ketal bands. The compound is probably impure. The fingerprint region of the infrared spectrum was quite different from the hydrogenation product of XIV.

**Hydrogenation Experiments.**—The standard reaction conditions involved shaking a solution of 0.1 g. of steroidal sapogenin plus 0.1 g. of steroidal amine or *n*-propylamine in 30 ml. of glacial acetic acid, or 0.1 g. of steroidal amine in 15 ml. of glacial acetic acid, with an equal weight of platinum oxide at room temperature and 3 atmospheres pressure for 3 hours or 25 hours. The catalyst was then removed and the solvent evaporated *in vacuo*. The residue was acetylated in the usual manner with pyridine and acetic anhydride and after standard work up the infrared spectrum of the total sample was obtained. Then in the case of mixtures of steroidal sapogenins and steroidal amines a sharp separation between the sapogenin acetate and the sapogenin acetamide could be obtained by chromatography on Florisil, the sapogenin acetate being much more easily eluted than the acetamide. In cases in which only the steroidal amine was hydrogenated, all pertinent data could be obtained from the infrared spectrum of the acetylated total reaction product. In this case absorption bands at 1735 cm.$^{-1}$ can come only from the acetylated C$_{26}$-hydroxyl formed as a consequence of side-chain opening. Since the O-acyl and N-acyl bands are well separated (1735 *vs.* 1680-1685 cm.$^{-1}$, respectively) the intensity of O-acyl bands can be estimated with reasonable accuracy. The intensity of the 1735 cm $^{-1}$ band of 3-desoxydihydrotigogenin acetate was used as a standard and the degree of side chain hydrogenation calculated from the intensity ratios. In cases involving only sapogenin acetates or mixtures in which the sapogenin had been previously separated from the amine by chromatography, the degree of side chain attack could be estimated by the decrease in intensity of the strong 982–985 cm.$^{-1}$.[10a] In the case of the 3,5-cyclosapogenins, all of the compounds studied, without regard to the nature of the 6$\beta$-substituent, had an infrared absorption band at 3060 cm.$^{-1}$ characteristic of methylene groups in the cyclopropane ring and found in all steroids with such structure.[17] Presence or absence of this infrared band provided a simple means of determining whether the 3,5-cyclo group had been hydrogenated. Other features of the molecule could be examined as described previously.

PHILADELPHIA 19, PENNA.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, TULANE UNIVERSITY, AND THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF LEIDEN (HOLLAND)]

# The Chemistry of Polythienyls. II[1-3]

BY HANS WYNBERG AND A. BANTJES

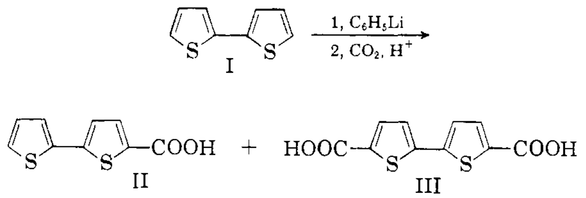
RECEIVED JULY 28, 1959

The acylation and metal–hydrogen interchange of 2,2′-bithienyl, 2,3′-bithienyl and 2,2′,5′,2″-terthienyl are described. The structures of the resulting products were determined by reductive desulfurization to aliphatic compounds. A formal total synthesis of *d,l*-muscone is recorded. An attempt is made to evaluate the directive influence of the thiophene ring.

In order to determine the orienting affect of a thiophene ring *as a substituent* upon aromatic substitution reactions it becomes necessary to design a bi- or polyaryl in which the thiophene itself does not undergo substitution. Thus a phenylthiophene would be inadequate since substitution occurs in the thiophene ring.[4,5]

