4,5-Dihydro-1-benzoxepin-3(2*H*)-one, *N*-Substituted 2,3-Dihydro-1,5-benzoxazepin-4(5*H*)-ones, and Related Compounds

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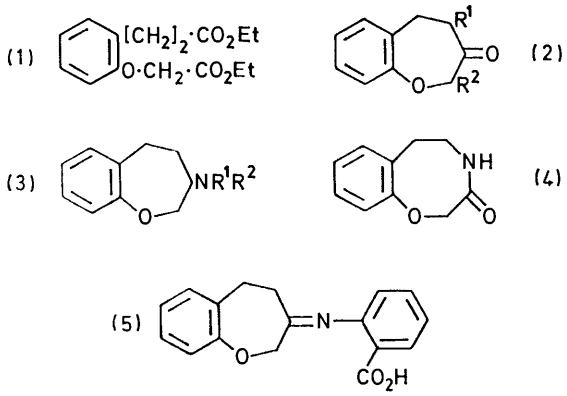
The preparation of 4,5-dihydro-1-benzoxepin-3(2*H*)-one and its conversion into 2,3,4,5-tetrahydro-1-benzoxepin-3-amines and related compounds are reported. Ring cleavage of 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one to give an acrylamide readily occurs when *N*-alkylation is attempted. Methods are described for the preparation of some 5-substituted 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-ones.

In a conventional Dieckmann cyclisation of ethyl 3-[*o*-(ethoxycarbonylmethoxy)phenyl]propionate (1), ethyl 2,3,4,5-tetrahydro-3-oxo-1-benzoxepin-2- or 4-carboxylate [2; $R^1 = H$, $R^2 = CO_2Et$ (or $R^1 = CO_2Et$, $R^2 = H$)] was only obtained in low yield.[1] We have found that the use of a high dilution technique vastly improved the yield (from about 4 to 70%) in this cyclisation. With a subsequent hydrolysis and decarboxylation, a ready synthesis of 4,5-dihydro-1-benzoxepin-3(2*H*)-one (2; $R^1 = R^2 = H$) was thus available.



A number of 2,3,4,5-tetrahydro-1-benzoxepin-3-amines (3) have been prepared by reductive amination of the 1-benzoxepin-3-one, and catalytic reduction of the ketone afforded 2,3,4,5-tetrahydro-1-benzoxepin-3-ol. 4,5-Dihydro-1-benzoxepin-3(2*H*)-one oxime was an oil that afforded the appropriate 1-benzoxepin-3-amine on reduction with lithium aluminium hydride. On being subjected to the Beckmann rearrangement, the oxime was converted into 5,6-dihydro-2*H*-1,4-benzoxazocin-3(4*H*)-one (4) as shown by the n.m.r. spectrum of the product. There was no positive evidence for the presence of the alternative Beckmann rearrangement product although the possibility of its formation could not be discounted.

On condensation of the 1-benzoxepin-3-one (2; $R^1 = R^2 = H$) with anthranilic acid in a manner similar to that described by Cromwell and Nielsen,[2] *N*-(2,3,4,5-tetrahydro-1-benzoxepin-3-ylidene)anthranilic acid (5) was obtained and not the cyclisation product.

Attempts to *N*-alkylate the readily prepared 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one (6; R = H) by addition of morpholinoethyl chloride or methyl iodide in the presence of sodium hydride or sodamide have in our hands resulted in ring cleavage to give acrylamides of type (7). Where slightly more than 1 equiv. of morpholinoethyl chloride was used, the *O*-substituted product (7; R^1 = morpholinoethyl, $R^2 = H$), was obtained, whereas with excess of methyl iodide the dialkyl compound (7; $R^1 = R^2 = Me$) was isolated.

