Synthesis of *N*-Ethoxycarbonyl-7-azabicyclo[4.2.1]nonane and *N*-Ethoxycarbonyl-9-azabicyclo[4.2.1]nonane (1)

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The synthesis of *N*-ethoxycarbonyl-7-azabicyclo[4.2.1]nonane and *N*-ethoxycarbonyl-9-azabicyclo[4.2.1]nonane, starting from bicyclo[5.1.0]octan-2-one, is described. The key step is the cyclopropyl ring fission by pyridinium chloride.

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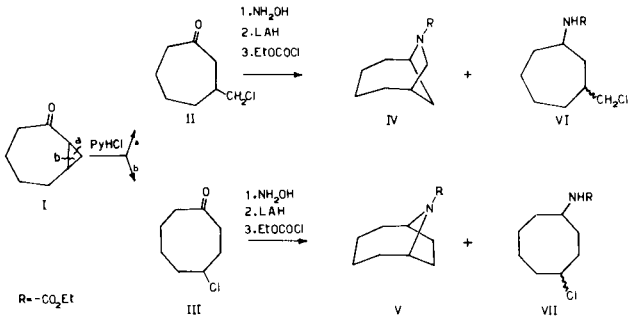
Several ring opening reactions involving mono- or diactivated cyclopropyl rings have recently been established (2a-d). Most of these reactions afforded 1,4-difunctionalised skeletons which may be applied in further synthetic transformations.

We also reported a mild method for the cyclopropane ring opening of α-cyclopropyl ketones by means of pyridinium chloride (3a,b). The γ-chloroketones so obtained may be converted by oximation and lithium aluminum hydride reduction to azabicycloalkanes containing a five membered nitrogen ring. In this way, formally in three steps, α,β-unsaturated ketones may produce azabicycloalkanes.

We wish to report here a typical example of the synthetic utility of such a ring opening reaction where both types of ring fission occur (a and b) giving derivatives of 7-azabicyclo[4.2.1]nonane and of 9-azabicyclo[4.2.1]nonane.



A mixture of the two chloroketones (4) II and III resulting from the pyridinium chloride treatment (acetonitrile, reflux, 42 hours) of bicyclo[5.1.0]octan-2-one (I) (5) was converted to a mixture of oximes. After lithium aluminum hydride reduction followed by treatment with ethyl chlorocarbonate, *N*-ethoxycarbonyl-7-azabicyclo-[4.2.1]nonane (IV) (10%) and *N*-ethoxycarbonyl-9-azabicyclo[4.2.1]nonane (V) (19%) were produced, together with the chlorourethanes VI (52%) and VII (19%), resulting from the corresponding amines. The four products showed increasing gc retention times in the order V, IV, VI, and VII and have been isolated by preparative gc. Structures were assigned on the basis of analytical and spectral data (ir, nmr, and ms).

The identity of IV, V and VII was confirmed by the independent synthesis of IV *via* catalytic reduction of the known *N*-ethoxycarbonyl-7-azabicyclo[4.2.1]nona-2,4-diene (6) and by repeating the usual sequence of oximation-reduction on an authentic sample of 4-chlorocyclooctanone (7).

EXPERIMENTAL

Gc analyses were performed on a Perkin-Elmer F 11 gas chromatograph equipped with a column of 2% OV 17 (2 m × 2 mm) or on a Carlo Erba Fractovap GI gas chromatograph equipped with a capillary column of 5% Apiezon "L"; preparative gc was performed on a Carlo Erba Fractovap GV gas chromatograph equipped with a column of 2% OV 17 (2 m × 4 mm).

Proton magnetic resonance spectra were obtained on a Perkin Elmer R 32 90 MHz spectrometer, using TMS as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 257 Infracord instrument. Gc-ms were obtained on an AEI-MS 12 spectrometer at 70 eV, coupled to a Varian 1400 gas chromatograph using a column of 2% OV 17 (2 m × 2 mm).

Treatment of I with Pyridinium Chloride.

