Rearrangement of Isoxazoline-5-spiro Derivatives. Part 3.[1] Indolizine, Quinolizine and Pyrido[1,2-*a*]azepine Derivatives by Sequential Rearrangement-Annulation.[2]

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4,5-Dihydrospiro[isoxazole-5-cyclopropane] derivatives (**3**), having a functionalized side-chain in position 3, have been prepared by cycloaddition. Under thermolytic conditions, compounds (**3**), undergo rearrangement to the intermediate 5,6-dihydro-4-pyridones (**4**) followed immediately by a further cyclization to *N*-bridgehead bicyclic compounds. A side-product, ascribed a wrong structure in a preliminary communication,[2] is proved by crystallographic analysis to be 2,3,4,4a,5,6-hexahydroquinolin-7(1*H*)-one (**7**).

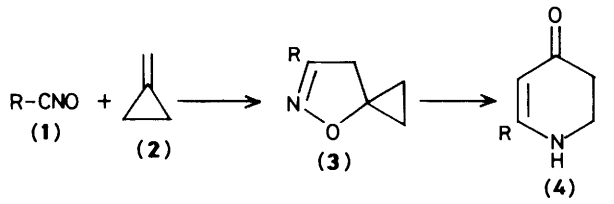
The scope of the title reaction can be extended beyond the synthesis of monocyclic derivatives with the pyridine skeleton, in several ways: (i) by starting from a ring-fused methylenecyclopropane, as already reported;[3] (ii) by starting from a cyclic dipole (a cyclic nitrone) and carrying out the analogous rearrangement on the tetrahydroisoxazole-5-spirocyclopropane adduct;[1,4] (iii) by preparing an intermediate dihydroisoxazole-5-spirocyclopropane with a side chain in position 3 suitable for ring-closure on the *N*-atom of the rearranged product.[2] The last procedure, reported in the present paper, leads to derivatives of the indolizine, quinolizine, and pyrido[1,2-*a*]azepine nuclei, whose interest in connection with several alkaloid families has already been pointed out.[2]

The annulation on nitrogen is realized by alkylation from a halide function or by acylation from an ester function. Attempted cyclisation to the *ortho*-position of a phenyl or a benzyl group adjacent to nitrogen[3] with phosgene, formaldehyde, or orthoformate failed.

Results and Discussion

The appropriate nitrile oxides (**1**) were prepared *in situ*, either from the primary nitro compounds by Mukaiyama's method[5] (**1a**—**e**) or from the corresponding oxime (**1f**). Methylenecyclopropane (**2**) was present in excess, affording good yields of the expected cycloadducts (**3**); the regioisomeric adducts were barely detectable by g.c.–m.s. in some cases, the cycloadditions being highly regioselective (Scheme 1).

Thermal rearrangement of the adducts (**3**) was carried out in dimethylformamide (DMF) solution: in order to facilitate further annulation of the expected intermediates (**4**), solid potassium carbonate was added to the halogeno derivatives (**3a**—**c**) and brine to the esters (**3d**—**f**).[6] In fact, under these conditions, the intermediates (**4**) were, in general, not detected [with the exception of (**4d**)] and the final *N*-bridgehead heterocycles were directly isolated (Scheme 2). A significant yield of an isomer of (**6**) was obtained from (**3b**). This isomer was tentatively assigned the incorrect structure reported [formula (**7**) in ref. 2] on the basis of its spectral data.[2] By *X*-ray crystallographic analysis, we found the structure illustrated (**7**) (Figure) to be the correct one. Apparently, the open-chain diradical intermediate (**15**) undergoes cyclization either to the dihydropyridone (**4b**), as expected, or to the isomer (**7**) by a competing homolytic displacement of bromine followed by a further cyclization (Scheme 3).



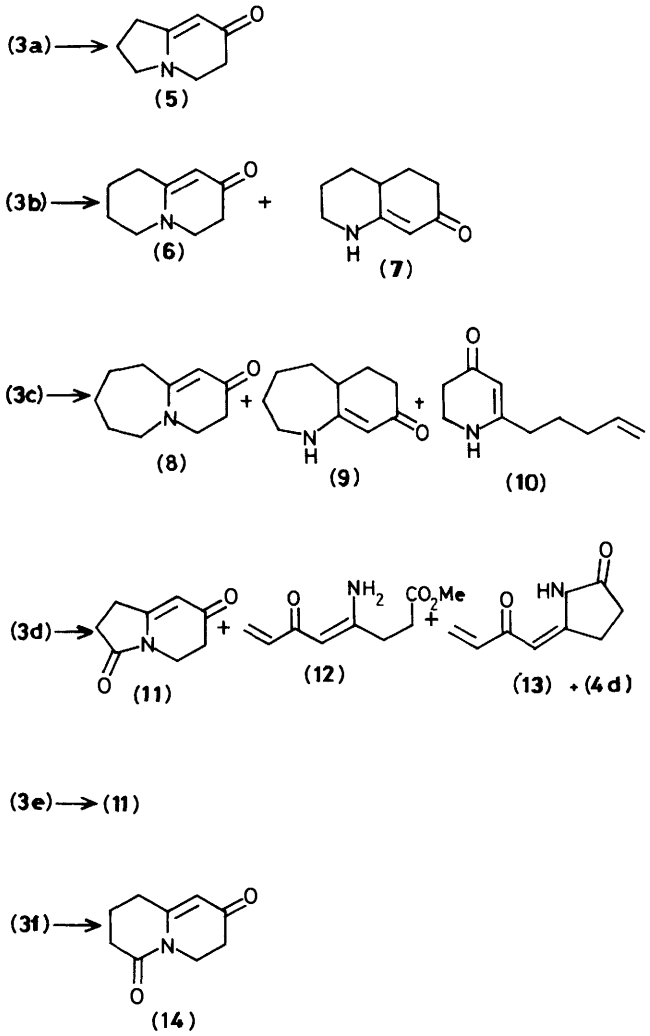
a; R = $CH_2CH_2CH_2Cl$
b; R = $CH_2CH_2CH_2CH_2Br$
c; R = $CH_2CH_2CH_2CH_2CH_2Br$
d; R = $CH_2CH_2CO_2Me$
e; R = $CH_2CH(CO_2Me)_2$
f; R = $CH_2CH_2CH(CO_2Me)_2$

Scheme 1.

