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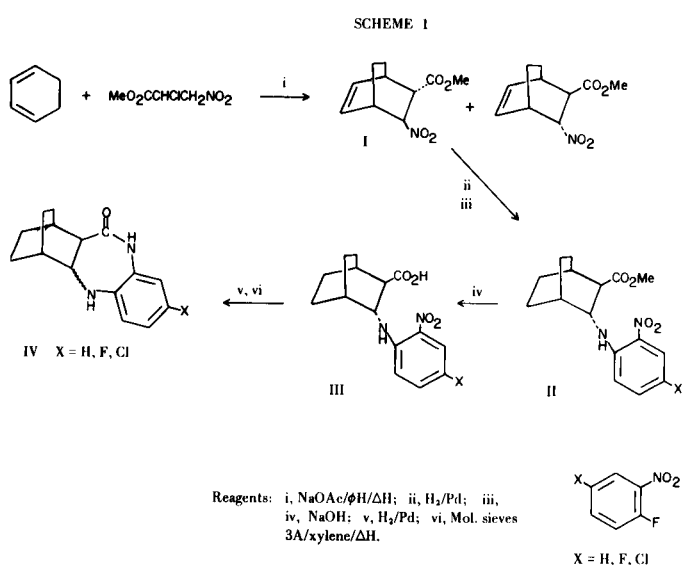
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The synthesis of the novel bicyclo[2.2.2]octanyl[1,4]benzodiazepinone ring system (IV) and its facile acid catalysed rearrangement to the corresponding bicyclo[2.2.2]oct-2-enylbenzimidazole system (IX) is described.

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Our interest in novel tricyclic compounds containing a 7-membered heterocyclic nucleus for their potential activities in the central nervous system (1) led us to synthesize the novel bicyclo[2.2.2]octanyl-1,4-benzodiazepinone IV. The route is outlined in Scheme I.

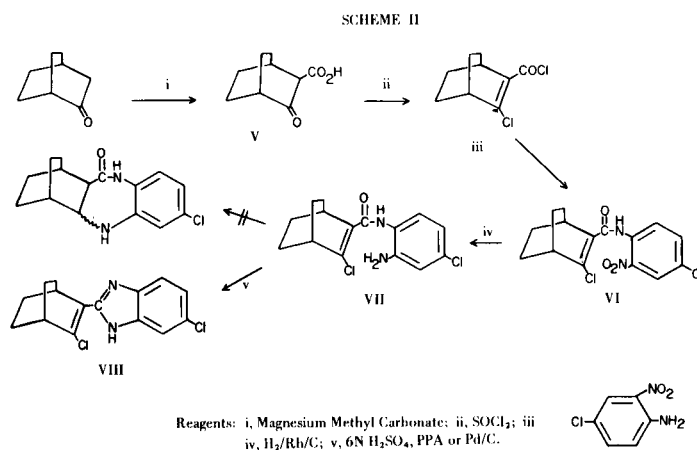


Cyclohexa-1,3-diene reacted with methyl 2-nitroacrylate, generated *in situ* from methyl 2-chloro-3-nitropropionate (2) and sodium acetate, in refluxing benzene. Under these conditions we found that cyclohexa-1,3-diene, usually a poor diene in the Diels-Alder reaction (3), formed the adducts as a 4.6:1 mixture of the *trans* isomers in excellent yield (83%). Catalytic reduction of the mixture I gave the corresponding *trans*-amine which was condensed with a variety of *o*-fluoronitrobenzenes to give II. Base hydrolysis of the ester yielded the *trans*-nitroacid III which on catalytic reduction gave the air sensitive diamine. Assignments of the *trans* stereochemistry of the above compounds I-III were based on the nmr coupling constants ( $J = 4-6.5$  Hz) of the two substituted bicyclooctane protons (see Experimental), and by correlation with known examples of *cis* and *trans* 2,3 disubstituted bicyclooctanes (7), where *cis* isomers have larger coupling constants ( $J = 6.7-10.5$  Hz). The best conditions found to cyclize this product directly to the desired benzodiazepinone IV was under neutral conditions by refluxing over molecular sieves (3A) in xylene.

