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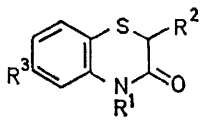
Acetylation and Acetoxylation of 4-Hydroxy-1,4-benzothiazin- and -benzoxazin-3(4*H*)-ones (Cyclic Hydroxamic Acids)

By **R. T. Coutts** * and **N. J. Pound**, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada

Treatment of 4-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one (Ia) and its 6-methyl derivative (Ie) with acetyl chloride yielded 4-acetoxy-derivatives (Ib and f); however, when acetic anhydride was the acetylating agent, 2-acetoxy-lactams (Ic and g) were obtained. In contrast, only 4-acetoxy-2*H*-1,4-benzothiazin-3(4*H*)-one 1,1-dioxide (IIb) was isolated when the sulphone corresponding to (Ia) was heated with either acetyl chloride or acetic anhydride. Whereas the 4-acetoxy-lactam (IIIb) was formed by the action of acetyl chloride on 4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (IIIa), treatment of this hydroxamic acid with acetic anhydride gave a mixture of the corresponding 6- and 7-acetoxy-lactams (IIIc and e). Mechanisms for the formation of these acetoxy-compounds are suggested, and some of their reactions are described.

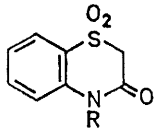
DURING a recent study on cyclic hydroxamic acids,[1] it was necessary to prepare the *O*-acetyl derivative of 4-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one (Ia). When it was found that treatment with acetyl chloride yielded a product that was isomeric, but not identical, with the acetate prepared by the interaction of compound (Ia) with acetic anhydride,[2] a more detailed investigation of the acetylation of this and related compounds [(Ie), (IIa), and (IIIa)] was carried out.

Treatment of compound (Ia) with excess of acetyl chloride yielded 4-acetoxy-2*H*-1,4-benzothiazin-3(4*H*)-one (Ib), identified by analysis and spectral data.



(I)

	R^1	R^2	R^3
a;	OH	H	H
b;	OAc	H	H
c;	H	OAc	H
d;	H	O_2CEt	H
e;	OH	H	Me
f;	OAc	H	Me
g;	H	OAc	Me



(II)

	R
a;	OH
b;	OAc

The mass spectrum showed ions at *m/e* 223 (M^+) and 181 ($M - 42$), and a metastable ion at *m/e* 146·9, the presence of which supported the direct loss of CH_2=C=O from the molecular ion.[3] Two i.r. carbonyl bands were observed at 1705 and 1802 cm^{-1}; carbonyl stretching near 1800 cm^{-1} is characteristic of the *N*-acetoxy-group.[2,4-8] The n.m.r. spectrum showed signals at τ 7·66 (3H, s, Me), 6·43 (2H, s, CH_2), and 2·55—3·20 (4H, m, aromatic).

An isomeric product was obtained when compound (Ia) was treated with acetic anhydride. Its mass spectrum (*m/e* 223, 181, and 43) indicated that it was also an acetate derivative. Two i.r. carbonyl peaks were observed at 1675 and 1753 cm^{-1}; the absence of absorption in the 1800 cm^{-1} region indicated that the *N*-acetoxy-function was not present. The n.m.r. spectrum showed signals at τ 8·00 (3H, s), 3·69 (1H, s), 2·58—3·18 (4H, aromatic), and —0·10br (1H, exchangeable). Reaction, therefore, must have occurred at the 2-position. It was concluded that acetoxylation, not acetylation, had occurred to give 2-acetoxy-2*H*-1,4-benzothiazin-3(4*H*)-one (Ic). This was confirmed by comparison with an authentic sample.[9]

Whereas treatment of the 4-acetoxy-compound (Ib) with glacial acetic acid gave a good yield of the 2-acetoxy-derivative (Ic), no reaction occurred when the hydroxamic acid (Ia) was treated similarly. In view of this, a mechanism for the formation of (Ic) from (Ib) can be proposed (Scheme 1). The attacking acetate ion appa-

