

Benzazoles. Part 12.¹ Synthesis of 2-(Tetrahydro-2-thienyl)benzimidazoles and their Unsaturated Derivatives by the Reaction of 2-Mercaptoalkylbenzimidazoles with β -Electrophilic Ketones

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2-(α -Mercaptoalkyl)benzimidazoles (3) reacted with β -halogenoalkylketones (1) or with α,β -unsaturated ketones (2) to form the vinylogue adducts (4) which cyclised to give 2-(3-hydroxytetrahydro-2-thienyl)benzimidazoles (6). Compounds (4) or (6) reacted with acetic anhydride at room temperature to give the mono- (8) and diacetylated (9) derivatives of (6). At higher temperature dehydroacetylation occurs to give 2-(2,3-dihydro-2-thienyl)benzimidazoles (11).

It had been found earlier that the carbonyl group of 3-(2-thiobenzimidazolyl)propiofenone, which is formed in the reaction of 2-mercaptobenzimidazole with β -chloropropiofenone, does not react with the nitrogen of the benzimidazole, and that ring-closure with the benzimidazole-NH group can be carried out only by the reduction of the ketone group to a hydroxy-group which is, in turn, converted into a halogen atom.²

However, it is known that 2-mercaptobenzimidazole reacts with α -halogenoketones to form 3-hydroxy-2,3-dihydrothiazolo[3,2-*a*]benzimidazoles which exist in equilibrium with their open-chain amino-ketone tautomers.³ The reaction of 2-(mercaptomethyl)benzimidazole (3a) with β -halogenoketones (1a,b) gave the products (4a,b),^{4,5} but the workers claimed that the ring-closure gave a thiazepinobenzimidazole compound (5) as a result of a reaction between the imidazole nitrogen and the carbonyl group when the ketones (4a,b) were heated in polyphosphoric acid, and mention that an attempted ring-closure by heating the ketones (4a,b) in pyridine-acetic anhydride failed.^{4,5}

When (3a) reacted with either the β -halogenoketones (1a,b) or the α,β -unsaturated ketones (2a,b) the saturated ketones (4a,b) which are formed are partially cyclized at room temperature in a few hours to give 2-(3-hydroxytetrahydro-2-thienyl)benzimidazoles (6a,b) instead of the thiazepinobenzimidazoles (5).

The nearest analogues to this ring-closure reaction^{6,7} are the reactions of ethyl thioglycolate with α,β -unsaturated ketones which afforded 2-ethoxycarbonyl-3-hydroxytetrahydrothiophens^{8,9} or those of ethyl thioglycolate with β -chlorovinyl ketones¹⁰ or aldehydes¹¹ yielding 2-ethoxycarbonylthiophens. The 2-(2-thienyl)benzimidazoles have been hitherto prepared from *o*-phenylenediamine and thiophencarbaldehydes¹² by the Weidenhagen method.¹³

Since the ring-closure reaction of (4a,b) is a Knoevenagel-type reaction which occurs between the carbonyl and the active methylene groups (route b) and takes place in a good yield at room temperature and no formation of (5) (route a) was observed, the reaction was investigated in detail.

RESULTS AND DISCUSSION

When the saturated ketone (4) was heated under reflux in chloroform-acetone (1:1) in the presence of piperidine, this proved to be suitable for the preparation for a wide range of 2-(3-hydroxytetrahydro-2-thienyl)benzimidazoles (6). Different ketones (4a-j) reacted at different rates. The ring-closure reaction always took place more readily when R⁵ = H than when R⁵ = Me. When R⁴ = H the cyclization is significantly quicker. The ring-closure in acetic acid also took place more readily, due to the carbonyl reactivity of ketones with R¹ = Me compared to those derivatives with R¹ = Ph [*e.g.* Method B: (6e) *cf.* (6j)].