*Trans*-stereochemistry in IV may not be assumed as equilibration to the less strained *cis*-isomer may have occurred under the thermal reaction conditions. The nmr spectrum of IV ( $X = H, J_{2,3} = 8$  Hz) was not definitive in this respect. The high coupling constant may indicate *cis* fusion, but unambiguous assignment is not possible as the magnetic properties and preferred conformation of this novel ring system are complex parameters.

An alternative route investigated is outlined in Scheme II.

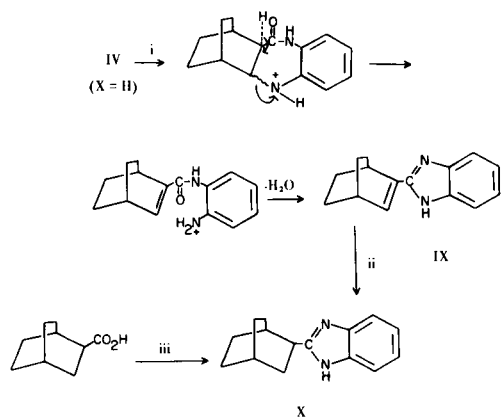
Bicyclo[2.2.2]octan-2-one (4) was smoothly carboxy-



lated with magnesium methyl carbonate (5). The  $\beta$ -keto acid V was treated with excess thionyl chloride followed by 4-chloro-2-nitroaniline to give the condensate VI. We were unable to obviate the facile formation of the vinyl chloride. Attempted catalytic reduction of VI over palladium carbon gave a multicomponent mixture (by tlc analysis). However rhodium on charcoal smoothly reduced the nitro group to the amine leaving the vinyl chloride group intact. Attempts to reduce the vinyl chloride VII under more vigorous conditions (Palladium carbon) followed by displacement to give the desired benzodiazepinone were unsuccessful. The vinyl benzimidazole VIII was the only product identified. Acid catalysis, (polyphosphoric acid and sulphuric acid) also effected ready formation of the benzimidazole.

The benzodiazepinone IV was found to rearrange readily to the benzimidazole IX under acidic conditions

(titanium tetrachloride, boron trifluoride etherate and *p*-toluenesulphonic acid). The mechanism of the facile rearrangement most likely involves protonation, or coordination to the Lewis acids, followed by proton loss from the bicyclic structure effecting ring opening and finally acid catalysed condensation.



Reagents: i,  $\text{TiCl}_4$ /anisole/*N*-methylpiperazine or  $\text{BF}_3$  etherate or *p*-toluenesulphonic acid/anisole/ $\Delta$ H; ii,  $\text{H}_2$ /Pd/C; iii, *o*-phenylenediamine/ $\Delta$ H.

The structure of the benzimidazole was proven by its characteristic uv spectrum and further supported by ir, nmr and mass spectral data (see Experimental). Also, catalytic reduction gave the saturated benzimidazole X which was independently synthesised by condensation of bicyclo[2.2.2]octane-2-carboxylic acid with *o*-phenylenediamine.

The products, and product ratios, of the rearrangement of benzo-1,4-diazepines and benzo-1,4-diazepinones to either benzimidazoles or benzimidazolones had been described in the literature as being highly sensitive to the structure of the reactant as well as to reaction conditions employed (6). In our hands, the novel bicyclo[2.2.2]-octanylbenzodiazepinones IV only gave the vinyl benzimidazoles IX as products.