[1] R. T. Coutts and N. J. Pound, *Canad. J. Chem.*, 1970, **48**, 1859.
[2] R. T. Coutts, K. W. Hindmarsh, S. J. Powell, J. L. Pound, and E. M. Smith, *Canad. J. Pharm. Sci.*, 1968, **3**, 49.
[3] H. Budzikiewicz, C. Djerassi, and D. H. Williams, 'Mass Spectrometry of Organic Compounds,' Holden-Day, San Francisco, 1967, p. 191.
[4] J. D. Loudon and I. Wellings, *J. Chem. Soc.*, 1960, 3462.
[5] J. D. Loudon and I. Wellings, *J. Chem. Soc.*, 1960, 3470.
[6] J. D. Loudon and G. Tennant, *J. Chem. Soc.*, 1960, 3466.
[7] A. Ohta and E. Ochiai, *Chem. and Pharm. Bull.* (*Japan*), 1962, **10**, 1260.
[8] L. A. Paquette, *J. Amer. Chem. Soc.*, 1967, **87**, 1407.
[9] K. Zahn, *Ber.*, 1923, **56**, 578.

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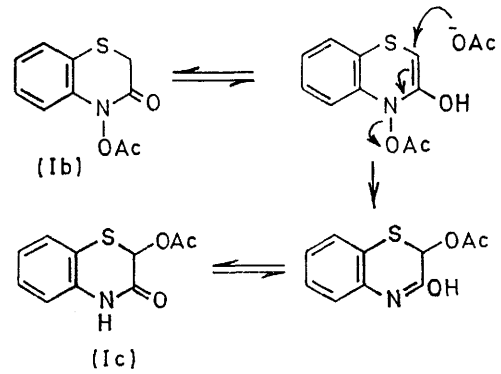
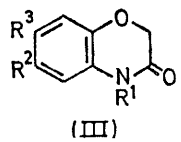
rently arises from the solvent; when compound (Ib) was treated with propionic acid the product was 2-propionyloxy-2*H*-1,4-benzothiazin-3(4*H*)-one (Id).



SCHEME 1

Analogous results were obtained when 4-hydroxy-6-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one (Ie) was treated with acetyl chloride and with acetic anhydride. The former reaction yielded 4-acetoxy-6-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one (If), identified from microanalysis and n.m.r. and i.r. spectra. When compound (Ie) was heated under reflux with acetic anhydride, 2-acetoxy-6-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one (Ig), identified similarly, was isolated.

It was previously [2] reported that the action of acetic anhydride on 4-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one 1,1-dioxide (IIa) produced the 4-acetoxy-derivative (IIb). In view of the foregoing results, this reaction was reinvestigated. Treatment of the hydroxamic acid (IIa) with either acetyl chloride or acetic anhydride gave product (IIb).



(III)

	R^1	R^2	R^3
a;	OH	H	H
b;	OAc	H	H
c;	H	OAc	H
d;	H	H	Cl
e;	H	H	OAc
f;	H	OH	H
g;	H	OBz	H
h;	H	H	H
i;	H	O_2CEt	H

The reactions of 4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (IIIa) with acetyl chloride and acetic anhydride gave surprising results. Treatment with acetyl chloride gave 4-acetoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (IIIb), $\nu_{max.}$ 1705 and 1803 cm^{-1} (CO); the n.m.r. spectrum possessed a two-proton signal that could be attributed to the methylene 2-protons. However, in contrast with the behaviour of the benzothiazine derivatives (Ia and e), heating a solution of the benzoxazine (IIIa) with acetic anhydride in acetic acid did not yield the 2-acetoxy-derivative. The following observations revealed that the product isolated (A) was 6-acetoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (IIIc). Analysis and the mass spectrum [*m/e* 207 (M^+), 165, and 43] indicated that it was isomeric with the 4-acetoxy-derivative (IIIb). The i.r. spectrum displayed carbonyl absorption at 1695 and 1760 cm^{-1} as well as NH stretching. The n.m.r. spectrum contained a two-proton methylene signal at τ 5·43 and a three-proton aromatic signal. Substitution had obviously occurred in the aromatic ring and not at the 2-position.