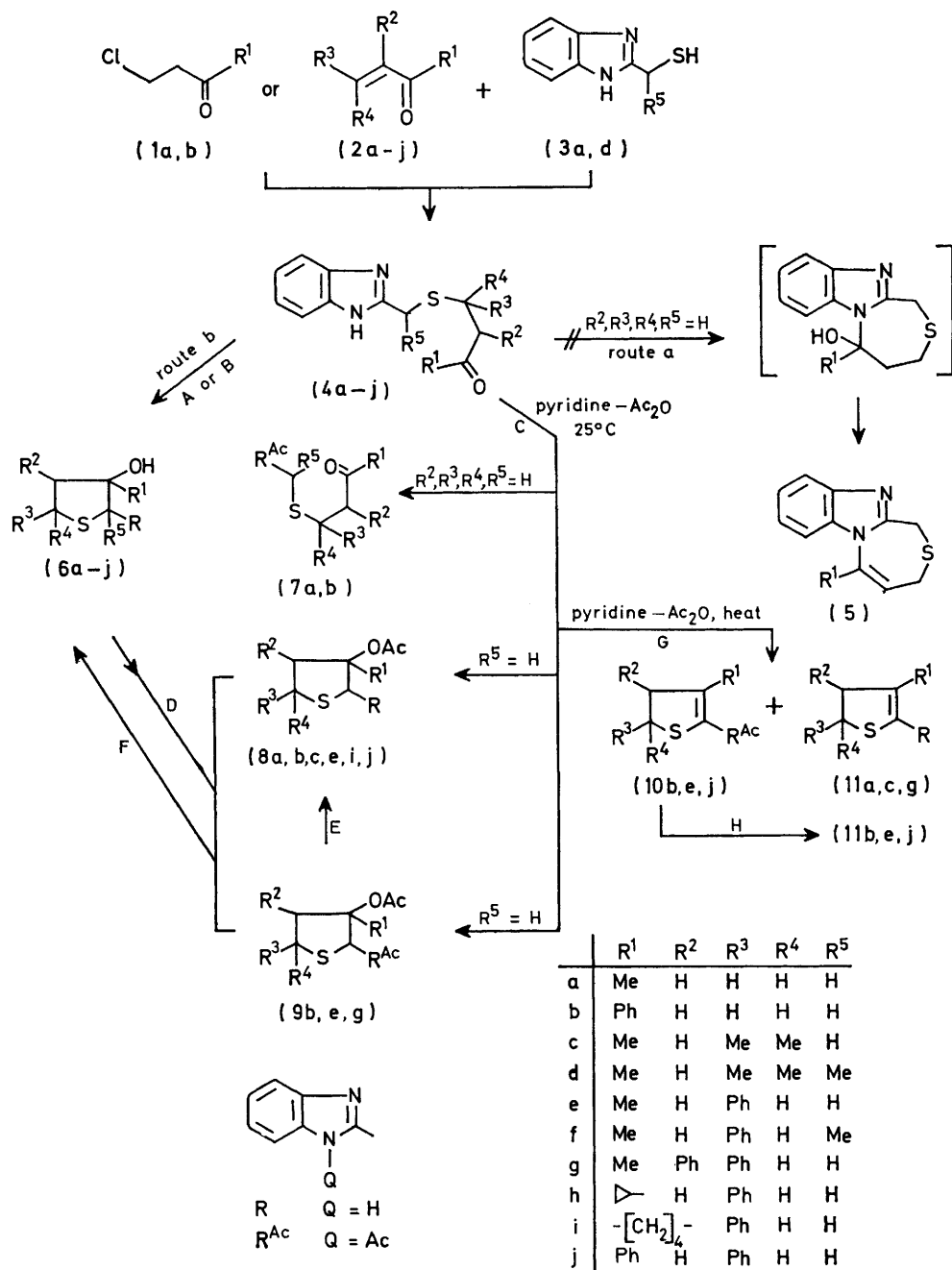
In pyridine-acetic anhydride (excess) at room temperature (4a) and (4b) gave the *N*-acetylated ketones (7a) and (7b) as main products, whereas from the analogues with R³ = Ph [(4e) and (4j)] under identical conditions (8e) and (9e) [from (4e)] and (8j) [from (4j)] were formed, respectively.

The diacetyl compounds (9) were hydrolysed in ethanol containing catalytic amounts of sodium hydroxide at room temperature to give the *O*-monoacetyl compounds (8). The derivatives (8) and (9) were hydrolysed with an equivalent amount of alkali to provide the corresponding hydroxy-compounds (6).

When the ring-closure was carried out at higher temperature, *i.e.* at the boiling point of pyridine-acetic anhydride, acetoxytetrahydrothiophens were dehydroacetylated, forming dihydrothiophens (10) and (11). These products could be isolated directly [(11a) and (11g)] or by hydrolysis through their *N*-acetyl derivatives [*e.g.* (10)].

The elimination is regiospecific, with the double bond formed between C-2 and C-3, as shown by the ¹H n.m.r. spectra, in which the H-2 signal is absent in the case of the dihydro-derivatives. In accord with this the intensities of the H-4 and H-5 signals are unchanged.

