Photocyclisation of Enamides. Part IV.[1] A New Stereoselective Synthesis of (±)-Crinan [2]

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(±)-Crinan (XIII) has been synthesised by stereoselective photocyclisation of *N*-(2-allylcyclohex-1-enyl)-*N*-benzylpiperonylamide (VIIa).

THE preceding paper reports the stereoselective photocyclisation of *N*-benzoylenamines of cyclic ketones to give *trans*-fused lactams. This method has now been applied to the synthesis of (±)-crinan (XIII) (the basic ring system of the Lycoris alkaloids, *e.g.* crinine and lycorine). Alternative syntheses of (±)-crinan have been reported.[3]

First, the effect of the presence of a methylenedioxy-group on the orientation of cyclisation was examined. The imine prepared from cyclohexanone and benzylamine was acylated with piperonyloyl chloride to afford the enamide (I) in good yield [δ 5·33 (=CH), $\nu_{max.}$ 1600—1630 cm^{-1} (amide CO)]. Irradiation of a methanolic solution of the enamide (I) as described previously [1] gave two photoproducts [(II) (13%) and (III) (15%)], separated by chromatography and identified from their n.m.r. spectra. Conversion of the product (III) into the known phenanthridone (IV) [4] confirmed the skeletal structure.

In view of the foregoing result and of our previous

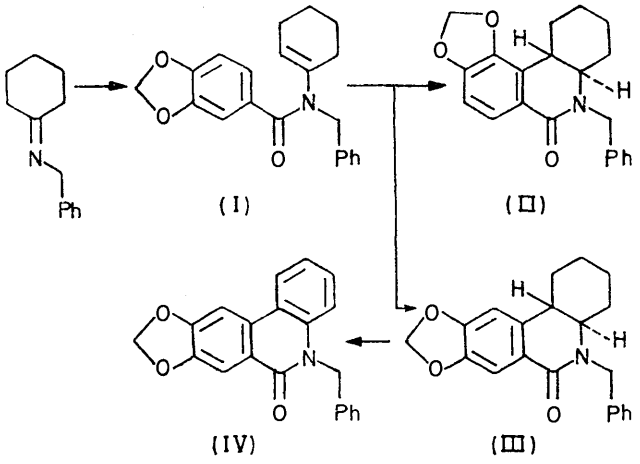
[1] Part III, I. Ninomiya, T. Naito, and T. Kiguchi, preceding paper.

[2] Preliminary communication, I. Ninomiya, T. Naito, and T. Kiguchi, *Chem. Comm.*, 1970, 1669.

[3] (*a*) W. C. Wildman, *J. Amer. Chem. Soc.*, 1956, **78**, 4180; (*b*) H. Muxfeldt, R. S. Schneider, and J. B. Mooberry, *J. Amer. Chem. Soc.*, 1966, **88**, 3670.

[4] K. Mitsuhashi, *J. Pharm. Soc. Japan*, 1952, **72**, 344.

