Pharmacologically Active 4-Oxo-4*H*-chromen-2-carboxylic Acids (2-Carboxychromones). Part I. The Synthesis of 4-Oxo-4*H*-chromen-2-carboxylic Acids containing a Fused Thiazole Ring

By **A. O. Fitton,* B. T. Hatton, M. P. Ward,** and (in part, the late) **R. Lewis,** Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT

The synthesis of five 2-carboxychromones containing a fused 2-methylthiazole ring is described. All were obtained from appropriately substituted acetylhydroxybenzothiazoles which were synthesised by several routes but mainly by acetylation of methoxybenzothiazoles under various conditions. A note on the mass spectral fragmentation of the 2-methylthiazolochromone acids is included.

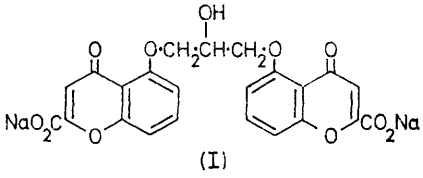
2-Carboxychromones and their salts frequently possess special activity [1,2] as inhibitors of the antigen–antibody reaction.[3] In addition, disodium 5,5′-(2-hydroxypropane-1,3-diyldioxy)-4,4′-dioxodi-4*H*-chromen-2,2′-dicarboxylate ('Intal') [4] (I) has recently found extensive use in the treatment of allergic asthma. We describe here the syntheses of five chromone-2-carboxylic acids which possess a fused thiazole ring, as part of a programme aimed at synthesising chromone acids with pharmacological activity related to that of Intal.

The thiazolochromones were synthesised by condensation of appropriately substituted acetylhydroxybenzothiazoles with diethyl oxalate, followed by cyclisation of the resulting diketone. In most cases, the acetylhydroxybenzothiazoles were obtained either from methoxybenzothiazoles by direct Friedel–Crafts acetylation, or, indirectly, from a hydroxybenzothiazole by *O*-acetylation and subsequent Fries rearrangement.

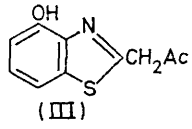
Treatment of 6-methoxy-2-methylbenzothiazole [5,6] (IIa) with boron trifluoride–acetic acid complex gave 7-acetyl-6-hydroxy-2-methylbenzothiazole (IIb) and 6-hydroxy-2-methylbenzothiazole [7] (IIc). Under similar conditions, 4-methoxy-2-methylbenzothiazole [5,6] (IId) did not react; however, it did react with acetyl chloride in the presence of aluminium chloride. With carbon disulphide as solvent, the product was 7-acetyl-4-methoxy-2-methylbenzothiazole (IIe) whereas in ethylene dichloride, 5-acetyl-4-hydroxy-2-methylbenzothiazole (IIf) and a small amount of 4-hydroxy-2-methylbenzothiazole [5] (IIg) were formed. Fries rearrangement of 4-acetoxy-2-methylbenzothiazole [8] (IIh) also gave the ketone (IIf), and in addition 2-acetonyl-4-hydroxybenzothiazole (III), by acetylation of the 2-methyl group.

[1] B.P. 1,024,645/1966.
[2] B.P. 1,116,562/1968.
[3] A. Wilson and H. O. Schild, 'Applied Pharmacology,' Churchill, London, 1968, p. 107.
[4] J. S. G. Cox, *Nature*, 1967, **216**, 1328.
[5] Y. Mizuno and J. Adachi, *Reports of the Faculty of Pharmacy, University of Kanazawa, Japan*, 1951, 8.
[6] Y. Mizuno and K. Adachi, *J. Pharm. Soc. Japan.*, 1950, **70**, 10; 1956, **76**, 329.
[7] M. A. Al'perovich and I. K. Ushenko, *Zhur. obshchei Khim.*, 1959, **29**, 989.
[8] A. I. Kiprianov and B. I. Dashevskaya, *Zhur. obshchei Khim.*, 1949, **19**, 1158.