It is known [1] that the action of chloride anion on compound (IIIa) gives the 7-chloro-lactam (IIId). This suggested that the acetoxylation of (IIIa) could have involved a similar nucleophilic attack by acetate anion at the 7-position to give 7-acetoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (IIIe).

Both the 6-acetoxy-lactam (IIIc) and the 7-acetoxy-lactam (IIIe) are known.[10] The m.p. of compound (A), however, was the same as that reported for (IIIc). Identification as the 6-acetoxy-lactam (IIIc) was confirmed by comparison with an authentic sample prepared from 2,5-dimethoxyaniline and chloracetyl chloride.[10] The phenol (IIIf) and its benzoate (IIIg) prepared from the authentic sample of (IIIc) were identical with those obtained from product (A).

4-Acetoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (IIIb) can be converted into the 6-acetoxy-derivative (IIIc) by treatment with glacial acetic acid. On one occasion this reaction gave a small amount of a second product, which had i.r. and n.m.r. spectra identical with those of 7-acetoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (IIIe).[10] Attempts to isolate more of this compound were unsuccessful, but g.l.c. of the reaction mixture indicated the presence of three products possessing retention times of 6·0, 7·4, and 8·3 min. By peak augmentation, it was shown that the second and third peaks were compounds (IIIc) and (IIIe), respectively, and that the mixture contained 85% of (IIIc), 10% of (IIIe), and 5% of an unidentified third product.

To help establish a mechanism for the formation of compound (IIIc) from (IIIb), the hydroxamic acid (IIIa) was treated with glacial acetic acid, and the action of acetic anhydride on the lactam, 2*H*-1,4-benzothiazin-3(4*H*)-one (IIIh) was studied. In neither instance did reaction occur. When the hydroxamic acid (IIIa) was heated with propionic anhydride, a product was obtained which was identified by analysis and i.r. and n.m.r. spectra as 6-propionyloxy-2*H*-1,4-benzoxazin-3(4*H*)-one (IIIi). Hydrolysis of (IIIi) yielded the 6-hydroxy-lactam (IIIf). The same propionate (IIIi) was formed when the acetate (IIIb) was heated with propionic acid. In contrast, the 6-acetoxy-derivative (IIIc) did not react with propionic acid.

A mechanism which involves an intermolecular rearrangement can be proposed for the formation of compound (IIIc) from (IIIb) (Scheme 2). The conversion of the 4-acetoxybenzoxazine (IIIb) to the 6-propionyloxy-compound (IIIi) by the action of propionic acid can be explained by this mechanism only if the conversion involves an ester exchange (Scheme 3) prior to the rearrangement, since ester exchange does not occur when the 6-acetoxy-lactam (IIIc) is heated under reflux in propionic acid.

[10] J. D. Loudon and J. Ogg, *J. Chem. Soc.*, 1955, 739.

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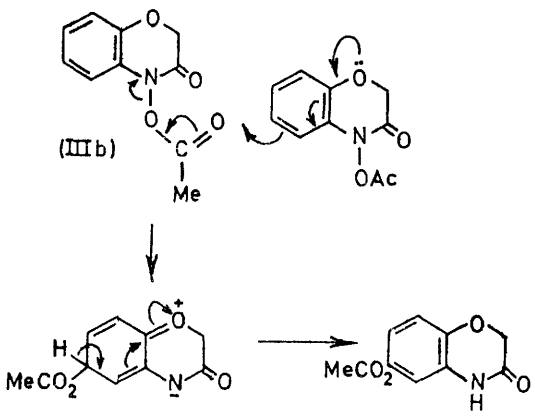
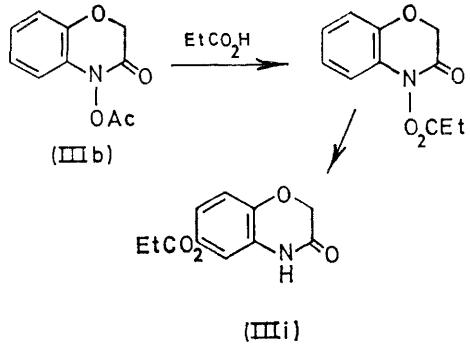