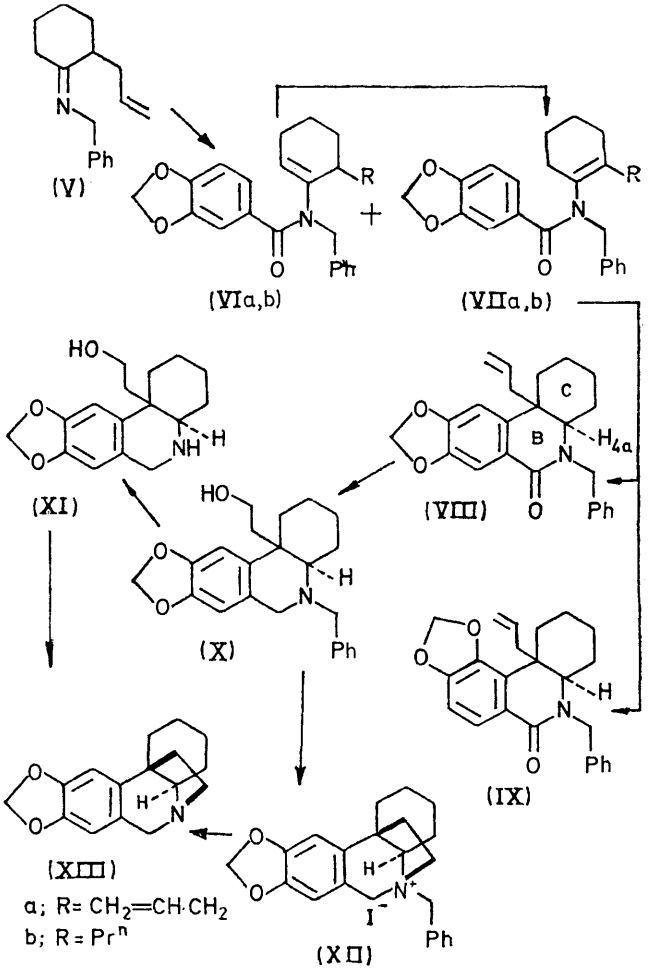
results in the photocyclisation of 2-alkylcyclohexanone enamides,[1] we could then proceed to the crinan synthesis. 2-Allylcyclohexanone was treated with benzylamine to give the imine (V), which was immediately acylated



with piperonyloyl chloride to afford a mixture of enamides (VIa) and (VIIa). Hydrogenation of the mixture afforded a mixture of the propylenamides (VIb) and (VIIb) in a ratio of 4 : 1 (n.m.r.). Prolonged heating or, more conveniently, irradiation with a high-pressure mercury lamp directly above the mixture of (VIa) and (VIIa) for only 30 min completed isomerisation to afford the homogeneous enamide (VIIa) in good yield.

A methanolic solution of the enamide (VIIa) was irradiated with a low-pressure mercury lamp at room temperature for 15 h. T.l.c. showed the presence of two products, one major (VIII) and another very minor component (IX). Chromatography on silica gel afforded a readily crystallised compound (VIII) in 20% yield, which was almost homogeneous and showed n.m.r. signals for two aromatic protons at δ 7·70 and 6·65, each as a singlet; thus the orientaton of cyclisation as shown was established. Assignment of the B/C-*trans* ring junction was assumed from the 4a-proton n.m.r. signal, which appears as a doublet of doublets (*J* 11 and 5 Hz). This assignment agreed with expectation on the basis of the electrocyclic mechanism suggested previously,[5] and was confirmed by the identity with crinan of the final product (XIII) derived from (VIII).

Ozonolysis of the lactam (VIII) in ethanol followed by reduction with lithium aluminium hydride afforded the benzylamino-alcohol (X) in 54% yield, which was debenzylated with 40% palladium–charcoal to afford the amino-alcohol (XI) in good yield. Treatment of the amino-alcohol (XI) with thionyl chloride in dioxan resulted in spontaneous ring closure to give (±)-crinan (XIII), which was homogeneous and whose i.r. spectrum was identical with that of an authentic sample.[6] Alternatively, the amino-alcohol (X) was converted in good yield into the quaternary ammonium iodide (XII) by heating under reflux with toluene-*p*-sulphonyl chloride in pyridine, followed by treatment with aqueous potassium iodide. This salt (XII) was hydrogenolysed with 40% palladium–charcoal, affording (±)-crinan together with a considerable amount of the starting material (XII). This synthesis of (±)-crinan confirms the stereochemistry of the enamide photocyclisation and



offers a novel approach to the total synthesis of alkaloids of this group [7] which bear additional substituents only on ring C.

EXPERIMENTAL

N.m.r. spectra were determined for solutions in deuteriochloroform with a Varian A-60D instrument (tetramethylsilane as internal reference). M.p.s were determined with a Kofler hot-stage apparatus. The photochemical reactions were carried out as described in the previous paper.[1]

N-Benzyl-N-cyclohex-1-enylpiperonylamide (I).—A solution of cyclohexanone (9·8 g) and benzylamine (11·8 g)

[5] Part I, I. Ninomiya, T. Naito, and T. Mori, *J.C.S. Perkin I*, 1973, 505.

[6] W. C. Wildman, 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1960, vol. VI, p. 290.

