Synthetic Studies in the Piperidine Alkaloid Field. Part 1. The 2-Azabicyclo[2.2.2]octan-5-one Approach to Prosopine

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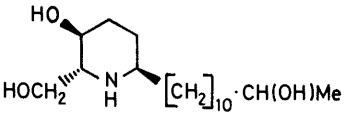
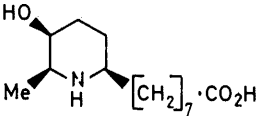
An approach to the synthesis of the *Prosopis* alkaloids utilising the Baeyer–Villiger reaction of methyl 2-benzyloxycarbonyl-5-oxo-2-azabicyclo[2.2.2]octane-3-carboxylate (6; R = CO_2Me) is described. The boron trifluoride–ether catalysed cycloaddition to cyclohexadiene of methyl 2-(benzyloxycarbonylimino)acetate (8; R = CO_2 Me), generated *in situ* from methyl *N*-benzyloxycarbonyl-2-methoxyglycinate, gave a mixture of bicyclic adducts (9) and (10). Oxymercuriation of (9) gave the alcohol (11; R = H), and subsequent oxidation gave the ketone (6; R = CO_2Me). Baeyer–Villiger oxidations of (6; R = CO_2Me or $CH_2{\cdot}O_2CPh$) gave the lactones (14) and (15), respectively, and none of the desired lactone (7).

THE alkaloid prosopine was first isolated from *Prosopis africana* (African mimosa),[1] and its structure was shown to be (1).[2] It is closely related to carpamic acid (2), derived from carpaine (3) (occurring in *Carica papaya*),[3] whose pharmacological properties are well documented.[4] Prosopine itself acts as a local anaesthetic, as well as exhibiting antibiotic activity.[5]



(1)



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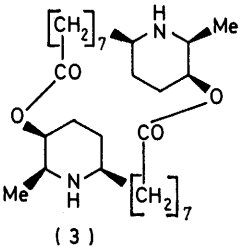
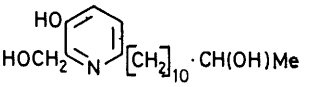


(3)

The synthesis of carpamic acid and some analogues has been reported by Brown,[6] and Fodor has described the synthesis of dehydroprosopine (4), and its catalytic reduction to all-*cis*-prosopine (5).[7] This compound could in principle be converted into prosopine by epimerisation at C-2 *via* the C-2 aldehyde.[8]

In our approach to the synthesis of prosopine we envisaged the preparation of the bicyclic lactone (7; R = $CH_2{\cdot}OH$) which has the correct relative configuration at each of the three chiral centres of the piperidine ring and which should readily be convertible into prosopine by appropriate chain extension at the carboxylic carbon atom. Such a lactone should be available from the Bayer–Villiger reaction of the 2-azabicyclo[2.2.2]-octan-5-one (6; R = $CH_2{\cdot}OH$).



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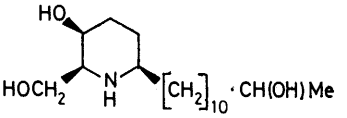
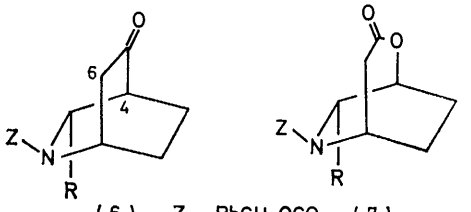


(5)

The azabicyclo[2.2.2]octane skeleton present in (6) is accessible *via* boron trifluoride catalysed cycloaddition of



(6) Z = $PhCH_2OCO$- (7)

an appropriately substituted iminoacetate (8; R = CO_2Me) to cyclohexadiene.[9] The iminoacetate was generated by the action of boron trifluoride–ether in benzene on *N*-benzyloxycarbonyl-2-methoxyglycinate,[10] or the corresponding methyl glyoxylate bis(benzylcarbamate), and was used *in situ* with cyclohexadiene. This resulted in a 35% yield of a 4 : 1 mixture of the *exo*- (9) and the *endo*-adduct (10), separated by column chromatography; the individual isomers could be characterised by ^1H n.m.r.