SCHEME 2



SCHEME 3

EXPERIMENTAL

I.r. spectra were recorded for Nujol mulls with a Beckman IR-10 spectrophotometer. Mass spectra were measured with an A.E.I. MS9 spectrometer at 70 eV (direct insertion technique), and n.m.r. spectra were recorded with a Varian A60 spectrometer, with tetramethylsilane as standard.

4-*Acetoxy*-2H-1,4-*benzothiazin*-3(4H)-*one* (Ib).—A solution of 4-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one [11] (1·08 g) in hot dry benzene (75 ml) was treated with acetyl chloride (3 ml) and heated under reflux for 2·5 h. The mixture was evaporated to dryness, leaving an oil which, when triturated with ethanol, gave *compound* (Ib) (1·01 g) as a white solid, m.p. 89—90° (from aqueous ethanol) (Found: C, 53·7; H, 4·2; N, 6·4. $C_{10}H_9NO_3S$ requires C, 53·8; H, 4·1; N, 6·3); see Discussion section for spectra.

2-*Acetoxy*-2H-1,4-*benzothiazin*-3(4H)-*one* (Ic).—(i) Acetic anhydride (2·5 ml) was added to a suspension of 4-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one (1 g) in glacial acetic acid (5 ml) and the mixture was heated under reflux for 30 min. The hot solution was poured on ice and the resulting suspension was neutralised with solid sodium carbonate. The mixture was extracted with ether. Evaporation of the extract left a yellow solid (0·9 g). Crystallisation from ethanol yielded compound (Ic), m.p. 172—174° (lit.,[9] 172—173°); for spectra see Discussion section.

(ii) A solution of 4-acetoxy-2*H*-1,4-benzothiazin-3(4*H*)-one (0·53 g) in glacial acetic acid (3 ml) was heated under reflux for 30 min, diluted with water (10 ml), and extracted with chloroform. Evaporation of the extract left a brown solid (0·51 g) which gave compound (Ic), m.p. 170—173° (from benzene), identical (i.r. spectrum) with that prepared by method (i).

2-*Propionyloxy*-2H-1,4-*benzothiazin*-3(4H)-*one* (Id).—A solution of 4-acetoxy-2*H*-1,4-benzothiazin-3(4*H*)-one (0·62 g) in propionic acid (8 ml) was heated under reflux for 3 h then poured on crushed ice. The product (0·47 g) crystallised from aqueous ethanol to give *compound* (Id) as a pale yellow solid, m.p. 128—129°, $\nu_{max.}$ 1670, 1749, 3060, 3130, and 3200 cm^{-1}, τ [$(CD_3)_2SO$] 9·06 (3H, t, *J* 7 Hz), 7·73 (2H, q, *J* 7 Hz), 3·75 (1H, s), 2·48—3·20 (4H, m), and —1·12br (1H, s, NH) (Found: C, 55·6; H, 4·9; N, 6·1. $C_{11}H_{11}NO_3S$ requires C, 55·7; H, 4·7; N, 5·9%).

4-*Acetoxy*-6-*methyl*-2H-1,4-*benzothiazin*-3(4H)-*one* (If).—Acetyl chloride (2 ml) was added to a solution of 4-hydroxy-6-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one [12] (0·43 g) in dry benzene (30 ml). This solution was heated under reflux for 90 min, then concentrated to a dark oil. Trituration with ethanol gave *compound* (If) as a grey solid (0·37 g), m.p. 97—98° (from ethanol), $\nu_{max.}$ 1701 and 1793 cm^{-1}, τ ($CDCl_3$) 7·68 (3H, s), 7·64 (3H, s), 6·46 (2H, s), and 2·68—3·30 (3H, m) (Found: C, 55·4; H, 4·7; N, 5·9. $C_{11}H_{11}NO_3S$ requires C, 55·7; H, 4·7; N, 5·9%).