[7] T. Kametani, 'The Chemistry of The Isoquinoline Alkaloids,' Hirokawa, Tokyo, 1968, p. 176.

in toluene (100 ml) was refluxed for 4 h, with removal of water as it formed. The resulting yellow solution was evaporated under reduced pressure. The residual oil was distilled *in vacuo* to give *N*-cyclohexylidenebenzylamine (15·7 g) as a pale yellow oil, b.p. 124—132° at 4 mmHg. To a cooled solution of the imine and triethylamine (12 g) in anhydrous chloroform (100 ml), a solution of piperonyloyl chloride (18·4 g) in anhydrous chloroform (90 ml) was added dropwise with stirring. After refluxing for 2 h, the mixture was diluted with chloroform, washed with water, dried (Na_2SO_4), and evaporated to give an oil, which was chromatographed on silica gel with chloroform as eluant. Distillation of the resulting oil afforded the *enamide* (I) (16·8 g, 50%) as a pale yellow oil, b.p. 200° (bath temp.) at 2×10^{-3} mmHg, $\nu_{max.}$ ($CHCl_3$) 1630—1600br (C=C–N–CO) and 940 cm^{-1}, δ ($CDCl_3$) 5·95 (2H, s, O·CH_2·O). 5·33 (1H, m, HC=C–N), and 4·81 (2H, s, N·CH_2Ph) (Found: C, 74·9; H, 6·15; N, 3·95. $C_{21}H_{21}NO_3$ requires C, 75·2; H, 6·3; N, 4·2%).

Irradiation of the N-*Piperonyloylenamine* (I).—A 0·02-M-solution of the *N*-piperonyloylenamine (I) (2·5 g) in methanol (800 ml) was irradiated for 17 h. (Prolonged irradiation caused decomposition of the products.) The solvent was removed and the residue was chromatographed on silica gel with chloroform as eluant. The residue from the first fraction was recrystallised from n-hexane to give 5-*benzyl*-1,2,3,4,4a,11c-*hexahydro*[1,3]*dioxolo*[4,5-k]*phenanthridin*-6(5H)-*one* (II) (310 mg, 13%), m.p. 156—157·5°, $\nu_{max.}$ (Nujol) 1640 cm^{-1} (NCO), 1610, and 925 cm^{-1}, δ($CDCl_3$) 8·15 (1H, d, *J* 9 Hz, 7-H), 7·00 (1H, d, *J* 9 Hz, 8-H), 6·05 (2H, s, O·CH_2·O) and 5·40 (2H, s, N·CH_2Ph) (Found: C, 75·55; H, 6·35; N, 4·1. $C_{21}H_{21}NO_3$ requires C, 75·2; H, 6·3; N, 4·2%). Recrystallisation of the second fraction from ether yielded 5-*benzyl*-1,2,3,4,4a,11b-*hexahydro*[1,3]-*dioxolo*[4,5-j]*phenanthridin*-6(5H)-*one* (III) (370 mg, 15%), m.p. 165—166°, $\nu_{max.}$ (Nujol) 1650 (NCO), 1610, 1585, 935, and 925 cm^{-1}, δ($CDCl_3$) 7·87 (1H, s, 7-H), 6·97 (1H, s, 11-H), 6·02 (2H, s, O·CH_2·O), and 5·41 (2H, s, N·CH_2Ph) (Found: C, 74·95; H, 5·95; N, 4·35%).

5-*Benzyl*[1,3]*dioxolo*[4,5-j]*phenanthridin*-6(5H)-*one* (IV).—A mixture of the lactam (III) and 10% palladium–charcoal was heated at 220—240 °C for 3 h. Extraction with chloroform afforded a crystalline *product* (IV), m.p. 180—183° (from 80% ethanol), $\lambda_{max.}$ (95% EtOH) 250, 253, 269, 287, 300, 309, 324, and 340 nm (lit.,[8] 250, 270, 285, 299, 310, 325, and 340) (Found: M^+, 329·105. $C_{21}H_{15}NO_3$ requires *M*, 329·105).