A mixture of 1.24 g. (10 mmoles) of bicyclo[5.1.0]octan-2-one (5) and 2.3 g. (20 mmoles) of pyridinium chloride in 25 ml. of acetonitrile (distilled from calcium hydride) was refluxed 42 hours. The cooled reaction mixture was poured into a saturated sodium chloride solution and repeatedly extracted with ether; the organic layer was dried and the solvent was removed. The residue was chromatographed on silica gel and eluted with benzene-ethyl acetate 9:1 to afford 1.3 g. of a mixture of the two chloroketones II (41%) and III (35%) (4); ir (carbon tetrachloride): 1703 cm^{-1}; nmr (deuteriochloroform): δ 4.2 (m, CHCl), 3.45 (m, CH_2Cl), 2.8-1.1 (m); ms: m/e (relative intensity) 162 (4), 160 (14, M^+), 55 (100).

Oximation of II and III.

A mixture of 1.2 g. of II and III T, 1.1 g. of hydroxylamine hydrochloride, and 1.4 g. of sodium acetate trihydrate in 7 ml. of ethanol and water to complete dissolution was refluxed for 6 hours. After the work-up, 1.15 g. (88%) of the corresponding oximes were obtained as oils; ir (carbon tetrachloride): 3600, 3240 cm^{-1}; nmr (carbon tetrachloride): δ 9.4 (broad, NOH), 4.1 (m, CHCl), 3.35 (m, CH_2Cl), 2.8-0.9 (m); ms: m/e (relative intensity) 177 (2), 175 (5, M^+), 140 (100).

Lithium Aluminum Hydride Reduction.

The oximes (0.85 g.) in 66 ml. of anhydrous diethyl ether were added over a period of 30 minutes to a refluxing suspension of 1.9 g. of lithium aluminum hydride in 47 ml. of ether. After 3.5 hours of reflux, the mixture was hydrolyzed with 2*N* hydrochloric acid and extracted with ether. The aqueous layer was made alkaline with sodium hydroxide and ex-

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tracted with ether. The ethereal phase was treated with ethyl chlorocarbonate (8) to give 0.44 g. of crude urethanes. The gc showed four peaks (19, 10, 52, and 19% in the order of increasing retention times). The four components were separated by preparative gc. The analytical and spectral data reported below suggested the structures V, IV, VI, and VII, respectively.

Compound V.

This compound had ir (carbon tetrachloride): 1690 cm^{-1}; nmr (carbon tetrachloride): δ 4.4-3.9 (q + m, 4H, CH_2O + H-1 + H-6), 2.1-1.4 (m, 12H), 1.27 (t, 3H, CH_3); ms: m/e (relative intensity) 197 (26, M^+), 168 (24), 154 (12), 142 (11), 141 (20), 140 (100), 124 (50), 112 (12), 110 (10), 96 (15), 82 (37), 81 (20), 79 (13), 70 (26), 68 (95), 57 (12), 56 (20), 44 (44).

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.78; H, 9.63; N, 7.15.

Compound IV.

This compound had ir (carbon tetrachloride): 1690 cm^{-1}; nmr (carbon tetrachloride): δ 4.05 (q + m, 3H, CH_2O + H-1), 3.4 (dd, 1H, H-8 exo, $J_{H\text{-}8\ exo,\ H\text{-}8\ endo}$ = 11 Hz, $J_{H\text{-}8\ exo,\ H\text{-}7}$ = 7 Hz), 3.05 (d, 1H, H-8 endo, $J_{H\text{-}8\ endo,\ H\text{-}7}$ = 0 Hz), 2.45 (m, 1H, H-7), 2.2-1.3 (m, 8H), 1.22 (t, 3H, CH_3); ms: m/e (relative intensity) 197 (12, M^+), 141 (9), 140 (100), 112 (11), 83 (4), 68 (60), 67 (10), 55 (9).

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.65; H, 9.83; N, 7.02.

Compound VI.