It appeared that ring cleavage was occurring in the presence of basic reagents. *N*-Methylation was therefore attempted in the presence of thallium(I) ethoxide[3] and the *N*-methylbenzoxazepinone (6; R = Me) was obtained. However, a more satisfactory preparation of this compound involved addition of sodium hydride

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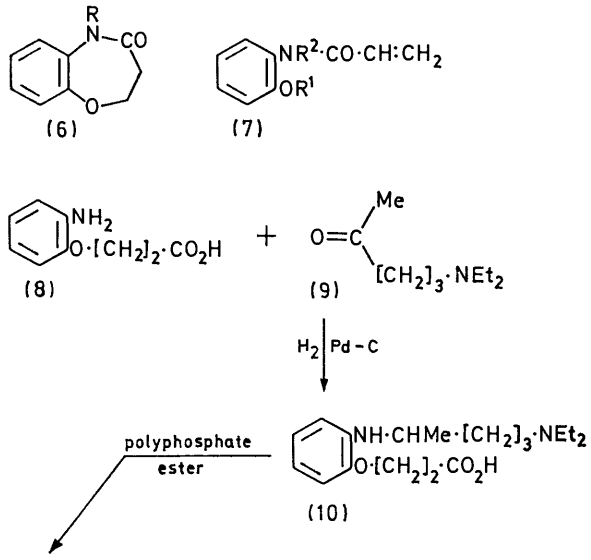
[1] G. Fontaine, *Ann. Chim.* (*France*), 1968, **3**, 469.
[2] N. H. Cromwell and L. A. Nielsen, *J. Heterocyclic Chem.*, 1969, **6**, 361.
[3] E. C. Taylor, G. H. Hawks, and A. McKillop, *J. Amer. Chem. Soc.*, 1968, **90**, 2421.

in portions to the benzoxazepinone–alkyl halide mixture.



Reduction of the *N*-methylbenzoxazepinone (6; R = Me) with lithium aluminium hydride afforded 2,3,4,5-tetrahydro-5-methyl-1,5-benzoxazepine hydrochloride, identical with that obtained on methylation of the previously reported [4] 2,3,4,5-tetrahydro-1,5-benzoxazepine.

Ring cleavage still occurred, however, when attempts were made to *N*-alkylate with morpholinoethyl chloride. An alternative approach would therefore be necessary for the preparation of basic benzoxazepinones [*e.g.* (6; R = morpholinoethyl)]. Some success has been achieved in this direction. Hydrogenation of a mixture of 3-(*o*-aminophenoxy)propionic acid (8) and 5-diethylaminopentan-2-one (9) afforded the crude substituted aminophenoxypropionic acid (10), which was cyclised in the presence of polyphosphate ester [5] to the appropriate *N*-substituted benzoxazepinone (6; R = CHMe·[CH$_2$]$_3$·NEt$_2$).

Similar problems were not encountered in the *N*-alkylation of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one with piperidinoethyl chloride.

EXPERIMENTAL

Ethyl 2,3,4,5-*Tetrahydro*-3-*oxo*-1-*benzoxepin*-2- *or* 4-*carboxylate* [2; R^1 = H, R^2 = CO$_2$Et (or R^1 = CO$_2$Et, R^2 = H)].—Sodium hydride (80 g; 50% dispersion in oil) was washed with light petroleum (b.p. 40—60°) and dry xylene, and suspended in azeotropically dried xylene (2·5 l). t-Butyl alcohol (3 ml) was added and the suspension was stirred at reflux temperature under nitrogen. Ethyl 3-[*o*-(ethoxycarbonylmethoxy)phenyl]propionate (180 g, prepared in 83% yield from 2,3-dihydrocoumarin and ethyl bromoacetate [1]) in xylene (giving 2 l of solution) was added through a 'high-dilution head,' similar to that described by Leonard and Sentz,[6] at a rate of 40 ml h^{-1} by use of a calibrated micro-pump. After addition of the diester was complete (50 h) the brown solution was refluxed for a further 2 h and cooled in ice–water. Glacial acetic acid (100 ml) was added, the solution was filtered, and the xylene was separated. The keto-ester was isolated from the xylene as a brown oil (91 g). On distillation of a sample, a deep yellow liquid was obtained of b.p. 168—178° at 1·5—2·5 mmHg (lit.,[1] 123—124° at 0·1 mmHg), n_D^{28} 1·5220, $\nu_{max.}$ (oil) 1720 and 1740 cm^{-1} (CO).

