[CONTRIBUTION NO. 519 FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

The Nitration of 5-Methyl-2-thenoic Acid[1]

BY E. CAMPAIGNE AND HERSCHEL G. GROSE

Improved yields of 5-methyl-4-nitro-2-thenoic acid were obtained by nitrating 5-methyl-2-thenoic acid in sulfuric acid at −5°. Above this temperature the replacement of the carboxyl group to give 3,5-dinitro-2-methylthiophene occurred readily, lowering the yield of acid. Derivatives of 5-methyl-4-nitro-2-thenoic acid reported are the acid chloride, ethyl ester, β-diethylaminoethyl ester hydrochloride and free base and γ-di-*n*-butylaminopropyl ester hydrochloride. β-Diethylaminoethyl 5-methyl-4-amino-2-thenoate hydrochloride was prepared by reducing the nitro ester hydrochloride over palladium.

Discussion

5-Methyl-2-thenoic acid has been nitrated by Rinkes,[2] using acetic anhydride and fuming nitric acid at −5 to −10°, to give as the *main* product (*sic*) 4-nitro-5-methyl-2-thenoic acid and small quantities of 5-nitro-2-methylthiophene and 3,5-dinitro-2-methylthiophene. This reaction has been repeated in this work using red fuming nitric acid (trial I), and pure, colorless nitric acid (trial II), each with acetic anhydride at −5 to −10°. The results are given in Table I along with those of Rinkes.

TABLE I

NITRATION OF 5-METHYL-2-THENOIC ACID

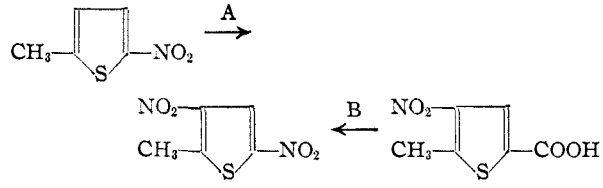
	5-Methyl-4-nitro-2-thenoic acid, %	2-Methyl-3,5-dinitrothiophene, %	2-Methyl-5-nitrothiophene, %	Starting Compound converted to $BaSO_4$, %
Trial[a] 1	39.0	None	15.5	10.1
Trial[a] 2	36.6	Trace[b]	17.3	12.0
Rinkes	"Main product"	4.7	0.31	Not detd.

[a] A small amount of tar was formed in each of these trials. [b] Enough was obtained for several melting points.

In addition, the nitration of this compound has been carried out 25 times by a shortened procedure in which no attempt was made to isolate the nitrated by-products or to determine the amount of the starting compound oxidized to the sulfate form. The yields have been found to vary from 30 to 50% with an average of about 40%. The reason for using pure, colorless nitric acid was to learn what effect, if any, nitrogen oxides had on the course of the reaction. Table I clearly indicates no difference between the two acids in the nitration reaction. When the nitration was conducted at −25°, only starting compound was obtained. Concentrated nitric acid alone at −5° did not nitrate 5-methyl-2-thenoic acid.

The literature does not record the use of concentrated nitric and sulfuric acids for nitrating 5-methyl-2-thenoic acid. It was found that this nitrating agent could nitrate the compound in 61% yields providing the temperature was kept below −5°. Even with this control of temperature, a 12% yield of 3,5-dinitro-2-methylthiophene was obtained also. At 20° the reaction gave 41% 4-nitro-5-methyl-2-thenoic acid and 12% of 3,5-dinitro-2-methylthiophene.

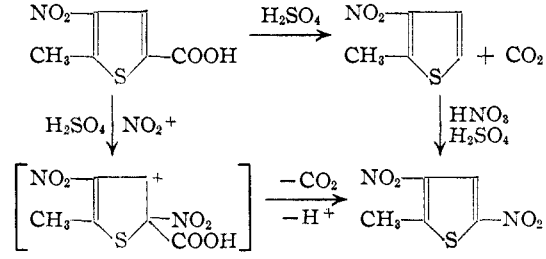
A study of the products of the nitration reaction by the methods described poses the question as to the path the reaction follows in giving 3,5-dinitro-2-methylthiophene. This compound could arise from the nitration of 5-nitro-2-methylthiophene (A) or it could come about by direct replacement of



the carboxyl group in 4-nitro-5-methyl-2-thenoic acid by a nitro group (B).

To determine what course the reaction undergoes, the following experiments were conducted. 5-Nitro-2-methylthiophene was nitrated with acetyl nitrate at −5°, giving only a 5% yield of 3,5-dinitro-2-methylthiophene and a 74% recovery of starting compound. Rinkes[2] nitrated this same compound to the dinitro derivative in quantitative yields by using concentrated nitric and sulfuric acids.