[1] G. Ratle, X. Monseur, B. C. Das, J. Yassi, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. chim. France*, 1966, 2945.

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[3] M. Spiteller-Friedmann and G. Spiteller, *Monatsh.*, 1964, **95**, 1234.

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[5] P. Bourrinet and A. Quevauviller, *Compt. rend. Soc. biol.*, 1968, **162**, 1138 (*Chem. Abs.*, 1969, **70**, 95,233k; *Ann. pharm. franç.*, 1968, **26**, 787 (*Chem. Abs.*, 1969, **71**, 29,012g); Omnium Chimique S.A., Fr. P. 1,524,395, 1968 (*Chem. Abs.*, 1969, **71**, 91,733w).

[6] E. Brown, R. Dhal, and J. Lavoue, *Tetrahedron Letters*, 1971, 1055; E. Brown and R. Dhal, *Bull. Soc. chim. France*, 1972, 4292; E. Brown, R. Dhal, and P. F. Casals, *Tetrahedron*, 1972, **28**, 5607; E. Brown and A. Bourgouin, *Chem. Letters*, 1974, 109; *Tetrahedron*, 1975, **31**, 1047; E. Brown and R. Dhal, *Tetrahedron Letters*, 1974, 1029; *J.C.S. Perkin I*, 1976, 2190; E. Brown and A. Bonte, *Tetrahedron Letters*, 1975, 2881.

[7] G. Fodor, J.-P. Fumeaux, and V. Sankaran, *Synthesis*, 1972, 464.

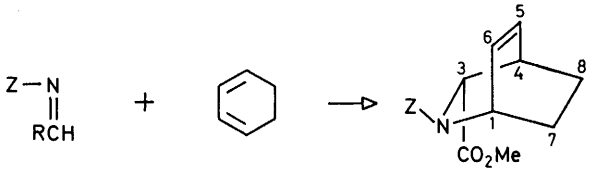
[8] G. Fodor, V. Sankaran, R. Sprecher, and A. Arakali, Abstracts of Ninth I.U.P.A.C. Symposium on the Chemistry of Natural Products, Ottawa, 1974, p. 17A; G. Fodor, personal communication.

[9] G. Krow, R. Rodebaugh, R. Carmosin, W. Figures, H. Pannella, G. DeVicaris, and M. Grippi, *J. Amer. Chem. Soc.*, 1973, **95**, 5273.

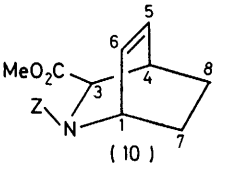
[10] U. Zoller and D. Ben-Ishai, *Tetrahedron*, 1975, **31**, 863.

spectroscopy in [$^2H_8$]toluene at 100 °C, at which temperature rotations about the C–N bond are relatively fast.[11] Attempts to increase the yield of the adducts (9) and (10) using a variety of conditions were unsuccessful. The competing acid catalysed side reactions of cyclohexadiene apparently set an upper limit of 30—40% yield on this reaction, which can only be exceeded if the iminoacetate can be isolated. Thus the isolable iminoacetate (8; R = CCl_3, Z = CO_2Et) gives high yields of cyclohexadiene adducts.[9]

The major difference between the *exo*- (9) and the *endo*-adduct (10) is the presence, in the n.m.r. spectrum, of W-plan coupling (J 1.5 Hz) between H-3 (δ 3.94), also vicinally coupled (J 3 Hz) to H-4, and one of the 8-protons on the methylene bridge of (9), whereas H-3 in (10) gives a simple doublet at δ 4.21, showing a 2.5 Hz vicinal coupling to H-4.[9,12] These assignments were confirmed by extensive double irradiation studies.