A mixture of 5- and 7-methoxybenzothiazoles results [6] from the oxidative cyclisation of *m*-methoxythionacetanilide, but separation of the mixture (*via* picrate formation) was difficult. The solid 7-methoxy-2-methylbenzothiazole (IIi) was readily obtained pure, but the liquid 5-methoxy-isomer (IIj) was always obtained contaminated, and was more conveniently prepared by an alternative route related to that of



(I)



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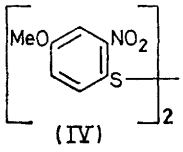

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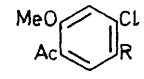
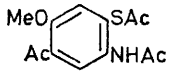


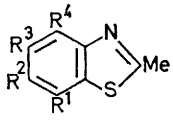
(V)a; R = H

b; R = NO_2



(VI)

a; $R^1 = R^3 = R^4 = H$, $R^2 = OMe$
b; $R^1 = Ac$, $R^2 = OH$, $R^3 = R^4 = H$
c; $R^1 = R^3 = R^4 = H$, $R^2 = OH$
d; $R^1 = R^2 = R^3 = H$, $R^4 = OMe$
e; $R^1 = Ac$, $R^2 = R^3 = H$, $R^4 = OMe$
f; $R^1 = R^2 = H$, $R^3 = Ac$, $R^4 = OH$
g; $R^1 = R^2 = R^3 = H$, $R^4 = OH$
h; $R^1 = R^2 = R^3 = H$, $R^4 = OAc$
i; $R^1 = OMe$; $R^2 = R^3 = R^4 = H$
j; $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
k; $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = Ac$
l; $R^1 = R^2 = R^4 = H$, $R^3 = OH$
m; $R^1 = OH$, $R^2 = Ac$, $R^3 = R^4 = H$
n; $R^1 = OH$, $R^2 = R^3 = H$, $R^4 = Ac$
o; $R^1 = R^4 = H$, $R^2 = OH$, $R^3 = Ac$
p; $R^1 = R^4 = H$, $R^2 = OMe$; $R^3 = Ac$



(II)

Deichmeister and Sveshnikov.[9] Thus, 4-chloro-3-nitroanisole [10] was converted by sodium disulphide into bis-4-methoxy-2-nitrophenyl disulphide (IV), which was reduced by zinc and acetic acid. The resulting zinc salt of the aminobenzenethiol, when heated with acetyl chloride, gave 5-methoxy-2-methylbenzothiazole.

Acetylation of this compound by acetyl chloride in ethylene dichloride in the presence of aluminium chloride gave 4-acetyl-5-hydroxy-2-methylbenzothiazole (IIk) and a small amount of 5-hydroxy-2-methylbenzothiazole [7] (III). Similar acetylation of 7-methoxy-2-methylbenzothiazole gave 6-acetyl-7-hydroxy-2-methylbenzothiazole (IIm) together with 4-acetyl-7-hydroxy-2-methylbenzothiazole (IIn). The four products from these reactions were all obtained when the mixture of 5- and 7-methoxy-2-methylbenzothiazoles was acetylated. Since the products were easily and cleanly separated chromatographically, it was unneccessary to separate the mixture of 5- and 7-methoxy-2-methylbenzothiazoles.

[9] M. V. Deichmeister and N. N. Sveshnikov, *Kinotekn., Nauchn. Tekhn. Sb.*, 1963, **4**, 117 (*Chem. Abs.*, 1963, **58**, 9043b).

5-Acetyl-6-hydroxy-2-methylbenzothiazole (IIo) was prepared by an alternative method. 4-Chloro-2-methoxyacetophenone [11] (Va) on nitration gave 4-chloro-2-methoxy-5-nitroacetophenone (Vb), which on treatment with sodium hydrogen sulphide and acetyl chloride gave a mixture of 5-acetyl-6-methoxy-2-methylbenzothiazole (IIp) and 5-acetamido-4-acetylthio-2-methoxyacetophenone (VI). On heating with aluminium chloride both yielded 5-acetyl-6-hydroxy-2-methylbenzothiazole.

The orientations of the various acetylhydroxybenzothiazoles were established or confirmed by their n.m.r. spectra (Table 1).

