

## Condensed Heterotricycles: Potential Metabolites of Dibenz[*b,f*][1,4]oxazepine Antidepressant, Sintamil\*†

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The synthesis of several potential metabolites of the antidepressant, Sintamil (1) is described. Nitrolactams 3, 6 and 10, aminolactams 4, 7 and 11, and the aminoalkyl derivatives 8, 9, 12 and 13 have been described before [*Indian J. Chem.*, 12 (1974), 227]. Treatment of 1 with H<sub>2</sub>O<sub>2</sub> gave the N-oxide 2. Several syntheses of the desmethyl derivative 5 have been achieved: alkylation of 3 with N-(3-chloropropyl)-N-methylformamide followed by hydrolysis; demethylation of 1 with CNBr, followed by acid cleavage of the cyano group in 15 and with ethyl chloroformate, followed by treatment with HBr in acetic acid. Treatment of the intermediate urethane 16 from the last reaction with alcoholic alkali afforded the ring cleaved product 17. The methylaminopropyl lactam 5 was converted into the acetate 18 and urea 19. It was also reduced to the diamine 20. Treatment of the chlorolactam 14 with the sodium salt of *p*-toluenesulphonamide led to the derivative 21. Alkali-catalysed addition of lactam 3 to acrylonitrile gave 22; addition to methyl acrylate gave the ester 23 which was hydrolysed to the acid 24 on the one hand and reduced to the amino ester 28 on the other. Propionitrile 25 and propionic ester 26 were similarly prepared. N-(2-Chloro-5-nitrobenzoyl)-4-benzyloxy-2-hydroxyaniline (30) was cyclized to the lactam 31, which was aminoalkylated to 32. Treatment of 32 with hot acid cleaved the benzyl group to afford the phenolic lactam 33.

THE synthesis of the antidepressant Sintamil (1) [10-[(3-dimethylamino)propyl]-2-nitrodibenz[*b,f*][1,4]oxazepin-11-(10H)-one] was described in earlier papers<sup>1,2</sup>. The biological characterization<sup>3</sup> of Sintamil as well as structure-activity relationships<sup>4</sup> in this class of compounds have also been reported. In connection with the metabolism of Sintamil<sup>5</sup>, it was of interest to synthesize the possible metabolites in animals and in the human. Based upon the reported metabolism of imipramine<sup>6</sup> and benzoctamine<sup>7</sup>, it was expected that the metabolism of 1 would lead to N-oxidation, N-demethylation, oxidative deamination to an acid, total loss of side-chain and nuclear hydroxylation in addition to the expected reduction of the nitro group and combinations of these processes. Among these compounds 3-13 had been made<sup>1,2</sup> for structure-activity relationship studies. Others were specially made for the metabolic work and are reported in this paper.

**N-Oxide** — Hydrogen peroxide oxidation of 1 afforded the N-oxide (2) which was crystalline but analysed with approximately 2.5 moles of water of crystallization. The picrate was obtained analytically pure, as also the HCl salt.

**Desmethyl derivatives: Des-monomethyl derivative** — The desmethyl derivative 5 of Sintamil was briefly mentioned in an earlier paper<sup>1</sup>. It was considered to be an important metabolite (cf. desmethylimipramine) and hence considerable effort was expended upon its synthesis. Alkylation of 3 with 3-methylaminopropyl chloride was not a very satisfactory route to 5. The reaction of the chloropropyl derivative 14 with methylamine was reported

to yield 5, but produced other products as well. Alkylation of 3 with N-(3-chloropropyl)-N-methylformamide followed by acid hydrolysis offered a satisfactory route to 5. Demethylation of 1 as a route to 5 was considered to be even more interesting. Reaction of 1 with cyanogen bromide gave the cyanamide 15. This could be hydrolysed to 5 by hot HCl or PPA. However, the procedure that gave most reproducible results was the following. 1 was allowed to react with ethyl chloroformate in refluxing toluene, when a mixture of neutral products consisting largely of 16 and some 14 was formed. Treatment of 16 with hydrogen bromide in acetic acid afforded 5 as the hydrobromide salt. If ethanolic KOH was used for hydrolysis of 16, the product was only the phenol 17, arising by the familiar base-promoted cleavage of the diphenyl ether link in 2-nitrodibenzoxazepines<sup>1</sup>.

