On 6-(Thenoyl)-7,8-dichloro-4-oxo-4*H*-1-benzopyran-2-carboxylic Acid

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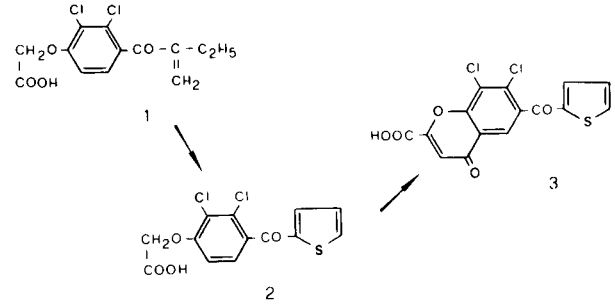
Received April 11, 1988

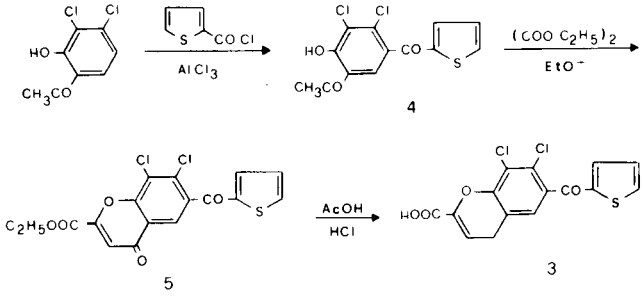
The annulation of the oxyacetic chain of thienylic acid into a γ-pyrone ring is described. The resulting 6-(2-thenoyl)-7,8-dichloro-4-oxo-4*H*-1-benzopyran-2-carboxylic acid retains almost 80% of the diuretic activity of the parent compound.

J. Heterocyclic Chem., **25**, 1277 (1988).

Since the discovery of ethacrinic acid **1**, a number of related high threshold diuretics (aryloxyacetic acid derivatives) has been successfully prepared [1]. Major improvements have been observed by modifying the α-methylenebutyryl side chain of the parent compound (*e.g.* indacrinone, thienylic acid) [2,3] as well as by annulation of the oxyacetic chain in a furan ring (*e.g.* 5-acyl-6,7-dichlorobenzofuran and dihydrobenzofuran-2-carboxylic acid derivatives) [4]. Since we have been interested for some time in the medicinal chemistry of benzo-γ-pyrone derivatives, we have experimented with the incorporation of the oxyacetic chain of thienylic acid **2** into a γ-pyrone ring as follows:



Compound **3** has been prepared by the usual route to chromone-2-carboxylic acid [5], in three steps starting from 2-hydroxy-3,4-dichloroacetophenone [6] following the scheme:



Preliminary pharmacological results seem to indicate that the diuretic activity of **3** is retained to a significant degree corresponding to about 80% of that of thienylic acid.

EXPERIMENTAL

2-Hydroxy-3,4-dichloro-5-(2-thenoyl)acetophenone **4**.

To a stirred solution of 2-hydroxy-3,4-dichloroacetophenone (20.5 g, 0.1 mole) and 2-thiophenecarbonyl chloride (14.6 g, 0.1 mole) in carbon disulfide (300 ml) 16 g (0.12 mole) of anhydrous aluminium chloride was added with cooling. The mixture was warmed on a water bath for 1 hour and then the solvent evaporated. The residue was cooled, poured into ice and extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate, concentrated to a small volume and then chromatographed on silica gel eluting with dichloromethane-cyclohexane (7:3). The first product obtained in the chromatographic separation was unreacted starting phenol (10.2 g, 50%). The required compound was eluted last. The solvent was removed *in vacuo* to afford 9.4 g (30%) of compound mp 172-174° (ligroin); ^{1}H nmr (deuteriochloroform): δ 2.66 (s, 3H, CH_3), 7.1-7.9 (m, 4H, aromatic); ms: 315 (M^+).

Anal. Calcd. for $C_{13}H_8Cl_2O_3S$: C, 49.52; H, 2.56; Cl, 22.51. Found: C, 49.41; H, 2.67; Cl, 22.58.

Ethyl 6-(2-Thenoyl)-7,8-dichloro-4-oxo-4*H*-1-benzopyran-2-carboxylate **5**.

To a stirred solution of sodium ethoxide [from sodium (0.57 g, 0.025 mole)], 3.15 g (0.01 mole) of **4** and 2.2 g (0.015 mole) of diethyl oxalate were added. The reaction mixture was refluxed for 4 hours. The cooled mixture was filtered and the precipitate was recrystallized from ethanol to give 3.2 g (80%) of **5**, mp 190-192°; ^{1}H nmr (deuteriochloroform): δ 1.46 (t, 3H, CH_3), 4.52 (q, 2H, CH_2), 7.1-8.2 (m, 5H, H-3 and aromatic); ms: 397 (M^+).

Anal. Calcd. for $C_{17}H_{10}Cl_2O_5S$: C, 51.38; H, 2.54; Cl, 17.86. Found: C, 51.46; H, 2.65; Cl, 17.61.

6-(2-Thenoyl)-7,8-dichloro-4-oxo-4*H*-1-benzopyran-2-carboxylic Acid **3**.

A solution of **5** (1.98 g, 0.005 mole) in acetic acid (25 ml) and hydrochloric acid (5 ml) was refluxed for 4 hours. The cooled mixture was filtered and the precipitate was recrystallized from ethanol to give 1.2 g (70%) of **3** mp 278-280°; ^{1}H nmr (DMSO-d_6): 7.32 (s, 1H, H-3), 7.5-8.7 (m, 4H, aromatic); ms: 369 (M^+).

Anal. Calcd. for $C_{15}H_6Cl_2O_5S$: C, 48.78; H, 1.64; Cl, 19.22. Found: C, 47.55; H, 1.71; Cl, 19.03.

REFERENCES AND NOTES

[1] E. M. Schultz, E. J. Cragoe, J. B. Bicking, W. A. Bolhofer and J. M. Sprague, *J. Med. Chem.*, **5**, 660 (1962).

[2] O. W. Woltersdorf, S. J. de Solms, E. H. Schultz and E. J. Cragoe, *J. Med. Chem.*, **20**, 1400 (1977).

[3] G. Thuillier, J. La Forest, B. Carion, P. Bessin, J. Bonnet and J. Thuillier, *Eur. J. Med. Chem.*, **9**, 625 (1974).

[4] W. F. Hoffman, O. W. Woltersdorf, F. C. Novello, E. J. Cragoe, J. P. Springer, L. S. Watson and G. M. Fanelli, *J. Med. Chem.*, **24**, 865 (1981).

[5] G. P. Ellis, "Chromenes, Chromanones and Chromones", John Wiley-Interscience, 1977.

[6] K. A. Trakar and P. R. Muley, *J. Indian Chem. Soc.*, **52**, 243 (1975).