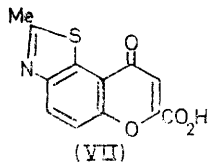
TABLE 1

Chemical shifts (τ) and coupling constants (*J* in Hz) of acetylhydroxy-2-methylbenzothiazoles

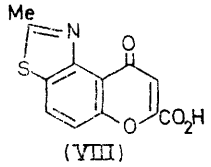
Compounds	Me	OH	Ac	Aromatic
(IIo)	7·20	−2·30 *	7·22	1·50, 2·54
(IIk)	7·15	−2·20 *	6·90	2·16 (d), 2·98 (d) (*J* 9·5)
(IIb)	7·17	−3·23 *	7·20	1·97 (d), 2·89 (d) (*J* 9·0)
(IIf)	7·15	−2·28 *	7·31	2·28 (d), 2·95 (d) (*J* 8·5)
(IIm)	7·17	−3·11 *	7·38	2·29 (d), 2·63 (d) (*J* 9·0)
(IIn) †	7·10	0·02 *	7·10	2·06 (d), 3·03 (d) (*J* 8·5)

* Exchangeable. † Solution in $(CD_3)_2CO$.

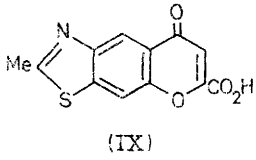
The thiazolochromones were prepared by base-catalysed condensation of the acetylhydroxy-2-methylbenzothiazoles with diethyl oxalate (1 equiv.), followed



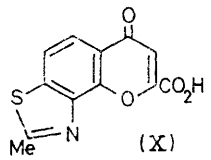
(VII)



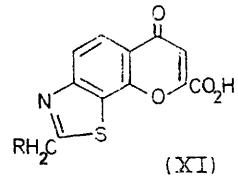
(VIII)



(IX)



(X)



(XI)

a; R = H

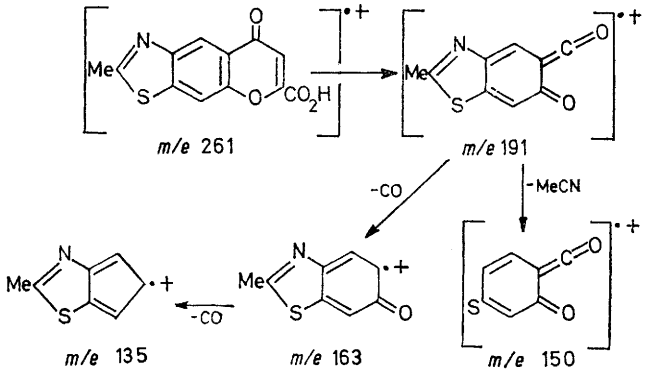
b; R = CO·CO_2H

by acid-catalysed cyclisation and hydrolysis of the resulting diketone esters. Use of an excess of diethyl

[10] H. H. Hodgson and J. H. Crook, *J. Chem. Soc.*, 1932, 1812.
[11] J. D. Bryan, A. A. Goldberg, and A. H. Wragg, *J. Chem. Soc.*, 1960, 1279.

oxalate led to condensation at the 2-methyl group as well as at the acetyl group. Thus 6-acetyl-7-hydroxy-2-methylbenzothiazole gave 2-oxalomethyl-6-oxopyrano-[3,2-*g*]benzothiazole-8-carboxylic acid (XIb).

The mass spectra of the thiazolochromone acids all displayed a similar fragmentation pattern (see Scheme). The base peak (*m/e* **191**) is the fragment formed by retro-Diels–Alder fission of the molecular ion (*m/e* 261). Further fragmentation occurs by loss [12] of methyl cyanide from the thiazole ring giving the ion at *m/e* **150**, or by successive loss of two carbon monoxide fragments [13] leading to ions at *m/e* **163** and **135**.



SCHEME

Details of the pharmacological activity of the thiazolochromones will be published elsewhere.

EXPERIMENTAL

N.m.r. spectra were recorded with a Varian A 60A spectrometer for solutions in deuteriochloroform unless otherwise stated, with tetramethylsilane as internal reference. Mass spectra were recorded with an A.E.I. MS12 spectrometer.

4-Chloro-2-methoxy-5-nitroacetophenone.—To a mixture of fuming nitric acid (60 ml.) and concentrated nitric acid (40 ml.) was added 4-chloro-2-methoxyacetophenone (10 g.) in portions during 15 min. The mixture was stirred for a further 15 min., then added to water (100 ml.). The precipitate gave *4-chloro-2-methoxy-5-nitroacetophenone* (9·3 g.) as needles, m.p. 121° (from aqueous ethanol) (Found: C, 47·2; H, 3·6. $C_9H_8ClNO_4$ requires C, 47·1; H, 3·5%), τ 7·37 (Ac), 5·92 (OMe), and 1·52 and 2·82 (aromatic protons).