When 4-nitro-5-methyl-2-thenoic acid was nitrated with sulfuric and nitric acids at 20°, a quantitative yield of 3,5-dinitro-2-methylthiophene was obtained. When the temperature was kept below −5°, no decarboxylation or nitration occurred and only starting material was obtained. When the reaction was started below −5° and the temperature allowed to rise slowly, it was quite evident that decarboxylation took place somewhere between −4 and −1°. The evolution of carbon dioxide was rapid, and 3,5-dinitro-2-methylthiophene was obtained. This acid could be recovered unchanged from the acetic anhydride–fuming nitric acid mixture after standing one hour at room temperature. Two paths for this reaction are possible



The first possibility involves the formation of 3-nitro-2-methylthiophene by decarboxylation, followed by its nitration to the dinitro compound. The alternate route involves the direct replacement of the carboxyl group by a nitronium ion. Evidence available at this time seems to indicate that the latter mechanism is correct. First, 4-nitro-5-methyl-2-thenoic acid is stable and does not undergo decarboxylation at its melting point of

(1) Taken from part of the thesis submitted by Herschel G. Grose in partial fulfillment of the requirements for the degree, Doctor of Philosophy, at Indiana University, February, 1951.

(2) I. J. Rinkes, *Rec. trav. chim.*, **51**, 1134 (1932).

181°. Secondly, 3-nitro-2-methylthiophene, previously prepared by Rinkes,[2] is not isolated from the reaction mixture. However, this is not significant in itself since if such were an intermediate it would probably undergo rapid nitration to the dinitro compound. Lastly, it has been found that 4-nitro-5-methyl-2-thenoic acid does not undergo decarboxylation at all in concentrated sulfuric acid alone at room temperature, but the addition of even a drop of concentrated nitric acid causes rapid evolution of carbon dioxide.

Analogous behavior in the decarboxylation of aromatic acids by nitric acid has been observed on several occasions in the benzene series.[3] Durylic acid may give a small amount of nitrotrimethylbenzene when nitrated with strong nitric acid while prehnitenecarboxylic acid forms dinitroprenitene quantitatively with fuming nitric acid and sulfuric acid at 10°.[4] It is quite interesting to note the similarity of products obtained from nitrating 5-methyl-2-thenoic acid and *p*-anisic acid. Thus, the latter gives 3-nitro-4-methoxybenzoic acid, 2,4-dinitroanisole and 2,4,6-trinitroanisole.[5]

Several derivatives of 5-methyl-4-nitro-2-thenoic acid were prepared and characterized. Thionyl chloride converted the acid to its chloride which was unstable to heat, decomposing explosively on attempted distillation at atmospheric pressure. The pure acid could be obtained by vacuum distillation, however, and from it the ethyl, β-diethylaminoethyl and γ-dibutylaminopropyl esters were obtained. β-Diethylaminoethyl 4-amino-5-methyl-2-thenoate hydrochloride was obtained by catalytic reduction of the corresponding nitro ester.

Experimental

Nitration of 5-Methyl-2-thenoic Acid. A. Method of Rinkes.[2]—When 54 g. (0.38 mole) of 5-methyl-2-thenoic acid[6] was nitrated by this method, and the product steam distilled, 8.5 g. (15.5%) of 5-nitro-2-methylthiophene, b.p. 66–68° (0.5 mm.), and 27.8 g. (39%) of 4-nitro-5-methyl-2-thenoic acid, m.p. 180.5–181.5°, were obtained. The water layer yielded 8.94 g. of $BaSO_4$, indicating 10.1% of the thiophene was oxidized.

B. **100% Nitric Acid and Acetic Anhydride.**—This experiment was conducted as before, except that pure, colorless nitric acid, obtained by distilling fuming nitric acid (sp. gr. 1.50) from concentrated sulfuric acid and blowing dry air through the yellow distillate until the liquid was water-clear, was used. The results are recorded in Table I.

C. **Concentrated Nitric and Sulfuric Acids.**—A flask was fitted with a stirrer and 48 ml. (0.76 mole) of concentrated nitric acid (sp. gr. 1.42) added. While keeping the temperature below −5°, 27.5 ml. (0.49 mole) of concentrated sulfuric acid (sp. gr. 1.84) was added, followed by 12 g. (0.09 mole) of 5-methyl-2-thenoic acid in small portions. Heat and brown fumes were evolved during the addition of the solid. The reaction mixture was poured onto cracked ice and water and then steam distilled. On cooling, the residue yielded 9.7 g. (61% yield) of 4-nitro-5-methyl-2-thenoic acid, m.p. 179–180.5°. When recrystallized from hot water–alcohol, the melting point was 181.0–181.5°.