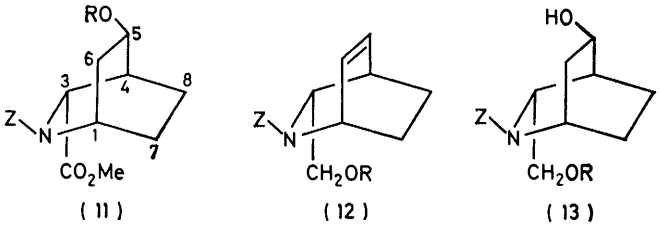


(8) (9)



(10)

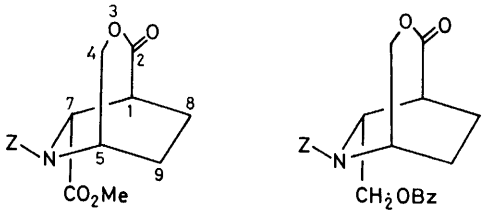
Various methods of hydrating the double bond of a 2-azabicyclo[2.2.2]oct-5-ene have been reported. Hydroboration [13] or epoxidation and subsequent reduction by hydride [14] are non-regioselective. A more attractive approach is oxymercuriation with mercury(II) acetate [15] or nitrate,[16] in which the carbamate carbonyl group may participate in delivering the mercury regioselectively to the double bond. Thus oxymercuriation of the *exo*-ester (9) with mercury(II) nitrate followed by reduction with borohydride gave the alcohol (11; R = H), which was converted into both the methoxymethyl acetal (11; R = CH_2·OMe) by treatment with phosphorus pentaoxide in dimethoxymethane,[17] and the corresponding ketone (6; R = CO_2Me) by oxidation with pyridinium chlorochromate.[18] The location of the oxygen substituent at C-5 in the oxymercuriation product was established by the n.m.r. spectrum of the acetal (11; R = CH_2·OMe), in which the H-5 signal occurs at δ 3.66, vicinally coupled (J 3.5 Hz) to H-4 (δ 2.29), which is in turn coupled (J 2.5 Hz) to H-3. The large (0.92 p.p.m.) downfield shift in the resonance due to H-3 of the acetal (11; R = CH_2·OMe) as compared with H-3 of the adduct (9) suggests a *quasi*-1,3-diaxial relationship between H-3 and the C-5 substituent in (11), which is consistent with overall *cis*-addition to the double bond of (9) during the oxymercuriation.[19]



(11) (12) (13)

The oxo-benzoate (6; R = CH_2·O_2CPh) was prepared in two ways. Selective reduction of the ester (9) by hydride gave the alcohol (12; R = H), which was benzoylated. Oxymercuriation of the benzoate (12; R = PhCO) gave the benzoate alcohol (13; R = PhCO). The same alcohol was obtained by selective hydride reduction of the hydroxy-ester (11; R = H) to give the diol (13; R = H) and subsequent benzoylation of the primary alcohol. The benzoate alcohol (13; R = PhCO) was oxidised to the oxo-benzoate (6; R = CH_2·O_2CPh) with pyridinium chlorochromate.

Bayer–Villiger reaction of the ketone (6; R = CO_2Me) with *m*-chloroperbenzoic acid in methylene chloride containing sodium hydrogen carbonate buffer gave the lactone (14) in 40% yield. This lactone was clearly characterised by the presence in the ^1H n.m.r. spectrum of an AB quartet at δ 4.06 and 3.65 due to the protons at C-4. The H-1 resonance occurs at δ 3.23. No other lactonic products such as (7) or hydroxy-acid products could be detected.



(14) (15)

The observed lactone (14) must have arisen from migration to oxygen of the methylene carbon atom in the ketone (6) rather than the expected migration of the bridgehead carbon atom. By contrast, Bayer–Villiger oxidation of bicyclo[2.2.2]octanone gives a good yield of the lactone derived from the migration of the bridge-

[11] W. E. Stewart and J. H. Siddall, *Chem. Rev.*, 1970, **70**, 517; E. W. B. de Leer and J. M. van der Toorn, *Rec. Trav. chim.*, 1975, **94**, 119.
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[13] J. I. DeGraw and J. G. Kennedy, *J. Heterocyclic Chem.*, 1967, **4**, 251.
[14] M. P. Cava, C. K. Wilkins, D. R. Dalton, and K. Bessho, *J. Org. Chem.*, 1965, **30**, 3772.
[15] G. Krow, R. Rodebaugh, M. Grippi, and R. Carmosin, *Synth. Comm.*, 1972, **2**, 211.
[16] G. R. Krow and D. Min Fan, *J. Org. Chem.*, 1974, **39**, 2674.
[17] K. Fuji, S. Nakano, and E. Fujita, *Synthesis*, 1975, 276.
[18] E. J. Corey and J. W. Suggs, *Tetrahedron Letters*, 1975, 2647.
[19] R. D. Bach and R. F. Richter, *J. Amer. Chem. Soc.*, 1972, **94**, 4747.