Reaction of 4-Chloro-2-methoxy-5-nitroacetophenone with Sodium Hydrogen Sulphide and Acetyl Chloride.—To a hot solution of 4-chloro-2-methoxy-5-nitroacetophenone (5 g.) in ethanol (100 ml.) was added sodium hydrogen sulphide solution [prepared by saturating a solution of sodium hydroxide (16 g.) in water (100 ml.) with hydrogen sulphide]. The mixture was heated under reflux for 1 hr., then cooled, acetyl chloride (10 ml.) was added, and this mixture was filtered. The filtrate was basified with 4N-sodium hydroxide, then extracted with chloroform, and the aqueous solution was retained. Evaporation of the extract gave a residue which yielded *5-acetyl-6-methoxy-2-methylbenzothiazole* (0·7 g.) as needles, m.p. 85° (from aqueous ethanol) (Found: C, 59·9; H, 4·95. $C_{11}H_{10}NO_2S$ requires C, 59·7; H, 5·0%), τ 7·35 (Ac) 7·22 (Me), 6·04 (OMe), and 1·77 and 2·67 (aromatic protons).

The extracted aqueous solution was neutralised with 4N-hydrochloric acid and re-extracted with chloroform. Evaporation of the dried ($MgSO_4$) extract gave a residue which yielded *5-acetamido-4-acetylthio-2-methoxyacetophenone* (4 g.) as needles, m.p. 208° (from ethanol) (Found: C, 55·6; H, 5·3. $C_{13}H_{15}NO_4S$ requires C, 55·5; H, 5·3%), τ 7·89 (NAc), 7·47 (SAc), 7·44 (Ac), 6·15 (OMe), 2·21 and 2·79 (aromatic protons), and 1·22 (NH, exchangeable).

Zinc Salt of 2-Amino-4-methoxybenzenethiol.—Zinc dust (12 g.) was added in portions to a hot solution of bis-4-methoxy-2-nitrophenyl disulphide (**3·1** g.) in acetic acid (250 ml.) during 0·5 hr. The mixture was heated for a further 1 hr., then filtered, and boiling water (500 ml.) was added to the filtrate. The mixture was cooled overnight, and the zinc salt of 2-amino-4-methoxybenzenethiol (2 g.) was filtered off.

5-Methoxy-2-methylbenzothiazole.—The foregoing zinc salt (4·6 g.) and acetyl chloride (3·5 ml.) were heated under reflux for 1 hr., and the product was digested with 5N-hydrochloric acid (20 ml.) before filtration. The filtrate was basified with 4N-sodium hydroxide, then filtered. The residue gave 5-methoxy-2-methylbenzothiazole (3·4 g.) as plates, m.p. 35° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 60·8; H, 5·2; N, 7·6. Calc. for C_9H_9NOS C, 60·4; H, 5·1; N, 7·8%).

7-Acetyl-4-methoxy-2-methylbenzothiazole.—A mixture of anhydrous aluminium chloride (1·85 g.) and 4-methoxy-2-methylbenzothiazole (1 g.) in carbon disulphide (10 ml.) was heated under reflux for 1 hr. Acetyl chloride (1 ml.) was added and heating was continued for 0·5 hr. before evaporation. The residue was heated at 100° for 4 hr. before the resulting complex was decomposed by addition to ice–4N-hydrochloric acid (50 g.). The mixture was neutralised with aqueous sodium hydrogen carbonate and filtered, and the filtrate was continuously extracted with ether. Evaporation of the extract gave a residue which yielded *7-acetyl-4-methoxy-2-methylbenzothiazole* (0·2 g.) as yellow prisms, m.p. 122° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 59·6; H, 4·8; N, 6·2. $C_{11}H_{11}NO_2S$ requires C, 59·8; H, 4·9; N, 6·3%), τ 7·31 (Ac), 7·13 (Me), 5·86 (MeO), and 2·03(d) and 3·03(d) (J 8·5 Hz, aromatic protons).