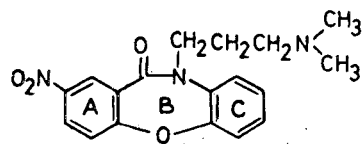
5 was further characterized as the N-acetyl derivative 18 and phenylurea 19 and also reduced to the amine 20. Formaldehyde-formic acid treatment of 5 afforded 1.

**Des-dimethyl derivative** — Although the des-di-N-methyl derivative of Sintamil was not synthesized, the tosyl derivative 21 was prepared from the chloro compound 14 by reaction with the sodium salt of *p*-toluenesulphonamide.

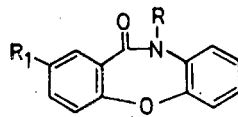
**Side chain oxidation products** — Taking advantage of the fact that the amide function in 3 formed the anion readily in the presence of alkali, it was added to acrylonitrile to yield 22, which was converted to the ester 23 in poor yields through the imidate. 23 was obtained directly in higher yields by the base-catalysed addition of 3 to methyl acrylate, and was hydrolysed under carefully defined conditions to the acid 24. The methoxy nitrolactam 6 was likewise converted to the nitrile 25 and ester 26. Treatment of nitrolactam 3 with methyl bromacetate

\*Sintamil, registered trade name of CIBA of India Ltd, for CIBA 2330-Go; 10-[3-(dimethylamino)propyl]-2-nitrodibenz[*b,f*][1,4]oxazepin-11(10H)-one hydrochloride.

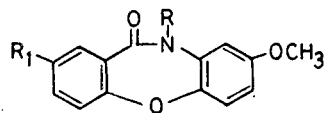
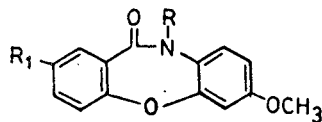
†CIBA contribution No. 350.



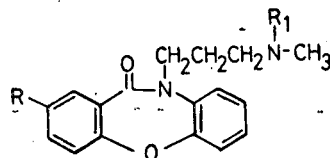
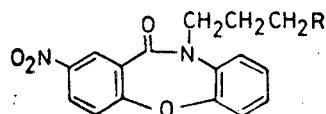
1 Sintamil (HCl salt)  
2 1-N-oxide



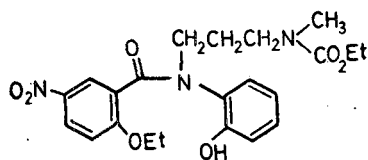
3 R=H; R<sub>1</sub>=NO<sub>2</sub>  
4 R=H; R<sub>1</sub>=NH<sub>2</sub>  
5 R=(CH<sub>2</sub>)<sub>3</sub>NHCH<sub>3</sub>; R<sub>1</sub>=NO<sub>2</sub>



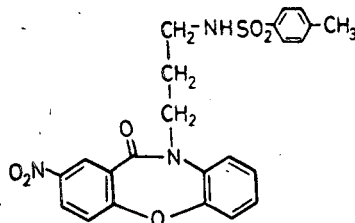
6 R=H; R<sub>1</sub>=NO<sub>2</sub>  
7 R=H; R<sub>1</sub>=NH<sub>2</sub>  
8 R=(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>3</sub>)<sub>2</sub>; R<sub>1</sub>=NO<sub>2</sub>  
9 R=(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>3</sub>)<sub>2</sub>; R<sub>2</sub>=NH<sub>2</sub>  
10 R=H; R<sub>1</sub>=NO<sub>2</sub>  
11 R=H; R<sub>1</sub>=NH<sub>2</sub>  
12 R=(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>3</sub>)<sub>2</sub>; R<sub>1</sub>=NO<sub>2</sub>  
13 R=(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>3</sub>)<sub>2</sub>; R<sub>1</sub>=NH<sub>2</sub>



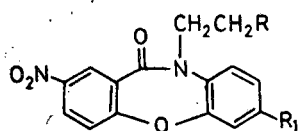
14 R=Cl  
15 R=N(CH<sub>3</sub>)<sub>2</sub>  
16 R=N(CH<sub>3</sub>)CO<sub>2</sub>Et  
17 R=NO<sub>2</sub>; R<sub>1</sub>=H  
18 R=NO<sub>2</sub>; R<sub>1</sub>=COCH<sub>3</sub>  
19 R=NO<sub>2</sub>; R<sub>1</sub>=CONHPh  
20 R=NH<sub>2</sub>; R<sub>1</sub>=H