A sequence analogous to that of Scheme 3 might rationalize the formation of the by-product (**9**), homologous with (**7**), obtained from (**3c**), besides the major product (**8**). Indeed, this pathway is observed for the bromo derivatives (**3b**) and (**3c**), but not for the chloroderivative (**3a**), where C-halogen homolysis is more difficult. The other side-products identified (see Scheme 2), are consistent with the proposed mechanism (Part 1):[3] thus the pyridone (**10**) is derived from (**4c**) by dehydrobromination, the ester (**12**) is the open-chain isomer of (**4d**) and (**13**) originates from lactamization of (**12**). The difficulty of forming 7-membered rings explains the lower yields obtained in the rearrangement of (**3c**) and the detection of the elimination product (**10**) and of two hydrolysis products observed in the presence of traces of water; *i.e.* the alcohol derived by hydrolysis from (**4c**) and its open-chain isomer (see Experimental section).

Some of the compounds prepared have been described previously, in connection with studies on alkaloids. Thus, the indolizine derivatives (**5**)[7] and (**11**)[8] are key intermediates towards Elaeocarpus alkaloids, and their syntheses by different procedures are known [the dione (**11**) appeared in the literature[8] while our work was in progress]. The quinolizinone (**6**) has been mentioned as a model compound in the course of a study on lupine alkaloids.[9]

The advantage of the present method is to offer a direct entry



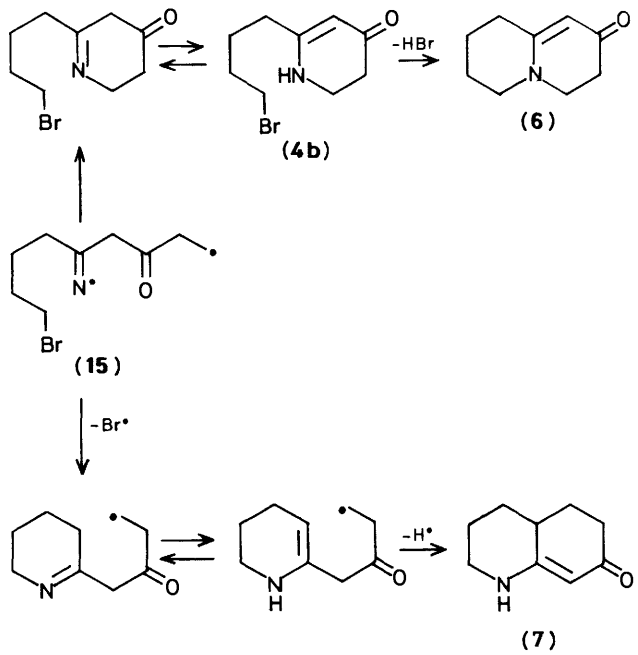
Scheme 2.

into *N*-bridgehead bicycles having an alkyl or a lactam ring junction. The possibility of introducing different functional groups in order to obtain an increased variety of functionalisation of the heterocyclic systems is under study.

Experimental

All reactions were carried out under nitrogen. M.p.s were observed with a microscope RCH Kofler apparatus. Kugelrohr distillations were carried out on a Büchi GKR-50 apparatus; the oven temperature is reported. Chromatographic separations were performed under pressure, using the 'flash-column' technique (silica gel); R_F values refer to t.l.c. carried out on 0.25 mm silica gel plates Merck F_{254}, with the same eluant indicated for the column chromatography. I.r. spectra were recorded on a Perkin-Elmer 283 spectrophotometer, n.m.r. spectra ($CDCl_3$ solutions) on Perkin-Elmer R 32 (^1H, 90 MHz), Varian XL-300 (^1H, 300 MHz) and Varian FT-80 A (^{13}C, 20 MHz) spectrometers: the chemical shifts are given in p.p.m. from TMS; coupling constants *J* are given in Hz. Mass spectra were recorded at 70 eV by G.C. inlet on a 5790A-5970A Hewlett-Packard instrument; exact mass measurements were performed, by direct inlet, with a VG 70-70 EG mass spectrometer, at an ionization potential of 70 eV. Microanalyses were carried out with a Perkin-Elmer 240 C elemental analyzer.

Methylenecyclopropane (**2**) was purchased from Fluka.



Scheme 3.

Nitrile oxides (**1**)—These compounds were prepared *in situ* from the appropriate nitro compounds[10] by Mukaiyama's procedure[5] (**1a**—**e**) or from the corresponding oxime (**1f**), as described.[11]

1-*Chloro*-4-*nitrobutane*.[10,12] $\nu_{max.}(CCl_4)$ 2 960, 2 920, 2 880, 1 690, 1 555, 1 450, 1 440, 1 385, and 1 375 cm^{-1}; δ_H(90 MHz) 4.42 (2 H, t, *J* 6.5), 3.58 (2 H, t, *J* 6), and 2.40—1.60 (4 H, m); δ_C 74.49 t, 43.47 t, 28.74 t, and 24.35 t; *m/z* 93 (2%), 91 (6), 63 (7), 62 (8), and 55 (100).

1-*Bromo*-5-*nitropentane*.[10] (Found: C, 30.7; H, 5.0; N, 7.0. Calc. for $C_5H_{10}BrNO_2$: C, 30.6; H, 5.1; N, 7.1%); $\nu_{max.}(CCl_4)$ 3 020, 2 960, 2 880, 1 560, 1 460, 1 440, 1 390, 1 380, and 1 360 cm^{-1}; δ_H(90 MHz) 4.42 (2 H, t, *J* 6.5), 3.42 (2 H, t, *J* 6.5), and 2.30—1.40 (6 H, m); δ_C 75.09 t, 32.66 t, 31.57 t, 26.23 t, and 24.63 t; *m/z* 149 (1%), 147 (1), 116 (6), 109 (7), 107 (7), 69 (48), and 41 (100).