head carbon atom.[20] The anomalous behaviour of the ketone (6; R = CO_2Me) has some parallels in the camphor series, which have been rationalised in terms of stereoelectronic factors operating in the rate-determining breakdown of the tetrahedral intermediate,[20] but similar arguments do not seem obviously applicable in this case. We supposed that the electron-deficient methoxycarbonyl group of (6; R = CO_2Me) reduced the tendency of C-4 to migrate, and therefore examined the Bayer–Villiger reaction of the oxo-benzoate (6; R = CH_2·O_2CPh). However this reaction gave the undesired lactone (15) in 45% yield. The use of alternative oxidants such as hydrogen peroxide in glacial acetic acid at 50 °C,[21] peracetic acid in acetic acid and sulphuric acid at 20 °C,[20] $K_2S_2O_8$ in 50% sulphuric acid,[22] 90% hydrogen peroxide in methylene chloride containing acetic anhydride and 100% sulphuric acid at 2 °C,[23] sodium acetate buffered peracetic acid in acetic acid at 20 °C,[20] and hydrogen peroxide in acetate buffered acetic acid at 0 °C was investigated.[24] No improved yield of the lactone (14) was obtained, and in those cases where the yield was lower there was no evidence of formation of the alternative lactone (7; R = CO_2Me). Clearly, alternative methods will have to be devised to induce the reaction to follow the desired course.

EXPERIMENTAL

M.p.s were determined with a Köfler hot-stage apparatus. ^{1}H N.m.r. spectra were recorded at 100 MHz with a Varian HA-100 or XL-100 spectrometer, with tetramethylsilane as reference. I.r. spectra were recorded for 2.5% (w/v) solutions with a Perkin–Elmer 257 spectrometer, and electronic spectra with a Unicam SP 1800 spectrometer. Mass spectra were recorded with an A.E.I. MS 30 (low resolution) or MS 902 (high resolution) instrument. Microanalyses were carried out by Mr. D. Flory and his staff at the University Chemical Laboratory. Preparative layer chromatography was carried out on 20 × 20 cm glass plates coated to a thickness of 1 mm with Merck Kieselgel PF_{254}. The silica gel for column chromatography was Merck Kieselgel 60 (70—230 mesh).