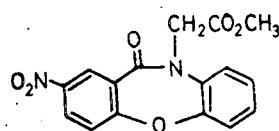
17



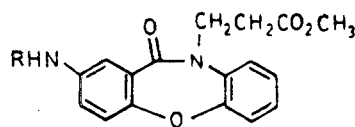
21



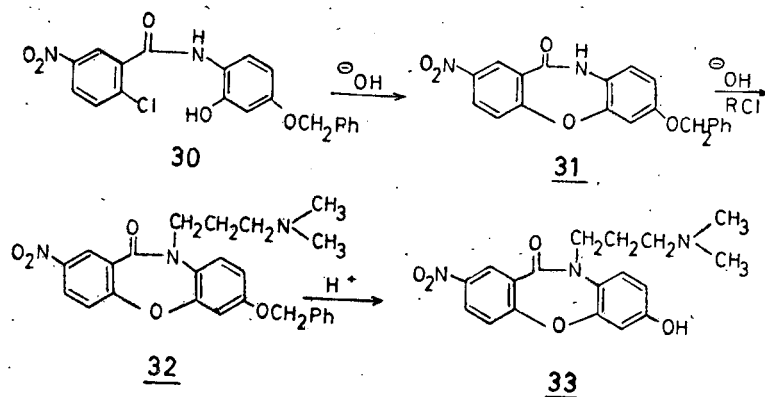
22 R=CN; R<sub>1</sub>=H  
23 R=CO<sub>2</sub>CH<sub>3</sub>; R<sub>1</sub>=H  
24 R=CO<sub>2</sub>H; R<sub>1</sub>=H  
25 R=CN; R<sub>1</sub>=OCH<sub>3</sub>  
26 R=CO<sub>2</sub>CH<sub>3</sub>; R<sub>1</sub>=OCH<sub>3</sub>



27



28 R=H  
29 R=COCH<sub>3</sub>



afforded the acetic ester 27. Catalytic reduction of the nitropropionic ester 23 led to the amine 28, which was further characterized as the acetyl derivative 29.

**Nuclear hydroxylated derivative**—Although the methyl ethers of plausible products of nuclear hydroxylation in the ring-C of 1 had been prepared before, we felt that the synthesis of the phenols themselves would be more useful for the ready identification of the relevant metabolites. Since hydroxylation *para* to the amide nitrogen was considered to be more likely, the synthesis of 33 was undertaken and achieved as follows: the amide 30 from 2-hydroxy-4-benzyloxyaniline was cyclized to the lactam 31 by aq. alkali. Alkylation with 3-dimethylaminopropyl chloride gave 32 which upon debenzoylation with hot HCl afforded 33.

### Experimental Procedure

M.p.s. are uncorrected. IR (nujol), UV (95% ethanol) and mass spectra were run respectively on a Perkin-Elmer infracord spectrophotometer, Beckmann DK 2A spectrometer and a Varian Mat CH7 mass spectrometer. NMR spectra were run on a Varian A 60 spectrometer. Chemical shifts are quoted in ppm downfield from TMS as the internal standard.

10-(3-Dimethylaminopropyl)-2-nitrodibenz[*b,f*][1,4]-oxazepin-11(10H)-one *N*-oxide (2)—A solution of 1 (2.5 g) in dioxane (10 ml) was mixed with aq. H<sub>2</sub>O<sub>2</sub> (30%, 5 ml) and the solution left at room temperature for 48 hr. It was then extracted with ether to remove unreacted 1 and evaporated to dryness. The residue crystallized from ethanol-ether to give 2 (1.5 g), m.p. about 128°;  $\nu_{\max}$  1640 cm<sup>-1</sup> (C=O); hydrochloride, m.p. 192° (d) (EtOH) (Found: C, 55.09; H, 5.35; N, 10.42. C<sub>18</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>5</sub> requires C, 54.89; H, 5.12; N, 10.67%); picrate, m.p. 180-82° (d) (acetone-EtOH) (Found: C, 48.82; H, 4.04; N, 14.44. C<sub>24</sub>H<sub>22</sub>N<sub>6</sub>O<sub>12</sub> requires C, 49.15; H, 4.04; N, 14.33%).