1-*Bromo*-6-*nitrohexane*. This compound was prepared by the reported procedure,[10] b.p. 100—120 °C/0.1 mmHg (yield 20%) (Found: C, 34.2; H, 5.75; N, 6.5. Calc. for $C_6H_{12}BrNO_2$: C, 34.3; H, 5.8; N, 6.7%); $\nu_{max.}(CCl_4)$ 3 010, 2 940, 2 860, 1 550, 1 435, 1 380, and 1 235 cm^{-1}; δ_H(90 MHz) 4.41 (2 H, t, *J* 6.5), 3.43 (2 H, t, *J* 6), and 2.20—1.20 (8 H, m); δ_C 75.27 t, 33.22 t, 31.98 t, 27.09 t, 26.88 t, and 25.15 t; *m/z* 163 (1%), 161 (1), 130 (13), 107 (7), 83 (22), 81 (21), 55 (96), and 41 (100).

Cycloadducts (**3a**—**e**): *General Procedure*.—Methylenecyclopropane (excess) and triethylamine (0.1 equiv.) were added to a cold (−60 °C) solution of the appropriate primary nitro derivative[10] (1 equiv.) and phenyl isocyanate (2.2 equiv.) in anhydrous diethyl ether (2 ml $mmol^{-1}$) and the reaction flask was stoppered. The temperature of the mixture was allowed to rise after which it was stirred and set aside at room temperature for 2 days. The precipitate (diphenylurea) was removed by filtration through Celite, and the ethereal solution concentrated. The residue was then column-chromatographed.

3-(3-*Chloropropyl*)-4,5-*dihydrospiro*[*isoxazole*-5-*cyclopropane*] (**3a**).—The title compound was prepared using the general procedure from: methylenecyclopropane (10.5 mmol), triethylamine (0.48 mmol), 1-chloro-4-nitrobutane[10] (4.78

mmol), and phenyl isocyanate (9.56 mmol) in anhydrous diethyl ether (10 ml). Column-chromatography using methylene dichloride–light petroleum b.p. (30—50 °C) (3:1) as eluant afforded the *adduct* (**3a**), R_F 0.18 (429 mg, 52%), b.p. 100 °C/0.2 mmHg (Found: C, 55.1; H, 6.7; N, 8.3. $C_8H_{12}ClNO$ requires C, 55.3; H, 7.0; N, 8.1%); $\nu_{max.}$(neat) 3 005, 2 960, 1 605, 1 445, 1 225, and 1 010 cm^{-1}; δ_H(90 MHz) 3.65 (2 H, t, *J* 6.5), 3.02 (2 H, s), 2.55 (2 H, t, *J* 7), 2.30—1.95 (2 H, m), 1.25—0.95 (2 H, m), and 0.90—0.60 (2 H, m); δ_C 158.14 s, 64.71 s, 43.96 t, 42.28 t, 28.63 t, 25.55 t, and 11.41 t (2 C); *m/z* 175 (0.4%), 173 (M^+, 1.2), 117 (8), 83 (11), 68 (6), 55 (11), and 42 (100).

By g.c.–m.s. we also identified in the crude reaction mixture the regioisomeric adduct, *m/z* 175 (5%), 174 (5), 173 (M^+, 16), 172 (8), 138 (6), 111 (18), and 83 (100); and the 3,4-bis(3-chloropropyl)-1,2,5-oxadiazole 2-oxide [a substituted furoxan, dimer of (**1a**)], *m/z* 242 (4%), 240 (25), 238 (M^+, 36), 210 (14), 208 (18), 205 (6), 203 (17), 180 (25), 178 (42), 176 (23), 143 (90), and 114 (100).

3-(4-*Bromobutyl*)-4,5-*dihydrospiro*[*isoxazole*-5-*cyclopropane*] (**3b**).—This compound was prepared from methylenecyclopropane (24 mmol), triethylamine (0.9 mmol), 1-bromo-5-nitropentane[10] (9 mmol), and phenyl isocyanate (19.8 mmol) in anhydrous diethyl ether (18 ml). Column chromatography (using methylene dichloride–light petroleum (3:1) as eluant afforded the *adduct* (**3b**), R_F 0.26 (963 mg, 46%), as an oil, purified by repeated column-chromatography using light petroleum–ethyl acetate (5:1) as eluant, R_F 0.30 (Found: C, 46.4; H, 5.9; N, 6.4. $C_9H_{14}BrNO$ requires C, 46.6; H, 6.1; N, 6.0%); $\nu_{max.}$(neat) 3 005, 2 955, 1 620, 1 435, 1 225, and 1 010 cm^{-1}; δ_H(90 MHz) 3.42 (2 H, t, *J* 6), 2.99 (2 H, s), 2.42 (2 H, t, *J* 7), 2.15—1.55 (4 H, m), 1.25—0.95 (2 H, m), and 0.90—0.60 (2 H, m); δ_C 158.87 s, 64.71 s, 41.89 t, 32.99 t, 31.77 t, 27.24 t, 24.42 t, and 11.45 t (2 C); *m/z* 233 (0.6%), 231 (M^+, 0.5), 175 (2), 152 (2), 135 (8), 124 (5), 110 (3), 96 (9), 82 (12), 68 (6), 55 (49), and 42 (100).

Some 3,4-bis(4-bromobutyl)-1,2,5-oxadiazole 2-oxide [a substituted furoxan, dimer of (**1b**)] was also collected, R_F 0.31, as an oil; $\nu_{max.}$(neat) 2 940, 2 860, 1 605, 1 470, and 1 430 cm^{-1}; δ_H(90 MHz) 3.65—3.30 (4 H, m), 2.90—2.40 (4 H, m), and 2.20—1.60 (8 H, m); δ_C 157.00 s, 115.12 s, 32.57 t, 32.39 t, 31.51 t, 31.44 t, 24.86 t, 24.58 t, 23.95 t, and 21.37 t; *m/z* 324 (1%), 277 (43), 275 (43), 230 (42), 228 (42), and 114 (100).