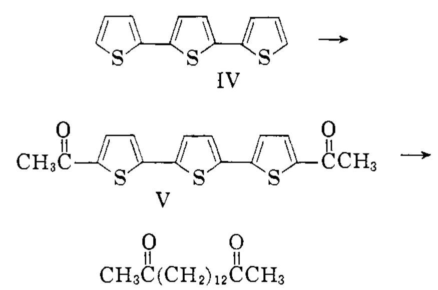
A biaryl possessing the desired characteristics would be a thienylfuran[6] since furan undergoes substitution reactions under milder conditions than those needed with thiophene. In the absence of such a biaryl, the bithienyls appear to be suited for a study of this kind. Consequently we have investigated the behavior of 2,2′-bithienyl (I),2,3′-bithienyl (VIII) and 2,2′,5′,2″-terthienyl (IV) under conditions of electrophilic substitution and of hydrogen–metal interchange.

The results with 2,2′-bithienyl were as expected—both acylation, which had been carried out previously[1], as well as hydrogen–metal interchange occurring in the 5- and 5′-positions, respectively



Carbonation followed by acidification of the reaction mixture obtained from phenyllithium and 2,2′-bithienyl furnished the mono- and dicarboxylic acids II and III in high yields. The structures of II and III were proved by their conversion to nonanoic and sebacic acid, respectively.

The acylation of 2,2′,5′,2″-terthienyl (IV) likewise proceeded in a predictable fashion to furnish as major product 5,5″-diacetyl-2,2′,5′,2″-terthienyl(V). This structure was confirmed by desulfurization followed by oxidation to the known[7] 2,15-hexadecanedione (VI), which has been used by Stoll in his synthesis of muscone.



$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}(CH_2)_{12}\overset{O}{\overset{\|}{C}}CH_3}$$

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(1) For the first paper in this series see H. Wynberg, A. Logothetis and D. VerPloeg, THIS JOURNAL, **79**, 1972 (1957).

(2) Part of this work was supported by the Office of Ordnance Research, Contract No. DA-01-009-ORD-500.

(3) From the doctoral dissertation of A. Bantjes.

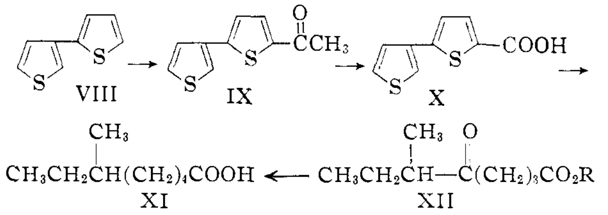
(4) A. Chrzaszczewska, *Roczniki Chem.*, **5**, 1,33 (1925); *C. A.*, **20**, 1078 (1926); A. S. Broun and M. G. Voronkov, *Doklady Akad. Nauk (USSR)*, **59**, 1293 (1941); *C. A.*, **43**, 2614 (1949); W. Steinkopf and H. J. Petersdorff, *Ann.*, **543**, 119 (1940).

(5) Some doubt has been thrown upon the assignment of structures resulting from substitution reactions with phenylthiophenes by I. V. N. Ivanov, *Zhur. Obschei Khim.*, **28**, 1232 (1958).

(6) The preparation of 3-thienylfuran has recently been reported by us (H. Wynberg and G. Schollmann, Abstracts of Papers, Division of Organic Chemistry, 135th National Meeting American Chemical Society Boston, Mass., April 5–10, 1959, p. 75-O).

(7) M. Stoll and A. Rouve, *Helv. Chim. Acta*, **30**, 2019 (1947).

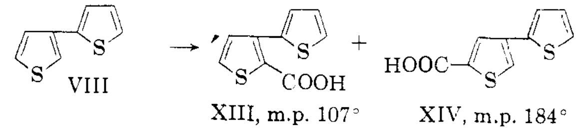
The acylation of 2,3′-bithienyl (VIII) has been described previously and a structure (IX) has been assigned to the ketone.[1] Additional confirmation of this assignment was obtained by oxidation of IX to the corresponding acid X and conversion of the latter *via* reductive desulfurization to the known[8] 6-methyloctanoic acid XI.



$$\underset{\mathrm{XI}}{CH_3CH_2\overset{CH_3}{C}H(CH_2)_4COOH} \longleftarrow \underset{\mathrm{XII}}{CH_3CH_2\overset{CH_3}{C}H—\overset{O}{\overset{\|}{C}}(CH_2)_3CO_2R}$$

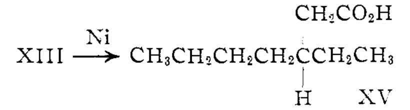
The latter was also prepared by reduction of the keto-acid (XII, R = H) resulting from the reaction of di-(2-butyl)-cadmium and γ-carboethoxybutyryl chloride.

