

Photocyclisation of Enamides. Part V.¹ Photocyclisation of $\alpha\beta$ -Unsaturated Anilides

By Ichiya Ninomiya,* Sadami Yamauchi, Toshiko Kiguchi, Atsuko Shinohara, and Takeaki Naito, Kobe Women's College of Pharmacy, Motoyamakita, Higashinada, Kobe, Japan

Irradiation of *N*-methyl- and *N*-benzyl-cyclohex-1-enecarboxanilide (Ia and b) and *N*-methyl-3,4-dihydronaphthalene-1-carboxanilide (VIII) with a low pressure mercury lamp afforded a mixture of *cis*- and *trans*-photocyclised products [the phenanthridones (II) and (III), and the benzophenanthridinones (IX) and (X), respectively], whose ratios were dependent upon the solvent employed. Equilibration and deuterium incorporation experiments provided important information on the reaction mechanism.

WE have developed a photocyclisation of various types of *N*-benzoylenamines² and shown its use for the

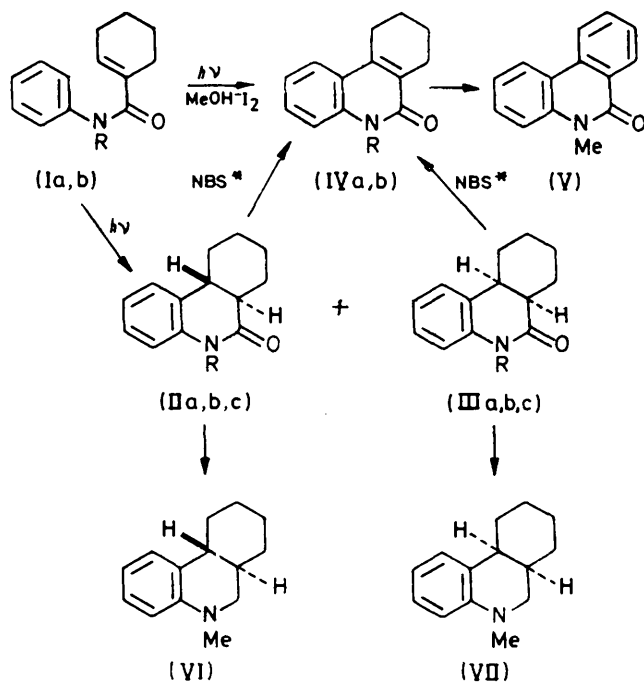
synthesis of a variety of heterocyclic systems. Chapman and his co-workers have previously reported the first

¹ I. Ninomiya, T. Naito, and T. Kiguchi, *J.C.S. Perkin I*, 1973, 2261.

² (a) I. Ninomiya, T. Naito, and T. Kiguchi, *J.C.S. Perkin I*, 1973, 2257; (b) I. Ninomiya, T. Naito, T. Kiguchi, and T. Mori, *ibid.*, p. 1696; (c) I. Ninomiya, T. Naito, and T. Mori, *ibid.*, p. 595.

non-oxidative photocyclisation of alkyl anilides,³ which can be regarded as a species of enamide. The stereochemistry of the reaction has not yet been clarified, although further examples of photocyclisation have been reported.⁴ We now report on stereochemical aspects of the photocyclisation of anilides and demonstrate the usefulness of this reaction for the synthesis of phenanthridine.

Acylation of *N*-alkylanilines with cyclohex-1-ene-carbonyl chloride⁵ afforded the corresponding anilides (Ia and b) in good yields. Irradiation² of a 0.02M-methanolic solution of the anilides (Ia and b) afforded mixtures of *trans*- and *cis*-epimeric products [(IIa and b), and (IIIa and b)] respectively, the *cis*-isomers (IIIa and b) being predominant on g.l.c. The ratios of



* NBS = *N*-bromosuccinimide
 a, R = Me; b, R = CH₂Ph; c, R = H

epimeric photoproducts were dependent upon the solvent employed during the irradiation; in protic solvents such as methanol, the *cis*-isomers (IIIa and b) were obtained predominantly while in aprotic solvents such as benzene, ether, and even dimethyl sulphoxide, the *trans*-isomers (IIa and b) were the major products (Table). Isolation of these epimeric products was accomplished by repeated chromatography.