10-(3-Methylaminopropyl)-2-nitrodibenz[*b,f*][1,4]-oxazepin-11-(10H)-one (5): (a) *Using N*-(3-chloropropyl)-*N*-methylformamide—A solution of 2-nitrodibenz[*b,f*][1,4]oxazepin-11-(10H)-one (3)<sup>2</sup> (5.1 g, 20 mmoles) in hot dioxane was added with stirring to sodamide (0.98 g, 25 mmoles) in dioxane (25 ml) during 10 min. The resultant clear solution was treated with *N*-(3-chloropropyl)-*N*-methylformamide<sup>8</sup> (3.4 g, 25 mmoles) during 10 min. The mixture was heated and stirred under reflux for 6 hr. Dioxane was then removed *in vacuo*, the residue treated with water and methylene chloride and filtered to remove recovered 3 (1.6 g) which was in-

soluble in both the phases. The methylene chloride layer was dried and evaporated to give *N*-formyl 5 as an oil (4.6 g). It was dissolved in ethanol (70 ml), mixed with aq. HCl (6*N*; 30 ml) and heated under reflux for 6 hr. Upon cooling in an ice-bath, a crystalline precipitate separated, which was filtered and washed with acetone and ether to give 5 HCl (2.55 g), m.p. 215-17°. The mother liquor was worked up to give the basic part (0.7 g), which yielded additional 5 HCl (0.35 g). The total product crystallized from ethanol-ether; m.p. 218-20° (Found: C, 55.90; H, 4.99; N, 11.38. C<sub>17</sub>H<sub>18</sub>ClN<sub>3</sub>O<sub>4</sub> requires C, 56.13; H, 4.99; N, 11.55%);  $\nu_{\max}$  1620 cm<sup>-1</sup> (C=O);  $\lambda_{\max}$  224, 264 nm (log  $\epsilon$  4.26, 4.05); NMR (D<sub>2</sub>O): 2.2 (*qu*; CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>), 2.87 (*s*, NCH<sub>3</sub>), 3.25 (*t*, CH<sub>2</sub>NHCH<sub>3</sub>), 4.28 (*t*, CON-CH<sub>2</sub>).

(b) *By demethylation of 1*: (i) *Using cyanogen bromide*—A solution of cyanogen bromide (2.1 g, 20 mmoles) in dry ether (15 ml) was added dropwise with stirring into a solution of 1 (5 g) in the same solvent (25 ml) at room temperature during 15 min. A crystalline precipitate was formed immediately. The mixture was stirred for 4 hr at room temperature, treated with water and filtered to give the cyanamide 15 (3.2 g), m.p. 131°, raised to 135-36° by crystallization from CHCl<sub>3</sub>-hexane (Found: C, 61.21; H, 4.87; N, 15.79. C<sub>18</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub> requires C, 61.36; H, 4.58; N, 15.90%);  $\nu_{\max}$  2200 (C≡N), 1630 cm<sup>-1</sup> (C=O).

A suspension of 15 (3 g) in aq. HCl (4*N*; 75 ml) was heated under reflux for 3 hr, cooled and extracted with ether to remove neutral material. The aq. layer was separated, made basic with conc. aq. ammonia and extracted with methylene chloride to give a basic product (2.2 g) which was converted into the HCl salt. Crystallization from EtOH gave 5 HCl (0.7 g), m.p. 215-18°.

Hydrolysis of the cyanamide 15 (4.2 g) with PPA (55 g) at 160° for 3 hr and workup as before gave crude 5 (2.4 g) from which pure 5 HCl (1 g), m.p. 215-18° was obtained.

(ii) *Using ethyl chloroformate*—To a stirred solution of 1 (from 3.8 g, 10 mmoles HCl salt) in dry xylene (10 ml) was added dropwise ethyl chloroformate (4.3 g, 40 mmoles) in xylene (20 ml). The mixture was then heated under reflux for 7 hr and treated with water. The xylene layer was separated, washed with dil. HCl and then with water. The aq. layers were combined, basified and extracted with ether to give recovered 1 (1.8 g). The xylene layer was dried and evaporated to give urethane 16 as an oil (2 g);  $\nu_{\max}$  1680 and 1635 cm<sup>-1</sup> (C=O).

The crude urethane **16** (9 g) was treated with HBr in AcOH (30%; 100 ml) and the solution set aside for 48 hr. Addition of ether gave a crystalline precipitate of **5** HBr which was filtered and washed with ether. The filtrates were washed repeatedly with water, dried and evaporated to give the chloropropyl lactam (**14**) which was purified by crystallization from ether (yield 1.5 g), m.p. 106-07° (Found: C, 57.15; H, 4.25; N, 8.30.  $C_{16}H_{13}ClN_2O_4$  requires C, 57.77; H, 3.94; N, 8.42%);  $\nu_{\max}$  1630  $cm^{-1}$  (C=O); NMR ( $CDCl_3$ ): 2.25 (*qu*,  $CH_2-CH_2-CH_2$ ), 3.62 (*t*, N- $CH_2$ ), 4.33 (*t*, Cl- $CH_2$ ).

