

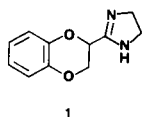
Richard C. M. Butler, Christopher B. Chapleo*, Peter L. Myers,
and Anthony P. Welbourn

Department of Medicinal Chemistry, Reckitt and Colman plc,
Dansom Lane, Hull, HU8 7DS, England
Received June 11, 1984

An investigation into the synthesis of benzoxazine, benzoxathiane and benzothiazine derivatives of 2-(2-imidazolynyl)-1,4-benzodioxane has been carried out.

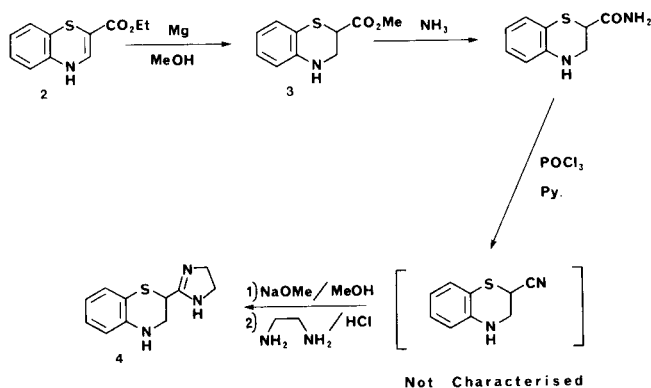
J. Heterocyclic Chem., **22**, 177 (1985).

The rational design of idazoxan (**1**), a potent and selective antagonist of α_2 -adrenoreceptors, has previously been described [1]. In view of the potential therapeutic value of a compound possessing this pharmacological profile a number of analogues of **1** have been prepared. In particular we recently reported [2] the synthesis of a series of chroman and dihydrobenzofuran compounds. Encouraged by the high level of biological activity possessed by some of these compounds, the synthesis of derivatives in which either one or both of the oxygen atoms of the 1,4-dioxane ring in **1** was replaced by sulphur or nitrogen atoms was investigated.



Conversion of ethyl 4*H*-1,4-benzothiazine-2-carboxylate (**2**) [3] to the required imidazolynyl dihydrobenzothiazine (**4**) was achieved as shown in Scheme I. Reduction of the double bond in **2** using magnesium in methanol gave the dihydro intermediate **3**; transesterification having also occurred. Previously described procedures [1] were used to convert the ester group to the imidazoline moiety.

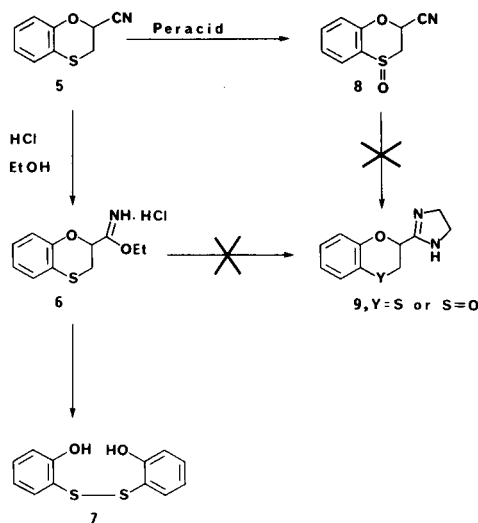
Scheme I



Attempts to prepare the corresponding imidazolynyl benzoxathiane imidazoline (**9** Y = S) were unsuccessful

due to the inherent instability of the ring system (see Scheme II). Reaction of 1,4-benzoxathiane-2-carbonitrile (**5**) [4] with ethanol and ethereal hydrogen chloride gave the imidoate **6** which on treatment with ethylenediamine gave a complex mixture. The only isolable product was the disulphide **7**. In an attempt to overcome this instability the nitrile **5** was converted to the benzoxathiane 4-oxide **8** prior to the formation of the imidazoline ring. The nmr spectrum of this oxide revealed it to be a 2:1 mixture of the two diastereomers. Subsequent reaction of **8** with ethanol and ethereal hydrogen chloride followed by ethylenediamine again gave a complex reaction mixture from which no products could be isolated or identified.