3-(5-*Bromopentyl*)-4,5-*dihydrospiro*[*isoxazole*-5-*cyclopropane*] (**3c**).—This compound was prepared from methylenecyclopropane (14.9 mmol), triethylamine (0.79 mmol), 6-bromo-1-nitrohexane (7.9 mmol) and phenyl isocyanate (17.4 mmol) in anhydrous diethyl ether (16 ml). Column-chromatography using methylene dichloride–light petroleum (5:1) as eluant afforded the *adduct* (**3c**), R_F 0.28 (1.096 g, 56%) as an oil (Found: C, 48.9; H, 6.4; N, 6.05. $C_{10}H_{16}BrNO$ requires C, 48.8; H, 6.55; N, 5.7%); $\nu_{max.}$(neat) 3 010, 2 955, 1 625, 1 440, 1 215, and 1 005 cm^{-1}; δ_H (300 MHz) 3.38 (2 H, t, *J* 6.7), 2.96 (2 H, s), 2.37 (2 H, t, *J* 7.3), 1.85 (2 H, m), 1.67—1.40 (4 H, m), 1.09 (2 H, m), and 0.68 (2 H, m); δ_C 159.17 s, 64.57 s, 41.93 t, 33.23 t, 32.11 t, 27.91 t, 27.47 t, 25.11 t, and 11.39 t (2 C); *m/z* 247 (0.5%), 245 (M^+, 1), 218 (1), 216 (1), 191 (1), 189 (1), 166 (4), 149 (2), 110 (13), 83 (20), 82 (15), 69 (31), 55 (19), and 42 (100).

By g.c.–m.s. we also identified in the crude reaction mixture the regioisomeric adduct, *m/z* 247 (3%), 245 (M^+, 3), 111 (73), 110 (31), 83 (93), and 41 (100); and the 3,4-bis(5-bromopentyl)-1,2,5-oxadiazole 2-oxide [a substituted furoxan, dimer of (**1c**)], *m/z* 369 (2%), 367 (3), 365 (2), 356 (2), 354 (3), 352 (2), 305 (39), 303 (41), 169 (15), and 41 (100).

3-(2-*Methoxycarbonylethyl*)-4,5-*dihydrospiro*[*isoxazole*-5-*cyclopropane*] (**3d**). This compound was prepared from: methylenecyclopropane (20 mmol), triethylamine (1 mmol), methyl 4-nitrobutyrate[13] (10 mmol) and phenyl isocyanate (22 mmol) in anhydrous diethyl ether (20 ml). Column-chromatography using methylene dichloride–light petroleum (5:1) as eluant afforded the *adduct* (**3d**), R_F 0.05 (1.25 g, 68%), (Found: C, 58.65; H, 6.9; N, 7.6. $C_9H_{13}NO_3$ requires C, 59.0; H, 7.15; N, 7.65%); $\nu_{max.}$(CCl_4) 1 750 and 1 600 cm^{-1}; δ_H(300 MHz) 3.68 (3 H, s), 2.99 (2 H, s), 2.66 (4 H, s), 1.10 (2 H, m), and 0.69 (2 H, m); δ_C 172.41 s, 157.85 s, 64.76 s, 51.47 q, 42.10 t, 29.94 t, 23.44 t, and 11.23 t (2 C); *m/z* 183 (M^+, 1%), 151 (20), 124 (8), 108 (19), 82 (12), and 42 (100).

In the crude reaction mixture we identified by g.c.–m.s. the regioisomeric adduct, *m/z* 183 (M^+, 26%), 152 (54), 151 (61), 124 (61), 123 (51), 96 (100), and 95 (56), while some chromatographic fractions contained impure 3,4-bis(2-methoxycarbonylethyl)-1,2,5-oxadiazole 2-oxide [a substituted furoxan, dimer of (**1d**)], δ_H (300 MHz) 3.67 (3 H, s), 3.64 (3 H, s), 3.02 (2 H, t, *J* 6.9), 2.83 (2 H, t, *J* 6.9), and 2.80—2.70 (4 H, m); *m/z* 228 (37%), 227 (17), 197 (100), 196 (25), 180 (24), 151 (29), and 150 (32).

3-(2,2-*Dimethoxycarbonylethyl*)-4,5-*dihydrospiro*[*isoxazole*-5-*cyclopropane*] (**3e**). This compound was prepared using: methylenecyclopropane (8 mmol), triethylamine (0.11 mmol), dimethyl (2-nitroethyl)malonate[14] (1.1 mmol) and phenyl isocyanate (2.19 mmol) in anhydrous diethyl ether (5 ml) during 4 days. Column chromatography using methylene dichloride–ethyl acetate (25:1) as eluant afforded the *adduct* (**3e**), R_F 0.31 (179 mg, 67%) (Found: C, 55.2; H, 6.3; N, 5.9. $C_{11}H_{15}NO_5$ requires C, 54.8; H, 6.3; N, 5.8%); $\nu_{max.}$($CDCl_3$) 3 010, 2 960, 1 760, 1 740, and 1 440 cm^{-1}; δ_H(300 MHz) 3.87 (1 H, t, *J* 7.7), 3.71 (6 H, s), 2.97 (2 H, s), 2.90 (2 H, d, *J* 7.7), 1.05 (2 H, m), and 0.66 (2 H, m); δ_C 168.66 s (2 C), 156.29 s, 65.17 s, 52.64 q (2 C), 48.22 d, 42.27 t, 27.42 t, and 11.34 t (2 C); *m/z* 241 (M^+, 5%), 209 (9), 177 (100), 150 (13), 122 (22), 113 (11), 109 (11), 55 (68), and 42 (94).

Some starting dimethyl (2-nitroethyl)malonate was also recovered, R_F 0.57 (33 mg).

3-(3,3-*Dimethoxycarbonylpropyl*)-4,5-*dihydrospiro*[*isoxazole*-5-*cyclopropane*] (**3f**).—(*a*) *Dimethyl* (3-*hydroxyiminopropyl*)-*malonate* was obtained as a mixture of *E*- and *Z*- isomers from dimethyl 3-oxopropylmalonate[15] and hydroxylamine in aqueous solution and extraction in diethyl ether: yield 93%, b.p. 150 °C/0.04 mmHg, m.p. 54—56 °C (pure *Z*-isomer) (Found: C, 47.15; H, 6.4; N, 6.9. $C_8H_{13}NO_5$ requires C, 47.3; H, 6.45; N, 6.9%); $\nu_{max.}$(CCl_4) 3 700—3 140, 2 960, 1 740, 1 435, and 1 150 cm^{-1}; δ_H(90 MHz, *Z*-isomer) 9.60 (1 H, br s), 6.80 (1 H, t, *J* 6), 3.75 (6 H, s), 3.46 (1 H, t, *J* 7.5), and 2.65—1.95 (4 H, m); δ_H(90 MHz, *E*-isomer) 7.50 (1 H, t, *J* 5.5); δ_C (*Z*-isomer) 169.06 s (2 C), 150.13 d, 52.18 q (2 C), 50.62 d, 24.74 t, and 22.38 t; δ_C (*E*-isomer) 169.06 s (2 C), 149.79 d, 52.18 q (2 C), 50.23 d, 26.72 t, and 25.08 t; *m/z* 186 ($M^+ - OH$, 25%), 154 (24), 145 (6), 140 (53), 132 (49), 112 (68), and 55 (100).