The *cis*-*N*-benzyl-lactam (IIIb) was debenzylated to afford the *cis*-*N*-nor-lactam (IIIc), identified by comparison with an authentic sample prepared by Masamune.⁶ Similarly, debenzylation of the *trans*-*N*-benzyl-

³ (a) P. G. Cleveland and O. L. Chapman, *Chem. Comm.*, 1967, 1064; (b) O. L. Chapman and W. R. Adams, *J. Amer. Chem. Soc.*, 1968, **90**, 2333.

⁴ (a) Y. Ogata, K. Takagiri, and I. Ishino, *J. Org. Chem.*, 1971, **36**, 3975; (b) M. Ogata and H. Matsumoto, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2264.

lactam (IIb) afforded the *trans*-*N*-nor-lactam (IIc), identical with the authentic sample.⁶ *N*-Methylation of a mixture of the *N*-nor-lactams (IIc) and (IIIc)

Solvent effect on the *trans* : *cis* ratio of products of photocyclisation of anilides

Anilide	Et ₂ O	Me ₂ SO	C ₆ H ₆	MeOH
(Ia)	4.0		0.9	0.3
(Ib)	15.6	4.0	1.6	0.4
(VIII)	6.3		1.5	0.7

afforded a mixture of the corresponding *N*-methyl-lactams which were identical with the photoproducts (IIa) and (IIIa) from the *N*-methylanilide (Ia) respectively.

Irradiation of the *N*-alkylanilides (Ia and b) in the presence of iodine afforded the corresponding didehydro-lactams (IVa^{6a} and b) respectively which were also obtained from the photoproducts [(IIa and b) and (IIIa and b)] upon treatment with *N*-bromosuccinimide. Further dehydrogenation of the didehydro-lactam (IVa) with selenium at an elevated temperature afforded the known phenanthridone (V).⁷ Lithium aluminium hydride reduction of the photoproducts (IIa) and (IIIa) afforded the corresponding tertiary amines (VI) and (VII)⁶ respectively.

Similar photocyclisation was also observed for the naphthalenecarboxanilide (VIII) which was prepared from *N*-methylaniline with 3,4-dihydronaphthoyl chloride in a good yield. The photoproducts were a mixture of *trans*- and *cis*-lactams (IX) and (X) in the ratio described in the Table. These were readily separated by chromatography and their structures were determined upon inspecting the coupling constants of the 4b-protons. The ratios of the *cis*- and *trans*-products coincided with those of the anilides (Ia and b). Irradiation of the enamide (VIII) in the presence of iodine afforded the expected didehydro-lactam (XI) along with the compound (XII) with a 4b-hydroxy-group.

The possibility of isomerisation between the *trans*- and *cis*-lactams (IIb) and (IIIb) during the course of their formation in the photocyclisation was examined. When a methanolic solution of either isomer, *cis*-(IIIb) or *trans*-(IIb), was irradiated or heated under reflux over 7 h, no isomerisation was observed. On the other hand, isomerisation was observed when potassium hydroxide was present: an alkaline methanolic solution of the anilide (IIb) or (IIIb) when heated under reflux for 7 h gave an equimolar mixture of both lactams (IIb) and (IIIb). This confirmed that the ratios observed in the photocyclisation of the anilides reflect the stereochemical course of the cyclisation.

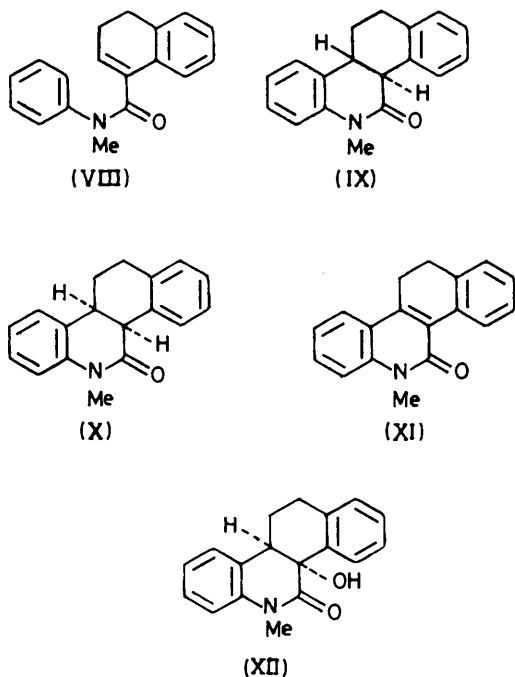
We also carried out experiments with deuteriated solvents in order to examine the possibility of solvent incorporation. When irradiation of the anilide (Ib) was carried out in an ethereal solution saturated with

⁶ G. H. Alt and A. J. Speziale, *J. Org. Chem.*, 1966, **31**, 1340.