## EXPERIMENTAL

Melting points were determined on a Kofler block under microscopic magnification and are not corrected. Nuclear magnetic resonance spectra were recorded on a Varian A-60A Instrument. Chemical shifts are given as  $\delta$  units, tetramethylsilane being used as internal standard. Ultra violet spectra were recorded on a Unicam S.P. 800 instrument. Solvents were removed in a Buchi rotary evaporator under water-pump vacuum. Microanalysis was by G. Maciak, Eli Lilly & Co., Indianapolis.

Endo- and exo-*trans*-2-carbomethoxy-3-nitrobicyclo[2.2.2]oct-5-ene (1).

Methyl 2-chloro-3-nitropropionate (2) (50.1 g., 0.30 mole), 1,3-cyclohexadiene (35 ml. of a 70% solution, 0.33 mole), benzene (30 ml.) and sodium acetate (35 g., 0.43 mole) were refluxed for 24 hours with rapid stirring. The mixture was filtered and the filtrate was evaporated *in vacuo* to give an oil which was distilled

to give an orange oil, yield 49.3 g., (83%), b.p. 100-104° at 0.2 mm; nmr (carbon tetrachloride):  $\delta_5 = 5.0$ ,  $J_{5,6} = 4$  Hz,  $\delta$  ( $\text{CH}_3$ ) = 3.74,  $\delta$  ( $\text{CH}_2$ ) = 3.67, ratio 4.6:1.

*trans*-3-Amino-2-carbomethoxybicyclo[2.2.2]octane.

Compound I (50 g., 0.23 mole) was dissolved in ethyl acetate (250 ml.) and hydrogenated under pressure (60 psi) in the presence of 10% palladium on charcoal (5 g.). After 24 hours the catalyst was filtered off and the filtrate dried (over anhydrous magnesium sulphate) then evaporated *in vacuo* to give an oil, yield 43 g. (100%), m.p. (as acetate salt) 119-120° (sublimes).

Anal. Calcd. for  $\text{C}_{12}\text{H}_{21}\text{NO}_4$ : C, 59.24; H, 8.70; N, 5.76; O, 26.30. Found: C, 58.99; H, 8.98; N, 5.58; O, 26.45; nmr (carbon tetrachloride):  $\delta_2 = 3.3$ ,  $J_{2,3} = 5.7$  Hz.

*trans*-2-Carbomethoxy-3-*N*-(2-nitrophenyl)aminobicyclo[2.2.2]octane (11).

The aminoester from above, (39 g., 0.21 mole), 2-fluoro-nitrobenzene (30 g., 0.21 mole) triethylamine (63 g., 0.62 mole) and xylene (500 ml.) were refluxed under nitrogen for 3 days. The solution was evaporated to give an oil which was dissolved in 5*N* hydrochloric acid and extracted with ether several times. The ether was washed with water, dried over magnesium sulphate and evaporated *in vacuo* to give an orange oil which solidified, yield 56 g., (86.4%), m.p. 85-86° (from methanol); nmr (deuteriochloroform):  $\delta_3 = 4.32$ ,  $J_{2,3} = 6.5$  Hz.

Anal. Calcd. for  $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_4$ : C, 63.14; H, 6.62; N, 9.21; O, 21.03. Found: C, 62.89; H, 6.89; N, 8.92; O, 21.03.

*trans*-3-*N*-(2-Nitrophenyl)aminobicyclo[2.2.2]octane-2-carboxylic Acid (III).

Sodium hydroxide (14 g., 0.35 mole) in water (50 ml.) was added to compound 11 (56 g., 0.18 mole) in ethanol (400 ml.) and stirred at 40° for 2 days. The solution was evaporated *in vacuo* to give an oil which, after adding water (200 ml.), was extracted several times with ether. The aqueous layer was acidified with 5*N* hydrochloric acid and extracted with ether. After drying the ether over magnesium sulphate the ether was evaporated *in vacuo* to give an orange solid, yield 36.3 g., (72%), m.p. 169-170° (from methanol); nmr (deuteriochloroform):  $\delta_3 = 4.28$ ,  $J_{2,3} = 6.5$  Hz.