(*b*) A solution of dimethyl (3-hydroxyiminopropyl)malonate (11 mmol), *N*-chlorosuccinimide (11 mmol) and triethylamine (0.1 ml) in methylene dichloride (25 ml) was stirred for 1 h and then cooled to −60 °C and treated with basic alumina (6.5 g) and with methylenecyclopropane (22 mmol). The stirred mixture was set aside for 1 day and then, since a g.c.–m.s. control showed that the reaction was incomplete, more triethylamine (0.76 ml) and methylenecyclopropane (17.2 mmol) were added, and stirring continued. After a further day the reaction was complete and the solvent was removed, and the residue extracted into tetrachloromethane (50 ml). After concentration, the residue was passed through a pad of silica gel and eluted with dichloromethane, in order to completely remove succinimide. On concentration, the *adduct* (**3f**) was obtained as a

yellow oil (1.95 g, 70%) (Found: C, 56.5; H, 6.6; N, 5.1. $C_{12}H_{17}NO_5$ requires C, 56.5; H, 6.7; N, 5.5%); $\nu_{max.}(CCl_4)$ 3 000, 2 950, 2 840, 1 750, 1 610, 1 435, 1 350, 1 250, 1 225, 1 200, and 1 150 cm^{-1}; δ_H(90 MHz) 3.81 (6 H, s), 3.54 (1 H, t, *J* 7), 3.04 (2 H, s), 2.55—2.15 (4 H, m), 1.25—0.95 (2 H, m), and 0.90—0.60 (2 H, m); δ_C 169.03 s (2 C), 157.94 s, 64.69 s, 52.28 q (2 C), 50.40 d, 41.75 t, 25.78 t, 24.82 t, and 11.26 t (2 C); *m/z* 255 (M^+, 3%), 192 (19), 191 (100), 99 (15), 69 (18), 59 (36), 55 (31), and 42 (60).

By g.c.–m.s. we also identified in the crude reaction mixture the regioisomeric adduct, *m/z* 255 (M^+, 13%), 224 (5), 223 (3), 222 (2), 208 (3), 196 (2), 193 (9), 192 (55), 191 (32), 190 (12), 164 (35), 124 (100), 96 (38), 59 (29), and 41 (21); and the 3,4-bis(3,3-dimethoxycarbonylpropyl)-1,2,5-oxadiazole 2-oxide [a substituted furoxan, dimer of (**1f**)], *m/z* 386 ($M^+ - O$, 1%), 385 (6), 372 (10), 371 (11), 341 (5), 340 (16), 339 (65), 321 (19), 308 (19), 305 (25), 244 (24), 159 (45), 145 (43), 132 (66), 113 (57), 100 (38), 59 (100), and 55 (87).

Rearrangement of (**3a**) *to give* 2,3,5,6-*Tetrahydroindolizin*-7(1H)-*one* (**5**).—*In solution.* The adduct (**3a**) (173 mg, 1 mmol) was heated in boiling anhydrous DMF (20 ml) in the presence of solid potassium carbonate (138 mg, 1 mmol) during 6 h. The solvent was removed under reduced pressure and the dark residue passed through a pad of silica gel using methylene dichloride and then methylene dichloride–methanol (10:1) as eluant. The second fraction gave, on concentration, the indolizinone (**5**)[7] (79 mg, 58%), $\nu_{max.}(CDCl_3)$ 2 960, 2 850, 1 620, and 1 575 cm^{-1}; δ_H(90 MHz) 5.03 (1 H, s), 3.60—3.25 (4 H, m), 2.80—2.35 (4 H, m), and 2.25—1.85 (2 H, m); δ_C 190.62 s, 169.60 s, 92.58 d, 53.10 t, 44.85 t, 34.41 t, 31.72 t, and 20.95 t; *m/z* 137 (M^+, 75%), 109 (32), 108 (100), 81 (54), and 80 (21) (Found: M^+, 137.0832, direct inlet. $C_8H_{11}NO$ requires *M*, 137.0840). Attempted distillation *in vacuo* caused partial decomposition.

By flash vacuum thermolysis (*f.v.t.*). The vapour of (**3a**) (213 mg) was passed at 0.03 mmHg through a quartz tube heated at 400 °C and then led into a cold trap. The condensed products were dissolved in hot acetone–methanol and the solvents removed to give the hydrochloride of (**5**) (130 mg, 61%), δ_H(90 MHz) 7.40 (1 H, br s), 5.87 (1 H, s), 4.10—3.70 (4 H, m), 3.15—2.75 (4 H, m), and 2.45—2.05 (2 H, m); δ_C 180.64 s, 177.15 s, 91.38 d, 55.65 t, 43.67 t, 34.31 t, 28.21 t, and 19.73 t. After treatment of the hydrochloride with sodium methoxide solution (from 26 mg of Na), the solution was concentrated and the residue extracted with methylene dichloride to give, on concentration, the indolizinone (**5**) (69 mg, 41%).