Scheme II



2-Substituted 1,4-benzoxazines are generally prepared from the cyclisation reaction of an aminophenol with 2,3-dibromopropionic acid esters [5]. In this way, 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (**11**, R = H) was prepared from the ethyl ester **10**. The nmr spectrum of this ester showed that the NH group is coupled to an adjacent methylene group and this demonstrates the regioselecti-

Table
Pharmacological Testing Results [a]

Compound	Presynaptic α_2 antagonist potency	Postsynaptic α_1 antagonist potency
1 [b]	1.0	1.0
5	0.09	0.21
14 R = H	0.014	< 0.02
14 R = Me	0	0.09
14 R = Et	0	0
14 R = CH ₂ Ph	0	1.0
14 R = Ts	0	0.1

[a] Compounds were examined for α_2 and α_1 -adrenoreceptor antagonist properties using standard testing procedures [1]. [b] Pre α_2 -pA₂ = 8.50; Post α_1 -pA₂ = 6.10 [1].

EXPERIMENTAL

Melting points were determined in a Büchi apparatus in glass capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 700 spectrophotometer. Mass spectra were obtained from an LKB 2091 instrument. Nuclear magnetic resonance spectra were taken at 60 MHz on a Varian Associates T60 spectrophotometer and chemical shifts are given relative to internal tetramethylsilane. Elemental analysis was performed on a Carlo Erba 1106 elemental analyser. The hygroscopic nature of other imidazoline compounds related to those reported here has been previously shown by the varying amounts of water found during elemental analysis [1,2]. Compounds **4** and **14** (R = Me) have also been found to be slightly hygroscopic.

Methyl 2,3-Dihydro-4*H*-1,4-benzothiazine-2-carboxylate (**3**).

To a stirred solution of ethyl 4*H*-1,4-benzothiazine-2-carboxylate (**2**) [3] (10 g, 0.045 mole) in 400 ml of methanol was added magnesium turnings (44 g, 1.81 moles). The mixture was warmed cautiously to initiate the reaction. Once the exothermic reaction started the mixture was maintained at 20–25° by cooling for 1 hour. The mixture was then allowed to stand at room temperature for 16 hours followed by the dropwise addition of 500 ml of 6*N* hydrochloric acid with cooling. After 2 hours, water was added and the mixture filtered. The filtrate was extracted with dichloromethane and the extracts were washed with water, dried and evaporated to leave 7.3 g (77%) of the methyl ester **3** as a brown oil; ir (bromofom): 3450 (NH), 1750 (C=O) cm⁻¹; nmr (deuteriochloroform/deuterium oxide): δ 7.2–6.5 (m, 4, aromatic H), 4.2–3.9 (m, 2, NH, CH), 3.90 (s, 3, CH₃), 3.80 (d, 2, CH₂).

2-(2-Imidazolyl)-2,3-dihydro-4*H*-1,4-benzothiazine Dihydrochloride (**4**).

Ester **3** (7.3 g, 0.035 mole) was dissolved in 190 ml of ethanol and ammonia was bubbled through the stirred solution for 14 hours. Removal of the reaction solvent gave a brown oil that was purified by column chromatography on silica with 5% methanol/chloroform. The carboxamide was obtained as a yellow solid which was crystallised from ethyl acetate/40–60° petrol to give 1.2 g (18%) of 2,3-dihydro-4*H*-1,4-benzothiazine-2-carboxamide, mp 121–122°; nmr (DMSO-*d*₆/deuterium oxide): δ 7.5 (broad s, 1, NH), 7.2 (broad s, 1, NH), 7.0–6.2 (m, 4, aromatic H), 6.10 (broad s, 1, NH), 3.9–3.4 (m, 3, CH₂, CH).

