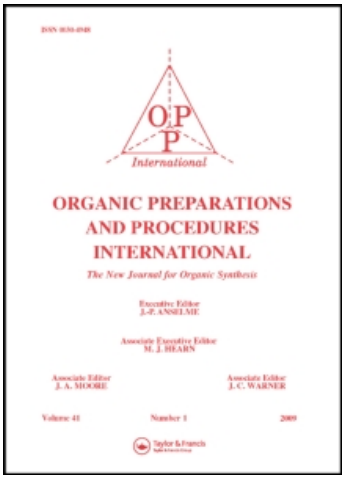

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SYNTHESIS OF 3-CARBOXYTHIOPHENE-2-ACETIC ACID AND ITS DERIVATIVES

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SYNTHESIS OF 3-CARBOXYTHIOPHENE-2-ACETIC ACID AND ITS DERIVATIVES

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(12/20/85)
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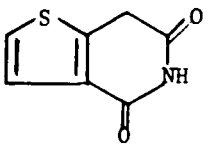
In our search for new hypoglycemic agents, it became important to prepare the thienopyridinedione 1 as an intermediate. Ames and Ribeiro[1] had already described isomeric compounds 2 and 3 and we now report the



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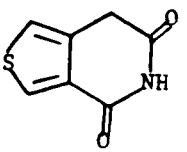

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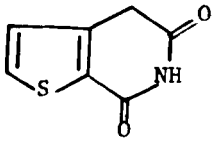
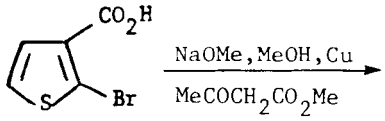


3

synthesis of 1 and of a representative condensation product 8. A slight modification of the published method[1] resulted in the condensation of 2-bromothiophene-3-carboxylic acid (4)[2] with methyl acetoacetate in methanol to afford 3-carboxythiophene-2-acetic acid methyl ester (5). Reaction of 5 with aqueous ammonia yielded 2-(2-amino-2-oxoethyl)-3-thiophenecarboxylic acid (6) which upon treatment with diazomethane in ether, gave 2-(amino-2-oxoethyl)-3-thiophenecarboxylic acid methyl ester (7). Since previous methods[1,3] failed to provide 1 in appreciable amounts, the cyclization of 7



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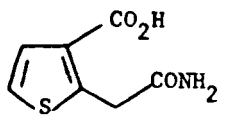

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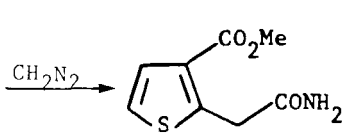

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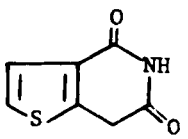

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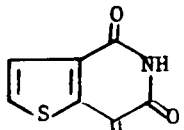

8

Ar = p-(PhCH$_2$CH$_2$O)C$_6$H$_4$

to 1 was achieved in dimethylformamide in the presence of sodium hydride.[5] Condensation of 1 with aromatic aldehydes (e.g. 9) afforded high yields of 8.

EXPERIMENTAL SECTION

3-Carboxythiophene-2-acetic Acid Methyl Ester (5).- To a stirred solution of 21.8 g (0.403 mol) of sodium methoxide in 500 ml of methanol was added 29.5 g (0.254 mol) of methyl acetoacetate, then 35 g (0.17 mol) of 2-bromothiophene-3-carboxylic acid (4)[2] and 1.75 g of copper powder. The mixture was heated to reflux for 16 hrs and then evaporated to dryness. The residue was dissolved in 1 L of water and the solution was filtered through Celite to remove the copper; it was then acidified with 18% hydrochloric acid and extracted three times with 500 ml of ethyl acetate. The combined ethyl acetate extract was extracted three times with 200 ml of 2N sodium hydroxide solution. The alkali extracts were acidified and extracted three times with 500 ml of ethyl acetate. The combined extracts were washed with water, dried over magnesium sulfate, and concentrated *in vacuo* to yield 40 g of a brown oil. The oil was stirred with 30 ml of a mixture of ethyl acetate and hexane to give 18.3 g (54%) of an off-white solid, mp. 105-107°. Recrystallization from ethyl acetate/pentane gave 5, mp. 110-112°. IR (KBr): 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.70 (s, 3H), 4.20 (s, 2H), 7.30 (q, 2H), 12.26 (s, 1H exchanged with D_2O).