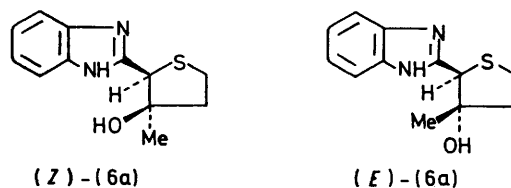
The structure of compounds (6) is shown by the OH band (4 320—3 300 cm⁻¹) and the diffuse NH band of benzimidazole (3 200—2 500 cm⁻¹) in the i.r. spectra. In the ¹H n.m.r. spectra the symmetrical AA'BB'



multiplet of aromatic protons, characteristic of an *N*-unsubstituted benzimidazole, is visible except when it is overlapped by the signals of aromatic substituents. The H-2 signal appears at *ca.* δ 5 ($\text{R}^5 = \text{H}$); in the derivatives with $\text{R}^5 = \text{Me}$ the methyl signal [(6d) Me at δ 1.76; (6f) Me at δ 1.92] is a singlet.

The question of diastereoisomerism arises with most of the compounds investigated. However, the ^1H n.m.r. data of the compounds (Tables 1–4) suggest that the ring-closure reactions have some stereoselectivity because fewer signals *e.g.* methyl signals, were observed than there might have been expected. To determine which isomer is actually formed selectively needs further in-

vestigation. In one case (6a), when both possible diastereoisomers (*Z* and *E*) were formed, the diastereoisomers were separated by fractional crystallization



(from chloroform). I.r. and ^1H and ^{13}C n.m.r. spectroscopy showed that the *Z*-isomer was the major product (5 : 1), in which the benzimidazolyl and hydroxy-groups

TABLE 1
(2-Benzimidazolylalkylthio) ketones (4)

	M.p. (°C)	Yield (%)	Molecular formula	Analysis (%) Found (Calc.)				Solvent	¹ H n.m.r (δ from SiM ₄)
				C	H	N	S		
(4a)	119—120 ^a	60	C ₁₂ H ₁₄ N ₂ OS	61.7 (61.5)	6.3 6.0	12.0 11.95	13.8 13.7	(CD ₃) ₂ SO	2.10 (s, 3 H, Me), 2.80 (s, 4 H, CH ₂ CH ₂), 4.0 (s, 2 H, CH ₂), 7.0—7.6 (m, 4 H, Ar-H)
(4b)	159—160 ^b	74	C ₁₇ H ₁₆ N ₂ OS	68.7 (68.9)	5.2 5.4	9.3 9.45	11.0 10.8	(CD ₃) ₂ SO	2.95, 3.35 (A ₂ B ₂ , 4 H, CH ₂ CH ₂), 4.05 (s, 2 H, CH ₂), 6.9—7.9 (m, 9 H, Ar-H)
(4d)	111—113	63	C ₁₅ H ₂₀ N ₂ OS	65.0 (65.2)	7.2 7.3	10.1 10.1	11.5 11.6	CDCl ₃	1.38 (s, 3 H, Me), 1.42 (s, 3 H, CH ₃), 1.75 (d, 3 H, Me), 1.98 (s, 3 H, Me), 2.62 (s, 2 H, CH ₂), 4.5 (q, 1 H, CH), 6.9—7.7 (m, 4 H, Ar-H)
(4e)	134—135	79	C ₁₈ H ₁₈ N ₂ OS	69.5 (69.65)	5.9 5.85	9.1 9.0	10.25 10.3	CDCl ₃	2.0 (s, 3 H, Me), 3.15 (d, 2 H, CH ₂), 3.80 (s, 2 H, CH ₂), 4.45 (AX ₂ m, 1 H, CH), 7.1—7.7 (m, 9 H, Ar-H)
(4f)	132—133	61	C ₁₉ H ₂₀ N ₂ OS	70.3 (70.3)	6.35 6.2	8.95 8.6	9.65 9.9	(CD ₃) ₂ SO	1.62 (d, 3 H, Me), 1.98 (s, 3 H, Me), 3.09 (d, 2 H, CH ₂), 4.12 (t, 1 H, CH), 4.28 (m, 1 H, CH), 6.9—7.6 (m, 9 H, Ar-H)
(4g)	134—135	52	C ₂₄ H ₂₂ N ₂ OS	74.7 (74.6)	5.85 5.7	7.35 7.25	8.0 8.3	CDCl ₃	2.14 (s, 3 H, Me), 3.80 (s, 2 H, CH ₂), 4.12 (d, 1 H, CH), 4.44 (d, 1 H, CH), 6.9—7.4 (m, 14 H, Ar-H)
(4h)	140—141	89	C ₂₀ H ₂₀ N ₂ OS	71.5 (71.4)	6.0 6.0	8.25 8.3	9.6 9.5	CDCl ₃	0.1—1.3 (m, 4 H, CH ₂ CH ₂), 1.6—2.1 (m, 1 H, CH), 3.12 (m, 2 H, CH ₂), 3.80 (s, 2 H, CH ₂), 4.27 (t, 1 H, CH), 7.2—7.7 (m, 9 H, Ar-H)
(4i)	121—123	68	C ₂₁ H ₂₂ N ₂ OS	71.7 (72.0)	6.3 6.3	8.1 8.0	9.4 9.15	CDCl ₃	1.3—3.2 (m, 9 H, [CH ₂] ₄ CH), 3.78 (s, 2 H, CH ₂), 4.0 (d, 1 H, CH), 7.1—7.7 (m, 9 H, Ar-H)
(4j)	152—153	89	C ₂₃ H ₂₀ N ₂ OS	76.0 (74.2)	5.6 5.4	7.3 7.5	8.7 8.6	(CD ₃) ₂ SO	3.58 (s, 2 H, CH ₂), 3.72 (d, 2 H, CH ₂), 4.50 (t, 1 H, CH), 6.9—7.9 (m, 14 H, Ar-H)