Anal. Calcd. for C₉H₁₀N₂OS: C, 55.64; H, 5.19; N, 14.42. Found: C, 55.53; H, 5.15; N, 14.15.

To a stirred solution of the amide (1.0 g, 0.005 mole) in 20 ml of anhydrous pyridine was added phosphorous oxychloride (1.34 g, 0.009 mole) at 0–5°. The mixture was stirred at 0–5° for 1 hour then allowed to warm to room temperature and stirred for a further 3 hours. The reaction mixture was poured into water and extracted with dichloromethane. The extracts were washed with water, dried and evaporated to give the crude nitrile. Ethyl acetate was added to the residue, an insoluble solid

was filtered off and the organic filtrate was evaporated to give 0.5 g (55%) of a brown solid; ir (bromofom): 3450, 2245 cm⁻¹; ms: (M⁺) *m/e* 176.

A mixture of this impure nitrile (0.43 g, 0.002 mole), sodium methoxide (catalytic amount) and 13 ml of methanol was stirred at room temperature for several days. The reaction mixture was cooled to 0–5° and ethylenediamine (0.176 g, 0.003 mole) was added followed by the dropwise addition of 1.7 ml of hydrogen chloride in methanol (4.25 *M* solution, 0.007 mole) over 25 minutes. After stirring at 0–5° for 4 hours the mixture was concentrated to a small volume and filtered. To the filtrate was added ethereal hydrogen chloride followed by an excess of anhydrous ether. The resulting suspension was filtered to give the hydrochloride salt as a brown solid. This solid was heated with excess isopropyl alcohol filtered and the filtrate evaporated. The residual dihydrochloride salt was recrystallised from ethanol/ethereal hydrogen chloride to give 0.084 g (12%) of the imidazoline dihydrochloride **4** as a white solid, mp 206–209°; ms: (M⁺) *m/e* 219; nmr (DMSO-*d*₆/deuterium oxide): δ 10.30 (broad s, 2, NH₂), 7.88 (broad s, 2, NH₂), 7.1–6.5 (m, 4, aromatic H), 4.66 (t, *J* = 3 Hz, 1, CH), 3.84 (s, 4, NCH₂CH₂N), 3.60 (d, *J* = 3 Hz, 2, CH₂).

Anal. Calcd. for C₁₁H₁₃N₃S·2HCl·½H₂O: C, 44.52; H, 5.77; N, 14.16. Found: C, 44.70; H, 5.45; N, 13.93.

Attempt to Prepare 2-(2-Imidazolyl)-2*H*-1,4-benzoxathiane Hydrochloride (**9**, Y = S).

A steady stream of gaseous hydrogen chloride was bubbled through a stirred cooled (0°) solution of 2*H*-1,4-benzoxathiane-2-carbonitrile (**5**) [4] (0.25 g, 0.0014 mole) in 10 ml of anhydrous ether and ethanol (0.07 g, 0.0015 mole) until saturated. After 16 hours at 0–10° solvent was removed under vacuum and the residue triturated with anhydrous ether. Filtration and drying gave 0.2 g (55%) of ethyl 2*H*-1,4-benzoxathiane-2-carboximidoate hydrochloride (**6**), mp 89–90°; ir (nujol): 1645 cm⁻¹; nmr (deuteriochloroform): δ 12.6 (broad s, 2, NH, HCl), 7.4–6.7 (m, 4, aromatic H), 6.60 (d × d, *J* = 5 and 7 Hz, 1, OCH), 4.74 (q, *J* = 6 Hz, 2, OCH₂), 3.50 and 3.46 (both d-overlapping, *J* = 5 and 7 Hz, together 2, SCH₂), 1.45 (s, 3, CH₃). Treatment of **6** with ethylenediamine and ethereal hydrogen chloride in an attempt to obtain the required imidazoline compound **9** (Y = S) gave a mixture. This crude reaction product was chromatographed on silica with chloroform to give 0.03 g (8% overall from **5**) of an impure sample of the disulphide **7** [11] as an oil; ms: (M⁺) *m/e* 250; nmr (deuteriochloroform): δ 7.6–6.6 (m, 8, aromatic H), 6.6–6.0 (broad s, 2, 2 × OH - exchanged in deuterium oxide).