4,5-*Dihydro*-1-*benzoxepin*-3(2H)-*one* (2; R^1 = R^2 = H).—The foregoing ester (50 g), methanol (200 ml), and 6N-hydrochloric acid (200 ml) were stirred and refluxed for 12 h. The cooled mixture was poured into ice–water (1 l), and extracted with ether (4 × 150 ml). The extracts were washed with water, dried (Na_2SO_4), and evaporated. Distillation of the residue afforded the 1-*benzoxepin*-3-*one* as a pale yellow liquid (20 g), b.p. 100—105° at 0·4—0·6 mmHg, n_D^{25} 1·5410 (Found: C, 74·1; H, 6·2. $C_{10}H_{10}O_2$ requires C, 74·0; H, 6·2%), $\nu_{max.}$ (liquid) 1710s cm^{-1} (CO); *oxime*, b.p. 145—147° at 1·5 mmHg (Found: C, 68·2; H, 6·5; N, 7·4. $C_{10}H_{11}NO_2$ requires C, 67·8; H, 6·3; N, 7·9%).

The ketone (3·5 g), 2-hydrazinopyridine (2·5 g), and glacial acetic acid (0·5 ml) in absolute ethanol (15 ml) were warmed on the steam-bath for 1·5 h. The crystals that separated on cooling gave 4,5-*dihydro*-1-*benzoxepin*-3(2H)-*one* 2-*pyridylhydrazone* as white plates (2·6 g), m.p. 129° (from ethanol) (Found: C, 71·2; H, 6·0; N, 16·6. $C_{15}H_{15}N_3O$ requires C, 71·0; H, 6·0; N, 16·6%). 4,5-*Dihydro*-1-*benzoxepin*-3(2H)-*one* 2-*quinolylhydrazone*, similarly prepared, had m.p. 143—144° (from ethanol) (Found: C, 75·1; H, 5·75; N, 13·8. $C_{19}H_{17}N_3O$ requires C, 75·2; H, 5·65; N, 13·85%).

2,3,4,5-*Tetrahydro*-1-*benzoxepin*-3-*amine* (3; R^1 = R^2 = H).—4,5-Dihydro-1-benzoxepin-3(2*H*)-one oxime (7 g) in ether (40 ml) was added to a stirred suspension of lithium aluminium hydride (2 g) in ether (10 ml). The stirred mixture was refluxed for 6 h and cooled, and saturated ammonium chloride solution (15 ml) was carefully added. The mixture was filtered and the residue was washed with ethyl acetate; basic material was isolated from the combined organic solutions. The *amine* was obtained as a pale yellow oil (2·3 g), b.p. 173° at 40 mmHg, n_D^{22} 1·5558 (Found: C, 73·4; H, 8·1; N, 8·4. $C_{10}H_{13}NO$ requires C, 73·6; H, 8·0; N, 8·6%); *hydrochloride*, prisms, m.p. 207—208° (from ethanol) (Found: C, 60·2; H, 7·2; N, 6·8. $C_{10}H_{14}ClNO$ requires C, 60·1; H, 7·1; N, 7·1%).

N-*Cyclopropyl*-2,3,4,5-*tetrahydro*-1-*benzoxepin*-3-*amine* (3; R^1 = H, R^2 = cyclopropyl) *Hydrochloride and Related Compounds*.—4,5-Dihydro-1-benzoxepin-3(2*H*)-one (5·4 g), cyclopropylamine (2·5 g), 10% palladium–charcoal (200 mg), and platinum dioxide (200 mg) were stirred in ethanol (50 ml), and the mixture was hydrogenated at atmospheric temperature and pressure. Filtration and evaporation left an oily residue which was converted into the *hydrochloride*, needles, m.p. 203—204° (from ethanol) (Found: C, 65·1; H, 7·8; N, 5·7. $C_{13}H_{18}ClNO$ requires C, 65·0; H, 7·5; N, 5·8%).

Other amines prepared by a similar procedure were 2,3,4,5-*tetrahydro*-N-*isopropyl*-1-*benzoxepin*-3-*amine* (3; R^1 = H, R^2 = Pr^i) *hydrochloride*, prisms, m.p. 236—

[4] V. A. Zagorevskii and N. V. Dudykina, *J. Gen. Chem.* (*U.S.S.R.*), 1963, **33**, 317.

[5] Y. Kanaoka, M. Machida, O. Yonemitsu, and Y. Ban, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 1065.

[6] N. J. Leonard and R. C. Sentz, *J. Amer. Chem. Soc.*, 1952, **74**, 1704.