Rearrangement of (**3b**) *to give* 3,4,6,7,8,9-*Hexahydro*-2H-*quinolizin*-2-*one* (**6**)[9] *and* 2,3,4,4a,5,6-*Hexahydroquinolin*-7(1H)-*one* (**7**).[16]—*In solution.* The same procedure described for (**3a**) gave from (**3b**) (164 mg, 0.7 mmol) a crude mixture of (**6**) and (**7**). Purification by column-chromatography using methylene dichloride–methanol (10:1) as eluant afforded the quinolizinone (**6**), R_F 0.44 (42 mg, 40%), $\nu_{max.}(CDCl_3)$ 2 960, 2 870, 1 625, and 1 560 cm^{-1}; δ_H(300 MHz) 4.86 (1 H, s), 3.37 (2 H, t, *J* 7.9), 3.17 (2 H, t, *J* 6.2), 2.45—2.38 (4 H, m), 1.89—1.80 (2 H, m), and 1.68—1.58 (2 H, m); δ_C 190.41 s, 163.37 s, 98.47 d, 50.45 t, 50.19 t, 35.19 t, 29.69 t, 23.15 t, and 19.63 t; *m/z* 151 (M^+, 64%), 123 (30), 122 (100), 95 (62), and 67 (41); and the quinolinone (**7**), R_F 0.27, (32 mg, 30%), m.p. 184—185 °C, from acetone [reported[16] m.p. 184—185 °C (from ethanol–diethyl ether)] (Found: C, 71.1; H, 8.8; N, 9.4. Calc. for $C_9H_{13}NO$: C, 71.5; H, 8.7; N, 9.3%); $\nu_{max.}(CDCl_3)$ 3 420, 2 950, 2 870, and 1 585 cm^{-1}; δ_H (300 MHz) 5.82 (1 H, br s), 5.11 (1 H, d, *J* 0.9), 3.39—3.30 (1 H, m), 3.23 (1 H, dt, *J* 4.2 and 11.7), 2.50—2.25 (3 H, m), 2.03—1.60 (5 H, m), and 1.42—1.25 (1 H, m); δ_C 196.03 s, 168.01 s, 98.34 d, 41.96 t, 36.75 t, 35.25 d, 29.65 t, 27.12 t, and 22.54 t; *m/z* 151 (M^+, 43%), 123 (100), 122 (72), 108 (23), and 95 (11).

By f.v.t. This was carried out as reported above for (**3a**): only the product (**6**) was obtained as an impure hydrobromide; δ_H(90 MHz) 5.85 (1 H, s), 5.80 (1 H, br s), 4.00—3.50 (4 H, m), 3.05—2.55 (4 H, m), and 2.15—1.60 (4 H m); δ_C 177.37 s, 173.87 s, 96.80 d, 51.67 t, 50.14 t, 30.59 t, 27.79 t, 21.48 t, and 17.26 t. The base (**6**) was isolated as above in 10% yield.

Rearrangement of (**3c**) *to give* 3,4,7,8,9,10-*Hexahydro*-6H-*pyrido*[1,2-a]*azepin*-2-*one* (**8**) *and* 1,2,3,4,5,5a,6,7-*Octahydro*-8H-1-*benzazepin*-8-*one* (**9**).—*In solution.* The adduct (**3c**) (492 mg, 2 mmol) was heated in boiling anhydrous DMF (40 ml) in the presence of solid potassium carbonate (276 mg, 2 mmol) during 6 h to give a complex reaction mixture containing the two title products. The solvent was removed under reduced pressure and the residue column-chromatographed using methylene dichloride–methanol (15:1) as eluant to give the *product* (**8**) as an oil, R_F 0.27, 68 mg (0.41 mmol, 21%) $\nu_{max.}$(neat) 1 620 and 1 550 cm^{-1}; δ_H(300 MHz) 4.92 (1 H, s), 3.53 (2 H, t, *J* 7.8), 3.45—3.37 (2 H, m), 2.38 (2 H, t, *J* 7.8), 2.37—2.32 (2 H, m), and 1.65—1.58 (6 H, m); δ_C 191.76 s, 168.69 s, 98.90 d, 54.19 t, 51.99 t, 35.63 t, 34.99 t, 29.20 t, 27.45 t, and 26.07, t; *m/z* 165 (M^+, 100%), 137 (26), 136 (92), 122 (32), 109 (79), and 108 (47) (Found: M^+, 165.1138, direct inlet. $C_{10}H_{15}NO$ requires *M*, 165.1153). Attempted distillation *in vacuo* caused partial decomposition.

The following by-products were identified within further fractions, collected from the chromatography with increased solvent polarity using methylene dichloride–methanol (5:1) as eluant: impure 2,3-dihydro-6-(pent-4-enyl)-4-pyridone (**10**), R_F 0.23 (referred to the first eluant); δ_H(300 MHz) 5.76 (1 H, ddt, *J* 17.3, 10.4 and 6.8), 5.02 (1 H, d, *J* 17.3), 5.01 (1 H, d, *J* 1.1), 4.97 (1 H, d, *J* 10.4), 4.84 (1 H, br s), 3.53 (2 H, t, *J* 7.6), 2.41 (2 H, t, *J* 7.6), 2.19 (2 H, t, *J* 7.7), 2.09 (2 H, dt, *J* 6.8 and 7.7), and 1.75—1.45 (2 H, m); δ_C 192.37 s, 165.91 s, 137.35 d, 115.51 t, and 98.72 d; *m/z* 165 (M^+, 34%), and 111 (100); and the *benzazepinone* (**9**), R_F 0.19 (referred to the first eluant), (41 mg, 0.25 mmol, 12%), m.p. 173—174 °C, from acetone (Found: C, 72.4; H, 9.3; N, 8.8. $C_{10}H_{15}NO$ requires C, 72.7; H, 9.2; N, 8.5%); $\nu_{max.}(CDCl_3)$ 3 430 and 1 580 cm^{-1}; δ_H(300 MHz) 6.37 (1 H, br s), 5.10 (1 H, s), 3.31 (2 H, m), 2.60 (1 H, m), 2.43—2.28 (1 H, m), 2.20—2.06 (2 H, m), 2.00—1.90 (1 H, m), 1.86—1.48 (5 H, m), and 1.45—1.28 (1 H, m); δ_C 195.82 s, 172.78 s, 98.17 d, 43.74 t, 35.35 d, 32.22 t, 32.18 t, 29.91 t, 29.84 t, and 29.31, t; *m/z* 165 (M^+, 80%), 137 (100), 136 (33), 122 (35), 109 (54), and 108 (58).

The presence of moisture in the reaction medium caused the formation, among the by-products, of the alcohol corresponding to hydrolysed (**4c**), obtained as an oil, R_F 0.07 using methylene dichloride–methanol (15:1) as eluant, $\nu_{max.}(CDCl_3)$ 3 450, 1 630, and 1 585 cm^{-1}; δ_H(300 MHz): 5.40 (1 H, br s), 4.97 (1 H, d, *J* 1.6), 3.63 (2 H, t, *J* 6.3), 3.54 (2 H, dt, *J* 2.4 and 7.7), 2.40 (2 H, t, *J* 7.7), 2.20 (2 H, t, *J* 7.6), 2.17 (1 H, br s), 1.65—1.52 (4 H, m), and 1.48—1.35 (2 H, m); δ_C 192.42 s, 166.41 s, 98.36 d, 62.25 t, 41.79 t, 35.13 t, 34.94 t, 32.08 t, 27.22 t, and 25.14, t; *m/z* 183 (M^+, 48%), 124 (57), and 111 (100).