⁶ (a) T. Masamune, M. Takasugi, H. Sugimoto, and M. Yokoyama, *J. Org. Chem.*, 1964, **29**, 681; (a) A. Michailidis, J.-P. Brouard, and A. Resplandy, *Compt. rend.*, 1972, **275**, 961.

⁷ T. Hase, *Acta Chem. Scand.*, 1964, **18**, 1806.

deuterium oxide, the photoproduct, which consisted of almost pure *trans*-isomer (IIb) (53%), had incorporated only 12% deuterium. On the other hand, the photoproducts from irradiation in deuterium methoxide solution, consisting of almost pure *cis*-isomer (IIIb) (36%), had incorporated 90% deuterium.



This marked contrast suggests the following mechanism for the photocyclisation of anilides: photochemical electrocyclic ring closure of the 6 π -electron enamide system⁸ gives an intermediate, which would then undergo a thermal hydrogen shift in both a stepwise and concerted manner, to afford a mixture of *cis*- and *trans*-lactams in the ratio observed. In an aprotic solvent, hydrogen would be shifted concertedly to afford the *trans*-lactam predominantly, while in a protic solvent, a stepwise hydrogen shift (deprotonation and protonation) occurs, therefore affording a mixture of *cis*- and *trans*-lactams; the reason for the preponderance of the *cis*-lactam is yet to be examined.

EXPERIMENTAL

I.r. spectra were recorded for solutions in chloroform, ¹H n.m.r. spectra for solutions in deuteriochloroform on a Varian A-60D instrument, and mass spectra on a JEOL-JMS-01SG machine. M.p.s were determined with a Kofler hot-stage apparatus. Photochemical reactions were carried out as described previously.¹

N-Methylcyclohex-1-enecarboxanilide (Ia).—To a stirred solution of *N*-methylaniline (3.4 g) and triethylamine (6.8 g) in anhydrous benzene (100 ml), a solution of cyclohex-1-enecarbonyl chloride⁵ (4.6 g) in anhydrous benzene (50 ml) was added dropwise with ice-cooling. The resulting solution was heated under reflux for 2 h, then diluted with benzene, washed with water, and dried. The solvent was removed and the residue chromatographed on alumina.

Elution with benzene afforded the *anilide* (Ia) as an oil (6.0 g, 88%), b.p. 123–127° at 2 mmHg, ν_{\max} 1625 cm^{-1} (N-CO-C=C), δ 5.83 (1H, m, CH=C) and 3.33 (3H, s, NMe) (Found: C, 77.75; H, 8.0; N, 6.7. $\text{C}_{14}\text{H}_{17}\text{NO}$ requires C, 78.1; H, 7.95; N, 6.5%).

N-Benzylcyclohex-1-enecarboxanilide (Ib).—A similar reaction of *N*-benzylaniline (6.3 g) with cyclohex-1-enecarbonyl chloride (5.5 g) afforded the *anilide* (Ib) (9 g, 90%), m.p. 75° (from *n*-hexane), ν_{\max} 1623 cm^{-1} (N-CO-C=C), δ 5.88 (1H, m, CH=C) and 4.99 (2H, s, NCH_2Ph) (Found: C, 82.7; H, 7.4; N, 4.55. $\text{C}_{20}\text{H}_{21}\text{NO}$ requires C, 82.45; H, 7.25; N, 4.8%).

cis- and *trans*-6a,7,8,9,10,10a-Hexahydro-5-methylphenanthridin-6(5H)-one (IIIa and IIa).—A 0.02M-solution of the anilide (Ia) (1.6 g) in methanol, ether, or benzene (400 ml) was irradiated with a low pressure mercury lamp at room temperature over 40 h. The solvent was removed *in vacuo* at room temperature to yield a residue which was chromatographed on silica gel. The fraction eluted with benzene afforded a pale yellow oil (30–59%), b.p. 138–143° (bath temp.) at 1 mmHg, ν_{\max} 1660 cm^{-1} (NCO), which was a mixture of the *cis*- and *trans*-lactams, and their ratios were determined by g.l.c. as in the Table. The stereoisomers were separated by preparative t.l.c. or g.l.c. The *cis*-lactam (IIIa) had b.p. 138–143° (bath temp.) at 1 mmHg, ν_{\max} 1660 cm^{-1} (NCO), δ 3.65 (3H, s, NMe) (Found: C, 78.5; H, 8.0; N, 6.55. $\text{C}_{14}\text{H}_{17}\text{NO}$ requires C, 78.1; H, 8.0; N, 6.5%). The *trans*-lactam (IIa) had m.p. 98–99° (from *n*-hexane), ν_{\max} 1660 cm^{-1} (NCO), δ 3.63 (3H, s, NMe) (Found: C, 77.95; H, 8.05; N, 6.6%).

