on Grade II alumina. Elution with 100 : 7 v/v chloroform–methanol gave unchanged azide (15) (recovery *ca.* 50%) and quinoline followed by a gum (150 mg) which from ether slowly deposited the *enamine* (14) as tiny crystals (20 mg, 6%), m.p. 100—102 °C, δ($CDCl_3$) 1.3—1.8br (2 H, NH_2), 1.68 (1 H, dd, J_1 4, J_2 13 Hz, *cis*-5-H), 2.50 (1 H, dd, J_1 7, J_2 13 Hz, *trans*-5-H), 3.93 (4 H, s, acetal CH_2), 3.8—4.0 (1 H, m, 1-H), 5.73 (1 H, dd, J_1 1.5, J_2 5 Hz, olefinic), and 6.02 (1 H, dd, J_1 2.0, J_2 5 Hz, olefinic), $\nu_{max.}$ ($CHCl_3$) 3 375, 3 300 (NH str), 3 060, 2 960, 2 885, 1 620, 1 580, and 1 075 cm^{-1} (Found: M^+, 141.079 2. $C_7H_{11}NO_2$ requires *M*, 141.079 0), *m/e* 99 ($M^+ - C_2H_4N$) and 44 (base).

Repetition of this experiment in the presence of more or less quinoline failed to give isolable quantities of (14).

4-*Oxocyclopent*-2-*enyl* N-*Phenylcarbamate* (16).—4-Hydroxycyclopent-2-enone (98 mg, 1 mmol) and freshly redistilled phenyl isocyanate (119 mg, 1 mmol) were mixed and set aside at room temperature for 64 h. The resulting buff crystalline mass was recrystallised from ether–hexane giving the *monocyclic urethane* (16) as plates (150 mg, 69%), m.p. 124—125 °C (decomp.) (Found: C, 66.3; H, 5.15; N, 6.45. $C_{12}H_{11}NO_3$ requires C, 66.35; H, 5.05; N, 6.45%), δ($CDCl_3$) 2.39 (1 H, dd, J_1 2.5, J_2 18 Hz, *cis*-5-H), 5.92 (1 H, m, 1-H), 6.35 (1 H, dd, J_1 1.5, J_2 5.5 Hz, 3-H), 6.72br (1 H, NH), 7.1—7.4 (5 H, m, ArH), and 7.64 (1 H, dd, J_1 2.5, J_2 5.5 Hz, 2-H), $\nu_{max.}$ (KBr) 3 320, 3 075, 1 720, 1 705, 1 600, 1 540, 1 500, 1 490, 1 445, 1 315, 1 215, 1 065, and 750 cm^{-1}.

4-*Anilinocyclopent*-2-*enone* (11).—The urethane (16) (300 mg) in dry tetrahydrofuran (2.0 ml) was treated with dry triethylamine (175 mg) in one portion at room temperature; carbon dioxide, which was slowly evolved, was swept into aqueous barium hydroxide solution in a stream of nitrogen, causing precipitation of barium carbonate. After 4¼ h at room temperature, the solvent was removed and the crystalline residue recrystallised from ether–hexane, giving 4-*anilinocyclopent*-2-*enone* (11) as buff prisms (230 mg, 96%), m.p. 67—69 °C (Found: C, 76.45; H, 6.6; N, 7.95. $C_{11}H_{11}NO$ requires C, 76.30; H, 6.35; N, 8.1%), δ($CDCl_3$) 2.20 (1 H, dd, J_1 2.2, J_2 18.6 Hz, *cis*-5-H), 2.92 (1 H, dd, J_1 6.1, J_2 18.6 Hz, *trans*-5-H), 3.77br

* Adogen 464 is methyltrialkyl(C_8—C_{10})ammonium chloride and was obtained from Aldrich Ltd.

(1 H, NH), 4.77 (1 H, m, 4-H), 6.28 (1 H, dd, J_1 1.7, J_2 5.7 Hz, 2-H), 6.5—6.9 (3 H, m, *o*- and *p*-ArH), 7.0—7.4 (2 H, m, *m*-ArH), and 7.68 (1 H, dd, J_1 2.3, J_2 5.7 Hz, 3-H), $\nu_{max.}$ (KBr) 3 340, 3 010, 2 905, 1 710 (weak), 1 695, 1 520, 1 495, and 475 cm^{-1}.

N-Benzyl-N-(4,4-ethylenedioxycyclopent-2-enyl)-N'-phenylthiourea (18).—The enamine (7; R = CH_2Ph) (693 mg, 3 mmol) in chloroform (2.0 ml) was treated with phenyl isothiocyanate (405 mg, 3 mmol) in one portion. After the initial exothermic reaction, the solution was kept at room temperature for 2 h, the solvent was removed, and the residual solid was recrystallised from chloroform–ether giving the *thiourea* (18) as needles (940 mg, 86%), m.p. 147—148 °C (Found: C, 68.85; H, 5.95; N, 7.7. $C_{21}H_{22}N_2O_2S$ requires C, 68.85; H, 6.0; N, 7.65%), δ($CDCl_3$) 1.96 (1 H, dd, J_1 5, J_2 15 Hz, *cis*-5-H), 2.74 (1 H, dd, J_1 8, J_2 15 Hz, *trans*-5-H), 3.96 (4 H, s, acetal CH_2), 4.76 (2 H, s, CH_2Ph), 6.00 (2 H, m, olefinic), 6.4—6.8 (1 H, m, 1-H), and 7.0—7.5 (11 H, m, ArH and NH), $\nu_{max.}$ (KBr) 3 340, 3 015, 2 960, 2 885, 1 593, 1 518, 1 495, 1 448, 1 325, 1 300, 795, 760, 725, and 700 cm^{-1}.