2-*Acetoxy*-6-*methyl*-2H-1,4-*benzothiazin*-3(4H)-*one* (Ig).—A suspension of 4-hydroxy-6-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one (0·47 g) in glacial acetic acid (6 ml) and acetic anhydride (2·5 ml) was heated under reflux for 30 min. The mixture was stirred with ice, then filtered. Crystallisation of the yellow product (0·41 g) from ethanol (charcoal) gave *compound* (Ig), m.p. 187—189°, $\nu_{max.}$ 1678, 1757, and 3200 cm^{-1}, τ ($CDCl_3$) 8·01 (3H, s), 7·74 (3H, s), 3·82 (1H, s), 2·66—3·27 (3H, m), and —1·00 (1H, s) (Found: C, 55·7; H, 4·7; N, 6·0. $C_{11}H_{11}NO_3S$ requires C, 55·7; H, 4·7; N, 5·9%).

4-*Acetoxy*-2H-1,4-*benzothiazin*-3(4H)-*one* 1,1-*Dioxide* (IIb).—(i) A solution of 4-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one 1,1-dioxide [13] (0·49 g) in dry benzene (50 ml) was treated with acetyl chloride (2·5 ml) as described in the preparation of (Ib) to give compound (IIb) (0·41 g), m.p. 159—161° (from ethanol) (lit.,[2] 161—162°), $\nu_{max.}$ 1705 and 1806 cm^{-1}, τ [$(CD_3)_2SO$] 7·57 (3H, s), 4·84 (2H, s), and 1·96—2·72 (4H, m).

(ii) Acetic anhydride (3 ml) was added to a solution of 4-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one 1,1-dioxide (0·51 g) in glacial acetic acid (7 ml). The mixture was heated under reflux for 35 min, then poured over ice to give compound (IIb) (0·5 g), m.p. 159—160° (from ethanol), identical (i.r. spectrum) with the product from method (i). When the reaction time was prolonged to 24 h, the same product was isolated.

4-*Acetoxy*-2H-1,4-*benzoxazin*-3(4H)-*one* (IIIb).—A suspension of 4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one [14] (1·92 g) in benzene (80 ml) was treated with acetyl chloride (2·8 ml) as described in the preparation of (Ib). The resulting grey solid (1·44 g) was crystallised from benzene–light petroleum and then aqueous ethanol to give *compound* (IIIb), m.p. 64—65°, $\nu_{max.}$ 1705 and 1803 cm^{-1}, τ ($CDCl_3$) 7·54 (3H, s), 5·25 (2H, s), and 2·93—3·26 (4H, m) (Found: C, 58·0; H, 4·3; N, 6·7. $C_{10}H_9NO_4$ requires C, 58·0; H, 4·4; N, 6·8%).

6-*Acetoxy*-2H-1,4-*benzoxazin*-3(4H)-*one* (IIIc).—A solution of 4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (1·03 g) in

[11] R. T. Coutts, D. L. Barton, and E. M. Smith, *Canad. J. Chem.*, 1966, **44**, 1733.
[12] R. T. Coutts, H. W. Peel, and E. M. Smith, *Canad. J. Chem.*, 1965, **43**, 3221.
[13] R. T. Coutts and D. G. Wibberley, *J. Chem. Soc.*, 1963, 4610.
[14] R. T. Coutts, D. Noble, and D. G. Wibberley, *J. Pharm. Pharmacol.*, 1964, **16**, 773.

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glacial acetic acid (10 ml) was treated with acetic anhydride (5 ml) as described in the preparation of (Ic). Crystallisation of the product (0·73 g) from benzene and ethanol yielded the 6-acetoxy-derivative (IIIc), m.p. 162—164° (lit.,[10] 162—163°), $\nu_{max.}$ 1691, 1760, and 3200 cm^{-1}, τ ($CDCl_3$) 7·74 (3H, s), 5·43 (2H, s), 2·96—3·44 (3H, m), and −0·27br (1H, s) (Found: C, 57·8; H, 4·3; N, 6·7. Calc. for $C_{10}H_9NO_4$: C, 58·0; H, 4·4; N, 6·8%).