^a Lit., ⁴ m.p. 89—90°. ^b Lit., ⁵ m.p. 135—136°.

TABLE 2
2-(3-Hydroxytetrahydro-2-thienyl)benzimidazoles (6)

Compd. no.	M.p. (°C)	Method	Reaction time/h	Yield (%)	Molecular formula	Analysis (%) Found (Calc.)				¹ H n.m.r. in (CD ₃) ₂ SO (δ from SiM ₄)
						C	H	N	S	
(Z)-(6a)	142—143	A(i)	48	15 ^a	C ₁₂ H ₁₄ N ₂ OS	61.7 (61.5)	6.2 6.0	12.0 12.0	13.8 13.7	1.40 (s, 3 H, Me), 1.9—2.3 (m, 2 H, CH ₂), 2.6—3.5 (m, 2 H, CH ₂), 4.55 (s, 1 H, C-2-H), 7.0—7.6 (m, 4 H, Ar-H)
(E)-(6a)	156—157	A(ii)	120	68 ^a		61.6 (61.5)	6.2 6.0	11.9 11.95	13.6 13.7	1.10 (s, 3 H, Me), 2.0—2.6 (m, 2 H, CH ₂), 2.9—3.3 (m, 2 H, CH ₂), 4.40 (s, 1 H, C-2-H), 7.0—7.7 (m, 4 H, Ar-H)
(6b)	154—155	A(i)	48	5	C ₁₇ H ₁₆ N ₂ OS	69.1 (68.9)	5.6 5.4	9.3 9.45	11.0 10.8	2.2—3.7 (m, 4 H, CH ₂ CH ₂), 5.0 (s, 1 H, C-2-H), 6.9—7.6 (m, 9 H, Ar-H)
(6c)	222—224	A(i)	6	74	C ₁₄ H ₁₈ N ₂ OS	63.95 (64.1)	6.9 6.9	10.5 10.7	12.0 12.2	1.23 (s, 3 H, Me), 1.42 (s, 3 H, Me), 1.62 (s, 3 H, Me), 2.04 (s, 2 H, CH ₂), 4.70 (s, 1 H, C-2-H), 6.9—7.6 (m, 4 H, Ar-H)
(6d)	167—169	A(i)	12	54	C ₁₅ H ₂₀ N ₂ OS	65.1 (65.2)	7.4 7.3	10.3 10.1	11.5 11.6	1.26 (s, 3 H, Me), 1.40 (s, 3 H, Me), 1.50 (s, 3 H, Me), 1.76 (s, 3 H, C-2-Me), 2.15 (2 H, brs, CH ₂), 6.9—7.6 (m, 4 H, Ar-H)
(6e)	178—180	A(i)	20	85	C ₁₈ H ₁₈ N ₂ OS	69.7 (69.65)	5.7 5.85	9.1 9.0	10.05 10.3	1.55 (s, 3 H, Me), 2.50 (d, 2 H, CH ₂), 5.15 (s, 1 H, C-2-H), 5.05 (t, 1 H, CH), 7.0—7.7 (m, 9 H, Ar-H)
(6f)	176—177	A(i)	24	62	C ₁₉ H ₂₀ N ₂ OS	70.3 (70.3)	6.45 6.2	8.8 8.6	10.1 9.9	1.32 (s, 3 H, Me), 1.94 (s, 3 H, C-2-Me), 2.30 (d, 2 H, CH ₂), 4.94 (t, 1 H, CH), 6.9—7.6 (m, 9 H, Ar-H)
(6g)	172—173	A(i)	16	60	C ₂₄ H ₂₂ N ₂ OS	74.4 (74.6)	5.5 5.7	7.1 7.25	8.1 8.3	1.28 (s, 3 H, Me), 3.65 (d, 1 H, CH), 5.18 (s, 1 H, C-2-H), 5.31 (d, 1 H, CH), 7.0—7.7 (m, 14 H, Ar-H)
(6h)	158—159	A(i)	5	36	C ₂₀ H ₂₀ N ₂ OS	71.1 (71.4)	6.0 6.0	8.1 8.3	9.4 9.5	0.0—0.6 (m, 4 H, CH ₂ CH ₂), 0.8—1.4 (m, 1 H, CH), 2.30 (d, 2 H, CH ₂), 5.02 (t, 1 H, CH), 5.12 (s, 1 H, C-2-H), 7.0—7.7 (m, 9 H, Ar-H)
(6i)	211—212	A(i)	4	50	C ₂₁ H ₂₂ N ₂ OS	72.1 (72.0)	6.1 6.3	8.05 8.0	8.9 9.15	0.7—2.5 (m, 9 H, [CH ₂] ₄ CH), 5.10 (s, 1 H, C-2-H), 5.50 (d, 1 H, CH), 6.9—7.7 (m, 9 H, Ar-H)
(6j)	164—165	A(i)	36	73	C ₂₃ H ₂₀ N ₂ OS	74.3 (74.2)	5.65 5.4	7.65 7.5	8.5 8.6	2.61 (d, 2 H, CH ₂), 5.0—5.5 (m, 1 H, CH), 5.44 (s, 1 H, C-2-H), 7.0—7.7 (m, 14 H, Ar-H)

