Tetrahedron. Vol. 29, pp. 1829 to 1832. Pergamon Press 1973. Printed in Great Britain

DITHIAINDENES

SYNTHESIS OF 6-THIA-7H-BENZO [*b*] THIOPHENE (1,6-DITHIAINDENE) AND 1,3-DIMETHYL-5-THIA-4H-BENZO [*c*] THIOPENE (1,3-DIMETHYL-2,5-DITHIAINDENE) AND ATTEMPTED SYNTHESIS OF 5-THIA-4H-BENZO [*b*] THIOPHENE (1,5-DITHIAINDENE)

I. ALAM[a] and G. THYAGARAJAN*
Regional Research Laboratory, Hyderabad 500009, India

(*Received in UK* 1 *February* 1973; *Accepted for publication* 16 *February* 1973)

Abstract—Synthesis of the heteroaromatic systems 6-thia-7H-benzo [*b*] thiophene (3) and 1,3-dimethyl-5-thia-4H-benzo [*c*] thiophene (5) have been achieved by reduction and dehydration of 1,6-dithiaindan-4-one (4) and 1,3-dimethyl-2,5-dithiaindan-7-one (8) respectively. A similar attempt to synthesise 5-thia-4H-benzo [*b*] thiophene (4) by dehydration of 7-hydroxy-1,5-dithiaindane (16) resulted in the formation of 7,7′-bis (1,5-dithiaindanyl) ether.

Dithiaindenes, of which ten isomers are theoretically possible, represent a relatively uninvestigated class of heterocyclic compounds. The structural types are of particular value and interest for tautomeric studies with the aid of modern physical tools, particularly NMR spectroscopy. Earlier, two examples of this class of compounds 5H-thieno [3,2-*b*] thiin and 6H-thieno [2,3-*b*] thiin (1 and 2 respectively) were known.[1] While this work was in progress, a report[2] presenting a description of some salts containing the isomeric thieno-thiapyrilium nuclei 3 and 4 appeared. We now wish to present our results on the synthesis and characterisation of the free heteroaromatic compounds 6-thia-7H-benzo[*b*]thiophene (3) and 1,3-dimethyl-5-thia-4H-benzo[*c*]thiophene (5), and an attempted preparation of 5-thia-4H-benzo[*b*]thiophene (4).

We considered that the most reasonable route to these systems lay in the preparation of the ketones 6, 7 and 8 which could then be reduced to the corresponding alcohols and these dehydrated to the dithiaindenes.

Synthesis of dithiainanones

1,6-*Dithiaindan-4-one* (6). Cagniant[3] reported the synthesis of this compound starting from 2-thienylmethanethiol and bromoethylacetate. Hydrolysis of the resultant ethyl 1-(2′-thienyl)-2-thia-4-butanoate gave the thienylthio acid, the acid chloride of which underwent cyclisation to give 6. This represented the first report on synthesis of dithiaindanones.

Employing a different approach, 6 was prepared from 2-chloromethylthiophene, easily accessible by direct chloromethylation of thiophene. Condensation with thioglycolic acid afforded 1-(2′-thienyl)-2-thiabutyric acid (9) which underwent cyclisation in moderate yields, to the desired ketone. The NMR and IR spectral data were in agreement with structure 6.

1,5-*Dithiaindan-7-one* (7). Cagniant[4] synthesised this system applying his original method, using 3-thienylmethanethiol as starting material. In the present investigation, the synthesis of 7 was accomplished by intramolecular cyclisation of 1(3′-thienyl)-2-thiabutyric acid (10), obtained by condensation of 3-bromomethylthiophene[5] and thioglycolic acid in a sequence analogous to that outlined for 6. Analytical and spectral characterisation confirmed the structure of 7.

1,3-*Dimethyl-2,5-dithiaindan-7-one* (8). Isolated instances of 3,4-annelated thiophene are reported. Stainkopf[6] synthesised the first of this kind, 4-oxo-1,3-dimethyl-4,5,6,7-tetrahydroisobenzothiophene (11). MacDowell[7] and Harrison[8] reported the preparation of thienocyclopentanones of the type 12, while Dann and Dammling[9] described the synthesis of 13.