Attempt to Prepare 2-(2-Imidazolyl)-2*H*-1,4-benzoxathiane 4-Oxide Hydrochloride (**9**, Y = SO).

a) 2*H*-1,4-Benzoxathiane-2-carbonitrile 4-Oxide (**8**).

To a cooled (0°) stirred solution of 2*H*-1,4-benzoxathiane-2-carbonitrile (**5**) [4] 1.2 g (0.007 mole) in 60 ml of dichloromethane, was added a solution of *m*-chloroperbenzoic acid (1.28 g, 0.0074 mole) in 20 ml of dichloromethane. The mixture was allowed to warm to room temperature and then poured into a mixture of saturated sodium bicarbonate solution and a 10% aqueous sodium sulphite solution. The organic layer was separated, dried and evaporated to leave 1.3 g (99%) of **8** as an oil which partially crystallised on standing. The nmr spectrum indicated the product to be a 2:1 mixture of the 2 diastereoisomers: nmr (deuteriochloroform): δ 8.0–7.0 (m, 4, aromatic H), 5.70 and 5.32 (2:1 ratio) both t, both *J* = 6 Hz, together 1, CH), 3.30 and 2.98 (1:2 ratio) both d, both *J* = 6 Hz, together 2, CH₂).

b) Methods described in the synthesis of **4** were used in an attempt to convert the above cyano-sulphoxide **8** to the required imidazoline compound **9** (Y = SO). Analysis (tlc) indicated that the reaction mixture was complex and no product could be isolated or identified.

Ethyl 3,4-Dihydro-2*H*-1,4-benzoxazine-2-carboxylate (**10**).

The ester **10** (bp 131–133°) was prepared according to the literature procedure [5]. Proof of the regioselectivity of the cyclisation reaction was obtained from the nmr spectrum; (DMSO-*d*₆): δ 6.62 (m, 4, aromatic H), 5.62 (broad t, *J* = 2 Hz, 1, NH), 4.84 (t, *J* = 4 Hz, 1, CH), 4.18 (q, *J* = 7

Hz, 2, CH₂), 3.41 (d × d, J = 2 and 4 Hz, 2, CH₂), 1.15 (t, J = 7 Hz, 3, CH₃). Addition of deuterium oxide: signal at δ 5.62 was exchanged and signal at δ 3.41 was converted to a doublet, J = 4 Hz.

Spin-Decoupling Experiments.

Irradiation at δ 5.62 converted signal at δ 3.41 to a doublet, J = 4 Hz; irradiation at δ 3.41 converted signals at δ 5.62 and δ 4.84 to singlets; irradiation at δ 4.84 converted signal at δ 3.41 to a doublet, J = 2 Hz.

2-(2-Imidazolyl)-3,4-dihydro-2H-1,4-benzoxazine Dihydrochloride (**14**, R = H).

3,4-Dihydro-2H-1,4-benzoxazine-2-carboxamide (**11**, R = H) [5] was converted, *via* methods described in the synthesis of **4**, to the unstable imidazoline dihydrochloride **14** (R = H), mp 197-202°; nmr (DMSO-d₆/deuterium oxide): 6.82 (s, 4, aromatic H), 5.40 (m, 1, OCH), 3.96 (s, 4, N(CH₂)₂N), 3.68 (m, 2, NCH₂); ms: (M⁺) m/e 203, (M⁺ - 1) m/e 202.

Anal. Calcd. for C₁₁H₁₃N₃O·2HCl: C, 47.84; H, 5.47; N, 15.22. Found: C, 47.01; H, 5.43; N, 14.88.

Satisfactory analytical data could not be obtained due to the instability of the compound.