^a The yields were calculated on the mixture of *E,Z*-isomers.

are *cis*.¹⁴ In accordance with the field effect¹⁵ an up-field shift of the ¹H n.m.r. signal of the methyl group can be expected in the *E*-isomer (Table 2) and of the *O*-acetyl group in the *Z*-isomer (8a) (Table 3).

EXPERIMENTAL

Melting points were determined in a Boeting micro-melting-point apparatus. I.r. spectra were obtained using

commercially were prepared by the Claisen-Schmidt reaction.¹⁶

The new compounds are presented in Tables 1—4.

General Procedure for the Preparation of the Ketones (4).—A mixture of 2-(2-mercaptoalkyl)benzimidazole (3a,b) (0.03 mol), chloroform-acetone (80 ml, 1:1), anhydrous potassium carbonate (5 g), and the unsaturated ketone (2) (0.03 mol) was stirred for 30 min at 0–5 °C (2a, b, or i), or

TABLE 3
Ketones (7) and the benzimidazoles (8) and (9)

	M.p. (°C)	Method	Yield (%)	Molecular formula	Analysis Found (Calc.)				¹ H n.m.r. (δ from SiMe ₄)	N.m.r. solvent
					C	H	N	S		
(7a)	107–109	C	70	C ₁₄ H ₁₆ N ₂ O ₂ S	61.0 (60.85)	5.8 5.8	10.3 10.1	11.8 11.6	2.12 (s, 3 H, Me), 2.75 (s, 4 H, CH ₂ -CH ₂), 2.90 (s, 3 H, NCOMe), 4.25 (s, 2 H, CH ₂), 7.2–7.8 (m, 4 H, Ar-H)	CDCl ₃
(7b)	107–108	C	61	C ₁₉ H ₁₈ N ₂ O ₂ S	67.6 (67.4)	5.7 5.4	8.45 8.3	9.4 9.5	2.85 (s, 3 H, NCOMe), 2.90 (m, 2 H, CH ₂), 3.35 (m, 2 H, CH ₂), 4.24 (s, 2 H, CH ₂), 7.1–7.9 (m, 9 H, Ar-H)	CDCl ₃
(E)-(8a)	163 164	C D	10 60	C ₁₄ H ₁₆ N ₂ O ₂ S ·H ₂ O	57.3 (57.1)	6.15 6.2	9.5 9.5	10.6 10.9	1.60 (s, 3 H, CH ₃), 1.78 (s, 3 H, OCOMe), 1.9–2.5 (m, 2 H, CH ₂), 2.6–3.3 (m, 2 H, CH ₂), 4.65 (s, 1 H, C-2-H), 6.9–7.6 (m, 4 H, Ar-H)	(CD ₃) ₂ SO
(Z)-(8a)	169–170	D	64	C ₁₄ H ₁₆ N ₂ O ₂ S	60.8 (60.85)	5.9 5.8	10.3 10.1	11.9 11.6	1.40 (s, 3 H, CH ₃), 2.08 (s, 3 H, OCOMe), 2.3–2.9 (m, 2 H, CH ₂), 2.9–3.3 (m, 2 H, CH ₂), 5.00 (s, 1 H, C-2-H), 7.0–7.7 (m, 4 H, Ar-H)	(CD ₃) ₂ SO
