the poisoning effects observed could be predicted reasonably well from a knowledge of the reactivity of these compounds in ordinary organic reactions.

Acknowledgment.—The authors are indebted to The Harshaw Chemical Company for financial support in the form of a fellowship.

Summary

A study of the poisoning of Raney nickel by hydrogen chloride and organic halides has indicated that there are at least two distinct types of active surface present on this catalyst. It has also been found that most of the poisoning effects observed could be predicted on the basis of the known reactivities of these halides. The notable exceptions to this rule are the apparent promoter effect of amyl chloride and the high toxicity of the propyl halides and compounds containing more than one halogen on the same carbon atom. Chlorides and bromides are in general moderately toxic whereas iodides are always highly toxic.

COLUMBUS, OHIO RECEIVED FEBRUARY 16, 1950

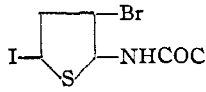
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

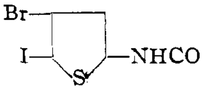
Reactions of Aceto-2-thiophenamide

BY CHARLES D. HURD AND JAMES MOFFAT

It was shown[1] recently that 2-acetamido-5-bromothiophene was remarkable in that the bromine atom was replaceable during nitration or diazo coupling operations. The present work extends this study.

Since 3-bromo-5-iodo-2-acetamidothiophene (I) readily lost its iodine atom during substitution reactions, one might have predicted the same for the 4-bromo-5-iodo analog (II). This did not occur, however, but instead a conventional substitution reaction occurred on nitration with acetyl nitrate, giving rise to III. Synthesis of II was achieved by mercuration of 2-acetamido-4-bromothiophene, followed by cleavage with iodine.


(I)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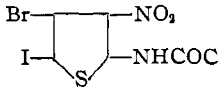
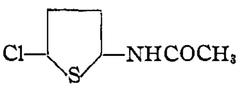

(III)


(IV)

Thiocyanation of aceto-2-thiophenamide gives rise to the 5-thiocyano derivative (IV). This is not surprising but it is interesting to point out that acetanilide[2] fails to react under comparable conditions. A similar difference in reactivities of aceto-2-thiophenamide and acetanilide was observed[1] with diazo coupling. The former reacted smoothly to yield an azo dye. On the other hand, acetanilide does not couple.

Chlorination experiments were performed also. Direct chlorination of aceto-2-thiophenamide in either chloroform or glacial acetic acid was unsatisfactory and no chloro derivatives were isolable. A 25% yield of ammonium chloride was isolated from the experiment using acetic acid.

N-Chloroacetamide proved to be an efficient chlorinating agent. The reaction could be controlled so that either the monochloro (V) or the dichloro (VI) derivatives could be prepared. The dichloro compound (VI) did not couple with sodium *p*-nitrobenzenediazoate but the monochloro compound (V) did. Coupling was at position 3, forming VII. This is the first example of a direct coupling of a diazo compound in a beta position of the thiophene nucleus. Of interest also is the fact that chlorine is not ejected in this process. This result is not entirely unexpected since it has been shown that 2,5-dibromothiophene,[3] 2,5-diiodothiophene,[3] 2,3,4,5-tetrabromothiophene[4] and 2,4,5-tribromo-3-methylthiophene[5] all react in the Friedel–Crafts reaction to form 2-acetyl derivatives with the ejection of halogen, whereas 2,5-dichlorothiophene reacts[6] to give 2,5-dichloro-3-acetylthiophene.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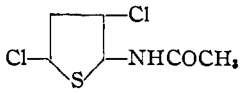
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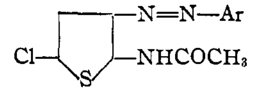
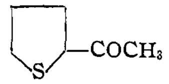

(VII)


(VIII)

The synthesis of aceto-2-thiophenamide from nitrothiophene leaves much to be desired; hence alternative syntheses from methyl 2-thienyl ketone were investigated, namely, the Beckmann rearrangement of the ketoxime and the Schmidt reaction using hydrazoic and sulfuric acids. The Beckmann reaction has been reported previously,[7] but the yields of amide were very poor. Several methods for carrying out this rearrangement were tested in the present study but none was satisfactory.