Methyl 2-Benzyloxycarbonyl-2-azabicyclo[2.2.2]*oct-5-ene-3-carboxylate* (9) *and* (10).—Boron trifluoride–ether (4 ml, 0.032 mol) was added to a stirred solution of methyl *N*-benzyloxycarbonyl-2-methoxyglycinate [10] (20.24 g, 0.08 mol) in dry benzene (60 ml) under nitrogen. The mixture was heated to reflux, and cyclohexa-1,3-diene [25] (8 ml, 0.085 mol) in dry benzene (16 ml) was added dropwise over 3 min. The mixture was heated under reflux for 1.5 h, then cooled and poured on to saturated aqueous sodium hydrogen carbonate (100 ml). The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate (100 ml), dried ($MgSO_4$), and concentrated to give a yellow oil. The oil was chromatographed on a silica column (600 g). Elution with petroleum (b.p. 40—60 °C)–ether (2 : 1) gave the exo-*adduct* (9) as an oil (8.5 g, 28%); δ([$^2H_8$]toluene, 100 °C) 7.16 (5 H, m, aromatic), 6.17 (2 H, m, H-5, -6), 5.15 and 4.95 (2 H, AB_q, *J* 13 Hz, CH_2Ph), 4.84 (1 H, m, H-1), 3.94 (1 H, dd, $J_{3,4}$ 3, $J_{3,8}$ 8 Hz, H-3), 3.44 (3 H, s, OMe), 2.68 (1 H, m, H-4), and 2.25—0.95 (4 H, m, H_2-7, -8); $\nu_{max.}$ ($CHCl_3$) 1 750s (ester CO) and 1 695s cm^{-1} (carbamate CO); *m/e* 301 (M^+, 5%), 242 (95), 195 (40), 170 (100), 150 (29), and 107 (100) (Found: C, 68.3; H, 6.6; N, 4.45%; M^+, 301.131 4. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.3; N, 4.6%; *M*, 301.131 3). The compound was homogenous in several different t.l.c. systems. Further elution with the same solvent gave the endo-*adduct* (10) (2.1 g, 7%) as crystals, m.p. 73.5—75.5 °C; δ([$^2H_8$]toluene; 100 °C) 7.2 (5 H, m, aromatic), 6.16 (1 H, ddd, $J_{5,6}$ 8, $J_{5,4}$ 7, $J_{5,1}$ 1 Hz, H-5), 5.93 (1 H, ddd, $J_{6,5}$ 8, $J_{6,1}$ 6, $J_{6,4}$ 2 Hz, H-6), 5.2 and 5.0 (2 H, AB_q, *J* 13 Hz, CH_2Ph), 4.84 (1 H, m, H-1), 4.21 (1 H, d, $J_{3,4}$ 2.5 Hz, H-3), 3.37 (3 H, s, OMe), 2.83 (1 H, m, H-4), and 1.8—1.0 (4 H, m, H_2-7, -8); $\nu_{max.}$ ($CHCl_3$) 1 760s (ester CO) and 1 690s cm^{-1} (carbamate CO); *m/e* 301 (M^+, 6%), 242 (83), 195 (6), 170 (100), and 107 (17) (Found: C, 68.1; H, 6.5; N, 4.45. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.3; N, 4.6%). The overall yield in the cycloaddition reaction could not be improved by varying the solvent (CCl_4, $CHCl_3$, CH_2Cl_2), catalyst amount (10—100 mol% BF_3,Et_2O), and type (CF_3CO_2H), reaction time (15 min to 2 h), and rate of addition of diene.

Methyl 2-Benzyloxycarbonyl-5-hydroxy-2-azabicyclo[2.2.2]*octane-3-carboxylate* (11; R = H).—A solution of the *exo*-ester (9) (2 g, 6.65 mmol) and mercury(II) nitrate monohydrate (2.3 g, 6.7 mmol) in 50% aqueous tetrahydrofuran (THF) (14 ml) was stirred at 20 °C for 3 days.[16] Aqueous 3M-NaOH (7 ml) was added, and then a solution of sodium borohydride (0.5M in $NaBH_4$) in aqueous 3M-NaOH (7 ml). The solution was saturated with NaCl, and the organic layer separated. The aqueous layer was extracted with ether (25 ml), and the combined organic layers were dried ($MgSO_4$) and concentrated to give the crude *alcohol* (11; R = H) (1.8 g, 88%), which was used without further purification.

Methyl 2-Benzyloxycarbonyl-5-methoxymethoxy-2-azabicyclo[2.2.2]*octane-3-carboxylate* (11; R = CH_2·OMe).—A solution of the alcohol (11; R = H) (368 mg, 1.12 mmol) and dimethoxymethane (8 ml) in dry chloroform (8 ml) containing phosphorus pentaoxide (4 g) was stirred at room temperature for 1/2 h.[17] The mixture was poured on to saturated sodium carbonate solution (150 ml) at 0 °C, and the resulting mixture was extracted with ether (2 × 100 ml). The combined organic layers were washed with saturated sodium chloride solution (50 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give an oil (0.4 g, 95%), which was further purified by preparative layer chromatography. Development in ether–petroleum (b.p. 40—60 °C) (2 : 1) gave the *acetal* (11; R = CH_2·OMe) as an oil; δ([$^2H_8$]toluene; 100 °C) 4.86 (1 H, d, $J_{3,4}$ 2.5 Hz, H-3), 4.18 (1 H, m, H-1), 3.66 (1 H, dt, $J_{5,4}$ 3.5, $J_{5,6}$ 8.5, $J_{5,6'}$ 3.5 Hz, H-5), and 2.29 (1 H, m, H-4); $\nu_{max.}$ ($CHCl_3$) 1 745m and 1 690s cm^{-1}; *m/e* 363 (M^+, 10%), 304 (30), 260 (30), 228 (33), 200 (45), and 172 (100) (Found: M^+, 363.171 2. $C_{19}H_{25}NO_6$ requires *M*, 363.174 7), judged pure by t.l.c. analysis in several different systems.