2-(2-Imidazolyl)-4-methyl-3,4-dihydro-2H-1,4-benzoxazine Dihydrochloride (**14**, R = Me).

A solution of methyl 3,4-dihydro-2H-benzoxazine-2-carboxylate (**10**) [5] (27.9 g, 0.135 mole) in 250 ml of formic acid was heated under reflux for 1 hour and then allowed to stand at room temperature a further 16 hours. The solution was evaporated to dryness and the residue partitioned between chloroform and saturated aqueous sodium bicarbonate solution. The organic phase was washed twice with bicarbonate solution, dried and evaporated to leave 12.1 g (38%) of the intermediate ethyl 4-formyl-3,4-dihydro-2H-benzoxazine-2-carboxylate as a solid. To a stirred, cooled (0-5°) solution of the above formyl compound (12 g, 0.051 mole) in 250 ml of anhydrous tetrahydrofuran was added a solution of diborane in 100 ml of tetrahydrofuran (1M solution, 0.1 mole) under an atmosphere of nitrogen. After 18 hours at room temperature ethanol was added dropwise with caution to destroy excess diborane. The solvent was removed under vacuum and the residue was stirred vigorously for 18 hours with a mixture of 50 ml of water, 250 ml of chloroform and 40 ml of concentrated hydrochloric acid. The mixture was then basified with concentrated ammonia solution and the organic layer was separated. The aqueous layer was extracted with chloroform (× 2) and the combined extracts were washed with water, dried and evaporated to leave an oil which slowly solidified on standing. The solid was triturated with petrol (40-60°) to leave 7.8 g (26% overall) of methyl compound **13**, R = Me, as a purple solid which was converted, *via* methods described in the synthesis of **4**, to the imidazoline dihydrochloride **14** (R = Me), mp 242-247°; nmr (DMSO-d₆/deuterium oxide): δ 6.76 (m, 4, aromatic H), 5.48 (t, J = 4 Hz, 1, CH), 3.94 (s, 4, N(CH₂)₂N), 3.60 (m, 2, CH₂), 2.78 (s, 3, NCH₃).

Anal. Calcd. for C₁₂H₁₅N₃O·2HCl·½H₂O: C, 48.90; H, 5.90; N, 14.26. Found: C, 48.71; H, 6.01; N, 13.86.

Using the procedures described above the following compounds were also prepared.

4-Ethyl-2-(2-imidazolyl)-3,4-dihydro-1,4-benzoxazine Dihydrochloride (**14**, R = Et).

This compound had mp 171-176° dec.

Anal. Calcd. for C₁₃H₁₅N₃O·2HCl: C, 50.57; H, 6.37; N, 13.61. Found: C, 50.62; H, 6.29; N, 13.37.

4-Benzyl-2-(2-imidazolyl)-3,4-dihydro-2H-1,4-benzoxazine Hydrochloride (**14**, R = CH₂Ph).

This compound had mp 233-243°.

Anal. Calcd. for C₁₈H₁₉N₃O·HCl: C, 65.55; H, 6.11; N, 12.74. Found: C, 65.68; H, 6.33; N, 12.74.

2-(2-Imidazolyl)-4-tosyl-3,4-dihydro-2H-1,4-benzoxazine Hydrochloride (**14**, R = Ts).

This compound had mp 235-241°.

Anal. Calcd. for C₁₈H₁₉N₃O₃·SHCl: C, 54.89; H, 5.12; N, 10.67. Found: C, 54.87; H, 5.18; N, 10.67.

Detosylation of 4-Tosyl-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide (**11**, R = Ts).

The *N*-tosylamide **11**, R = Ts (5.0 g, 0.015 mole) (prepared from ester **13** by standard procedure) and 20 ml of aqueous sulphuric acid (18 ml of concentrated acid + 2 ml of water) were mixed and heated on a steam bath for 15 minutes. The solution was cooled, poured into ice-water and basified with saturated sodium hydroxide solution. The warm solution was extracted with ethyl acetate and the combined extracts were washed with saturated sodium chloride solution, dried and evaporated to leave 1.2 g of an off white solid. Recrystallisation from ethanol gave 0.6 g (22%) of 3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide (**11**, R = H), mp 144-145.5 (lit [5] mp 145-148°). Mixed mp with an authentic sample of the amide showed no change.