The 3,4-annelated thiophene system (8) has now been prepared from 2,5-dimethylthiophene.[10] Chloromethylation using standard procedures[11–13] gave 3-chloromethyl-2,5-dimethylthiophene as the major product. Condensation of this with thioglycolic acid and subsequent cyclisation of the intermediate acid (14) afforded the new system 1,3-dimethyl-2,5-dithiaindan-7-one (8).

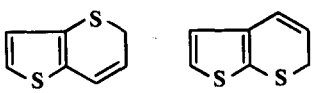
Reduction of dithiaindanones. The keto compounds (6, 7 and 8) were smoothly reduced by LAH or $NaBH_4$ to the corresponding alcohols, 4-hydroxy-1,6-dithiaindane (15), 7-hydroxy-1,5-dithia-

[a]Present address: Department of Chemistry, University of California, Berkeley, California 94720 USA.

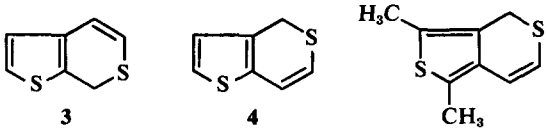
indane (16) and 7-hydroxy-1,3-dimethyl-2,5-dithiaindane (17). The IR and NMR spectral data of these products were consistent with their structure (Experimental). The $NaBH_4$ reduction of 6 and 7 to 15 and 16 respectively has been reported recently.[2]

Synthesis of dithiaindenes. The hydroxydithiaindanes were dehydrated using a variety of dehydrating agents such as *p*-toluenesulphonic acid, *p*-toluenesulphonyl chloride,[14,15] basic alumina[16] and phosphorus pentoxide in dry benzene. Thus, 4-hydroxy-1,6-dithiaindane (15) and 7-hydroxy-1,3-dimethyl-2,5-dithiaindane (17) gave the respective dithiaindenes 3 and 5.

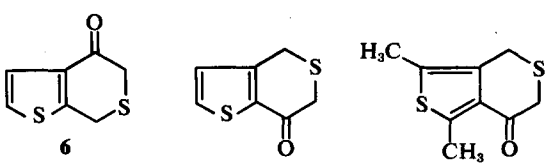
Dehydration of 7-hydroxy-1,5-dithiaindane (16) under similar conditions gave a white crystalline product which was different from the expected dithiaindene (4). Elemental and spectral analysis showed it to be a symmetrical ether and this compound has been assigned structure 18, 7,7′-bis(1,5-dithiaindanyl)ether.