Anal. Calcd. for  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_4$ : C, 62.05; H, 6.24; N, 9.65; O, 22.04; Found: C, 62.00; H, 6.14; N, 9.49; O, 21.80.

*trans*-3-*N*-(2-Aminophenyl)aminobicyclo[2.2.2]octane-2-carboxylic Acid.

Compound III (36 g., 0.125 mole) was hydrogenated under pressure (60 psi) in the presence of 5% palladium on charcoal (3.5 g.) in methanol (250 ml). After 1 day the catalyst was filtered off and the filtrate dried over magnesium sulphate then evaporated *in vacuo* to give a white solid, yield 28 g., (93%). The product rapidly turned to a purple colour and was used directly in the next experiment.

1,4-Ethano-1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo[*b,e*][1,4]-diazepin-11-one (IV).

The crude amino-acid from above (28 g., 0.11 mole), molecular sieves (28 g, type 3A powder supplied by B. D. H.) and xylene (600 ml.) were refluxed for 1 day with vigorous stirring. The sieves were filtered off and washed several times with boiling ethanol. The solution was evaporated *in vacuo* to give an off-white solid which was recrystallized from dioxane to give the product IV, yield 10.69 (40.7%) m.p. 259-265° (m.p. as HCl salt 245-247°).

Anal. Calcd. for  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}$ : C, 74.35; H, 7.49; N, 11.56; O, 6.60. Found: C, 74.57; H, 7.23; N, 11.30; O, 6.90.

Similarly prepared were:

*trans*-8-Chloro-1,4-ethano-1,2,3,4,4a,10,11,11a-octahydro-5H-dibenzob[e][1,4]diazepin-11-one, m.p. 214-216°.

*trans*-8-Fluoro-1,4-ethano-1,2,3,4,4a,10,11,11a-octahydro-5H-dibenzob[e][1,4]diazepin-11-one, m.p. 243-246°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>17</sub>FN<sub>2</sub>O: C, 69.20; H, 6.59; N, 10.76; O, 6.15. Found: C, 69.05; H, 6.48; N, 10.70; O, 6.45.

2-(Bicyclo[2.2.2]oct-2-en-2-yl)benzimidazole (IX).

Method A.

A mixture of *p*-toluene sulphonic acid (0.192 g., 0.001 mole) and compound IV (0.242 g., 0.001 mole) were refluxed in anisole (5 ml.) for 1 day. Saturated sodium bicarbonate solution (10 ml.) was added and the mixture extracted with methylene chloride. The organic solvents were combined then evaporated *in vacuo* to give a white solid (161 mg., 72%) which was recrystallised from ethanol to give product IX, yield 94 mg. (42%), m.p. 330° (sublimes);  $\lambda$  max 298.5 m $\mu$  ( $\epsilon$  = 18,505); 233 m $\mu$  ( $\epsilon$  = 10,094); methanol.

*Anal.* Calcd. for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.09; H, 7.18; N, 12.22.

Method B.

Titanium tetrachloride (189 mg, 1 mmole) in anisole (0.5 ml.) was added to a mixture of compound IV (242 mg., 1 mmole) and *N*-methylpiperazine (0.5 ml.) in anisole (1.5 ml.). The mixture was refluxed for 1 day then poured into water (10 ml.) and extracted several times with ether. The ether was washed with water, dried over magnesium sulphate and evaporated *in vacuo* to give a crude solid which was recrystallised from ethanol, yield 55 mg. (25%) m.p. 330° sublimes.

2-(Bicyclo[2.2.2]octan-2-yl)benzimidazole (X).

Method A.

Compound IX (21.2 mg.) was hydrogenated at atmospheric pressure in the presence of 5% palladium on charcoal (10 mg.) in ethyl acetate (5 ml.). After 1 day the catalyst was filtered off and the filtrate was evaporated *in vacuo* to give a white solid m.p. 275°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.92; H, 8.29; N, 12.30.