The Schmidt reaction did give rise to aceto-2-thiophenamide, but apparently as an eutectic with the isomeric 2-thenomethylamide, $C_4H_3S{-}CO{-}NHCH_3$. The latter compound was prepared for purposes of characterization by reaction of methylamine and 2-thenoyl chloride. Only two other

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(1) Hurd and Priestley, THIS JOURNAL, **69**, 859, 1174 (1947).

(2) Brewster and Dains, *ibid.*, **58**, 1364 (1936).

(3) Gattermann and Römer, *Ber.*, **19**, 689 (1886).

(4) Steinkopf, Jacob and Penz, *Ann.*, **512**, 162 (1934).

(5) Steinkopf and Jacob, *ibid.*, **515**, 276 (1935).

(6) Steinkopf and Köhler, *ibid.*, **532**, 265 (1937).

(7) (a) Rimini, *Chem. Ztg.*, **23**, 266 (1899); (b) Steinkopf, *Ann.*, **403**, 17 (1914).

ketones,[8] namely, benzylacetone and levulinic acid are reported to give rise to both isomeric amides in the Schmidt reaction.

Several of the azo derivatives prepared by Hurd and Priestley[1] were at hand; hence they were tested to see whether they could serve as acid-base indicators in strongly acid solution. They were found in general to have sharp color changes, but presumably because of the amide groups, most of them were unstable in strong acids. The compounds possessing carbamate structures were much more stable in acids, but were too insoluble in acids to be useful. The compounds were all dissolved in a few ml. of alcohol, then were diluted to 100 ml. with water giving concentrations of 3–5 mg. per 100 ml. Results are summarized in Table I. None of the amides remained colored more than one-half hour in 6 *N* acid and neither of the carbamates more than one-half hour in alkali.

TABLE I

COLOR CHANGES SHOWN BY THE AZO DYES

Cpd.[a]	Color In 6 *N* HCl	At *p*H 2–3	At *p*H 12	Fades rapidly in:
1	Red	Yellow	Purple	Acid
2	Rose-red	Brownish-yell.	Violet	Acid
3	Rose-red	Brownish-yell.	Violet	Acid
4	Rose-red	Brownish-yell.	Violet	Acid
5	Orange-red	Insoluble	Blue	Alkali
6	Red	Insoluble	Violet	Alkali
7	Rose-red		Violet	Acid

[a] 1, 2-Acetamido-5-(*p*-nitrophenylazo)-thiophene; 2, 2-acetamido-3-bromo-5-(*p*-nitrophenylazo)-thiophene; 3, 2-acetamido-3-iodo-5-(*p*-nitrophenylazo)-thiophene; 4, 2-acetamido-3,4-dibromo-5-(*p*-nitrophenylazo)-thiophene; 5, ethyl N-2-(5-(*p*-nitrophenylazo))-thienylcarbamate; 6, benzyl N-2-(5-(*p*-nitrophenylazo))-thienylcarbamate; 7, 2-acetamido-4-bromo-5-(*p*-nitrophenylazo)-thiophene.

Experimental

The thiophene and methyl 2-thienyl ketone used in this work were generously donated by the Socony–Vacuum Oil Company. Micro Dumas determinations were performed by M. M. Ledyard and V. Hobbs. Micro combustions for carbon and hydrogen were carried out by M. Hines and P. Craig.

Methyl 2-Thienyl Ketoxime.—This oxime was prepared in 63% yield in the conventional manner. The material melted at 110° following crystallization from alcohol and water. This is the m.p. reported in the literature.[7b] Further purification by crystallization from benzene brought the m.p. to 114–115°.

Anal. Calcd. for C_6H_7NOS: N, 9.92. Found: N, 9.64.

Methyl 2-Thienyl Ketoxime Acetate.—One part of this oxime was mixed with 6 parts each of glacial acetic acid and acetic anhydride. The crystals which separated after 24 hours were collected and filtered from alcohol–water; m.p. 129–130°.

Anal. Calcd. for $C_8H_9NO_2S$: N, 7.68. Found: N, 7.56.

***p*-Nitrobenzo-2-thiophenamide.**—This amide was prepared by H. M. Priestley of this Laboratory, but it was not analyzed. His procedure was to add *p*-nitrobenzoyl chloride in ether to an aqueous solution of thienylammonium chlorostannate, then with cooling and stirring to add dilute sodium hydroxide dropwise. The precipitate was collected and crystallized from dilute alcohol; m.p. 220°.