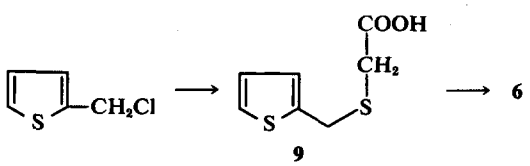
1 2



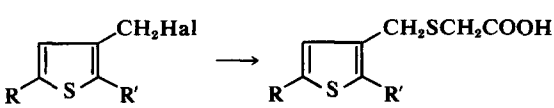
3 4 5



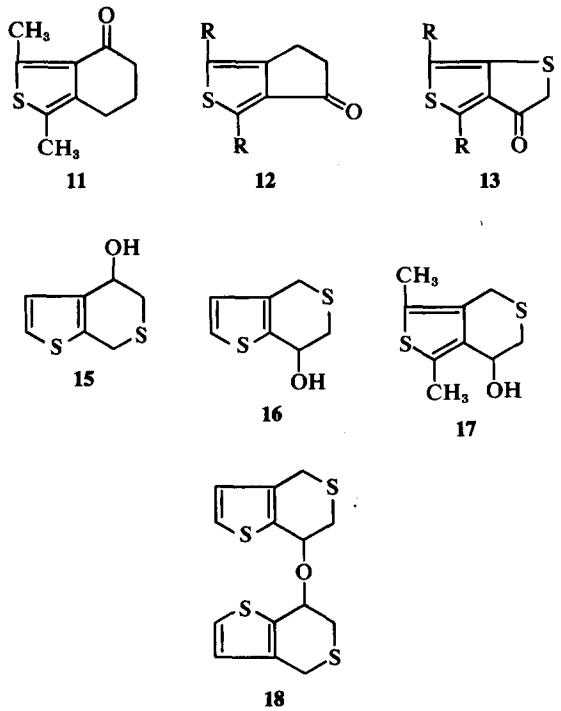
6 7 8



9



10: R = R′ = H ⟶ 7
14: R = R′ = CH_3 ⟶ 8



11 12 13 15 16 17 18

EXPERIMENTAL

All m.ps, taken in capillary tubes are uncorrected. IR spectra were conducted on a Perkin-Elmer model 221 spectrometer equipped with NaCl optics. NMR spectra were recorded on a Varian A-60A spectrometer. Chemical shifts are in δ values relative to internal TMS. TLC experiments were done on silica gel G plates.

2-Chloromethylthiophene[16] (b.p. 73–74°/11 mm, 41% yield), 3-bromomethylthiophene[4] (b.p. 75–78°/1 mm, 45% yield) and 2,5-dimethylthiophene[9] (b.p. 136°, 87% yield) were prepared as described in the literature.

3-Chloromethyl-2,5-dimethylthiophene. A mixture of 2,5-dimethylthiophene (10 g) and conc. HCl (50 ml) was cooled in an ice bath. A rapid stream of HCl was passed through this mixture with stirring while formalin (14 ml) was added dropwise during 1 hr. The temp was maintained below −5° throughout the addition, after which the mixture was diluted with water and extracted with benzene. The extract was washed with water, dried over $MgSO_4$ and concentrated. The residue was distilled under reduced pressure to give 3-chloromethyl-2,5-dimethylthiophene (5·2 g) b.p. 96–115°/13 mm (lit, b.p. 96–115/13 mm).

Preparation of thienylthioacids (only a typical experiment is reported here)

Method A. Thioglycollic acid (0·25 mole) was dissolved in 2 N NaOH (150 ml) and cooled to 0°. A soln of 2-chloromethylthiophene (0·25 mole) in acetone (50 ml) was added dropwise during 3 hr with stirring. The mixture was stirred for 24 hr at room temp, then diluted with water and shaken with CH_2Cl_2 (or chloroform) to remove any unreacted chloromethylthiophene. The aqueous soln was acidified with 1:1 HCl and extracted with chloroform. Evaporation (crystallisation) of the dried chloro-

form extract and distillation gave pure 1(2′-thienyl)-2-thiabutyric acid, b.p. 206°/15 mm, in 80 percent yield.

Method B. To a cooled and stirred soln of thioglycollic acid (0·25 mole) and triethylamine (0·25 mole) in dry benzene (150 ml) was added dropwise during 2 hr at 0–5°, a soln of 2-chloromethylthiophene (0·25 mole) in dry benzene (50 ml). The mixture was left overnight at room temp. The Et_3NHCl was filtered and the filtrate was extracted with $NaHCO_3$ aq. The alkaline soln was acidified and extracted with chloroform. Concentration of the dried chloroform extract and distillation under reduced pressure afforded the product. 1(2′-Thienyl)-2-thiabutyric acid (**9**) b.p. 206°/17 mm (Lit, b.p. 204/112 mm) was obtained in 75–80% yield. (Found: C, 44·69, S, 34·00, H, 4·23. $C_7H_8O_2S_2$ requires C, 44·69, S, 34·04, H, 4·29%); IR (film): 3065, 3030, 1665, 1300, 1275, 1285 cm^{-1}; NMR (CCl_4): δ 3·05, s, 2H(–S–C<u>H</u>$_2$–COOH), 4·00, s, 2H(–CH_2–S–), 7·00, m, 3H (aromatic), 11·8, s, 1H-(–COOH) ppm.