Method B.

Bicyclo[2.2.2]octane-2-carboxylic acid (9.2 g., 0.06 mole) and *o*-phenylenediamine (6.5 g., 0.06 mole) were refluxed 7 days to produce a black solid. This was dissolved in ethanol and heated with animal charcoal to give a colourless solution which, on cooling, deposited product X as white needles, yield, 8 g. (59.2%), m.p. 275-276° dec. (as the hydrochloride salt m.p. 245-248°). Mixed m.p. with product X obtained by method A 274-275.5° dec.

*Anal.* Calcd. for C<sub>15</sub>H<sub>19</sub>ClN<sub>2</sub>: C, 68.56; H, 7.29; N, 10.66; Cl, 13.49. Found: C, 68.26; H, 7.11; N, 10.53; Cl, 13.56.

2-Chlorobicyclo[2.2.2]oct-2-ene-3-carboxylic Acid Chloride.

The keto acid V (500 mg., 0.003 mole) was dissolved in dichloromethane (15 ml.) and an excess of thionyl chloride (redistilled 5 ml.) was added dropwise with stirring. The solution was stirred at room temperature overnight and then refluxed for 1 hour, leaving an orange solution. The excess thionyl chloride was removed by azeotroping with carbon tetrachloride leaving an oil which was distilled *in vacuo*, b.p. 112°, 0.8 mm. (530 mg.), 90% yield.

2-Chloro-3-(4-chloro-2-nitrophenyl)carboxamidobicyclo[2.2.2]-oct-2-ene (VI).

To a solution of 4-chloro-2-nitroaniline (8.71 g., 0.05 mole) and triethylamine (8 ml.) in dichloromethane (100 ml.), the acid chloride from above (11.5 g, 0.056 mole) was added dropwise with stirring. The solution was left overnight at room temperature and quenched by throwing onto ice-water. Basic material was washed out using 2*N* hydrochloric acid (2 X 30 ml.) and the organic extract washed with water (3 X 30 ml.), dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to give VI (12.8 g., 74%) as yellow needles m.p. 129.5-130.5°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O: C, 52.79; H, 4.11; N, 8.21; Cl, 20.22. Found: C, 53.00; H, 3.91; N, 8.14; Cl, 20.74.

2-Chloro-3-(2-amino-4-chlorophenyl)carboxamidobicyclo[2.2.2]-oct-2-ene (VII).

Compound VI (510 mg., 1.5mmoles) was hydrogenated at atmospheric pressure in ethyl acetate (20 ml.) using 5% Rhodium on charcoal as catalyst. The uptake of hydrogen was slow over 16 hours, the catalyst was filtered off and the solution reduced to give a yellow solid, VII (430 mg., 92%) m.p. 138-140°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>2</sub>O: C, 57.87; H, 5.14; N, 9.00; Cl, 22.82. Found: C, 58.11; H, 5.10; N, 9.00; Cl, 22.66.

2-(2-Chlorobicyclo[2.2.2]oct-2-enyl)-6-chlorobenzimidazole (VIII).

To VII (3.00 g., 0.009 mole) was added polyphosphoric acid (20 g.) and the mixture heated at 120° under nitrogen. The reaction was complete after 1 hour. After basification of the solution with 2*N* sodium hydroxide, it was extracted with ethyl acetate (3 X 30 ml.), the organic extracts washed with water, dried over magnesium sulphate, filtered, and the solvent removed *in vacuo* to give a pale yellow solid VIII. The free base was recrystallised from ethanol-water, dried, and the hydrochloride salt prepared in ethereal hydrochloric acid and ethanol. m.p. 204-208° (60% yield).

*Anal.* Calcd. for C<sub>15</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>: C, 54.64; H, 4.58; N, 8.50; Cl, 32.26. Found: C, 54.74; H, 4.58; N, 8.40; Cl, 32.56.

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