**5** HBr was suspended in water and treated with conc. aq. ammonia. The liberated base was extracted into ether and converted to the hydrochloride salt; 4.5 g, m.p. 216-20°.

*Treatment of urethane 16 with alkali* — Crude **16** (450 mg), KOH (110 mg) and ethanol (2 ml) were warmed to give a clear solution which was set aside at room temperature for 3 hr. The solution was diluted with water and extracted with ether. The aq. layer was acidified to give an oil which solidified. This was filtered and crystallized from ether-hexane to give the phenolic urethane **17** (100 mg), m.p. 147-48° (Found: C, 58.96; H, 5.86; N, 9.69.  $C_{22}H_{27}N_3O_7$  requires C, 59.31; H, 6.11; N, 9.43%);  $\nu_{\max}$  1660 and 1640; (C=O), 3210  $cm^{-1}$  (OH);  $\lambda_{\max}$  282, 300 nm ( $\log \epsilon$  3.97, 3.97); NMR ( $CDCl_3$ ): 1.25 (*t*,  $J=7$  Hz,  $-CH_2-CH_3$ ), 1.47 (*t*,  $J=7$  Hz,  $-CH_2-CH_3$ ), 1.87 (*qu*,  $CH_2-CH_2-CH_2$ ), 2.92 (*s*, N $CH_3$ ), 3.45 (*t*,  $-CH_2-N-CH_3$ ), 3.92 (*t*, CO-N- $CH_2$ ), 4.12 (*q*,

2  $CH_2-CH_3$ ).

*N-Acetyl derivative of 5* — A mixture of **5** (3 g), acetic anhydride (5 ml) and triethylamine (2 ml) in ether (20 ml) was set aside at room temperature for 48 hr, when the acetyl derivative **18** separated as a crystalline precipitate (1 g) which recrystallized from MeOH-ether, m.p. 105-10° (Found: C, 61.82; H, 5.34; N, 11.16.  $C_{19}H_{19}N_3O_5$  requires C, 61.78; H, 5.19; N, 11.38%);  $\nu_{\max}$  1640  $cm^{-1}$  (C=O).

*Phenyl urea of 5* — **5** (1 g) and phenylisocyanate (0.4 g) were left in benzene (10 ml) at room temperature for 18 hr, when the urea **19** separated as a crystalline precipitate which recrystallized from MeOH to give pure **19** (1 g), m.p. 155-56° (Found: C, 64.74; H, 5.23; N, 12.56.  $C_{24}H_{22}N_4O_5$  requires C, 64.56; H, 4.97; N, 12.55%);  $\nu_{\max}$  1650 and 1620; (C=O), 3280  $cm^{-1}$  (NH).

*Reduction of 5* — A solution of **5** HCl (2 g) in methanol (100 ml) was shaken with hydrogen at atmospheric pressure and room temperature in the presence of Adam's catalyst (0.2 g) for 6 hr till there was no more hydrogen uptake. The mixture was filtered and the filtrate evaporated to dryness to give 20 HCl which crystallized from methanol (1.5 g), m.p. 210-14° (Found: C, 60.89; H, 6.22; N, 12.26.  $C_{17}H_{20}ClN_3O_2$  requires C, 61.16; H, 6.04; N, 12.59%);  $\nu_{\max}$  1630 (C=O); 3240, 3340 and 3400  $cm^{-1}$  (NH).

*Conversion of 5 to 1* — A mixture of **5** (200 mg), aq. formaldehyde (40%, 1.5 ml) and formic acid (2 ml) was heated on a steam-bath for 4½ hr. The resultant solution was diluted with water, made alkaline and extracted with chloroform. The chloroform layer was evaporated to give an oil (0.2 g), which was converted to the HCl salt of **1** (200 mg), m.p. 221-23°, m.m.p. remained undepressed.