2-(2-Amino-2-oxoethyl)-3-thiophenecarboxylic Acid (6).- A solution of 4.1 g (0.02 mol) of 3-carboxythiophene-2-acetic acid methyl ester (5) in 50 ml of conc. ammonium hydroxide was allowed to stand at room temperature for 18 hrs. The solution was concentrated *in vacuo* and poured into 200 ml of cold water; it was acidified with 18% hydrochloric acid to yield 3.5 g (95%) of 6, mp. 200-202°. IR (KBr): 3406 (NH), 1697 (C=O), 1636 (C=O) cm^{-1}; ^1H NMR (DMSO): δ 4.02 (s, 2H), 6.95 (broad, 1H, exchanged with D_2O), 7.32 (q,

2H), 7.36 (broad, 1H, exchanged with D_2O), 12.63 (broad, 1H, exchanged with D_2O); MS: m/e 186 (M+H).

2-(2-Amino-2-oxoethyl)-3-thiophenecarboxylic Acid Methyl Ester (7).- To a slurry of 3 g (0.016 mol) of 2-(2-amino-2-oxoethyl)-3-thiophenecarboxylic acid (6) in 100 ml of ether was added a solution of diazomethane in 75 ml of ether, prepared from 5 g (0.05 mol) of N-methyl-N-nitroso urea and 50% potassium hydroxide, and the mixture was stirred at room temperature for 1 hr. The solid was collected and washed with ether to yield 2.2 g of 7, mp. 105-107°. Concentration of the ether solution gave 0.6 g of 7, mp. 108-110°, for a total of 2.8 g (89%). IR (KBr) 3403 (NH), 1713 (C=O), 1653 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.87 (s, 3H), 4.09 (s, 2H), 6.07 (broad, 1H, exchanged with D_2O), 6.47 (broad, 1H, exchanged with D_2O), 7.28 (q, 2H); MS: m/e 200 (M+H).

Thieno[3,2-c]pyridine-4,6(5H,7H)-dione (1).- To a slurry of 0.5 g (0.021 mol) of sodium hydride in 100 ml of dimethylformamide[5] was added 4.2 g (0.021 mol) of 2-(2-amino-2-oxoethyl)-3-thiophenecarboxylic acid methyl ester (7) and the mixture was heated to 145° for 1 hr. The solvent was evaporated *in vacuo*, the residue was dissolved in water and the solution was acidified. The solution was extracted twice with ethyl acetate and the combined ethyl acetate extract was washed with 2N hydrochloric acid, then with brine, dried over magnesium sulfate, concentrated *in vacuo* to give 2 g of residue. The residue was dissolved in 100 ml of hot ethanol and the charcoal was added; the solution was then filtered through Celite and gave upon cooling 1.5 g (43%) of 1, mp. 185-187°. IR (KBr): 3210 (NH), 1705 (C=O), 1677 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 14.10 (s, 2H), 7.42 (q, 2H), 8.26 (broad, 1H, exchanged with D_2O); MS: m/e 168 (M+H).

Anal. Calcd for $C_7H_5NO_2S$: C, 50.28; H, 3.01; N, 8.38

Found: C, 50.28; H, 3.02; N, 8.42

7-[[4-(2-Phenylethoxy)phenyl]methylene]thieno[3,2-c]pyridine-4,5[5H,7H]-dione (8).- A solution of 1.5 g (0.009 mol) of thieno[3,2-c]pyridine-4,6(5H,7H)-dione (1) and 2 g (0.009 mol) of 4-(2-phenylethoxy)benzaldehyde (9)[4] in 20 ml of pyridine was allowed to stand at room temperature for 60 hrs. The precipitated solid was collected and yielded 2.45 g (73%) of solid, mp. 182-85°; the solid was dissolved in 600 ml of hot ethanol and the solution was filtered and upon cooling afforded 1.86 g of 8, mp. 190-193° (dec.). IR (KBr): 3610 (NH), 1697 (C=O) cm^{-1}; ^1H NMR (DMSO): δ 3.22 (t, 2H), 4.32 (t, 2H), 7.13 (d, 2H), 7.43 (m, 6H), 7.57 (m, 3H), 8.09 (s, 1HO, 11.55 (s, 1H, exchanged with D_2O); MS: m/e 375 (M+).

Anal. Calcd for $C_{22}H_{17}NO_3S$: C, 70.38; H, 4.57; N, 3.73; S, 8.54

Found: C, 70.49; H, 4.62; N, 3.87; S, 9.02

REFERENCES

1. D. E. Ames and O. Ribeiro, J. Chem. Soc. Perkin I, 1390 (1975).

2. S. Gronowitz and B. Holm, Acta, Chem. Scand., 23 (6) 2207 (1969).

3. P. Singh and S. M. Weinreb, Tetrahedron, 32, 2379 (1976); O. Grummit, R. Egan, and A. Buck, Org. Synth. Coll. Vol. III, 449 (1955); M. I. Ali et al., Naturforsch., 31b, 589 (1976).

4. N. P. Buu-Hoi et al., J. Org. Chem., 18, 121 (1953).

5. **CAUTION**: Sodium hydride may react with DMF to yield hydrogen gas and carbon monoxide [Powers et al., J. Org. Chem., 31, 2623 (1966)].