When 2,3′-dithiophene (VIII) was treated with phenyllithium and the resulting product was carbonated, a mixture of monocarboxylic acids was obtained in 75% yield. Fractional crystallization of this mixture permitted the isolation of two pure components, acid XIII and XIV in yields of 38 and 52%, respectively.

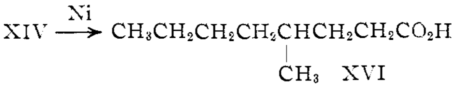


XIII, m.p. 107° XIV, m.p. 184°

In view of the high melting point (m.p. 204°) and low solubility of acid X it is of considerable significance that no acid corresponding to X could be detected in the mixture. The structures of XIII and XIV were unambiguously determined by degradation to 3-ethylheptanoic acid (XV) and 4-methyloctanoic acid (XVI). These in turn were prepared by described routes.[9] The comparisons were carried out in each case by mixture melting point determinations of the carefully purified S-benzylisothiuronium salts of the acids (see Table II).



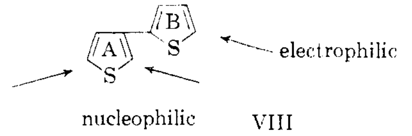
$$\mathrm{XIII} \xrightarrow{\mathrm{Ni}} CH_3CH_2CH_2CH_2\overset{CH_2CO_2H}{\underset{H}{C}}CH_2CH_3 \qquad \mathrm{XV}$$



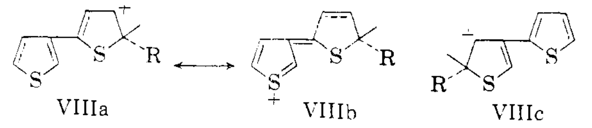
$$\mathrm{XIV} \xrightarrow{\mathrm{Ni}} CH_3CH_2CH_2CH_2\underset{CH_3}{C}HCH_2CH_2CO_2H \qquad \mathrm{XVI}$$

## Discussion

In the substitution reactions with 2,2′-bithienyl (I) it appears that the influence of the sulfur atom often outweighs any influence due to the presence of a thiophene ring as a substituent.[10] The same considerations apparently apply to the linear 2,2′,5,2″-terthienyl (IV). However a different situation prevails with the unsymmetrical 2,3′-bithienyl (VIII). The three α-positions at which substitution occurs are non-equivalent. The electrophilic substitution becomes understandable and comparable to the results with biphenyl which acylates almost exclusively in the *p*-position. A consideration of a possible transition state structure (VIIIa ↔ VIIIb) for electrophilic substitution indicates its possible stabilization through contributions by limiting structures involving electron shifts out of the *other* ring. No such limiting structures contributing to the stability of the transition state can easily be formulated if initial attack occurs at the 5′-position (VIIIc).



VIII



VIIIa VIIIb VIIIc

Jean[11] has presented convincing evidence based on the rate of racemization of an optically active 3-phenylthiophene that the steric requirements of a thiophene ring are less than those of a phenyl ring. Thus coplanar limiting structures, of importance in discussing conjugative effects in biaryls, might contribute to a greater extent to the structure of 2,3′-bithienyl than in the case of biphenyl. In this light the difference in the reactivity of the 5- and 5′-positions of 2,3′-bithienyl toward electrophilic substitution becomes understandable since an increase in conjugative interactions would tend to distinguish more sharply between these two points of attack.