(8b)	190–191	C D E	12 30 65	C ₁₉ H ₁₈ N ₂ O ₂ S	67.5 (67.4)	5.5 5.4	8.3 8.3	9.4 9.5	1.95 (s, 3 H, OCOMe), 2.7–3.5 (m, 4 H, CH ₂ CH ₂), 5.0 (s, 1 H, C-2-H), 6.9–7.6 (m, 9 H, Ar-H)	(CD ₃) ₂ SO
(8c)	151–153	E	65	C ₁₆ H ₂₀ N ₂ O ₂ S	63.35 (63.1)	6.8 6.6	9.5 9.2	10.8 10.5	1.55 (s, 3 H, Me), 1.60 (s, 3 H, Me), 1.76 (s, 3 H, Me), 1.98 (s, 3 H, OCOMe), 2.80 (s, 2 H, CH ₂), 5.74 (s, 1 H, C-2-H), 7.1–7.9 (m, 4 H, Ar-H)	CDCl ₃
(8e)	177–178	C E	15 82	C ₂₀ H ₂₀ N ₂ O ₂ S	68.3 (68.2)	5.95 5.7	8.05 7.95	9.2 9.1	1.80 (s, 3 H, Me), 2.10 (s, 3 H, OCOMe), 2.50 (d), 3.58 (d), (2 H, CH ₂), 4.75 (dd, 1 H, CH), 5.10 (s, 1 H, C-2-H), 7.1–7.8 (m, 9 H, Ar-H)	CDCl ₃
(8i)	127–128	C	56	C ₂₃ H ₂₄ N ₂ O ₂ S ·H ₂ O	67.3 (67.3)	6.5 6.4	7.0 6.8	8.05 7.8	1.0–1.8 (br, 6 H, [CH ₂] ₃), 1.92 (s, 3 H, OCOMe), 2.0–2.6 (br, 2 H, CH ₂), 3.2–3.8 (br, 1 H, CH), 5.13 (d, 1 H, CH), 5.44 (s, 1 H, C-2-H), 7.1–7.9 (m, 9 H, Ar-H)	CDCl ₃
(8j)	226–227	C	72	C ₂₅ H ₂₂ N ₂ O ₂ S	72.3 (72.4)	5.45 5.35	6.7 6.8	7.5 7.7	2.26 (s, 3 H, OCOMe), 3.2–3.7 (m, 2 H, CH ₂), 4.95 (t, 1 H, CH), 5.20 (s, 1 H, C-2-H), 7.0–7.8 (m, 14 H, Ar-H)	(CD ₃) ₂ SO
(9b)	169–170	C D	8 30	C ₂₁ H ₂₀ N ₂ O ₃ S	66.45 (66.3)	5.2 5.3	7.5 7.4	8.6 8.4	1.60 (s, 3 H, OCOMe), 2.80 (s, 3 H, NCOMe), 2.5–3.3 (m, 2 H, CH ₂ -CH ₂), 5.95 (s, 1 H, C-2-H), 7.2–7.9 (m, 9 H, Ar-H)	(CD ₃) ₂ SO
(9e)	144–145	C	76	C ₂₂ H ₂₂ N ₂ O ₃ S	66.6 (67.0)	5.7 5.6	7.1 7.1	8.4 8.1	1.80 (s, 3 H, Me), 1.94 (s, 3 H, OCOMe), 2.53 (2 d), 3.40 (2 d), (2 H, CH ₂), 2.78 (s, 3 H, NCOMe), 5.05 (t, 1 H, CH), 5.90 (s, 1 H, C-2-H), 7.1–7.9 (m, 9 H, Ar-H)	(CDCl ₃)
(9g)	235–236	C	65	C ₂₈ H ₂₆ N ₂ O ₃ S	71.6 (71.5)	5.45 5.6	5.9 5.95	6.7 6.8	1.70 (s, 3 H, Me), 1.94 (s, 3 H, OCOMe), 2.80 (s, 3 H, NCOMe), 3.49 (d, 1 H, CH), 5.54 (d, 1 H, CH), 6.44 (s, 1 H, C-2-H), 7.0–8.0 (m, 14 H, Ar-H)	CDCl ₃

Nujol suspensions (Zeiss Specord 71) or KBr pellets (Perkin-Elmer 577). N.m.r. spectra were recorded with a Perkin-Elmer R12 instrument using tetramethylsilane as internal standard.