Methyl 2-Benzyloxycarbonyl-5-oxo-2-azabicyclo[2.2.2]*octane-3-carboxylate* (6; R = CO_2Me).—The alcohol (11; R = H) (0.8 g, 2.56 mmol) in dry methylene chloride (2.5 ml) was added to a stirred mixture of pyridinium chlorochromate [18] (0.822 g, 3.84 mmol) and dry methylene chloride

[20] J. Meinwald and E. Frauenglass, *J. Amer. Chem. Soc.*, 1960, **82**, 5235.
[21] G. Mehta and P. N. Pandey, *Synthesis*, 1975, 404.
[22] N. C. Deno, W. E. Billups, K. E. Kramer, and R. R. Lastormirsky, *J. Org. Chem.*, 1970, **35**, 3080.
[23] J. H. Markgraf and S. J. Basta, *Synth. Comm.*, 1972, **2**, 139.
[24] P. A. Grieco, *J. Org. Chem.*, 1972, **37**, 2363.
[25] J. P. Schaefer and L. Endres, *Org. Synth.*, Coll. Vol. V, 1973, p. 285.

(5 ml). After stirring at room temperature (1 h), the mixture was diluted with ether (30 ml), and the resulting solid was filtered off and washed once with ether (30 ml). The combined filtrates were concentrated under reduced pressure and the resulting orange oil was purified by layer chromatography. Development in ether followed by elution gave the *ketone* (6; R = CO_2Me) [0.6 g, 70% from the ester (9)] as an oil; δ([$^2H_8$]toluene; 100 °C) 4.50 (1 H, m, H-1), 4.46 (1 H, d, $J_{3,4}$ 2.5 Hz, H-3), and 2.56 (1 H, m, H-4); $\nu_{max.}$ ($CHCl_3$) 1 735s (ester and ketone CO) and 1 700s cm^{-1} (carbamate CO); *m/e* 317 (M^+, 4%), 258 (81), 214 (42), 172 (50), and 108 (100) (Found: C, 64.1; H, 6.0; N, 4.2. $C_{17}H_{19}NO_5$ requires C, 64.4; H, 6.0; N, 4.4%).

2-Benzyloxycarbonyl-2-azabicyclo[2.2.2]*oct-5-en-3-ylmethanol* (12; R = H).—A solution of the ester (9) (1.47 g, 4.9 mmol) in anhydrous ether (5 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.102 g, 2.7 mmol) in anhydrous ether (50 ml) at −78 °C under nitrogen. The mixture was stirred for 3 h, during which time the temperature rose to 25 °C. Sodium hydroxide solution (0.5 ml; 1.25M) was added, and the resulting mixture was dried ($MgSO_4$) and evaporated to leave an oil, which was purified by chromatography on a silica column. Elution with ether–petroleum (b.p. 40—60 °C) (1 : 1) gave first some ester (9) (0.39 g), and then the *alcohol* (12; R = H) (0.64 g, 65% based on starting material consumed) as an oil; δ ($CDCl_3$) 4.72 (1 H, m, H-1), 3.90 (1 H, dd, *J* 6, 10 Hz, CH_AH_BOH), 3.65 (1 H, dd, *J* 4, 10 Hz, CH_AH_BOH), 3.40 (1 H, ddd, *J* 6, 4, 1 Hz, H-3), and 2.79 (1 H, m, H-4); $\nu_{max.}$ ($CHCl_3$) 3 400m (OH) and 1 670s cm^{-1} (carbamate CO); *m/e* 273 (M^+, 2%), 242 (97), 170 (100), 137 (16), 108 (56), and 107 (47) (Found: M^+, 273.137 9. $C_{16}H_{19}NO_3$ requires *M*, 273.136 4), judged pure by t.l.c. analysis in several solvent systems.