This compound had ir (carbon tetrachloride): 3440, 1715 cm^{-1}; nmr (carbon tetrachloride): δ 4.9 (broad, 1H, NH), 4.4-3.9 (q + m, 3H, CH_2O + H-1), 3.4 (m, 2H, CH_2Cl), 2.2-1.4 (m, 11H), 1.2 (t, 3H, CH_3); ms: m/e (relative intensity) 235 (< 1), 233 (2, M^+), 198 (21), 184 (67), 176 (22), 132 (14), 128 (55), 115 (13), 109 (73), 108 (50), 104 (13), 102 (40), 95 (34), 93 (15), 91 (14), 90 (100), 84 (15), 82 (16), 81 (15), 79 (20), 70 (14), 69 (15), 68 (20), 67 (54), 62 (28), 58 (10), 57 (12), 56 (83), 55 (37), 54 (12), 53 (16).

Anal. Calcd. for $C_{11}H_{20}ClNO_2$: C, 56.52; H, 8.62; N, 5.99. Found: C, 56.31; H, 8.51; N, 5.85.

Compound VII.

This compound had ir (carbon tetrachloride): 3440, 1715 cm^{-1}; nmr (carbon tetrachloride): δ 4.6 (broad, 1H, NH), 4.3-3.9 (q + m, 4H, CH_2O + H-1 + H-4), 2.2-1.4 (m, 12H), 1.2 (t, 3H, CH_3); ms: m/e (relative intensity) 235 (< 1), 233 (2, M^+), 129 (13), 128 (94), 116 (15), 115 (57), 109 (27), 108 (32), 107 (12), 102 (16), 93 (29), 92 (14), 90 (38), 82 (22), 81 (17), 80 (18), 79 (35), 77 (12), 70 (12), 69 (11), 68 (16), 67 (56), 62 (18), 57 (14), 56 (100), 55 (33), 54 (16), 45 (15), 44 (71), 43 (60), 42 (22), 40 (72).

Anal. Calcd. for $C_{11}H_{20}ClNO_2$: C, 56.52; H, 8.62; N, 5.99. Found: C, 56.29; H, 8.48; N, 5.88.

N-Ethoxycarbonyl-7-azabicyclo[4.2.1]nonane (IV).

N-Ethoxycarbonyl-7-azabicyclo[4.2.1]nona-2,4-diene (6) (438 mg., 2.22 mmoles) in 5 ml. of ethanol was hydrogenated at room temperature for 18 hours in the presence of 50 mg. of platinum oxide. After filtration and solvent evaporation, 406 mg. (93%) of IV were obtained, b.p. 142-145° (external bath) at 25 mm Hg. All spectral data were in agreement with those recorded for IV coming from preparative gc.

4-Chlorocyclooctanone Oxime (*Syn* + *Anti*).

Following the above indicated procedure, 1.3 g. (8.1 mmoles) of III (7) gave 1.3 g. (92%) of an oil, b.p. 160-165° (external bath) at 15 mm Hg; ir (carbon tetrachloride): 3590, 3230 cm^{-1}; nmr (carbon tetrachloride): δ 9.2 (broad, 1H, NOH), 4.1 (m, 1H, CHCl), 2.8-1.3 (m, 12H); ms: m/e (relative intensity) 177 (1), 175 (3, M^+), 160 (2), 158 (5), 149 (10), 147 (30), 140 (60), 139 (10), 124 (13), 122 (20), 120 (17), 112 (10), 111 (10), 109 (10), 107 (20), 98 (26), 96 (10), 95 (20), 94 (40), 93 (20), 91 (23), 82 (27), 81 (46), 80 (37), 79 (64), 78 (20), 77 (26), 73 (67), 69 (15), 68 (20), 67 (100), 66 (13), 65 (20), 57 (13), 56 (27), 55 (79), 54 (53), 53 (46), 51 (24).

N-Ethoxycarbonyl-9-azabicyclo[4.2.1]nonane (V) and *N*-Ethoxycarbonyl-4-chlorocycloocytlamine (VII).

Following the above indicated procedure, 0.65 g. of 4-chlorocyclooctanone oximes (*syn* + *anti*) after lithium aluminum hydride reduction and ethyl chlorocarbonate treatment afforded 0.34 g. of crude urethanes, whose gc showed two peaks of the same area. Their retention times corresponded to V and VII, respectively. The identity of the products, separated by preparative gc T,with V and VII was finally confirmed by spectral data (ir, nmr, and ms).

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