The thiophene group in the "ortho" position, adjacent to the 2′-position in structure VIII, may be responsible for the lack of substitution at this position.[12]

Since electrophilic substitution in 2,3′-bithienyl (VIII) takes place in the 5-position it may be argued that this position is liable to become more electronegative than the 5′-position. The results of the hydrogen–metal exchange reaction are in accord with this reasoning, since no acid corresponding to exchange at the 5-position could be found, while the hydrogen at the 5′-position was exchanged to an extent of 38% based on the acid isolated. The high yield (52%) of carboxylic acid XIII corresponding to exchange at the 2′-position could well be ascribed to electron attraction by thiophene as an (*ortho*) substituent. The possibility exists also that coördination of the lithium atom with the sulfur atom of *either* ring prior to exchange at the 2′-position has influenced the extent of exchange at this position

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(8) J. Cason and F. S. Prout, THIS JOURNAL, **66**, 46 (1944); P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **95**, 153 (1933); **103**, 299 (1933); S. Wilkinson, *Nature*, **164**, 622 (1949); L. Crombie and J. H. Harper, *J. Chem. Soc.*, 2688 (1950).

(9) (a) H. Kenyon and M. C. R. Symons, *J. Chem. Soc.*, 2129 (1953); (b) W. Keil, *Z. physiol. Chem.*, **274**, 175 (1942).

(10) See a recent discussion by S. Gronowitz, *Arkiv. Kemi*, **13**, 295 (1959).

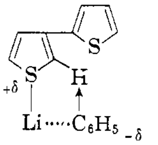
(11) G. N. Jean, *J. Org. Chem.*, **21**, 419 (1956).

(12) R. D. Brown, *Experientia*, **6**, 376 (1950), considers this steric factor for the biphenyl case.

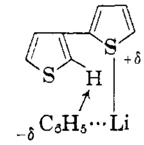
TABLE I

POLYTHIENYLCARBOXYLIC ACIDS

| No. | 95% EtOH $\lambda_{max}$, m$\mu$ | log $\epsilon$ | M.p., °C. | Yield, % | Carbon, % Calcd. Found | Hydrogen, % Calcd. Found |
|---|---|---|---|---|---|---|
| | 237 | 3.7 | | | | |
| II | 257 | 3.7 | 183–184 | 74 | 51.41 | 2.86 |
| | 328 | 4.3 | | | 51.21 | 2.88 |
| X | 238 | 3.8 | 203–205 | 91 | 51.41 | 2.86 |
| | 311 | 4.3 | | | 51.46 | 2.94 |
| XIII | 248 | 4.1 | 107–109 | 52 | 51.41 | 2.86 |
| | 285 | 4.0 | | | 51.73 | 2.95 |
| XIV | 247 | 4.1 | 173–175 | 38 | 51.41 | 2.86 |
| | 305 | 4.1 | | | 51.21 | 2.88 |
| III | | | 371–375 d. | 48 | 47.26 | 2.36 |
| | | | | | 47.16 | 2.49 |

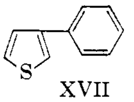


and



Electron attraction by thiophene might well affect the relative basicity of the two sulfur atoms and accordingly render the sulfur atom in ring B (structure VIII) less capable of coördination with the lithium atom prior to hydrogen–metal exchange. This hypothesis is strengthened by the work of Gronowitz[10] who found that in the metalation of 3-phenylthiophene (XVII) the main product resulted from exchange at the 5-position. A combination of: (a) stronger electron attraction by thiophene than by phenyl; (b) coördination by the lithium with either sulfur atom instead of with one; (c) increased basicity of one sulfur atom relative to the other; and (d) smaller steric requirement of thiophene with respect to phenyl, might readily have altered the point of attack during hydrogen–metal exchange. It is well to bear in mind, however, that in thiophene as in benzene one might expect the donor-acceptor properties of the C–C $\pi$-bonds as well as the 3p-electrons of the sulfur atom "to adapt themselves to variations in electronic demand."[13]