*Synthesis of tosyl derivative 21* — Chloropropyl lactam **14** (6.66 g, 20 mmoles), sodium *p*-toluenesulphonamide (3.47 g, 18 mmoles) and DMF (30 ml) were heated at 110° for 16 hr. The solvent was removed *in vacuo*; water was added to the residue and the mixture extracted with chloroform. The chloroform extract was evaporated and the residue chromatographed on an alumina column in benzene. Elution of the column with benzene gave a gum, which was rejected. Elution with chloroform gave **21**, which crystallized from chloroform-methanol, 0.7 g, m.p. 192-94° (Found: C, 59.48; H, 4.85; N, 8.96.  $C_{23}H_{21}N_3O_6S$  requires C, 59.10; H, 4.53; N, 8.99%);  $\nu_{\max}$  1650 (C=O), 3280  $cm^{-1}$  (NH).

*Nitropropionitrile 22* — Acrylonitrile (1.08 g) was added to a stirred suspension of nitrolactam **3** (1.2 g) and powdered NaOH (20 mg) in dioxane (6 ml) at 60° and the mixture heated under reflux for 4 hr. Dioxane and excess acrylonitrile were removed *in vacuo* and water (20 ml) added to the residue, followed by conc. HCl to the point of acidity. The solid that separated was filtered and purified by filtration through a column of silica gel in chloroform to give **22** (1.2 g), m.p. 155-57° (Found: C, 62.42; H, 3.90; N, 13.38.  $C_{16}H_{11}N_3O_4$  requires C, 62.13; H, 3.59; N, 13.59%);  $\nu_{\max}$  2240 (C≡N), 1650  $cm^{-1}$  (C=O).

*Nitropropionic ester 23*: (i) *Directly from lactam 3* — To a suspension of nitrolactam **3** (15.36 g, 60 mmoles) and powdered NaOH (0.1 g) in dry dioxane (25 ml) was added with stirring at 80° methyl acrylate (25.8 g, 300 mmoles). The mixture was stirred at 110° for 12 hr and the solvent evaporated *in vacuo*. Water was added to the residue and the mixture extracted with ether. The dried ether extract, on concentration, deposited crystals which were filtered and recrystallized from ether to give the methyl ester **23** (14 g), m.p. 106-08° (Found: C, 59.62; H, 4.34; N, 8.39.  $C_{17}H_{14}N_2O_6$  requires C, 59.65; H, 4.12; N, 8.18%);  $\nu_{\max}$  1730 and 1640  $cm^{-1}$  (C=O); NMR ( $CDCl_3$ ): 2.87 (*t*,  $CH_2CO_2Me$ ), 3.65 (*s*, O $CH_3$ ), 4.45 (*t*, CON- $CH_2$ ).

(ii) *From propionitrile 22* — A solution of propionitrile **22** (0.3 g) in dioxane (15 ml) containing absolute methanol (0.2 ml) was saturated with dry HCl gas at 0° and set aside at room temperature for 4 days. The resultant crystalline methyl imidate HCl salt was filtered, washed with water and dried (0.15 g), m.p. 159-61° (d). This was treated with water (10 ml) and the solution heated at 100° for 15 min, cooled and extracted with chloroform to give ester **23**, which was purified by passing through a column of silica gel in  $CHCl_3$ ; yield 0.1 g, m.p. 106-08°.

*Nitropropionic acid 24* — A solution of the above ester **23** (4 g) in gl. AcOH (20 ml) and conc. HCl (20 ml) was heated at 110° for 3 hr and then evaporated to dryness. The residue was treated with aq. sodium bicarbonate and extracted with methylene chloride. The aq. layer was acidified and the liberated acid extracted into methylene chloride. Evaporation of the methylene chloride layer and crystallization of the residue from ether gave acid **24** (2.4 g), m.p. 167-69°. One batch showed m.p. 129-32° (Found: C, 58.48; H, 3.87; N, 8.47.  $C_{16}H_{12}N_2O_6$  requires C, 58.54; H, 3.68; N, 8.53%);  $\nu_{\max}$  1720, 1700 and 1660  $cm^{-1}$  (C=O).

**Propionitrile 25** — Treatment of the nitromethoxy lactam **6** (2.7 g) with acrylonitrile (2.5 g) as before gave **25** (1.8 g), m.p. 146-48° (benzene-hexane) (Found: C, 61.04; H, 3.95; N, 12.67.  $C_{17}H_{13}N_3O_5$  requires C, 60.17; H, 3.86; N, 12.39%).