Acetylhydroxybenzothiazoles.—*Method A*. An intimate mixture of 4-methoxy-2-methylbenzothiazole (17·8 g.) and anhydrous aluminium chloride (34 g.) was added in portions to ethylene dichloride (75 ml.), and the mixture was heated under reflux for 1 hr. Acetyl chloride (14 ml.) was added, and heating was continued for a further 1 hr. before the solvent was evaporated. The residue was heated at 140° for 1 hr. then decomposed by addition to ice–4N-hydrochloric acid (500 ml.). Filtration yielded *5-acetyl-4-hydroxy-2-methylbenzothiazole* (13·1 g.) as needles, m.p. 214—216° (from aqueous ethanol) (Found: C, 57·7; H, 4·4; N, 6·9. $C_{10}H_9NO_2S$ requires C, 58·0; H, 4·4; N, 6·8%).

The acidity of the filtrate was reduced to pH 5 with addition of 2N-sodium hydroxide. Filtration gave 4-hydroxy-2-methylbenzothiazole (1·8 g.), m.p. 146° (lit.,[6] 145°).

[12] B. J. Millard and A. F. Temple, *Org. Mass. Spectrometry*, 1968, **1**, 285.

[13] W. M. Scott and M. E. Wacks, *Org. Mass. Spectrometry*, 1968, **1**, 847.

By a similar procedure, 5-methoxy-2-methylbenzothiazole (8·9 g.) yielded *4-acetyl-5-hydroxy-2-methylbenzothiazole* (2·38 g.) as needles, m.p. 104—105° (from aqueous ethanol) (Found: C, 57·9; H, 4·4; N, 6·7. $C_{10}H_9NO_2S$ requires C, 58·0; H, 4·4; N, 6·8%), and 5-hydroxy-2-methylbenzothiazole (1·24 g.), m.p. 187° (lit.,[7] 187°).

Similarly, 7-methoxy-2-methylbenzothiazole (10 g.) gave *6-acetyl-7-hydroxy-2-methylbenzothiazole* (2·2 g.) as needles, m.p. 91—93° (from aqueous ethanol) (Found: C, 58·0; H, 4·4; N, 6·8. $C_{10}H_9NO_2S$ requires C, 58·0; H, 4·4; N, 6·8%), together with *4-acetyl-7-hydroxy-2-methylbenzothiazole* (1·3 g.) as yellow needles, m.p. 227° (from aqueous ethanol) (Found: C, 58·1; H, 4·5; N, 6·7. $C_{10}H_9NO_2S$ requires C, 58·0; H, 4·4; N, 6·8%) (compound precipitated from acid solution at pH 3·5).

A mixture of 5- and 7-methoxy-2-methylbenzothiazoles (6 g.) on acetylation gave all four products from a chloroform extraction of the neutral solution, following decomposition of the reaction complex. The mixture was separated chromatographically on a silica gel column. Successive elutions with 5, 20, 50, and 75% chloroform–benzene gave 4-acetyl-5-hydroxy-2-methylbenzothiazole (0·64 g.), 6-acetyl-7-hydroxy-2-methylbenzothiazole (0·84 g.), 4-acetyl-7-hydroxy-2-methylbenzothiazole (0·51 g.), and 5-hydroxy-2-methylbenzothiazole (0·35 g.), respectively.

Method B. 7-Acetyl-6-hydroxy-2-methylbenzothiazole. A solution of 6-methoxy-2-methylbenzothiazole (3 g.) in boron trifluoride–acetic acid complex (20 ml.) was heated under reflux for 24 hr., then added to water (150 ml.). The mixture was basified with 2N-sodium hydroxide and filtered, and the filtrate was acidified to pH 5 with N-hydrochloric acid. Filtration gave *7-acetyl-6-hydroxy-2-methylbenzothiazole* (1·5 g.) as needles, m.p. 188—189° (from aqueous ethanol) (Found: C, 57·6; H, 4·2; N, 6·6. $C_{10}H_9NO_2S$ requires C, 58·0; H, 4·4; N, 6·8%).

The mother liquor from crystallisation was evaporated to dryness, and the residue was crystallised from benzene–light petroleum (b.p. 60—80°) to give 6-hydroxy-2-methylbenzothiazole (0·4 g.) as plates, m.p. 161—162° (lit.,[7] 162°).

Method C. Fries rearrangement of 4-acetoxy-2-methylbenzothiazole. A mixture of 4-acetoxy-2-methylbenzothiazole (1·6 g.) and anhydrous aluminium chloride (2 g.) in ethylene dichloride (20 ml.) was heated under reflux for 2 hr., then evaporated. The residue was heated at 170° for 1 hr., then cooled, ground up, and added to ice–4N-hydrochloric acid (100 g.). The mixture was filtered, and the residue gave 5-acetyl-4-hydroxy-2-methylbenzothiazole (0·6 g.), identical with the sample obtained by method A.