Acylation of N-(2-*Allylcyclohexylidene*)*benzylamine* (V) *with Piperonyloyl Chloride*.—Acylation, as before, of the imine (V) [prepared from 2-allylcyclohexanone (1·2 g) and and benzylamine] with piperonyloyl chloride (1·6 g) at room temperature afforded an oily product, which was chromatographed several times on silica gel with chloroform as eluant to give a pale yellow oil (2 g, 62%), homogeneous on t.l.c. However, this was found to be a mixture of *N*-(6-allylcyclohex-1-enyl)-*N*-benzylpiperonylamide (VIa) and *N*-(2-allylcyclohex-1-enyl)-*N*-benzylpiperonylamide (VIIa) in a ratio of *ca.* 4 : 1 (n.m.r.). Rapid distillation afforded a sample of b.p. 190° at 2×10^{-3} mmHg, $\nu_{max.}$ ($CHCl_3$) 1630—1600br (C=C–NCO), 995, 915 (CH=CH_2), and 940 cm^{-1}, δ($CDCl_3$) 5·95 (2H, s, O·CH_2·O) and 5·50 (*ca.* 0·8H, approx. t, HC=C–N) (Found: C, 77·05; H, 6·65; N, 3·9. Calc. for $C_{24}H_{25}NO_3$: C, 76·75; H, 6·7; N, 3·75%). Removal of the low boiling fraction of the crude oil by slow distillation left a brown residue, which was chromatographed on alumina with benzene as eluant to give the homogeneous *enamide* (VII) (t.l.c. and n.m.r. spectrum). Distillation gave a sample of b.p. 200° (bath temp.) at 2×10^{-3} mmHg, $\nu_{max.}$ ($CHCl_3$) 1630—1600br C=C–NCO), 995, 920 (CH=CH_2), and 940 cm^{-1}, δ($CDCl_3$) 5·95 (2H, s, O·CH_2·O), 4·95 and 4·60 (2H, AB-type q, *J* 14 Hz, N·CH_2Ph), and 2·90—2·00br (2H, eight lines, CH_2·CH=CH_2) (Found: C, 77·05; H, 6·85; N, 3·75. $C_{24}H_{25}NO_3$ requires C, 76·75; H, 6·7; N, 3·65%). Isomerisation of the enamide (VIa) to (VIIa) was observed in good yield on irradiation of the mixture (neat) with a 1 kW high-pressure mercury lamp.

Catalytic Hydrogenation of the N-*Piperonyloylenamine* (VIIa).—The *N*-piperonyloylenamine (VIIa) in methanol was hydrogenated at room temperature over Raney nickel. Distillation of the product afforded N-*benzyl*-N-(2-*propylcyclohex*-1-*enyl*)*piperonylamide* (VIIb) as an oil in high yield; b.p. 200° (bath temp.) at 2×10^{-3} mmHg, $\nu_{max.}$ ($CHCl_3$) 1630—1600br (C=C–NCO) and 940 cm^{-1}, δ($CDCl_3$) 5·90 (2H, s, O·CH_2·O) and 4·90 and 4·60 (2H, AB-type q, *J* 14 Hz, N·CH_2Ph) (Found: C, 76·4; H, 7·2; N, 3·6. $C_{24}H_{27}NO_3$ requires C, 76·35; H, 7·2; N, 3·7%).

Hydrogenation of the 4 : 1 *Mixture of Enamides* (VIa) *and* (VIIa).—Similar hydrogenation of the mixture of enamides afforded an oil, homogeneous on t.l.c., in good yield. The n.m.r. spectrum showed it to be a mixture of *N*-benzyl-*N*-(6-propylcyclohex-1-enyl)piperonylamide (VIb) and *N*-benzyl-*N*-(2-propylcyclohex-1-enyl)piperonylamide (VIIb) in a ratio of *ca.* 4 : 1. Rapid distillation afforded a sample of b.p. 200° (bath temp.) at 2×10^{-3} mmHg, $\nu_{max.}$ ($CHCl_3$) 1630—1600br (C=C–NCO) and 935 cm^{-1}, δ($CDCl_3$) 5·95 (2H, s, O·CH_2·O), 5·45br (*ca.* 0·8H, t, HC=C–N), 5·25 and 4·43 (*ca.* 1·6H, AB-type q, *J* 14·5 Hz, N·CH_2Ph), and 4·95 and 4·55 (*ca.* 0·4H, AB-type q, *J* 14 Hz, N·CH_2Ph) (Found: C, 76·6; H, 7·3; N, 3·65. Calc. for $C_{24}H_{27}NO_3$: C, 76·35; H, 7·2; N, 3·7%).