metalation ——→



XVII

**Acknowledgment.**—The authors wish to thank Professor Dr. E. Havinga for many helpful discussions.

## Experimental[14]

**5-(2'-Thienyl)-2-thenoic Acid (II).**—A solution of 0.2 mole of phenyllithium was prepared by adding a solution of 3.12 g. (0.02 mole) of bromobenzene in 10 ml. of sodium dried ether slowly to 0.28 g. (0.04 mole) of very finely cut lithium ribbon, dispersed in 50 ml. of dry ether. The reaction was carried out in a modified Grignard apparatus consisting of a three-necked Morton stirring flask equipped with a reflux condenser, a separatory funnel with pressure equalizer and a gas inlet connected to a helium cylinder. The reflux condensor was connected to a mercury valve to maintain a slight helium pressure during the reaction. When all of the lithium had gone into solution 3.32 g. (0.02 mole) of 2,2'-bithienyl,[15] dissolved in 50 ml. of dry ether was added all at once. The solution was heated under reflux for 15 minutes after the addition and finally poured over solid carbon dioxide and kept for one hour protected from moisture by a drying tube. The ether was evaporated and the remaining cake was dissolved in a 5% sodium hydroxide solution, with stirring and heating. The hot solution was filtered and after cooling to room temperature the filtrate was acidified with concentrated hydrochloric acid. A green white precipitate was removed by filtration and washed with cold water, yielding 3.1 g. (74%) of crude monocarboxylic acid, m.p. 175–179°. Recrystallization from heptane or methanol-water furnished long white needles of II, melting at 183–184°; for analysis see Table I.

TABLE II

REDUCTIVE DESULFURIZATION OF POLYTHIENYLCARBOXYLIC ACIDS

| Starting acid | Product | Desulfurization yield, % | M.p. or b.p. (mm.), °C. Acid | S-Benzylisothiuronium salt | Amide |
|---|---|---|---|---|---|
| II | Pelargonic | 85 | 8 | | 94–95[a] |
| XVII | Tridecanoic | 74 | 41 | | 98–99[b] |
| III | Sebacic | 67 | 133–134 | | |
| XIV | 4-Methyloctanoic | 79 | 82–84 (2.5)[g] | 134.6–135.1[c] | |
| XIII | 3-Ethylheptanoic | 80 | 109–113 (3) | 143.5–144[d] | |
| X | 6-Methyloctanoic | 74 | 69–70 (0.1)<br>$n^{24}$D 1.4382 | 147.5–148.2[e,f] | |

[a] Reported m.p. 95°. [b] Reported m.p. 100°. [c] Mixture m.p. with the S-benzylisothiuronium salt of 4-methyloctanoic acid (ref. 8a) 134.9–135.4°. [d] Mixture m.p. with the S-benzylisothiuronium salt of 3-ethylheptanoic acid (ref. 8b) 143.7–144.2°. [e] Mixture m.p. with 6-methyloctanoic acid (ref. 7) 147.3–147.9°. [f] The mixture melting points of the S-benzylisothiuronium salts of non-identical acids showed depressions of 6–12°. [g] Ethyl ester.

**Methyl 2,2'-Bithienyl 5-carboxylate.**—The methyl ester, obtained in 89% yield by heating the acid for 12 hr. under reflux in excess absolute methanol and a few drops of sulfuric acid, melted at 74–75°.

*Anal.* Calcd. for $C_{10}H_8O_2S_2$: C, 53.57; H, 3.57. Found: C, 53.45; H, 3.53.

**Dimethyl 2,2'-Bithienyl-5,5'-dicarboxylate.**—The dibasic acid III was esterified *via* the diacid chloride because of the insolubility of the free acid in alcohol to furnish the diester as pale yellow crystals, m.p. 211–212°.

*Anal.* Calcd. for $C_{12}H_{10}O_4S_2$: C, 51.04; H, 3.58. Found: C, 50.89; H, 3.53.