This crude compound was twice recrystallized from aqueous alcohol in the present work and analyzed; m.p. 223–224°.

Anal. Calcd. for $C_{11}H_8N_2O_3S$: C, 53.20; H, 3.25. Found: C, 53.18; H, 3.61.

2-Acetamido-3-nitro-4-bromo-5-iodothiophene.—2-Acetamido-4-bromo-5-iodothiophene, m.p. 162–163°, was synthesized[1] and 0.28 g. of it was dissolved in a mixture of 0.3 ml. of glacial acetic acid and 0.1 ml. of fuming nitric acid (d. 1.60). An immediate yellow precipitate formed which was filtered off. A second crop was obtained by diluting the filtrate with water. The first crop was recrystallized from aqueous alcohol yielding 0.10 g. of bright yellow needles, m.p. 248–248.5° (dec.).

Anal. Calcd. for $C_6H_4BrIN_2O_3S$: C, 18.43; H, 1.03. Found: C, 18.50; H, 1.11.

2-Acetamido-5-thiocyanothiophene.—Aceto-2-thiophenamide (0.7 g.) was dissolved with 3.24 g. of sodium thiocyanate in 200 ml. of hot water. Into this was added 5 g. of cupric sulfate pentahydrate in 50 ml. of water during 5 minutes. The solution was kept one-half hour on the steam-bath at which time the black cupric thiocyanate had changed to the white cuprous salt. The mixture was filtered hot and cooled and extracted several times with carbon tetrachloride. The solvent was diluted with petroleum pentane yielding 0.21 g. of 2-acetamido-5-thiocyanothiophene, m.p. 180–185° (dec.). On recrystallization from chloroform and pentane, there was obtained 0.12 g. of product melting at 201–203° (dec.) (The melting point of this compound is extremely variable according to the rate of heating. The sample melting from 201–203° melts at 180–190° on slower heating.)

Anal. Calcd. for $C_7H_6N_2OS_2$: C, 42.40; H, 3.04. Found: C, 42.60; H, 3.48.

Chlorination.—A solution of 0.76 g. (0.0050 mole) of aceto-2-thiophenamide, 1.84 g. (0.0197 mole) of N-chloroacetamide prepared by the method of Mauguin,[9] and 1 ml. of concentrated hydrochloric acid in 50 ml. of water was heated on the steam-bath for 15 minutes. The solution became very dark colored and a black, charred-looking mass separated. The solution on cooling deposited a mass of fine white needles. The needles were separated, dissolved in ether and the ether solution was decolorized twice with Norit. On evaporation, there was left 0.56 g. of yellowish crystalline material (53.5% as dichloro compound). This was recrystallized from ligroin yielding 0.49 g. of white crystalline dichloride, m.p. 123–124°.

Anal. Calcd. for $C_6H_5Cl_2NOS$: C, 34.30; H, 2.40. Found: C, 34.30; H, 2.48.

In 31 ml. of water was dissolved 1.04 g. (0.0074 mole) of aceto-2-thiophenamide, 0.69 g. (0.0074 mole) of N-chloroacetamide and three drops of concentrated hydrochloric acid. The solution was allowed to stand at room temperature for 15 hours and was then heated on the steam-bath for 45 minutes. The solution was cooled and filtered and the product was recrystallized twice (with great loss) from aqueous ethanol; yield of the monochloride, 0.12 g. (9%), m.p. 177.5–178°.

Anal. Calcd. for C_6H_6ClNOS: C, 41.03; H, 3.44. Found: C, 40.98; H, 3.37.

3-*p*-Nitrophenylazo-2-acetamido-5-chlorothiophene.—A solution of 0.08 g. of 2-acetamido-5-chlorothiophene in 10 ml. of glacial acetic acid was treated with a solution of 0.20 g. of sodium *anti-p*-nitrobenzenediazoate in 5 ml. of glacial acetic acid. The red solution was kept at 5° for one week, then filtered and the precipitate washed thoroughly with aqueous alcohol, alcohol and ether. A second crop of the compound was obtained from the filtrate by dilution with water; yield 0.10 g. first crop and 0.04 g. second crop. The first crop was recrystallized from a mixture of pyridine and water and dried in a desiccator over sulfuric acid. This melted from 184–185° with decomposition.