Hydrolysis of the product with 10% sodium hydroxide at 25° gave 6-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one (IIIf), m.p. 252—254° (decomp.) (from ethanol) (lit.,[10] 249—250°), identical (i.r., n.m.r., and u.v. spectra) with an authentic sample.[10]

Benzoylation of (IIIf) with benzoyl chloride gave 6-*benzoyloxy*-2H-1,4-*benzoxazin*-3(4H)-*one* (IIIg) as a white solid, m.p. 201—202°, $\nu_{max.}$ 1698, 1738, and 3200 cm^{-1}, τ [$(CD_3)_2SO$] 5·41 (2H, s), 1·80—3·34 (8H, m), and −0·71 (1H, s) (Found: C, 67·1; H, 4·4; N, 5·5. $C_{15}H_{11}NO_4$ requires C, 67·0; H, 4·1; N, 5·2%).

Treatment of 4-*Acetoxy*-2H-1,4-*benzoxazin*-3(4H)-*one with Acetic Acid.*—A solution of the acetoxy-compound (0·45 g) in glacial acetic acid (3 ml) was heated under reflux for 30 min. The mixture was poured on ice and a white solid (0·35 g) separated. The filtrate was neutralised with solid sodium carbonate and extracted with chloroform. Removal of the chloroform left more white solid (0·09 g). Crystallisation of the combined solids yielded 6-acetoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (IIIc) (0·25 g), m.p. 159—160°, identical (i.r. spectrum) with that isolated in the preceding reaction.

The filtrate from these crystallisations was evaporated to dryness to leave a white solid (0·16 g), m.p. 135—140°. G.l.c. of this solid in methanol (0·25 in × 6 ft glass column of 3% silicone rubber OV-17 on Chromosorb at 185°) showed three peaks of relative intensities 2 : 16 : 7 with retention times 6·0, 7·4, and 8·3 min, respectively. Addition of authentic samples of 6-acetoxy- and 7-acetoxy-2*H*-1,4-benzoxazin-3(4*H*)-one [10] to the sample solution resulted in augmentation of the second and third peaks, respectively.

6-*Propionyloxy*-2H-1,4-*benzoxazin*-3(4H)-*one* (IIIi).—(i) A solution of 4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (1·65 g) in propionic anhydride (7 ml) and propionic acid (15 ml) was heated under reflux for 30 min. The mixture was poured on ice and an off-white solid (1·13 g) separated. The filtrate was neutralised with solid sodium carbonate and extracted with chloroform. Evaporation of the extract left a solid (0·41 g). The combined solids yielded *compound* (IIIi), m.p. 146—147° (from ethanol), $\nu_{max.}$ 1703, 1762, and 3200 cm^{-1}, τ ($CDCl_3$) 8·78 (3H, t, *J* 7 Hz), 7·44 (2H, q, *J* 7 Hz), 5·45 (2H, s), 3·00—3·46 (3H, m), and 0·50br (1H, s) (Found: C, 59·5; H, 4·8; N, 6·4. $C_{11}H_{11}NO_4$ requires C, 59·7; H, 5·0; N, 6·3%).

Stirring a sample of compound (IIIi) (0·77 g) with 10% sodium hydroxide (25 ml.) at 25° yielded 6-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (0·59 g), m.p. 255—257° (decomp.) (from ethanol) (lit.,[10] 249—250°).

(ii) 4-Acetoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (0·61 g) dissolved in propionic acid (5 ml) was heated under reflux for 25 min. The solution was poured on ice and treated as described in method (i). The combined products (0·60 g) yielded compound (IIIi), m.p. 145—147° (from ethanol), identical (i.r. spectrum) with the compound isolated in (i).

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