**Reduction and Desulfurization of 2,2'-Bithienyl-5,5'-dicarboxylic Acid.**—To 100 ml. of water in which 4 g. of Raney nickel was dispersed was added 0.300 g. of the diammonium salt of 2,2'-dithiophene-5,5'-dicarboxylic acid. This mixture was refluxed and stirred for 16 hours. The Raney nickel was separated from the now colorless water solution by filtration through a Soxhlet extraction thimble and was extracted with water for 16 hours. The extract and filtrate were combined and evaporated to 5 ml. The solution was acidified with concentrated hydrochloric acid

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(13) G. S. Hammond and C. E. Reeder, THIS JOURNAL, **80**, 574 (1958).

(14) All melting points and boiling points are uncorrected. Representative lithiation, esterification and desulfurization experiments are described. Unless otherwise mentioned the acids listed in Tables I and II have been prepared by these described techniques.

(15) H. Wynberg and A. Logothetis, THIS JOURNAL, **78**, 1958 (1956).

in the cold to furnish 136 mg. (67% yield) of colorless platelets melting at 133.5–134.0°. The mixed melting point with commercial sebacic acid (m.p. 133–134°) was 133–134°.

**5,5''-Diacetyl-2,2',5',2''-terthienyl (V).**—A solution of 105 mg. of pure IV m.p. 94–95°, and one drop of 85% phosphoric acid in 1.25 ml. of acetic anhydride was heated for one hour at 110°, while protected from moisture. The solution was then poured over 25 g. of crushed ice and the brown-yellow solid (130 mg.) removed by filtration. One recrystallization from dioxane yielded 86 mg. (61%) of red-orange platelets melting at 242–245°. Sublimation at 225–230° (0.3 mm.) furnished 72 mg. (51%) of pure yellow platelets of V, m.p. 249–250°.

*Anal.* Calcd. for $C_{16}H_{12}O_2S_3$: C, 57.83; H, 3.61. Found: C, 57.84; H, 3.64.

**Reductive Desulfurization of V.**—When 35 mg. of V was desulfurized in the usual manner 21 mg. (80% yield) of colorless platelets, m.p. 67–68°, was obtained. Oxidation of this (presumed) 2,15-hexadecane diol with 1.5 ml. of glacial acetic acid and 50 mg. of chromium trioxide furnished 18 mg. (69% from V) of hexadecane-2,15-dione, m.p. 83–85°, after one recrystallization from aqueous methanol (reported[6] m.p. 82.5°).

**Separation of Monocarboxylic Acids XIII and XIV.**—The lithiation and carbonation of 2.10 g. of 2,3'-bithienyl[15] was carried out as described above for 2,2'-bithienyl, using 2.10 g. of bromobenzene and 1.90 g. of lithium in 130 ml. of ether. The crude carbonated mixture was dissolved in 5 N sodium hydroxide solution. Insoluble material furnished 0.3 g. (15%) recovered 2,3'-bithienyl. Acidification of the filtrate yielded 1.71 g. (75%) of crude mixture of acids. This dried acid mixture was stirred with heptane–benzene (4:1) and the solid remaining (80 mg.) removed by filtration. This solid, m.p. 270–280°, presumably consisting of dibasic acid(s) was not investigated further. Upon cooling the organic filtrate in ice, 0.62 g. (38%) of crude acid, m.p. 156–168°, crystallized. Several crystallizations from the same solvent mixture furnished pure 2,3'-bithienyl-5'-carboxylic acid (XIV), m.p. 173–175° (for analysis see Table I). The filtrate was concentrated to a small volume to furnish 0.85 g. (52%) of acid XIII, m.p. 94–105°. Three crystallizations from petroleum ether (b.p. 60–80°) furnished pure 2,3'-bithienyl-2'-carboxylic acid, m.p. 107–109° (for analysis see Table I).

New Orleans, La.
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[Contribution from the Research and Development Department, Organic Chemicals Division, American Cyanamid Co.]