Anal. Calcd. for $C_{12}H_9ClO_3N_4S$: C, 44.38; H, 2.79. Found: C, 44.47; H, 3.02.

Sodium *anti-p*-nitrobenzenediazoate (0.10 g.) was moistened with 0.10 ml. of water and then dissolved in 10 ml. of cold glacial acetic acid. This was poured into a cold solution of 0.10 g. of 2-acetamido-3,5-dichlorothiophene dissolved in 5 ml. of acetic acid and the solution was placed in the cold room. No precipitate was formed even after 40 days (a sample of the diazoate solution gave an immediate reaction with dimethylaniline).

The Schmidt Reaction. At 0–10°.—To a cold solution of 5.40 g. of methyl 2-thienyl ketone in 100 ml. of chloroform

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(8) Smith, THIS JOURNAL, **70**, 320 (1948); Moyer and Wolff, "Organic Reactions," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 315.

(9) Mauguin, *Ann. chim. phys.*, [viii] **22**, 305 (1911).

was added 5 ml. of 96% sulfuric acid and 46 ml. of a 1.3 *N* solution of hydrazoic acid in chloroform. The solution was kept at 0–10° for 15 minutes with stirring and then poured onto ice. The layers were separated and the aqueous layer extracted repeatedly with chloroform. The chloroform solution was washed with dilute alkali and evaporated. The product was recrystallized from benzene and a second crop obtained by the addition of pentane. The first crop (1.43 g.) melted over the range 110–135° and the second crop (1.33 g.) melted sharply at 101–102°.

Repeated recrystallizations of the material melting at 101–102° failed to raise the melting point. The aceto-2-thiopheneamide present in the first crop above was removed by dissolving 0.58 g. of it in a solution of 1.41 g. of mercuric acetate and 1.13 g. of sodium acetate in 30 ml. of water. The solution was heated several hours at 100°. A solution of sodium chloride was then added and the heavy flocculent precipitate formed was filtered off and dried. The solution was extracted several times with chloroform. The chloroform solution was dried and the solvent evaporated. The product was recrystallized from benzene and petroleum hexane; m.p. 108–109°; mixed m.p. with an authentic sample of 2-thenomethylamide of m.p. 113–114°, 110–112°.

At 25–80°.—This reaction was run starting with 2.14 g. (0.0170 mole) of methyl 2-thienyl ketone, 5 ml. of concentrated sulfuric acid and 0.0191 mole of hydrazoic acid in 75 ml. of benzene. The mixture was heated on the steam-bath for 10 minutes, allowed to stand overnight and the layers were separated but nothing was found in the benzene layer. The acid layer was poured into ice water, the aqueous solution then being extracted with chloroform. The aqueous solution was neutralized hot with barium carbonate, filtered and evaporated to dryness. The residue was a small amount of black glassy material, which was partly decolorized to a yellow color, but which would not crystallize. This material was a barium salt of a sulfonic acid, presumably of acetamidothiophenesulfonic acid, but it was not characterized further.

The residue from the chloroform solution was crystallized from benzene; m.p. 109–112°. This was 2-thenomethylamide. That it was not 2-thienyl methyl ketoxime (m.p. 114°) was demonstrated, since a mixed m.p. determination of these two substances melted at 75–78°. Saponification of a 0.04-g. sample gave rise to 2-thenoic acid, m.p. and mixed m.p., 129°.

2-Thenomethylamide.—This material was prepared by interaction of methylamine and 2-thenoyl chloride. After crystallization from benzene, it melted at 113–114°.

Anal. Calcd. for C_6H_7NOS: N, 9.92. Found: N, 9.94.

2-Acetamido-3,5-thiophenedisulfonyl Chloride.—Aceto-2-thiophenamide (2.18 g.) was melted and allowed to solidify to a thin crust on the bottom of the flask. Then 26 ml. of chlorosulfonic acid was added. The flask was swirled in an ice-bath until solution was complete, then the mixture was heated 18 minutes on a steam-bath. The solution was poured into ice-water and the light brown, gummy sulfonyl chloride filtered off, dissolved in benzene, dried over sodium sulfate and the crude product decolorized once in benzene solution and then once in ether solution. It was then suspended in hot ligroin (b.p. 85–100°) and 15 ml. of benzene was added, which was just enough to dissolve all the material. On cooling, the solution deposited small hard crystals which were filtered off and desiccated overnight; m.p. 114° (uncor.); yield 2.18 g. or 44%.