The *cis*-lactam (IIIa) was identical with a sample prepared by methylation of the *N*-nor-lactam (IIIc) provided by Professor Masamune.⁶

cis- and *trans*-5-Benzyl-6a,7,8,9,10,10a-hexahydrophenanthridin-6(5H)-one (IIIb and IIb).—A similar irradiation of the anilide (Ib) (2.3 g) in methanol, ether, or benzene, as in the case of (Ia) afforded the photocyclised product as a mixture of *cis*- and *trans*-stereoisomers [(IIIb) and (IIb)]. Their ratios were determined by g.l.c. as in the Table. The product was obtained in 48–67% yield, as crystals, m.p. 109–111° (Found: C, 82.65; H, 7.25; N, 4.8. $\text{C}_{20}\text{H}_{21}\text{NO}$ requires C, 82.45; H, 7.25; N, 4.8%), and was separated by preparative g.l.c. The *cis*-lactam (IIIb) had δ 5.10 and 5.35 (2H, ABq, J 16 Hz, NCH_2Ph). The *trans*-lactam (IIb) gave crystals, m.p. 118–119° from *n*-hexane, ν_{\max} 1670 cm^{-1} (NCO), δ 4.95 and 5.45 (2H, ABq, J 16 Hz, NCH_2Ph) (Found: C, 82.6; H, 7.35; N, 4.75%).

7,8,9,10-Tetrahydro-5-methylphenanthridin-6(5H)-one (IVa).—(a) *Oxidative photocyclisation of the enamide* (Ia). The enamide (Ia) (1.6 g) in methanol (400 ml) was irradiated in the presence of iodine (1.0 g) over 48 h. The solvent was evaporated and the dark brown residue was dissolved in chloroform and washed with aqueous sodium thiosulphate, water, and dried. Evaporation of the solvent afforded a residue which was chromatographed on silica gel. Elution with chloroform gave a viscous oil, which was distilled, b.p. 170–180° (bath temp.) at 1 mmHg, to give the didehydro-lactam (IVa),^{6a} as a pale yellow oil (0.5 g, 30%), ν_{\max} 1634 cm^{-1} (N-CO-C=C), δ 3.72 (3H, s, NMe) (Found: C, 78.8; H, 6.95; N, 6.35. Calc. for $\text{C}_{14}\text{H}_{15}\text{NO}$: C, 78.85; H, 7.1; N, 6.55%).

(b) *Dehydrogenation of the trans- or cis-lactam* (IIa or IIIa). A mixture of the *trans*-lactam (IIa) (144 mg) and

⁶ R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry,' Academic Press, New York, 1970.

N-bromosuccinimide (95 mg) in carbon tetrachloride (8 ml) was stirred at 30–40° for 6 h. The succinimide formed was filtered off and the filtrate was evaporated to give a residue which was purified by preparative t.l.c. to afford the didehydro-lactam (IVa) ⁶ (35 mg, 31%), and starting material (56 mg). The product was identical with the sample obtained from the oxidative photocyclisation described in (a).

Similarly, the didehydro-lactam (IVa) (11 mg, 10%) was obtained from the *cis*-lactam (IIIa) (112 mg) along with recovered starting material (88 mg).

5-Methylphenanthridin-6(5H)-one (V).—A mixture of the didehydro-lactam (IVa) (48 mg) and selenium (73 mg) was heated at 240–250° (metal-bath) for 3.5 h. The mixture was extracted with hot chloroform, and the chloroform layer was filtered and evaporated to give a residue which was purified by preparative t.l.c. to give crystals of (Va) (20 mg, 43%), m.p. 106–108° (lit.,⁷ 107–108°), identical with an authentic sample.