Irradiation of the N-*Piperonyloylenamine* (VIIa).—According to the procedure given for (I), irradiation of the *N*-piperonyloylenamine (VIIa) (16·5 g) in methanol (2·2 l; 0·02M) for 15 h, and chromatography of the crude product on silica gel with chloroform as eluant followed by repeated preparative t.l.c., afforded *trans*-11c-allyl-5-benzyl-1,2,3,4,4a,11c-hexahydro[1,3]dioxolo[4,5-*k*]phenanthridin-6(5*H*)-one (IX) as an oil, which was homogeneous on t.l.c. but contained a very small amount of the lactam (VIII) (n.m.r. spectrum), although this could not be isolated; $\nu_{max.}$ ($CHCl_3$) 1640, 1610, 995, 950, and 915 cm^{-1}, δ($CDCl_3$) 7·85 (*ca.* 0·7H, d, *J* 8·5 Hz, 7-H), 7·70 [*ca.* 0·3H, s, 7-H of (VIII)], 6·83 (*ca.* 0·7H, d, *J* 8·5 Hz, 8-H), 6·65 [*ca.* 0·3H, s, 11-H of (VIII)], 5·93 (*ca.* 1·4H, s, O·CH_2·O), and 6·00 [*ca.* 0·6H, s, O·CH_2·O of (VIII)].

Recrystallisation of a second fraction from ether afforded trans-11b-*allyl*-5-*benzyl*-1,2,3,4,4a,11b-*hexahydro*[1,3]*dioxolo*[4,5-j]*phenanthridin*-6(5H)-*one* (VIII) (3·3 g, 20%), m.p. 157—158°, $\nu_{max.}$ (Nujol) 1640, 1615, 995, 930, and 910 cm^{-1}, δ($CDCl_3$) 7·70 (1H, s, 7-H), 6·65 (1H, s, 11-H), 6·00 (2H, s, O·CH_2·O), 5·40 and 4·40 (2H, AB-type q, *J* 16 Hz, N·CH_2Ph), 3·70 (1H, dd, *J* 11 and 5 Hz, 4a-H), and 2·40br (2H, d, *J* 6·5 Hz, CH_2·CH=CH_2) (Found: C, 77·0; H, 6·75; N, 3·85. $C_{24}H_{25}NO_3$ requires C, 76·75; H, 6·7; N, 3·75%).

trans-5-*Benzyl*-2,3,4,4a,5,6-*hexahydro*-1H-[1,3]*dioxolo*-[4,5-j]*phenanthridine*-11b-*ethanol* (X).—Into a solution of

[8] T. Ikeda, W. I. Taylor, Y. Tsuda, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 1956, 4749.

the lactam (VIII) (1·6 g) in anhydrous ethanol (250 ml), ozone gas was bubbled slowly with cooling (ice) for 5 h. T.l.c. then showed complete disappearance of the starting material. Removal of the solvent at room temperature under reduced pressure left a yellow oil, which was dissolved in anhydrous ether (200 ml), and lithium aluminium hydride (4·5 g) was added in small portions with cooling. The mixture was refluxed for 5 h, then the excess of lithium aluminium hydride was decomposed by adding water with cooling. The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated to give a solid, which was recrystallised from ethanol to afford the *amino-alcohol* (X) (860 mg, 54%), m.p. 190—191°, $\nu_{max.}$ (Nujol) 3100br (OH) and 930 cm^{-1}, δ($CDCl_3$) 6·65 (1H, s, 11-H), 6·31 (1H, *approx.* s, 7-H), 5·85 (2H, s, O·CH_2·O), 4·35 and 2·87 (2H, AB-type q, *J* 12 Hz), 3·65 and 3·20 (2H, AB-type q, *J* 15 Hz), and 2·45 (1H, dd, *J* 11 and 3 Hz, 4a-H) (Found: C, 75·5; H, 7·4; N, 3·85. $C_{23}H_{27}NO_3$ requires C, 75·6; H, 7·45; N, 3·85%).