With an increased quantity of water (as in commercial DMF), the above-mentioned alcohol became the main product (up to 25% isolated) and some of the open-chain isomer [CH_2=CHCO–CH=C(NH_2)$(CH_2)_5$OH] was also identified, δ_H(300 MHz) 10.20 (1 H, br s), 6.31 (1 H, dd, *J* 17.3 and 10.2), 6.11 (1 H, dd, *J* 17.3 and 1.9), 5.70 (1 H, br s), 5.48 (1 H, dd, *J* 10.2 and 1.9), 5.14 (1 H, s), 3.62 (2 H, t, *J* 6.3), 2.35 (1 H, br s), 2.19 (2 H, t, *J* 7.8), and 1.73—1.28 (6 H, m); *m/z* 183 (M^+, 25%), 166 (4), 165 (6), 156 (9), 138 (7), 124 (92), 111 (34), 110 (38), 11 (34), 110 (38), 96 (43), 83 (62), 82 (78), and 55 (100).

By f.v.t. The same procedure reported for (**3a**) afforded from (**3c**) (1 mmol) the base (**8**) (crude 45 mg, 27%).

Rearrangement of (**3d**) *to give* 1,2,5,6-*Tetrahydroindolizine*-3,7-*dione* (**11**).[8]—A solution of (**3d**) (3.75 mmol) in DMF (75

Table 1. Fractional coordinates for non-hydrogen atoms with the estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
O(W)	3 185(4)	4 936(3)	6 676(2)
N(1)	−1 203(3)	8 078(3)	8 917(2)
C(2)	−2 715(4)	9 039(4)	9 201(2)
C(3)	−4 061(4)	8 002(4)	9 612(2)
C(4)	−4 507(4)	6 456(4)	9 077(2)
C(4a)	−2 730(3)	5 468(3)	9 089(2)
C(5)	−3 025(4)	3 899(3)	8 573(2)
C(6)	−1 181(4)	2 995(3)	8 589(2)
C(7)	336(3)	4 050(3)	8 312(2)
O(7)	1 666(3)	3 373(2)	8 025(1)
C(8)	201(3)	5 754(3)	8 409(2)
C(8a)	−1 195(3)	6 479(3)	8 783(1)

Table 2. Bond lengths (Å) and angles (°) and hydrogen bonds parameters

C(2)–C(3)	1.505(4)
C(2)–N(1)	1.468(3)
C(3)–C(4)	1.510(4)
C(4)–C(4a)	1.509(3)
C(4a)–C(5)	1.503(4)
C(4a)–C(8a)	1.517(3)
C(5)–C(6)	1.514(4)
C(6)–C(7)	1.510(3)
C(7)–C(8)	1.412(4)
C(7)–O(7)	1.249(3)
C(8)–C(8a)	1.374(3)
C(8a)–N(1)	1.329(3)
C(8a)–N(1)–C(2)	126.9(2)
C(3)–C(2)–N(1)	112.4(2)
C(4)–C(3)–C(2)	110.0(2)
C(8a)–C(4a)–C(4)	111.1(2)
C(8a)–C(4a)–C(5)	110.5(2)
C(5)–C(4a)–C(4)	114.5(2)
C(4a)–C(4)–C(3)	110.4(2)
C(6)–C(5)–C(4a)	111.8(2)
C(7)–C(6)–C(5)	112.7(2)
O(7)–C(7)–C(6)	118.4(2)
C(8)–C(7)–O(7)	123.3(2)
C(8)–C(7)–C(6)	118.2(2)
C(4a)–C(8a)–N(1)	118.1(2)
C(8)–C(8a)–C(4a)	120.9(2)
C(8)–C(8a)–N(1)	121.0(2)
C(8a)–C(8)–C(7)	122.8(2)
O(w) ... O(7)	2.857(4)
O(w) ... O(7)^{i}	2.801(4)
O(w) ... N(1)^{i}	2.921(4)
O(7) ... H(w′)^{i}	2.24(4)
H(1) ... O(w)^{i}	2.15(4)
H(w) ... O(7)	2.02(4)
O(7) ... H(w)–O(w)	168.0(3)
O(7) ... H(w′)^{i}–O(w)^{i}	174.0(3)
N(1)–H(1) ... O(w)^{i}	171.0(3)

^{i} Symmetry operation 0.5 − *x*, 0.5 + *y*, 1.5 − *z*.

ml), containing NaCl (3.5 mmol) and water (0.13 ml), was refluxed during 4.5 h. The solvent was removed under reduced pressure and the residue column chromatographed using chloroform–methanol (25:1) as eluant, to give the indolizinedione (**11**), R_F 0.30 (275 mg, 55%), *m/z* (Found M^+, 151.0626, direct inlet. Calc. for $C_8H_9NO_2$ *M* 151.0633). All spectral data are in agreement with the reported values.[8] However, the description of the ^{1}H n.m.r. spectrum (300 MHz) should be

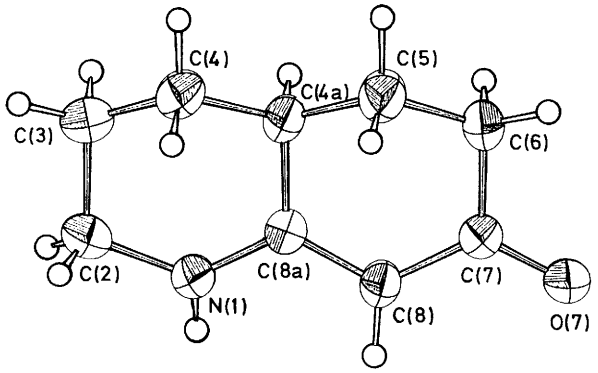


Figure. ORTEP view[19] for compound (**7**). 50% Thermal ellipsoids and crystallographic numbering are shown for non-hydrogen atoms.

corrected as follows: 5.31 (1 H, t, *J* 1.3, 8-H), 3.86 (2 H, t, *J* 7.6, 5-H_2), 2.92—2.85 (2 H, m, 1-H_2), 2.65—2.58 (2 H, m, 2-H_2), 2.52 (2 H, t, *J* 7.6, 6-H_2). Double resonance experiments show coupling of the 1-H protons with 8-H (allylic) and with 2-H_2 as well as the coupling between 5-H_2 and 6-H_2. The ^{13}C n.m.r. assignments[8] to 5-C and 6-C should be inverted, *i.e.* 37.29 (5-C) and 33.39 (6-C).