5-Benzyl-7,8,9,10-tetrahydrophenanthridin-6(5H)-one (IVb).—A similar irradiation in the presence of iodine was carried out on the *N*-benzylanilide (Ib) (2.0 g) and afforded the didehydro-lactam (IVb) (0.7 g, 35%), m.p. 123–124°, as pale yellow crystals from *n*-hexane, ν_{\max} 1643 cm⁻¹ (N–CO–C=C), δ 5.58 (2H, s, NCH₂Ph) (Found: C, 83.15; H, 6.5; N, 4.8. C₂₀H₁₉NO requires C, 83.0; H, 6.6; N, 4.85%).

cis-6a,7,8,9,10,10a-Hexahydrophenanthridin-6(5H)-one (IIIc).—To a mixture of the *N*-benzyl-lactam (IIb) (0.4 g) in liquid ammonia (200 ml), metallic sodium (0.25 g) was added in small pieces over a period of 30 min. The mixture was stirred for a further 1 h before excess of ammonium chloride was added to stop the reaction. Ammonia was evaporated off and water was added to the residue. This was extracted with chloroform, and the chloroform layer was dried and evaporated to give a residue which crystallised upon trituration with methanol to give the lactam (IIIc) (0.13 g, 39%), m.p. 208–211° (lit.,⁶ 211–212°), ν_{\max} 3430 (NH) and 1675 cm⁻¹ (NCO), identical with an authentic sample supplied by Professor Masamune.^{6a}

trans-6a,7,8,9,10,10a-Hexahydrophenanthridin-6(5H)-one (IIc).—Similar treatment as in the case of the *cis*-isomer (IIIb) of the *trans-N*-benzyl-lactam (IIb) (0.5 g) afforded the *trans*-lactam (IIc) (0.21 g, 61%), m.p. 227° (lit.,^{6a} 220–221°), ν_{\max} 3430 (NH) and 1675 cm⁻¹ (NCO) (Found: C, 77.45; H, 7.3; N, 6.7. Calc. for C₁₃H₁₅NO: C, 77.6; H, 7.5; N, 7.0%). This compound was identical with the compound reported ⁶ (i.r. and n.m.r. spectra).

cis-6a,7,8,9,10,10a-Hexahydro-5-methylphenanthridin-6(5H)-one (IIIa).—A mixture of the *cis*-lactam (IIIc) (45 mg) and sodium hydride (12 mg) in anhydrous benzene (15 ml) was heated under reflux for 15 min and cooled. Methyl iodide was added and the mixture was heated under reflux for 7 h. After cooling, the mixture was diluted with water, extracted with benzene, and the benzene layer was washed with water, dried, and evaporated. The residue was purified by preparative t.l.c. to afford the *cis-N*-methyl-lactam (IIIa), which was identical with the photocyclised *cis*-lactam (IIIa) (i.r. spectra and g.l.c.).

trans-6a,7,8,9,10,10a-Hexahydro-5-methylphenanthridin-6(5H)-one (IIa).—By a similar methylation, the *trans*-lactam (IIc) (45 mg) was converted into the *trans-N*-methyl-lactam (IIa) (20 mg, 42%), which was identical

with the sample obtained from the photocyclisation of the *N*-methylanilide (Ia).

trans-5,6,6a,7,8,9,10,10a-Octahydro-5-methylphenanthridine (VI).—An anhydrous suspension of the *trans*-lactam (IIIa) (100 mg) and lithium aluminium hydride (80 mg) in ether (60 ml) was refluxed for 1 h on a steam-bath. Water was added to decompose excess of lithium aluminium hydride and the resulting mixture was extracted with ether. The combined ether extracts were washed with water, dried, and evaporated to afford an oily residue, which was distilled to give compound (VI) as an oil,⁶ (89 mg, 95%), b.p. 150–160° (bath temp.) at 1 mmHg.

cis-5,6,6a,7,8,9,10,10a-Octahydro-5-methylphenanthridine (VII).—Similarly, reduction of the *cis*-lactam (IIIa) (100 mg) with lithium aluminium hydride afforded the *cis*-phenanthridine (VII) ⁶ (92 mg, 99%), b.p. 125–130° (bath temp.) at 1 mmHg.

N-Methyl-3,4-dihydronaphthalene-1-carboxanilide (VIII).—Acylation of *N*-methylaniline (3.5 g) with 3,4-dihydro-1-naphthoyl chloride (4.83 g) was carried out as in the preparation of (Ia) and (Ib) and the product was purified by chromatography on silica gel. The anilide (VIII) (5.57 g, 84.5%) was obtained, b.p. 140–150° (bath temp.) at 3×10^{-3} mmHg, ν_{\max} 1640 cm⁻¹ (NCO) and 1615 cm⁻¹, δ 5.97 (1H, t, *J* 4.2 Hz, HC=C–CO) and 3.47 (3H, s, NMe) (Found: C, 82.05; H, 6.45; N, 5.4. C₁₃H₁₇NO requires C, 82.1; H, 6.5; N, 5.3%).