**Propionic ester 26** — Nitromethoxy lactam **6** (1.3 g) was treated with methyl acrylate (2.5 ml) to give **26** (0.85 g), m.p. 102-04° ( $CH_2Cl_2$ -ether) (Found: C, 58.32; H, 4.50; N, 7.73.  $C_{18}H_{16}N_2O_7$  requires C, 58.06; H, 4.33; N, 7.52%);  $\nu_{max}$  1738 and 1650  $cm^{-1}$  (C=O); NMR ( $CDCl_3$ ); 2.82 (t,  $CH_2CO_2Me$ ), 3.63 (s,  $OCH_3$ ), 3.80 (s,  $OCH_3$ ), 4.38 (t,  $N-CH_2$ ).

**Nitroacetic ester 27** — A mixture of nitrolactam **3** (2.5 g), methyl bromacetate (4.5 g), powdered NaOH (0.4 g) and dioxane (40 ml) was stirred under reflux for 12 hr. Most of the solvent was then distilled off and water (20 ml) and ether (100 ml) added to the residue. The insoluble material was filtered to give the recovered **3** (1.15 g). The etherial layer in the filtrate was separated and evaporated to give a gum which was chromatographed on a column of neutral alumina in benzene-chloroform (1:2). Elution with the same solvent mixture gave **27**, which crystallized from  $CH_2Cl_2$ -ether (yield 1.35 g), m.p. 122-24° (Found: C, 58.83; H, 3.91; N, 8.82.  $C_{16}H_{12}N_2O_6$  requires C, 58.54; H, 3.68; N, 8.53%);  $\nu_{max}$  1760 and 1660  $cm^{-1}$  (C=O).

**Aminopropionic ester 28** — A solution of nitropropionic ester **23** (5 g) in methanol (250 ml) was hydrogenated at atmospheric pressure and room temperature, using Adam's catalyst (0.15 g), to give **28**, characterized as the HCl salt (4.3 g), m.p. 210-12° (MeOH-ether) (Found: C, 58.27; H, 5.12; N, 8.37.  $C_{17}H_{17}ClN_2O_4$  requires C, 58.54; H, 4.91; N, 8.03%); The acetyl derivative **29** was prepared by reaction of **28** with acetic anhydride and pyridine; m.p. 128-30° ( $CH_2Cl_2$ -ether) (Found: C, 64.28; H, 5.49; N, 8.14.  $C_{19}H_{18}N_2O_5$  requires C, 64.40; H, 5.12; N, 7.91%).

**2-Nitro-7-hydroxy-10-(3-dimethylaminopropyl)dibenz[b,f][1,4]oxazepin-11(10H)-one (33)** — Condensation<sup>2</sup> of 2-chloro-5-nitrobenzoyl chloride (1.32 g, 6 mmoles) with 2-hydroxy-4-benzyloxyaniline<sup>9</sup> (1.92 g, 6 mmoles) gave the crude amide **30** (2 g), m.p. 170-80°, which was cyclized<sup>2</sup> by heating with aq. NaOH (1N, 5 ml) to give the lactam **31** (1 g),

m.p. 242-45° (acetone) (Found: C, 66.40; H, 4.20; N, 7.68.  $C_{20}H_{14}N_2O_5$  requires C, 66.29; H, 3.89; N, 7.73%).

A solution of **31** (1 g, 2.5 mmoles) in acetone (20 ml) and aq. NaOH (2N, 1.4 ml) was treated with 3-dimethylaminopropyl chloride (0.31 g, 2.5 mmoles) and heated under reflux for 1 hr. The mixture was treated with two further lots of the chloride and worked up as usual<sup>1</sup>. The product was converted to the HCl salt. Crystallization from ethanol gave **32** HCl (0.7 g), m.p. 219-20° (Found: C, 61.70; H, 5.77; N, 8.55.  $C_{25}H_{26}ClN_3O_5$  requires C, 62.04; H, 5.42; N, 8.68%).

A solution of the above HCl salt (0.5 g) in hydrochloric acid (6N, 10 ml) was heated at 100° for 1 hr and set aside overnight. The crystals that separated were filtered and recrystallized from MeOH to give **33** HCl (0.2 g), m.p. 235-38° (Found: C, 54.87; H, 5.32; N, 10.96.  $C_{18}H_{20}ClN_3O_5$  requires C, 54.89; H, 5.12; N, 10.67%);  $\lambda_{max}$  235, 275 nm (log  $\epsilon$  4.24, 4.00).

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