238° (from ethanol) (Found: C, 64·8; H, 8·4; N, 5·8. $C_{13}H_{20}ClNO$ requires C, 64·75; H, 8·3; N, 5·8%); N-[3-(*dimethylamino*)*propyl*]-2,3,4,5-*tetrahydro*-1-*benzoxepin*-3-*amine* (3; R^1 = H, R^2 = $[CH_2]_3$·NMe_2) *dihydrochloride*, prisms, m.p. 147—149° (from ethanol) (Found: C, 53·2; H, 8·5; N, 8·5. $C_{15}H_{26}Cl_2N_2O,H_2O$ requires C, 53·1; H, 8·3; N, 8·3%); N-[2-(*diethylamino*)*ethyl*]-2,3,4,5-*tetrahydro*-1-*benzoxepin*-3-*amine* (3; R^1 = H, R^2 = $[CH_2]_2$·NEt_2) *dihydrochloride*, prisms, m.p. 198—200° (from ethanol) (Found: C, 57·5; H, 8·5; N, 8·4. $C_{16}H_{28}Cl_2N_2O$ requires C, 57·4; H, 8·4; N, 8·4%); and 2,3,4,5-*tetrahydro*-NN-*dimethyl*-1-*benzoxepin*-3-*amine* (3; R^1 = R^2 = Me) as an oil, b.p. 90° at 1 mmHg (Found: C, 75·0; H, 9·2; N, 7·2. $C_{12}H_{17}NO$ requires C, 75·35; H, 9·0; N, 7·3%).

2,3,4,5-*Tetrahydro*-1-*benzoxepin*-3-*ol*.— 4,5-Dihydro-1-benzoxepin-3(2*H*)-one (5·0 g) in ethanol (50 ml) was hydrogenated over 10% palladium–charcoal (200 mg) and platinum oxide (200 mg) at 60° and atmospheric pressure. Filtration and evaporation afforded the 1-*benzoxepin*-3-*ol* (5·0 g) as a microcrystalline solid [from light petroleum (b.p. 40—60°)], m.p. 86—88° (Found: C, 72·9; H, 7·2. $C_{10}H_{12}O_2$ requires C, 73·1; H, 7·4%).

5,6-*Dihydro*-2H-1,4-*benzoxazocin*-3(4H)-*one* (4).—4,5-Dihydro-1-benzoxepin-3(2*H*)-one oxime (10 g) was stirred with polyphosphoric acid (100 g) at 90° for 10 min. The mixture was poured into ice–water (500 ml) and adjusted to pH 6 with 2N-sodium hydroxide. The solution was extracted with chloroform; the combined extracts were washed with water, dried (Na_2SO_4), and evaporated. The semi-solid residue (8·0 g) was extracted with light petroleum (b.p. 60—80°) for 6 h. The solid that separated on cooling was recrystallised from 4 : 1 benzene–light petroleum (b.p. 40—60°). The 1,4-benzoxazocin-3-one (1·5 g) was obtained as a white microcrystalline solid, m.p. 158·5—159·5° (Found: C, 67·8; H, 6·4; N, 7·6. $C_{10}H_{11}NO_2$ requires C, 67·8; H, 6·3; N, 7·9%), homogeneous (R_F 0·46) on t.l.c. [silica precoated plate, Kodak 6060; acetone–benzene (1 : 2) as developing solvent], τ ($CDCl_3$) 5·35 (2H, s), 6·1 (2H, m), and 7·05 (2H, t) (3 × CH_2), τ ($CDCl_3$–D_2O) 5·4 (2H, s), 6·1 (2H, t), and 7·05 (2H, t).

N-(2,3,4,5-*Tetrahydro*-1-*benzoxepin*-3-*ylidene*)*anthranilic Acid* (5).—4,5-Dihydro-1-benzoxepin-3(2*H*)-one (8·1 g) was stirred at 80° with anthranilic acid (6·9 g) for 5 min; the mixture had then solidified. Heating was continued at 150° until the solid melted and the melt was stirred at 200° for 30 min. After cooling, the product rapidly crystallised on trituration with benzene. Recrystallisation from benzene–ether followed by acetone, afforded the (1-*benzoxepin*-3-*ylidene*)*anthranilic acid* (5·5 g) as needles, m.p. 183—184° (Found: C, 72·6; H, 5·4; N, 4·9. $C_{17}H_{15}NO_3$ requires C, 72·6; H, 5·4; N, 5·0%).