trans-2,3,4,4a,5,6-*Hexahydro*-1H-[1,3]*dioxolo*[4,5-j]*phenanthridine*-11b-*ethanol* (XI).—A solution of the *N*-benzyl alcohol (X) (260 mg) in methanol (30 ml) containing conc. hydrochloric acid (1 ml) was shaken in the presence of 40% palladium–charcoal (80 mg) at room temperature and 4·5 atm for 5 h. Filtration and evaporation left a residue, which was washed with ether, treated with aqueous potassium carbonate, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a powder (170 mg, 8%). Recrystallisation from ethanol gave the *alcohol* (XI) m.p. 177—178°, $\nu_{max.}$ (Nujol) 3250 (NH), 3300—3000br (OH) and 940 cm^{-1} (Found: C, 69·55; H, 7·55. $C_{16}H_{21}NO_3$ requires C, 69·8; H, 7·7%).

(±)-5-*Benzylcrinanium Iodide* (XII).—A solution of the *N*-benzyl alcohol (X) (180 mg) and toluene-*p*-sulphonyl chloride (95 mg) in anhydrous pyridine (8 ml) was refluxed for 3 h. The solvent was removed under reduced pressure and the residue was treated with aqueous potassium carbonate and extracted with ether. The aqueous layer was extracted thoroughly with chloroform and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated to give a powder (240 mg). This was dissolved in hot water, and aqueous potassium iodide (100 mg) was added. The resulting crystals (200 mg, 85%) were collected and recrystallised from water to give the *quaternary salt* (XII) as needles, m.p. 188—191°, $\nu_{max.}$ (Nujol) 1615 and 930 cm^{-1} (Found: C, 57·8; H, 5·4; N, 2·85. $C_{23}H_{26}INO_2$ requires C, 58·1; H, 5·5; N, 2·95%).

(±)-*Crinan* (XIII).—(a) *From the alcohol* (XI). Freshly distilled thionyl chloride (0·5 ml) was added to an ice-cooled solution of the amino-alcohol (XI) (220 mg) in anhydrous dioxan (8 ml), which was then kept at room temperature overnight. The mixture was diluted with water, treated with potassium carbonate, and extracted thoroughly with ether. The combined extracts were washed with brine, dried (K_2CO_3), and evaporated. The residue was chromatographed on alumina with ether as eluant to give the tertiary amine (XIII) (70 mg, 34%), δ($CDCl_3$) 6·70 (1H, s, 11-H), 6·45 (1H, approx. s, 7-H), 5·87 (2H, s, O·CH_2·O), and 4·35 and 3·71 (2H, AB-type q, *J* 17 Hz, 6-H_2), identical (i.r. spectrum) with authentic (−)-crinan. Recrystallisation of the *hydrochloride* of (XIII) from acetone afforded crystals of m.p. 252—254° (decomp.) (Found: C, 65·05; H, 6·7; N, 4·8. $C_{16}H_{20}ClNO_2$ requires C, 65·4; H, 6·85; N, 4·75%).

(b) *From the quaternary salt* (XII). A solution of the quaternary salt (XII) (200 mg) in methanol (5 ml) containing conc. hydrochloric acid (2 drops) was stirred in the presence of 40% palladium–charcoal (100 mg) at room temperature and 5·3 atm for 6 h. Filtration and evaporation left a residue, which was washed with ether, treated with aqueous potassium carbonate, and extracted with ether. The salt (XII) (160 mg) was recovered by extraction with chloroform from the insoluble fraction. The ether extracts were washed with brine, dried (K_2CO_3), and evaporated to give the base (XIII) (20 mg, 92%), identical with the sample obtained in (a) (t.l.c. and i.r. spectra).

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