2-Mercaptomethylbenzimidazole (3a)¹⁶ and 2-(1-mercaptoethyl)benzimidazole (3d)¹⁷ were prepared, respectively, by the Philips method¹⁸ from *o*-phenylenediamine and thio-glycolic acid, and from 2-mercaptopropionic acid in 5*N*-hydrochloric acid. Ketones which were not available

in other cases at the boiling point of the solvent mixture. The precipitated product was filtered off and washed with water to remove inorganic material. If no precipitate formed, the filtrate was evaporated, and the residue was dissolved in alcohol-water. All products were recrystallized from ethanol-water.

Compounds (4a) and (4b) have been prepared previously by Singh and Singh^{4,5} by reaction of (3a) with, respectively, (1a) and (1b) in ethanol in the presence of sodium hydroxide.

General Procedures for the Preparation of 2-(3-Hydroxy-tetrahydro-2-thienyl)benzimidazoles (6).—*Method A.* (i) A solution of the ketone (4) (0.01 mol) in chloroform-acetone (50 ml, 1:1) containing a few drops of piperidine was heated under reflux (for 4–48 h, see Table 2). The reaction mixture was evaporated *in vacuo*, and the residue was crystallized from ethanol-water. The crude product (6) was dissolved in dimethyl sulphoxide-ethanol, and heated with charcoal. Addition of water to the filtered solution induced crystallization of the product.

Method A. (ii) A solution of the ketone (4) (0.01 mol) in

Method D. Acetic anhydride (2 ml) was added to a solution of the 3-hydroxytetrahydrothiophen derivative (6) (0.01 mol) in pyridine (20 ml) and the mixture was worked up as in Method A. In the fractional recrystallization the *NO*-diacetyl derivative (9), if any was formed, crystallized out first, and then the *O*-acetyl derivative (8). The analytical samples were obtained by recrystallization from ethanol-water.

Preparation of O-Acetyltetrahydrothiophens (8) by the Hydrolysis of the NO-Diacetyl Compounds (9). *Method E.*—A catalytic amount of sodium hydroxide (10%) was added

TABLE 4
1-Acetyl-2-(2,3-dihydro-2-thienyl)benzimidazoles (10) and 2-(2,3-dihydro-2-thienyl)benzimidazoles (11)

	M.p. (°C)	Method	Yield (%)	Molecular formula	Analysis Found (Calc.)				¹ H N.m.r. in (CD ₃) ₂ SO (δ from SiMe ₄)
					C	H	N	S	
(10b)	112–113	G	82	C ₁₉ H ₁₆ N ₂ OS	71.25 (71.2)	5.2 5.0	8.9 8.7	10.1 10.0	2.52 (s, 3 H, NCOMe), 3.38 (br s, 4 H, CH ₂ CH ₂), 7.0 (br s, 5 H, Ar-H), 7.1–8.1 (m, 4 H, Ar-H)
(10e)	117–119	G	78	C ₂₀ H ₁₈ N ₂ OS	71.6 (71.8)	5.5 5.4	8.5 8.4	9.3 9.6	1.85 (s, 3 H, Me), 2.75 (s, 3 H, NCOMe), 3.20 (d, 2 H, CH ₂), 5.08 (t, 1 H, CH), 7.2–8.2 (m, 9 H, Ar-H)
(10j)	108–109	G	84	C ₂₆ H ₂₀ N ₂ OS	75.6 (75.7)	5.0 5.1	7.1 7.1	8.2 8.1	2.60 (s, 3 H, NCOMe), 3.68 (d), 3.76 (d) (2 H, CH ₂), 5.32 (t, 1 H, CH), 7.10 (s, 5 H, Ar-H), 7.2–8.2 (m, 9 H, Ar-H)
(11a)	198–200	G	76	C ₁₂ H ₁₂ N ₂ S	66.5 (66.6)	5.6 5.6	12.75 12.95	14.9 14.8	2.30 (s, 3 H, Me), 2.9–3.5 (m, 4 H, CH ₂ -CH ₂), 7.1–7.7 (m, 4 H, Ar-H)
(11b)	202–203	H	92	C ₁₇ H ₁₄ N ₂ S	73.5 (73.35)	5.1 5.1	10.1 10.1	11.5 11.5	3.32 (s, 4 H, CH ₂ CH ₂), 7.10 (s), 7.0–7.6 (m, 9 H, Ar-H)
(11c)	206–208	G	75	C ₁₄ H ₁₆ N ₂ S	68.8 (68.8)	6.6 6.6	11.6 11.5	13.0 13.1	1.55 (s, 6 H, 2 Me), 2.25 (s, 3 H, Me), 2.80 (s, 2 H, CH ₂), 7.0–7.6 (m, 4 H, Ar-H)
(11e)	224–226	H	93	C ₁₈ H ₁₆ N ₂ S	73.8 (73.9)	5.4 5.5	9.65 9.6	10.9 11.0	2.18 (s, 3 H, Me), 3.22 (d), 3.26 (d), (2 H, CH ₂), 4.95 (t, 1 H, CH), 7.0–7.6 (m, 9 H, Ar-H)
(11g)	298–300	G	91	C ₂₄ H ₂₀ N ₂ S	78.1 (78.2)	5.5 5.5	7.8 7.6	8.8 8.7	2.02 (s, 3 H, Me), 4.40 (d), 4.82 (d), (2 H, CH ₂), 7.28 (s), 7.0–7.7 (m), (14 H, Ar-H)
(11j)	223–224	H	92	C ₂₃ H ₁₈ N ₂ S	77.85 (77.9)	5.2 5.1	8.1 7.9	9.25 9.05	3.43 (d), 3.71 (d), (2 H, CH ₂), 5.12 (t, 1 H, CH), 7.1–7.6 (m, 14 H, Ar-H)