Anal. Calcd. for C₉H₁₀N₂O₂: C, 60.67; H, 5.66; N, 15.72. Found: C, 60.45; H, 5.74; N, 15.65.

Detosylation of **14** (R = Ts) was also carried out using the above procedure to give the parent compound **14** (R = H).

Attempts to Prepare 3-(2-Imidazolyl)-3,4-dihydro-2H-1,4-benzoxazine (**16**) and Its 4-Acetyl Derivative **18**.

a) To a stirred solution of 4-acetyl-3,4-dihydro-2H-1,4-benzoxazine-3-carbonitrile (**15**) [5] (0.7 g, 0.0035 mole) in 2 ml of anhydrous dichloromethane at 0° was added a solution of triethyloxonium tetrafluoroborate (1.51 g, 0.008 mole) in 7 ml of anhydrous dichloromethane. The mixture was stirred at 0° for 20 minutes and then at room temperature for 3 hours. On recooling to 0° 5 ml of anhydrous methanol was added and stirring continued for 2 hours. Ethylenediamine (0.46 g, 0.0077 mole) was then added and the mixture stirred a further 18 hours. Solvent was removed *in vacuo* and the residue was chromatographed on silica with dichloromethane to yield 0.15 g of recovered starting material **15** and 0.15 g (34%) impure 3,4-dihydro-2H-1,4-benzoxazine-3-carbonitrile (**17**) as an oil; ms: (M⁺) 160 m/e; nmr (deuteriochloroform): δ 7.0-6.4 (m, 4, aromatic H), 4.6-4.0 (m, 4, OCH₂, NCH and NH-exchanged in deuterium oxide).

b) A solution of the 4-acetyl benzoxazine **15** [5] (0.6 g, 0.003 mole) and a catalytic amount of sodium methoxide (35 mg) in 2.5 ml of anhydrous methanol was stirred at room temperature for 18 hours. The solution was cooled to 0° and ethylenediamine (0.21 g, 0.0035 mole) in 2 ml of anhydrous methanol was added. After 10 minutes 0.3 ml of a 10M solution of methanolic hydrochloric acid was added and stirring continued for 1 hour. Analysis (tlc) indicated a complex reaction mixture with no major product being formed.

c) The reaction described in (b) above was repeated using the impure 3,4-dihydro-2H-1,4-benzoxazine-3-carbonitrile (**17**). Again tlc indicated a complex reaction mixture from which no product could be isolated.

4-Benzyl-3,4-dihydro-2H-1,4-benzoxazine (**19**).

Reduction of the 4-benzoyl precursor [8] with diborane using the procedure described in the preparation of **14** (R = Me) gave the benzyl product **19** in 68% yield, mp 42.5-44.5°; ms: (M⁺) m/e 225.

Anal. Calcd. for C₁₅H₁₅NO: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.83; H, 6.76; N, 6.27.

Attempt to Prepare 4-Benzyl-3,4-dihydro-2H-1,4-benzoxazine-3-carbonitrile (**21**).

To a cooled (0°) solution of **19** (1.9 g, 0.0084 mole) in 19 ml of anhydrous dichloromethane was added over 5 minutes a solution of *m*-chloroperbenzoic acid (1.7 g, of 95% pure material, 0.0094 mole) in 25 ml of anhydrous dichloromethane. After 18 hours stirring at room temperature the mixture was chromatographed on alumina (basic grade) with dichloromethane initially and then with 10% methanol/dichloromethane to give the crude *N*-oxide **20** as an oil. To a cooled (0°) solution of **20**, under an atmosphere of argon gas, in 15 ml of anhydrous dichloromethane was added 4 ml of acetic anhydride. The solution darkened during the first 5 minutes. After 18 hours stirring at room temperature aqueous sodium bi-