The acidity of the filtrate was reduced to pH 3·5 with 2N-sodium hydroxide; filtration then gave *2-acetonyl-4-hydroxybenzothiazole* (0·45 g.) as needles, m.p. 132° (from ethanol) (Found: C, 57·8; H, 4·1; N, 6·7. $C_{10}H_9NO_2S$ requires C, 58·0; H, 4·4; N, 6·8%), τ 7·23 (Ac), 7·33 (CH_2), 1·78 (OH, exchangeable), 2·02—3·10 (complex, aromatic protons).

Method D. 5-Acetyl-6-hydroxy-2-methylbenzothiazole. (*a*) An intimate mixture of 5-acetyl-6-methoxy-2-methylbenzothiazole (2 g.) and anhydrous aluminium chloride (4 g.) was heated at 100° for 1 hr., and the complex was added to ice–4N-hydrochloric acid (100 ml.). Filtration gave *5-acetyl-6-hydroxy-2-methylbenzothiazole* (1·1 g.) as yellow prisms, m.p. 164—165° (from aqueous ethanol) (Found: C, 58·1; H, 4·2; N, 6·6. $C_{10}H_9NO_2S$ requires C. 58·0: H, 4·4; N, 6·8%).

(*b*) An intimate mixture of 5-acetamido-4-acetylthio-2-methoxyacetophenone (2 g.) and anhydrous aluminium chloride (4 g.) was heated at 200° for 1 hr., then added to ice–4N-hydrochloric acid (100 ml.). Isolation as in (*a*) gave 5-acetyl-6-hydroxy-2-methylbenzothiazole (0·7 g.), identical with the previous sample.

TABLE 2
Methylthiazolochromone acids

Starting hydroxy-ketone	Product	Yield (%)	M.p.	Found (%) *			Chemical shifts (τ) and coupling constants J (Hz) †		
				C	H	N	Me	3-H	Aromatic
(IIo)	(IX)	71	305—308° (decomp.)	54·8	2·8	5·0	7·17	3·12	1·59, 1·64
(IIk)	(VIII)	64	300 (decomp.)	55·1	2·5	5·2	7·23	3·03	2·14 (d), 2·88 (d) (J 8·0)
(IIb)	(VII)	63	310—312 (decomp.)	54·7	2·6	5·1	7·10	2·92	1·62 (d), 2·20 (d) (J 9·0)
(IIf)	(X)	82	290 (decomp.)	55·0	2·9	5·3	7·16	2·75	1·75 (d), 2·95 (d) (J 8·0)
(IIm)	(XIa)	71	300 (decomp.)	55·0	2·9	5·1	7·07	3·15	2·05 (d), 3·05 (d) (J 8·5)

* $C_{12}H_7NO_4S$ requires C, 55·2; H, 2·7; N, 5·4%. † Solutions in $(CD_3)_2SO$.

Pyranobenzothiazolecarboxylic Acids.—To sodium (1·0 g.) in ethanol (20 ml.) was added a solution of the acetylhydroxy-2-methylbenzothiazole (1·0 g.) in diethyl oxalate (1·2 ml.). The mixture was heated under reflux for 1·5 hr., then cooled and stirred into dry ether (100 ml.). The precipitated sodium salt was filtered off and dried, then heated under reflux with acetic acid (16 ml.) and concentrated hydrochloric acid (6 ml.) for 1 hr., The cooled product was filtered off and either reprecipitated from aqueous sodium hydrogen carbonate with 2N-hydrochloric acid, or crystallised from dimethyl sulphoxide (see Table 2).

By this procedure, but with an excess of diethyl oxalate, 6-acetyl-7-hydroxy-2-methylbenzothiazole (0·6 g.) yielded *2-oxalomethyl-6-oxopyrano*[3,2-g]*benzothiazole-8-carboxylic acid* (0·4 g.) as a yellow powder, m.p. 300° (decomp.) purified by repeated precipitation with 2N-hydrochloric acid from aqueous sodium hydrogen carbonate) (Found: C, 49·8; H, 2·3; N, 4·2. $C_{14}H_7NO_7S$ requires C, 50·2; H, 2·1; N, 4·2%).

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