dimethyl sulphoxide (10 ml) was set aside at room temperature for 7 d and then diluted by water. The product (6) was worked up as in method A(i).

Method B. A solution of the ketone (4) (0.01 mol) in acetic acid (30 ml; 96%) was kept at room temperature for 4–48 h, then poured onto ice and neutralized with an aqueous solution of sodium carbonate (5%). The product (6) was filtered off, washed with water and then with either a mixture of ethanol-ether (1:1) or *n*-hexane, and dried. The analytical sample was recrystallized as in method A.

General Procedures for the Preparation of Acetyltetrahydrothiophens (8) and (9).—*Method C.* Acetic anhydride (4 ml) was added to a solution of the ketone (4) (0.01 mol) in pyridine (20 ml). The mixture was kept for 24 h, and then poured onto ice. The initially oily product which separated solidified, and was filtered off, washed with water, and dried. A solution of the crude product in ethanol was heated with charcoal, filtered, and diluted with water. The material which separated out was fractionally crystallized.

Of the products obtained, those from (4a) and (4b) were the *N*-acetyl derivatives of the ketones (7a) (70%) and (7b) (61%), respectively, and from the mother-liquors the *O*-acetyl derivatives (8a) (10%) and (8b) (12%), respectively, of the cyclized product (6), and the diacetyl derivative (9b) (8%).

In the case of other ketones (4) the *N*-acetyl derivative of the saturated ketone could not be isolated, and the tetrahydrothiophen derivatives (8) and (9) were formed in higher yields.

to a solution of the *NO*-diacetyl derivative (9) (0.005 mol) in ethanol (10 ml). The solution was kept at room temperature for 2 h and the corresponding derivative (8) was then obtained by diluting the solution with water. The analytical samples were crystallized from ethanol-water.

Hydrolysis of Acetyl Compounds (8) and (9) to 3-Hydroxy-tetrahydrothiophens (6). *Method F.*—An aqueous solution (2 ml) of the equivalent amount of sodium hydroxide was added to a solution of the acetyl derivative (8) or (9) (0.005 mol) in ethanol (10 ml). The mixture was kept for 2–4 h at room temperature and then diluted with water until crystallization started. The derivatives (6) were filtered off and recrystallized from ethanol-water.

General Procedure for the Preparation of 1-Acetyl-2-(2,3-dihydro-2-thienyl)benzimidazoles (10). *Method G.*—A solution of the saturated ketone (4) or the cyclized product (6) (0.02 mol) in pyridine (20 ml) and acetic anhydride (6 ml) was boiled for 5 h and then poured onto ice. The precipitated solid was filtered off, washed with water, and dried. The crude products were 1-acetyl-2-(2,3-dihydro-2-thienyl)-benzimidazole derivatives (10); the analytical samples were crystallized from chloroform-hexane. In three cases, only the deacetylated derivatives (11a, c, and g) could be isolated. The *N*-acetyl group of derivatives (10) were spontaneously hydrolysed to the corresponding products (11) when warmed in aqueous ethanol.

Hydrolysis of Derivatives of 1-Acetyl-2-(2,3-dihydro-2-thienyl)benzimidazole (10) to (11). *Method H.*—A solution of sodium hydroxide (80 mg) in water (2 ml) was added to a

solution of (10) (0.02 mol) in ethanol (20 ml) and the mixture was kept for 30 min at room temperature and then diluted with water until the precipitation of crystals started. The product (11) was filtered off and recrystallized from aqueous ethanol.

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