carbonate solution was added and the mixture was extracted with dichloromethane. The extracts were dried and evaporated to leave a semi-solid which was triturated with ether and then recrystallised from ethanol to give 0.4 g (17% overall yield) of presumed 6-acetoxy-4-benzyl-3,4-dihydro-2H-1,4-benzoxazine (**22**), mp 117.5-120°; ir (nujol): 1765 (C=O) cm^{-1} ; ms: (M^+) 283 m/e; nmr (deuteriochloroform): δ 7.25 (s, 5, aromatic H of benzyl group), 6.78 (broad d, $J = 8$ Hz, 1, aromatic H-8), 6.36 (broad s, 1, aromatic H-5), 6.30 (d $\times$ d, $J = 2$ and 8 Hz, 1, aromatic H-7), 4.38 (s, 2, CH_2Ph), 4.20 (broad t, $J = 4$ Hz, 2, CH_2), 3.30 (broad t, $J = 4$ Hz, 2, CH_2), 2.16 (s, 3, CH_3).

Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{NO}_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.04; H, 6.20; N, 4.91.

Similar rearrangements have been described [10] giving a mixture of acetylated products but the 6-acetoxy derivative is usually the major product.

Acknowledgement.

The authors wish to express their thanks to Lawrence K. Chan for his assistance in the synthetic work and Pamela Parker for assistance in the preparation of this manuscript.

REFERENCES AND NOTES

- [1] C. B. Chapleo, P. L. Myers, R. C. M. Butler, J. C. Doxey, A. G. Roach and C. F. C. Smith, *J. Med. Chem.*, **26**, 823 (1983).
- [2] C. B. Chapleo, P. L. Myers, R. C. M. Butler, J. A. Davis, J. C. Doxey, S. D. Higgins, M. Myers, A. G. Roach, C. F. C. Smith, M. R. Stillings and A. P. Welbourn, *J. Med. Chem.*, **27**, 570 (1984).
- [3] G. Liso, G. Trapani, V. Berardi and P. Marchini, *J. Heterocyclic Chem.*, **17**, 377 (1980); G. Liso, G. Trapani, V. Berardi, A. Latrofa and P. Marchini, *J. Heterocyclic Chem.*, **17**, 793 (1980).
- [4] J. F. Caputo and A. R. Martin, *J. Heterocyclic Chem.*, **15**, 1403 (1978).
- [5] J. Augstein, A. M. Monro and G. W. Hessey, Great Britain Patent 1,057,568; *Chem. Abstr.*, **66**, 95058z (1967).
- [6] M. S. Chodnekhar, A. F. Crowther, W. Hepworth, R. Howe, B. J. McLoughlin, A. Mitchell, B. S. Rao, R. P. Slatcher, L. H. Smith and M. A. Stevens, *J. Med. Chem.*, **15**, 49 (1972).
- [7] H. Bartsch and O. Schwarz, *J. Heterocyclic Chem.*, **20**, 45 (1983).
- [8] The precursor 4-benzoyl-1,4-benzoxazine was prepared according to the procedure by G. Coudert, G. Buillaumet and B. Loubinoux, *Synth. Commun.*, **9**, 541 (1979).
- [9] Conversions of this type have been previously reported: W. C. Groutas, M. Essawi and P. S. Portoghese, *Synth. Commun.*, **10**, 495 (1980); see also A. Ahond, A. Cave, C. Kan-Fan, H. P. Husson, J. de Rostolan and P. Potier, *J. Am. Chem. Soc.*, **90**, 5622 (1968).
- [10] Y. Hasimoto, T. Ishizaki, K. Shudo and T. Okamoto, *Chem. Pharm. Bull.*, **31**, 3891 (1983).
- [11] B. Haitinger, *Monatsh. Chem.*, **4**, 166 (1883).