Similarly prepared employing either method were:

1(3′-*Thienyl*)-2-*thia-butyric acid* (**10**) from 3-bromomethylthiophene and thioglycolic acid, b.p. 201/14 mm (Lit, 200/14 mm), yield 70% (Found: C, 44·64, S, 34·00, H, 4·25. $C_7H_8O_2S_2$ requires: C, 44·69, S, 34·04, H, 4·29%); IR (film): 3085, 3030, 1665, 1550, 1400, 1285, 1175 cm^{-1}, NMR (CCl_4): δ 3·03, s, 2H(SC<u>H</u>$_2$ COOH), 3·85, s, 2H(–C<u>H</u>$_2$S–), 7·18, m, 3H (aromatic), 11·9, s, 1H(COO<u>H</u>) ppm.

1(2′,5′-*Dimethyl*-3′-*thienyl*)-2-*thia-butyric acid* (**14**) from 3-chloromethyl-2,5-dimethylthiophene and thioglycolic acid. The product was isolated by crystallisation, m.p. 170°, yield 55% (Found: C, 50·10, S, 29·60, H, 5·62. $C_9H_{12}O_2S_2$ requires: C, 50·00, S, 29·62, H, 5·60%); IR (KBr): 1685 cm^{-1} (C=O). NMR (CCl_4): δ 3·0, s, 2H(–SC<u>H</u>$_2$COOH), 3·65, s, 2H(–C<u>H</u>$_2$–S–), 3·33, s, 6H-(2′-C<u>H</u>$_3$ and 5′-C<u>H</u>$_3$), 6·58, s, 1H (aromatic), 11·6, s, 1H(COO<u>H</u>) ppm.

Cyclodehydration of thineylthioacids

General procedure. The thienylthioacid (1 part) was dissolved in dry benzene (12–15 parts by weight) and mixed with P_2O_5 (3–5 parts). The mixture was refluxed for 4–6 hr, cooled, and the benzene layer decanted. The solid mass was decomposed with ice and extracted several times with hot benzene. The combined benzene extract was washed with $NaHCO_3$ aq, then with water, dried (Na_2SO_4) and evaporated. The crude product was purified by chromatography and crystallisation.

Alternatively, the thienylthioacid (1 part) was mixed with 15–17 times its weight of polyphosphoric acid and heated on a steam bath for 5 hr. The dark mixture was cooled and poured over crushed ice. Extraction with chloroform, washing with $NaHCO_3$ aq and water, and drying gave the crude product which was purified over a silica gel column. Thus prepared were:

1,6-*Dithiaindan-4-one* (**6**), b.p. 168–69/16 mm (Lit, b.p. 168°/16 mm), yield 40%. (Found: C, 49·4, S, 37·60, H, 3·50. $C_7H_6OS_2$ requires: C, 49·42, S, 37·64, H, 3·56%); IR (film): 1670 cm^{-1} (C=O); NMR (CCl_4): δ 3·38, s, 2H(–S–C<u>H</u>$_2$–CO), 3·96, s, 2H(–C<u>H</u>$_2$–S–), 7·21, q, 2H (aromatic) ppm.

1,5-*Dithiaindan-7-one* (**7**), m.p. 66° (from benzene–light petroleum), yield 48% (Lit. m.p. 67°). (Found: C, 49·40, S, 37·61, H, 3·50. $C_7H_6OS_2$ requires: C, 49·42, S, 37·64, H, 3·56%); IR (KBr): 1650 cm^{-1} (C=O); NMR ($CDCl_3$): δ 3·45, s, 2H(–SC<u>H</u>$_2$–S–), 7·25, q, 2H (aromatic) ppm.

1,3-*Dimethyl*-2,5-*dithiaindan-7-one* (**8**), m.p. 68° (from benzene–light petroleum), yield 40% (Found: C, 54·50, S, 32·20, H, 5·03, $C_9H_{10}OS_2$ requires: C, 54·54, S, 32·32, H, 5·09%); IR (KBr): 1665 cm^{-1} (C=O), NMR (CCl_4): δ 2·3, s, 3H(C<u>H</u>$_3$), 2·66, s, 3H(C<u>H</u>$_3$), 3·2, s, 2H(–SC<u>H</u>$_2$-CO), 3·59, s, 2H(–CH_2–S) ppm.