4-Benzyl-3-phenylimino-2-thia-4-aza-cis-bicyclo[3.3.0]*octan-7-one* (19).—The thiourea (18) (549 mg, 1.5 mmol) in tetrahydrofuran (9.0 ml) was treated with 2N-hydrochloric acid (6.0 ml) and the solution was kept at room temperature for 2 h. The product was liberated by dilution with water and extraction into chloroform. Removal of the solvent from the dried extract and recrystallisation of the residue from ether–dichloromethane gave the *bicyclic imine* (19) as needles (360 mg, 75%), m.p. 138—139 °C (from dichloromethane–ether) (Found: C, 70.6; H, 5.45; N, 8.45. $C_{19}H_{18}N_2OS$ requires C, 70.8; H, 5.6; N, 8.7%), δ($CDCl_3$) 2.40—2.72 (4 H, m, 6- and 8-CH_2), 3.90—4.35 (2 H, m, 1- and 5-H), 4.27 (1 H, d, J 16 Hz, *H*CHPh), 5.21 (1 H, d, J 16 Hz, $^-$HC*H*Ph), 6.8—7.5 (5 H, m, $^=$NPh), and 7.35br (5 H, s, CH_2Ph), $\nu_{max.}$ (KBr) 2 950, 2 905, 1 738 (ketone C=O), 1 612vs (N=C), 1 584, 1 450, 1 405, 1 340, 1 185, 775, 740, and 700 cm^{-1}, *m/e* 322 (M^+, base), 240 (M^+ − 82), 239 (M^+ − 83), 137 (M^+ − 185), 136 (M^+ − 186), 91 ($PhCH_2^+$), and 77 (Ph^+).

T.l.c. (silica, developed in 4 : 1 v/v ether–hexane) indicated the presence of a trace impurity, R_F 0.24, in addition to the major component of R_F 0.50; the more polar component was subsequently identified as (20; R = CH_2Ph).

2,4-Diphenyl-3-thioxo-2,4-diaza-cis-bicyclo[3.3.0]*octan-7-one* (20; R = Ph).—4-Anilinocyclopent-2-enone (11) (173 mg, 1 mmol) in chloroform (20 ml) and triethylamine (100 mg, 1 mmol) was treated with phenyl isothiocyanate (135 mg, 1 mmol) in one portion and the resulting solution was set aside at room temperature for 72 h. The solvent was removed and the residue was recrystallised from chloroform–ether giving the *thiourea* (20; R = Ph) as off-white fibrous needles (121 mg, 40%), m.p. 267—268 °C (decomp.) (from ethanol) (Found: C, 70.05; H, 5.3; N, 9.0. $C_{18}H_{16}N_2OS$ requires C, 70.1; H, 5.2; N, 9.1%), δ($CDCl_3$) 2.65 (4 H, m, 6- and 8-CH_2), 5.10 (2 H, m, 1- and 5-H), and 7.44 (10 H, m, ArH), $\nu_{max.}$ (KBr) 3 040, 2 945, 2 910, 1 743 (ketone C=O), 1 593, 1 494 (thioamide II), 1 440, 1 400, 1 275 (thioamide I), 750, and 695 cm^{-1}, *m/e* 308 (M^+), 307 (M^+ − 1, base), 194 (M^+ − 114), 104 (M^+ − 204), 91 ($PhN^{+\cdot}$), and 77 (Ph^+).

2-Benzyl-4-phenyl-3-thioxo-2,4-diaza-cis-bicyclo[3.3.0]*octan-7-one* (20; R = CH_2Ph).—The imine (19) (120 mg) in dry dimethyl sulphoxide (2.5 ml) containing triethylamine (0.3 ml) was heated at 60 °C for 10 min. The solution was cooled and diluted with water; the product was isolated by extraction with ethyl acetate and preparative t.l.c. of the resultant gum on silica. Development with chloroform gave the *thiourea* (20; R = CH_2Ph) as prisms (60 mg, 50%), m.p. 134—135 °C (from ether–chloroform) (Found: C, 70.85; H, 5.6; N, 8.55; S, 10.0. $C_{19}H_{17}N_2OS$ requires C, 70.8; H, 5.6; N, 8.7; S, 9.95%), δ($CDCl_3$) 2.50 (4 H, m, 6- and 8-CH_2), 4.30—4.60 (1 H, m, 1-H), 4.46 (1 H, d, J 15 Hz, *H*CHPh), 4.80—5.00 [1 H, m, 5-H, strongly roofing to signal from 1-H with common splitting (taken as the first-order coupling constant) of $J_{H1\text{-}H5}$ 8.2 Hz], 5.52 (1 H, d, J 15 Hz, $^-$HC*H*Ph), and 7.38 (10 H, m, ArH), $\nu_{max.}$ (KBr) 2 895, 1 743 (ketone C=O), 1 598, 1 498 (thioamide II), 1 470, 1 450, 1 395, 1 255 (thioamide I), 740, and 705 cm^{-1} (Found: M^+, 322.113 6. $C_{19}H_{17}N_2OS$ requires M, 322.1 140) *m/e*, 289 (M^+ − SH), 240 (M^+ − 82), 207 (M^+ − 115), 135 (M^+ − 187), 91 ($PhCH_2^+$), and 77 (Ph^+).

Monitoring by ^1H n.m.r. showed the conversion (19) ⟶ (20; R = CH_2Ph) to proceed cleanly. When the reaction was performed in chloroform solution, complete rearrangement required 80—100 h at room temperature.

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