Reaction of 2,3-*Dihydro*-1,5-*benzoxazepin*-4(5H)-*one with Morpholinoethyl Chloride*.—Sodamide (2·7 g) was added to a solution of the benzoxazepinone [7] (10 g, 0·06 mol) in dioxan (90 ml) and the mixture refluxed for 3 h. Freshly prepared morpholinoethyl chloride (12 g, 0·08 mol) was added and refluxing was continued for a further 4 h. Methanol (12 ml) was added to the mixture with stirring and the suspension filtered (Supercel). Dioxan was distilled from the filtrate and the product was isolated from ethyl acetate as an oil (6·7 g). Repeated vacuum distillation afforded 2′-(2-*morpholinoethoxy*)*acrylanilide* (7; R^1 = morpholinoethyl, R^2 = H) as an oil, b.p. 176—178° at 0·15 mmHg, that crystallised as prisms, m.p. 86—88° (Found: C, 64·9; H, 7·6; N, 10·0. $C_{15}H_{20}N_2O_3$ requires C, 65·2; H, 7·3; N, 10·1%); *oxalate dihydrate*, m.p. 159—160° (Found: C, 50·7; H, 6·65; N, 6·9. $C_{17}H_{22}N_2O_7,2H_2O$ requires C, 50·7; H, 6·5; N, 7·0). On hydrogenation of the acrylanilide in ethanol over 5% palladium–charcoal, 1 equiv. of hydrogen was absorbed.

Reaction of 2,3-*Dihydro*-1,5-*benzoxazepin*-4(5H)-*one with Excess of Methyl Iodide*.—The benzoxazepinone [7] (6·8 g, 0·04 mol) was added to sodium hydride (5·5 g; 50% dispersion in oil; 0·117 mol) that had been washed with benzene and suspended in dry dioxan (100 ml). The mixture was refluxed with stirring for 3 h. Dry methyl iodide (13 ml) was added dropwise (an acetone–solid carbon dioxide cold-finger condenser was used to prevent loss by evaporation) and the solution was stirred under reflux for a further 2 h. The cooled mixture was filtered (supercel) and the solution evaporated. The product was isolated from ether and distilled *in vacuo* to give 2-*methoxy*-N-*methylacrylanilide* (7; R^1 = R^2 = Me) (2·25 g) as an oil, b.p. 140—142° at 3 mmHg (Found: C, 68·7; H, 7·2; N, 7·5. $C_{11}H_{13}NO_2$ requires C, 69·1; H, 6·85; N, 7·3%).

A sample of the above acrylanilide in ethanol (25 ml) was hydrogenated over 5% palladium–charcoal (0·5 g) at atmospheric temperature and pressure. Filtration, evaporation, and flash-distillation of the residue afforded N-*methyl*-N-*propionyl*-o-*anisidine* (Found: C, 68·4; H, 8·0; N, 7·4. $C_{11}H_{15}NO_2$ requires C, 68·4; H, 7·8; N, 7·25%), n_D^{22} 1·5250, identical with a sample (b.p. 116° at 15 mmHg) prepared by reaction of *o*-anisidine with propionic anhydride followed by methylation of the resulting amide with methyl iodide in the presence of sodium hydride.

2,3-*Dihydro*-5-*methyl*-1,5-*benzoxazepin*-4(5H)-*one* (6; R = Me).—*By use of thallium*(I) *ethoxide*. Thallium(I) ethoxide (*ca.* 4 g; prepared from thallium chippings and absolute ethanol [8]) in dioxan (20 ml) was added to 2,3-dihydro-1,5-benzoxepin-4(5*H*)-one (3·2 g) in dioxan (30 ml). The green mixture was stirred for 1 h. Methyl iodide (2 g) was added and stirring was continued for a further 2 h at room temperature. The mixture was filtered, the filtrate evaporated, and the product isolated from benzene. The 5-*methyl*-1,5-*benzoxazepinone* (6; R = Me) was obtained as an oil (1·3 g), b.p. 110—114° at 0·5 mmHg (Found: C, 67·7; H, 6·5; N, 7·6. $C_{10}H_{11}NO_2$ requires C, 67·8; H, 6·3; H, 7·9%).