# Novel Reactions of 2-Naphthol with Thioglycolic Acid and Other Mercaptans[1]

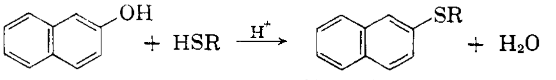
By F. M. Furman, J. H. Thelin, D. W. Hein and W. B. Hardy

Received May 29, 1959

Two unusual reactions of 2-naphthol with thioglycolic acid have been found. An alkaline-catalyzed reaction gave 2-hydroxy-1-naphthaleneacetic acid in 89% yield. Acid catalysis gave (2-naphthylthio)-acetic acid in 87% yield. The latter reaction is general for naphthols and other mercaptans, thus providing a useful synthetic route to alkyl and aryl naphthyl sulfides.

Thioglycolic acid (mercaptoacetic acid) has been found to react with 2-naphthol in two novel and divergent ways. With an alkaline catalyst, hydrogen sulfide is evolved and 2-hydroxy-1-naphthaleneacetic acid is formed. But with an acid catalyst, (2-naphthylthio)-acetic acid is obtained. The acid-catalyzed reaction was extended to alkyl and aryl mercaptans and the corresponding 2-naphthyl sulfides were obtained. Thioglycolic acid reacts similarly with 1-naphthol and 1,5-naphthalenediol. Thus, the acid-catalyzed reaction appears to be general with naphthols.

**The Acid-catalyzed Reaction.**[2]—2-Naphthol was heated at 110–120° with various mercaptans for about 16 hours in the presence of acid catalysts (*e.g.*, *p*-toluenesulfonic acid) without a solvent. 2-Naphthyl sulfides were conveniently obtained in good yields. Examples of this reaction, together with the yields, are

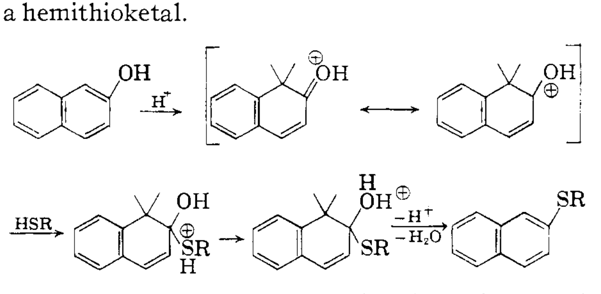


| | |
|---|---|
| R = $-CH_3$ | 99% yield |
| $-C_2H_5$ | 68% |
| $-(CH_2)_4CH_3$ | 22%[3] |
| $-(CH_2)_{11}CH_3$ | 79% |
| $-CH_3COOH$ | 87% |
| $-C_6H_5$ | 43%[3] |

1-Naphthol, 6-bromo-2-naphthol and 1,5-naphthalenediol reacted similarly with thioglycolic acid to yield the corresponding naphthylthioacetic acids.

No product was obtained in the absence of an acid catalyst. Toluenesulfonic acid and mixed alkanesulfonic acids were effective. Other catalysts which had activity were concentrated sulfuric acid, sodium bisulfate and polyphosphoric acid. The yields were lower if an appreciable amount of water was present.

This reaction, which is somewhat analogous to the Bucherer reaction, is another manifestation of the ability of naphthols to undergo attack by certain nucleophiles, such as methanol,[4] under acid catalysis and resembles formally the formation of a hemithioketal.



An alternative mechanism involves the attack of the mercaptan on the carbonium ion derived from 2-naphthol by protonation of the hydroxyl group and its loss as water. This may be the mechanism in case of compounds which form carbonium ions easily. For example, *s*-triphenyl-

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[1] This material was presented before the Organic Group of the North Jersey Section of the American Chemical Society Eleventh Annual Meeting in Miniature, South Orange, N. J., January 26, 1959.

[2] W. B. Hardy, J. H. Thelin and F. M. Furman, U. S. Patent 2,884,449.

[3] These values represent purified yields from a single experiment and do not necessarily represent the optimum conditions.

[4] L. Gattermann, *Ann.*, **244**, 72 (1888).