Photocyclisation of the Anilide (VIII).—According to the procedure given for (Ia) and (Ib), irradiation of the anilide (VIII) (455 mg) in methanol was carried out over 23 h and afforded, upon chromatography on silica gel, *trans-6,10b,11,12-tetrahydro-6-methylbenzo[i]-phenanthridin-5(4bH)-one* (IX) (80 mg, 17%), m.p. 177–178° from methanol, ν_{\max} 1670 (NCO) and 1605 cm⁻¹ (C=C), δ 3.48 (1H, d, *J* 13 Hz, 4b-H) and 3.45 (3H, s, NMe) (Found: C, 82.0; H, 6.45; N, 5.3. C₁₈H₁₇NO requires C, 82.1; H, 6.5; N, 5.3%), eluted by benzene, and the *cis*-isomer (X) (120 mg, 25.5%) eluted by benzene-chloroform, m.p. 138–140° from methanol, ν_{\max} 1663 (NCO) and 1600 cm⁻¹ (C=C), δ 3.85 (1H, d, *J* 6 Hz, 4b-H) and 3.37 (3H, s, NMe) (Found: *M*⁺, 279.12599. C₁₈H₁₇NO requires *M*, 279.12593).

The starting anilide (VIII) (110 mg, 26.2%) was eluted by chloroform. Further elution by chloroform yielded an oil which was purified by preparative g.l.c. to afford *11,12-dihydro-6-methylbenzo[i]phenanthridin-5(6H)-one* (XI) in low yield, ν_{\max} 1632 (C=C–CON) and 1590 cm⁻¹ (C=C), δ 8.70 (1H, m, 4-H), 3.75 (3H, s, NMe), and 3.00–2.80 (4H, m, 11- and 12-H₂), *m/e* 261 (*M*⁺).

Oxidative Photocyclisation of the Anilide (VIII).—According to the procedure given for (IVa), irradiation of the anilide (VIII) (553 mg) in the presence of iodine (233 mg) afforded pale yellow crystals, m.p. 181–183° from methanol, of *cis-6,10b,11,12-tetrahydro-4b-hydroxy-6-methylbenzo[i]-phenanthridin-5(4bH)-one* (XII) (159 mg, 27.2%), ν_{\max} 3480 (OH) and 1663 cm⁻¹ (NCO), δ (C₆D₅N) 4.58 (1H, s, OH, disappeared on D₂O addition), 3.53 (1H, ddd, *J* 8, 3, and 1 Hz, 10b-H), and 3.36 (3H, s, NMe) (Found: *M*⁺, 279.1260. C₁₈H₁₇NO₂ requires *M*, 279.1259). From the mother liquors of the crystallisation of the hydroxy-lactam (XII), the didehydro-lactam (XI) was obtained upon preparative g.l.c.

Photocyclisation of the N-Benzylanilide (Ib) in Deuteriated Solvent.—(a) In D₂O-treated ether. Irradiation of the *N*-benzylanilide (Ib) (300 mg) in ether (40 ml) which was saturated with D₂O was carried out over 22 h. After

evaporation of the solvent, chromatography on silica gel afforded a crystalline product (170 mg, 53%), eluted by benzene, which was recrystallised from ether to give crystals, m.p. 112—113°, which consisted of the almost pure *trans*-lactam (g.l.c.). The relative intensity of the peaks at m/e 292/291 (M^+) demonstrated deuterium incorporation by 12%.

(b) *In methan[^2H]ol solution.* The *N*-benzylanilide (Ib) (140 mg) was irradiated in MeOD (10 ml; 0.04M) over 22 h. The solvent was evaporated off to afford a residue

which was chromatographed on silica gel. Elution with benzene afforded a crystalline product (50 mg, 36%) which showed the ratio of *cis*:*trans* to be 10 (g.l.c.). The relative intensity of the m/e 292/291 peaks showed 90% deuterium incorporation.

We thank Professor T. Masamune for generous gifts of samples and Miss K. Saiki for mass spectral measurements.

[4/499 Received, 13th March, 1974]