By use of sodium hydride. Methyl iodide (6·5 ml) was added to a stirred solution of 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one [7] (3·5 g) in dioxan (25 ml). Sodium hydride (2·0 g; 50% oil dispersion washed with benzene) was suspended in dioxan (25 ml) and added in portions during 15 min. The mixture was stirred at room temperature for 1 h, refluxed for 1 h, and filtered. The filtrate was evaporated and the residue distilled *in vacuo* to give the 5-methylbenzoxazepinone (6; R = Me) as an oil (2·6 g), b.p. 94—96° at 0·2 mmHg, identical with the sample already prepared.

2,3,4,5-*Tetrahydro*-5-*methyl*-1,5-*benzoxazepine Hydrochloride*.—The foregoing 2,3-dihydro-5-methyl-1,5-benzoxazepin-4(5*H*)-one (1·3 g) in ether (50 ml) was added to a stirred suspension of lithium aluminium hydride (0·5 g) in ether (50 ml); the mixture was refluxed for 5 h then cooled. Saturated ammonium chloride solution (30 ml) was added and the mixture was refluxed for 1·5 h and filtered. 2,3,4,5-Tetrahydro-5-methyl-1,5-benzoxazepine (0·6 g) was isolated

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[8] N. V. Sidgwick and L. E. Sutton, *J. Chem. Soc.*, 1930, 1461.

from ether as an oil, b.p. 70° at 0·5 mmHg, which afforded a *hydrochloride* as prisms, m.p. 160—161° (from ethanol–ether) (Found: C, 59·8; H, 7·1; N, 6·8. $C_{10}H_{14}ClNO$ requires C, 60·2; H, 7·1; N, 7·0%).

5-[4-(*Diethylamino*)-1-*methylbutyl*]-2,3-*dihydro*-1,5-*benzoxazepin*-4(5H)-*one* (6; R = $CHMe\cdot[CH_2]_3\cdot NEt_2$).—*o*-Aminophenoxypropionic acid (26 g; prepared from *o*-nitrophenoxypropionic acid [9] by catalytic hydrogenation) and freshly distilled 5-diethylaminopentan-2-one (21 g) in glacial acetic acid (500 ml) were hydrogenated over 10% palladium–charcoal (1 g) at 60° and atmospheric pressure. Filtration and evaporation gave the crude substituted aminophenoxypropionic acid (10) as an oil (45 g). This oil in acetonitrile (450 ml) was refluxed with triethylamine (30 g) and polyphosphate ester [5] (215 g) with stirring for 3 days. The solvent was evaporated off, ice and 10N-sodium hydroxide were added to the residual oil, and the solution was stirred with ethyl acetate for 0·5 h. The organic layer was separated and the aqueous layer re-extracted with ethyl acetate. The combined organic solutions were extracted with 2N-hydrochloric acid. The acid extracts were basified (10N-NaOH) and extracted with ethyl acetate. Evaporation of the dried organic solution, followed by distillation of the residue *in vacuo*, afforded unchanged 5-diethylaminopentan-2-one (6·4 g) and the 5-*substituted* 1,5-*benzoxazepin*-4(5H)-*one* (6; R = $CHMe\cdot[CH_2]_3\cdot NEt_2$) as an oil (9·0 g), b.p. 164—166° at 0·4 mmHg (Found: C, 70·7; H, 9·4; N, 9·0. $C_{18}H_{28}N_2O_2$ requires C, 71·0; H, 9·3; N, 9·2%).

2,3-*Dihydro*-5-(2-*piperidinoethyl*)-1,5-*benzothiazepin*-4(5H)-*one*.—Sodamide (2·7 g) was added to 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one [10] (11·3 g) in dioxan (80 ml) and the stirred mixture was refluxed for 2 h. Piperidinoethyl chloride (8·4 g; freshly prepared from the hydrochloride) was slowly added and the suspension was stirred under reflux for a further 4·5 h. Methanol (15 ml) was added to the cooled mixture, which was stirred for 15 min, and filtered (Supercel). The *piperidinoethylbenzothiazepinone* was isolated from ether as a pale yellow liquid (11·95 g), b.p. 176° at 0·4 mmHg (Found: C, 65·8; H, 7·5; N, 9·7. $C_{16}H_{22}N_2OS$ requires C, 66·2; H, 7·6; N, 9·65%); *citrate*, prisms (from methanol–ethyl acetate), m.p. 147—148° (Found: C, 54·3; H, 6·3; N, 5·4. $C_{22}H_{30}N_2O_8S$ requires C, 54·6; H, 6·4; N, 5·8%).

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