2-Benzyloxycarbonyl-2-azabicyclo[2.2.2]*oct-5-en-3-ylmethyl Benzoate* (12; R = Bz).—Benzoyl chloride (0.21 ml, 177 mmol) was added to a stirred solution of the alcohol (12; R = H) (0.32 g, 1.17 mmol) in dry pyridine (15 ml). After stirring (0.5 h), the mixture was poured onto a mixture of M-HCl (20 ml) and ether (20 ml) at 0 °C. The ether layer was separated and washed with M-HCl (4 × 20 ml); the washings were then combined and extracted with ether (20 ml). The combined organic extracts were washed with saturated aqueous sodium chloride (20 ml), dried ($MgSO_4$), and concentrated to give a solid. Recrystallisation from petroleum (b.p. 60—80 °C) gave the *benzoate* (12; R = Bz) (0.44 g, 99%) as needles, m.p. 84—86 °C; δ ($CDCl_3$) 5.47 (2 H, m, H-5, -6), 4.79 (1 H, dd, *J* 5, 10 Hz, CH_AH_B-OBz), 4.78 (1 H, m, H-1), 4.29 (1 H, t, *J* 10, 10 Hz, CH_AH_B-OBz), 3.67 (1 H, m, H-3), and 2.88 (1 H, m, H-4); $\nu_{max.}$ ($CHCl_3$) 1 715s (ester CO) and 1 695s cm^{-1} (carbamate CO); *m/e* 377 (M^+, 0.2%), 255 (6), 242 (23), 183 (20), 170 (85), 131 (12), and 105 (100) (Found: C, 73.6; H, 6.25; N, 3.65. $C_{23}H_{23}NO_4$ requires C, 73.3; H, 6.1; N, 3.7%).

2-Benzyloxycarbonyl-5-oxo-2-azabicyclo[2.2.2]*octan-3-ylmethyl Benzoate* (6; R = CH_2OBz).—The benzoate (12; R = Bz) (0.125 g, 0.32 mmol) was oxymercuriated with mercury(II) nitrate (0.122 g, 0.32 mmol) in 50% aqueous THF (0.7 ml). Work-up as described previously using $NaBH_4$ (0.5M) in 3M-NaOH (0.35 ml) gave the crude *alcohol* (13; R = Bz), which was oxidised without further purification using pyridinium chlorochromate (0.1 g, 0.47 mmol) to give an oily product. This was purified by layer chromatography. Elution with 1 : 1 ether–petroleum (b.p. 40—60 °C) gave the *oxo-benzoate* (6; R = CH_2OBz) as an oil; δ ($CDCl_3$) 4.7—4.3 (4 H, m, H-1, -3, and CH_2OBz), and 2.73 (1 H, m, H-4); $\nu_{max.}$ ($CHCl_3$) 1 740—1 690s cm^{-1}; *m/e* 393 (M^+, 1%), 271 (51), 258 (15), 214 (27), 172 (16), 124 (16), 122 (15), and 105 (100) (Found: M^+, 393.156 0. $C_{23}H_{23}NO_5$ requires *M*, 393.157 6), judged pure by t.l.c. analysis in several solvent systems.

2-Benzyloxycarbonyl-3-hydroxymethyl-2-azabicyclo[2.2.2]*octan-5-ol* (13; R = H).—The hydroxy-ester (11; R = H) (1.4 g, 4.4 mmol) was reduced with lithium aluminium hydride (0.14 g, 3.7 mmol) in ether at −78 °C as described for the ester (9). After the usual work-up and column chromatography on silica (50 g), some starting material (11; R = H) (0.6 g) and then the *diol* (13; R = H) (0.47 g, 64% based on starting material consumed) were eluted with chloroform–methanol (30 : 1), the latter as an oil; δ ($CDCl_3$) 4.15—3.4 (7 H, m, H-1, -3, -5, CH_2OH, and OH), and 2.08 (1 H, m, H-4); $\nu_{max.}$ ($CHCl_3$) 3 600w (OH), 3 400m (OH), and 1 670s cm^{-1} (carbamate CO); *m/e* 291 (M^+, 0.4%), 260 (64), 216 (74), and 172 (100) (Found: M^+, 291.149 1. $C_{16}H_{21}NO_4$ requires *M*, 291.147 0), judged pure by t.l.c. analysis in several solvent systems.