Among the by-products, we identified in the fractions from chromatography the intermediate (**4d**), δ_H(300 MHz) 5.63 (1 H, br s), 4.90 (1 H, d, *J* 1.6), 3.68 (3 H, s), 3.50 (2 H, dt, *J* 2.4 and 7.5), 2.67—2.42 (4 H, m), and 2.37 (2 H, t, *J* 7.5); *m/z* 183 (M^+, 27%), 152 (9), 124 (100), 110 (41), 109 (23), and 55 (52); the enaminone (**12**), $\nu_{max.}$($CDCl_3$) 3 500, 1 740, 1 610, and 1 530 cm^{-1}; δ_H(300 MHz) 10.04 (1 H, br s), 6.28 (1 H, dd, *J* 17.3 and 10.2), 6.10 (1 H, dd, *J* 17.3 and 1.8), 5.79 (1 H, br s), 5.48 (1 H, dd, *J* 10.2 and 1.8), 5.10 (1 H, s), 3.67 (3 H, s), 2.63—2.57 (2 H, m), and 2.49—2.43 (2 H, m); δ_C 187.93 s, 173.05 s, 165.39 s, 137.73 d, 123.25 t, 94.05 d, 51.84 q, 32.30 t, and 30.86 t; *m/z* 183 (M^+, 26%), 124 (100), 110 (44), 109 (22), 98 (29), 96 (32), and 55 (64); and the corresponding lactam (**13**), δ_H (300 MHz) 10.95 (1 H, br s), 6.38 (1 H, dd, *J* 17.5 and 10.2), 6.23 (1 H, dd, *J* 17.5 and 1.6), 5.73 (1 H, dd, *J* 10.2 and 1.6), 5.66 (1 H, t, *J* 1.3), and 3.00—2.50 (4 H, m); *m/z* 151 (M^+, 51%), 150 (42), and 124 (100).

Rearrangement of (**3e**) *to give* 1,2,5,6-*Tetrahydroindolizine*-3,7-*dione* (**11**).—A solution of (**3e**) (0.96 mmol) in DMF (22 ml), containing NaCl (0.96 mmol) and water (2 mmol), was refluxed and stirred during 6 h. The solvent was removed under reduced pressure and the residue passed through a pad of silica gel and washed with methanol. The residue of the methanolic solution was extracted in chloroform and the solution concentrated to give the product (**11**) (48 mg, 33%).

Rearrangement of (**3f**) *to give* 3,4,6,7,8,9-*Hexahydro*-2H-*quinolizine*-2,6-*dione* (**14**).—A solution of (**3f**) (2 mmol) in DMF (40 ml), containing NaCl (2 mmol) and water (4 mmol), was refluxed during 6 h. The solvent was removed under reduced pressure and the residue column chromatographed using methylene dichloride–methanol (10:1) as eluant, to give the *quinolizinedione* (**14**), R_F 0.30 (144 mg, 44%), m.p. 101—103 °C (from diethyl ether) (Found: C, 65.1; H, 6.7; N, 8.3. $C_9H_{11}NO_2$ requires C, 65.4; H, 6.7; N, 8.5%); $\nu_{max.}$(KBr) 3 060, 2 960, 2 900, 1 695, 1 665, 1 655, and 1 590 cm^{-1}; δ_H (90 MHz) 5.30 (1 H, s), 4.19 (2 H, t, *J* 7.5), 2.85—2.35 (6 H, m), and 2.20—1.75 (2 H, m); δ_C 193.10 s, 168.77 s, 156.18 s, 106.50 d, 40.10 t, 35.23 t, 32.71 t, 29.52 t, and 18.67 t; *m/z* 165 (M^+, 61%), 109 (100), 108 (27), and 81 (20).

Crystallographic Analysis of Compound (**7**).—Crystals suitable for *X*-ray analysis were obtained from a solution in

acetone by allowing the solvent to evaporate slowly to dryness; m.p. 181—182 °C (Found: C, 63.5; H, 8.7; N, 7.9. $C_9H_{13}NO{\cdot}H_2O$ requires C, 63.9; H, 8.9; N, 8.3%).

Crystal Data.—$C_9H_{13}NO{\cdot}H_2O$ (**7**), M = 169.11, Monoclinic, a = 7.174 (1), b = 8.212 (3), c = 15.187 (6) Å, β = 100.42 (2)°, V = 880.1, space group $P2_1/n$, Z = 4, D_x × 1.27 g cm^{-3}, colourless prismatic crystal grown from acetone with approximate dimension 0.2 × 0.15 × 0.30 mm, μ = 0.53 cm^{-1}.

Data Collection and Structure Analysis.—Data were collected on fully automated Enraf-Nonius CAD4 four cycle diffractometer (graphite monochromated Mo-K_α, λ = 0.7107 Å), within $2\theta < 50°$ by $\omega - 2\theta$ step-scan technique. A total of 1 424 independent reflections were collected. After correction for Lorentz and polarization effects, 1 103 reflections with $I \geqslant 3\sigma(I)$ were considered observed and used in the structure solution and refinement. Absorption corrections were not applied.

The structure was solved by use of direct methods of SHELX86;[17] subsequent calculation by SHELX76.[18] The locations of all hydrogen atoms were found by difference Fourier maps. The solution was refined by full-matrix least squares with non-hydrogen atom anisotropic and hydrogen atoms isotropic. The weighting scheme used was $w^{-1} = \sigma^2(F_0) + 0.0219\,F_0^2$. Final R and R_w values were 0.069 and 0.070 respectively. Fractional atomic co-ordinates for the non-hydrogen atoms are given in Table 1. Table 2 lists bond lengths, bond angles and hydrogen bonds parameters. Thermal parameters and hydrogen atom co-ordinates are available on request from the Cambridge Crystallographic Data Centre.*

* For details see Instructions for Authors (1989), *J. Chem. Soc., Perkin Trans. 1*, 1989, Issue 1.

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