Reduction of dithiaindanones with lithium aluminium hydride

A soln of the dithiaindanone (0·2 mole) in THF (100 ml) was added dropwise to LAH (0·15 mole) slurried in THF (250 ml). The mixture was stirred and gently refluxed for 4 hr. After cooling in ice, the excess reducing agent was decomposed by the careful addition of 40% KOH aq (35 ml) and filtered. The ppt was washed with ether. The combined THF–ether soln was dried and concentrated leaving the crude product which was purified over a silica gel column using chloroform–light petroleum as eluent.

Reduction with sodium borohydride

The reduction was carried out in a 2-necked flask equipped with a reflux condenser and N_2 gas inlet. The dithiaindanone (0·2 mole) and $NaBH_4$ (0·08 mole) were mixed in 50% aq EtOH and refluxed under N_2 for 4 hr. The mixture was then poured into 15% NaCl aq (50 ml) and extracted with methylene chloride. The extract was washed with dil HCl and water and dried. Evaporation of the solvent gave the crude product which was purified over a silica gel column using chloroform.

Thus were prepared:

4-*Hydroxy*-1,6-*dithiaindane* (**15**), b.p. 123/0.3 mm (Lit. b.p. 123/0.3 mm), yield 75%. (Found: C, 48·85, S, 37·16, H, 4·65, $C_7H_8OS_2$ requires: C, 48·80, S, 37·23, H, 4·68%); IR (film): 3335, 2900, 1405, 1190, 1030, 775 cm^{-1}; NMR ($CDCl_3$): δ 3·66, s, 2H(–C<u>H</u>$_2$–S–), 2·75, s, 2H-(–S–C<u>H</u>$_2$–), 4·16, t, 1H(> C<u>H</u>), 3·81, s, 1H(O<u>H</u>), 6·99, q, 2H (aromatic) ppm.

7-*Hydroxy*-1,5-*dithiaindane* (**16**), b.p. 115–117/0·2 mm (Lit. b.p. 116/0·2 mm), yield 60% (Found: C, 48·79, S, 37·19, H, 4·69. $C_7H_8OS_2$ requires: C, 48·80, S, 37·23, H, 4·68%); IR (film): 3375, 2905, 1405, 1185, 1050, 940 cm^{-1}; NMR (CCl_4): δ 2·85, s, 2H(–S–C<u>H</u>$_2$–), 3·53, s, 2H(–C<u>H</u>$_2$–S–), 3·65, s, 1H(O<u>H</u>), 4·75, t, 1H(> C<u>H</u>–), 6·85, q, 2H (aromatic) ppm.

7-*Hydroxy*-1,5-*dimethyl*-2,5-*dithiaindane* (**17**), b.p. 121·5–122/0·5 mm, yield 50%. (Found: C, 54·01, S, 32·20, H, 6·01. $C_9H_{12}OS_2$ requires: C, 53·99, S, 31·96, H, 6·04%); IR (film): 3380, 2908, 1400, 1216, 1130, 1025, 775 cm^{-1}; NMR (CCl_4): δ 2·20, s, 3H(–C<u>H</u>$_3$), 2·33, s, 3H(–CH_3), 2·7, d, 2H(–S–C<u>H</u>$_2$–), 3·36, s, 2H(–C<u>H</u>$_2$–S), 4·58, t, 1H(>C<u>H</u>), 3·13, s, 1H(O<u>H</u>) ppm.

Dehydration of hydroxy dithiaindanes

Method A. Woelm basic alumina (5 parts), the hydroxy dithiaindane (one part) and benzene (50 ml) were refluxed with stirring for 4 hr. The mixture was then cooled, filtered and evaporated under reduced pressure. Distillation or column chromatography of the crude product over silica gel afforded the pure compound.