Preparation of the Oxo-benzoate (6; R = CH_2OBz) *from the Diol* (13; R = H).—The diol (13; R = H) (95 mg, 0.36 mmol) was benzoylated with benzoyl chloride (0.038 ml, 0.36 mmol) in dry pyridine (2 ml) as for the alcohol (12; R = H). After the usual work-up the crude product was oxidised with pyridinium chlorochromate (130 mg, 0.6 mmol) in methylene chloride (1 ml) as for the oxidation of the alcohol (11; R = H). The usual work-up and layer chromatography gave the purified oxo-benzoate (6; R = CH_2OBz) (45 mg, 35%), identical with that prepared by oxymercuriation of the benzoate (12; R = Bz) and subsequent oxidation.

Baeyer–Villiger Oxidation of the Ketone (6; R = CO_2Me).—*m*-Chloroperbenzoic acid (85% by titration; 0.476 g, 2.34 mmol) and sodium hydrogen carbonate (0.232 g, 2.75 mmol) were added to a stirred solution of the ketone (6; R = CO_2Me) in methylene chloride. The mixture was stirred at room temperature (3 days), filtered, and evaporated. The resulting oil was purified by layer chromatography. Development and elution with ether gave *methyl-6-benzyloxycarbonyl-2-oxo-3-oxa-6-azabicyclo*[3.2.2]*nonan-7-carboxylate* (14) (0.164 g, 40%) as an oil; δ([$^2H_8$]toluene; 100 °C) 7.16 (5 H, m, aromatic), 5.15 and 4.9 (2 H, ABq, *J* 12 Hz, CH_2Ph), 4.67 (1 H, d, $J_{7,1}$ 2.5 Hz, H-7), 4.37 (1 H, m, H-5), 4.06 (1 H, ddd, $J_{4n,4x}$ 12, $J_{4n,5}$ 4, $J_{4n,9}$ 1.5 Hz, H-4 *endo* to N-bridge), 3.65 (1 H, dd, $J_{4x,4n}$ 12, $J_{4x,5}$ 1.5 Hz, H-4 *exo* to N-bridge), 3.35 (3 H, s, OMe), 3.23 (1 H, m, H-1), and 2.2—1.2 (4 H, m, H_2-8, -9); $\nu_{max.}$ ($CHCl_3$) 1 760—1 680s cm^{-1}; *m/e* 333 (M^+, 32%), 274 (100), 258 (32), 230 (52), 198 (40), and 108 (30) (Found: M^+, 333.121 4. $C_{17}H_{19}NO_6$ requires *M*, 333.121 1), judged pure by t.l.c. analysis in various solvent systems.

Bayer–Villiger Oxidation of the Ketone (6; R = CH_2OBz).—*m*-Chloroperbenzoic acid (85%; 19 mg, 0.093 mmol) and sodium hydrogen carbonate (9 mg, 0.11 mmol) were added to a stirred solution of the ketone (6; R = CH_2OBz) (26 mg, 0.066 mmol) in methylene chloride (15 ml). The mixture was stirred at room temperature (3 days), filtered, and evaporated. Layer chromatography of the residual oil and elution with ether gave *6-benzyloxycarbonyl-2-oxo-3-oxa-6-azabicyclo*[3.2.2]*nonan-7-ylmethyl benzoate* (15) (12 mg, 45%) as an oil; δ ($CDCl_3$) 4.80 (1 H, m, H-5), 4.7—4.2 (5 H, m, H_2-4, H-7, and CH_2OBz), and 3.36 (1 H, m, H-1); $\nu_{max.}$ ($CHCl_3$) 1 750—1 680s cm^{-1}; *m/e*

409 (M^+, 9%), 287 (10), 274 (12), 230 (52), 196 (72), and 105 (100) (Found: M^+, 409.1542. $C_{23}H_{23}NO_6$ requires M, 409.152 4), judged pure by t.l.c. analysis in several solvent systems.

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