Anal. Calcd. for $C_6H_5Cl_2NO_5S_2$: Cl, 22.01. Found: Cl, 22.44.

Summary

Several new reactions of aceto-2-thiophenamide are recorded.

EVANSTON, ILLINOIS RECEIVED JULY 28, 1950

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

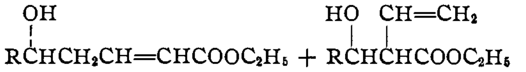
The Synthesis of Some δ-Lactones of α,β,δ-Trihydroxy Acids[1]

BY JAMES ENGLISH, JR., J. DELAFIELD GREGORY AND JAMES R. TROWBRIDGE, II

The synthesis of α,β,δ-trihydroxy acids was undertaken in view of the fact that the structural formula of auxin *a*, as proposed by Kögl,[2] places it in this otherwise unencountered class of compounds. Several δ-hydroxy-α,β-unsaturated esters have previously been prepared by the Reformatsky reaction of ethyl γ-bromocrotonate with various aldehydes.[3] A former investigation revealed that performic acid prepared from 90% hydrogen peroxide was a convenient reagent for the hydroxylation of α-β unsaturated acids and esters.[4] In the work to be described, the hydroxylation of two δ-hydroxy-α,β-unsaturated esters with performic acid yielded, in each case, an isomeric mixture of α,β,δ-trihydroxy acids which were isolated as δ-lactones.

The initial investigation[3] of the Reformatsky reaction of ethyl γ-bromocrotonate with several cyclic aldehydes showed that the crude products contained substantial quantities of esters which boiled 20–35° lower than the desired δ-hydroxy-α,β-unsaturated esters at pressures of less than 1 mm. A similar reaction of heptaldehyde with ethyl γ-bromocrotonate yielded in addition to the expected product, ethyl 5-hydroxy-2-hendecenoate (I, R = *n*-hexyl), an isomeric lower-boiling ester, ethyl 3-hydroxy-2-vinylnonanoate (II, R = *n*-hexyl).

$$\mathrm{RCHO + BrCH_2CH{=}CHCOOC_2H_5 \longrightarrow}$$



$$\mathrm{R\overset{OH}{\overset{|}{C}}HCH_2CH{=}CHCOOC_2H_5 + R\overset{HO}{\overset{|}{C}}H\overset{CH=CH_2}{\overset{|}{C}}HCOOC_2H_5}$$

I II

The ester II, R = *n*-hexyl, was quantitatively hydrogenated over a platinum oxide catalyst to ethyl 3-hydroxy-2-ethyl-nonanoate. This latter ester was also obtained as the product of the Reformatsky reaction of heptaldehyde with ethyl α-bromo-*n*-butyrate. Samples of the ester which had been prepared by each of two synthetic routes were hydrolyzed to the free acids which were then converted to crystalline *p*-bromophenacyl esters. These derivatives were proved to be identical by a determination of the mixed melting point.

The analogous reaction of cyclopentanecarboxaldehyde and ethyl γ-bromocrotonate also yielded two isomeric esters, ethyl 5-cyclopentyl-5-hydroxy-2-pentenoate (I, R = cyclopentyl), and ethyl 3-cyclopentyl-3-hydroxy-2-vinylpropanoate (II, R = cyclopentyl). The lower-boiling type II esters readily decolorized a test solution of 1% bromine in carbon tetrachloride. The type I esters reacted much less rapidly with this reagent as expected

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[1] This material is taken from dissertations submitted to the Faculty of the Graduate School of Yale University in partial fulfillment of the requirements for the Ph.D. degree by J. Delafield Gregory, 1947, and James R. Trowbridge, II, 1950.

[2] Kögl, *Ber.*, **68A**, 16 (1945).

[3] English and Gregory, THIS JOURNAL, **69**, 2123 (1947).

[4] English and Gregory, *ibid.*, **69**, 2120 (1947).