Method B. The hydroxydithiaindane was heated with a small amount of *p*-toluenesulfonic acid or tosyl chloride in dry benzene for 1–3 hr. After cooling, the organic layer was decanted and washed with $NaHCO_3$ aq and water to remove acidic impurities. The dried benzene layer was evaporated leaving the product which was purified by distillation and column chromatography.

1,6-*Dithiaindene* (**3**), b.p. 125–26/0·2 mm, yield 65% (Found: C, 54·40, S, 41·50, H, 3·92. $C_7H_6S_2$ requires:

C, 54·44, S, 41·53, H, 3·96%); IR (film): 2915, 2880, 1660, 1420, 1175, 775 and 745 cm^{-1}, NMR (CCl_4): δ 3·96, s, 2H(–C<u>H</u>$_2$–S), 6·92, q, 2H (vinylic), 6·48, q, 2H (aromatic) ppm.

7,7′-*Bis*(1,5-*dithiaindanyl*)*ether* (**18**), m.p. 152 (from benzene), yield 65%. (Found: C, 51·52, S, 39·12, H, 4·35. $C_{14}H_{14}OS_4$ requires: C, 51·54, S, 39·24, H, 4·33%); IR (KBr): 2900, 1420, 1310, 1050, 840 and 715 cm^{-1}; NMR ($CDCl_3$): δ 3·13, m, 4H(–C<u>H</u>$_2$–S–)$_2$, 3·6, m, 4H(–S–C<u>H</u>$_2$–, –S·C<u>H</u>$_2$–), 5·08, m, 2H(>C<u>H</u>–, >C<u>H</u>–), 7·02, q, 4H (aromatic) ppm.

1,3-*Dimethyl*-2,5-*dithiaindene* (**5**), b.p. 132/0·5 mm, yield 85%. (Found: C, 59·32, S, 35·15, H, 5·52. $C_9H_{10}S_2$ requires: C, 59·33, S, 35·13, H, 5·53%); IR (film): 3030, 2908, 1672, 1585, 1545, 1440, 1218, 795 and 730 cm^{-1}; NMR (CCl_4): δ 2·23, s, 3H(C<u>H</u>$_3$), 2·25, s, 3H(C<u>H</u>$_3$), 3·65, s, 2H(C<u>H</u>$_2$–S–), 6·25, q, 2H(vinylic) ppm.

REFERENCES

[1]J. T. Bos, *Rec. Trav. Chim.* **88**, 733 (1969).
[2]T. E. Young and C. R. Hamel, *J. Org. Chem.* **35**, 821 (1970).
[3]P. Cagniant and D. Cagniant, *Bull. Soc. Chim. Fr*, **7**, 1534 (1964).
[4]P. Cagniant and D. Cagniant, *Ibid.* **7**, 2591 (1967).
[5]E. Campaigne and B. F. Tullar, *Org. Synthesis* **33**, 96 (1953).
[6]N. Steinkopf and I. Poulsson, *Liebigs Ann.* **536**, 128 (1938).
[7]D. MacDowell and T. Patrick, *J. Org. Chem.* **32**, 1266 (1967).
[8]L. Harrison and T. Cantrell, *Tetrahedron Letters* **45**, 4477 (1967).
[9]O. Dann and W. Dammling, *Chem. Ber.* **87**, 373 (1954).
[10]G. Jean and F. Nord, *J. Org. Chem.* **20**, 1363 (1955).
[11]R. Gaerther and G. Tonkyn, *J. Am. Chem. Soc.* **73**, 5878 (1951).
[12]M. P. Cagniant and D. Cagniant, *Bull. Soc. Chim. Fr*, 713 (1953).
[13]Ya. L. Goldfarb and M. S. Kondakova, *Bull. Acad. Sci. USSR*, (Engl), 486 (1956).
[14]N. Gunnel, *Acta. Chem. Scand.* **16**, 1329 (1962).
[15]S. T. Cantrell, *Tetrahedron Letters*, No. **17**, 1299 (1969).
[16]R. H. Bible, *J. Org. Chem.* **26**, 1336 (1961).
[17]K. B. Wiberg and H. F. Meshane, *Org. Synthesis* **3**, 197.