Anal. Calcd. for $C_6H_5O_4NS$: N, 7.48. Found: N, 7.38.

The distillate gave 1.8 g. of 3,5-dinitro-2-methylthiophene (11.5% conversion), m.p. 98–99°, corrected. Rinkes reports the melting point at 99–100°.[2]

Anal. Calcd. for $C_5H_4N_2O_4S$: N, 14.90. Found: N, 15.23.

When this same reaction was run at 20°, a 41% yield of 4-nitro-5-methyl-2-thenoic acid and a 12.5% yield of 3,5-dinitro-2-methylthiophene was obtained.

Nitration of 2-Nitro-5-methylthiophene.—Ten grams (0.07 mole) of 2-nitro-5-methylthiophene was nitrated with 65 ml. of acetic anhydride and 19 ml. (0.48 mole) of red fuming nitric acid (sp. gr. 1.60) in the same manner as described for the case of 5-methyl-2-thenoic acid. The temperature was maintained at −5° during the entire experiment. The steam distillation gave a cloudy distillate which was extracted with ether. The ether extract gave 7.4 g. of 5-nitro-2-methylthiophene, b.p. 66–68° (0.5 mm.), a 74% recovery of starting compound.

Following the cloudy distillate, a solid formed in the condenser which when combined with the residue was found to weigh 0.64 g. (4.9% yield). The 3,5-dinitro-2-methylthiophene thus obtained had a m.p. of 98–99°, corrected.

Nitration of 4-Nitro-5-methyl-2-thenoic Acid.—In a tall, narrow beaker 8.4 g. (0.045 mole) of 4-nitro-5-methyl-2-thenoic acid was treated with 24 ml. of concd. sulfuric and 18 ml. of concd. nitric acid in the same manner as described for 5-methyl-2-thenoic acid. The temperature during this experiment was kept at −5°. From the reaction there was obtained a quantitative recovery of the starting compound which showed no melting point depression with another sample.

In a separate trial the temperature was allowed to rise slowly. At about −4° some slight bubble formation was observed and at −1° the evolution of carbon dioxide had become vigorous. When a weighed sample was nitrated by this procedure at 20°, a 96% yield of pure 3,5-dinitro-2-methylthiophene, m.p. 98–99°, was obtained.

5-Methyl-4-nitro-2-thenoyl Chloride.—A mixture of 16.4 g. (0.088 mole) of 5-methyl-4-nitro-2-thenoic acid and 30 ml. of thionyl chloride in 50 ml. of dry benzene was refluxed for 4 hours, and then the excess thionyl chloride and benzene were distilled. The residual yellow oil boiled at 124–127° at 3 mm., and solidified in the receiver to a pale yellow solid, melting at 45.5–47.5° (cor.). The yield was 11.1 g. or 62%.

Anal. Calcd. for $C_6H_4O_3NSCl$: N, 6.81. Found: N, 7.04.

The ethyl ester is a yellow oil, boiling at 158–161° (10 mm.).

Anal. Calcd. for $C_8H_9O_4NS$: S, 14.89. Found: S, 14.72.

β-Diethylaminoethyl 5-Methyl-4-nitro-2-thenoate Hydrochloride.—The acid chloride prepared from 18.7 g. (0.10 mole) of 5-methyl-4-nitro-2-thenoic acid as previously described, but without final vacuum distillation, was mixed with 100 ml. of dry benzene and 11.7 g. (0.10 mole) of diethylaminoethanol in 100 ml. of dry benzene was added dropwise with stirring. When all the alcohol had been added, the mixture was refluxed for two hours. The pink solid which formed on cooling was recrystallized from a mixture of anhydrous ethyl acetate and ethanol, to yield 23.3 g. of white crystals (72%) which melted at 172.5–174°.

Anal. Calcd. for $C_{12}H_{19}O_4N_2SCl$: N, 8.68; Cl, 10.98. Found: N, 9.04; Cl, 11.15.

The free ester, extracted from a bicarbonate solution of the hydrochloride, was an unstable yellow oil boiling at 160.5–162° at 1 mm., $n^{20}D$ 1.5338, d^{20}_4 1.1742. This free base turned black within 24 hours, even though stored in a refrigerator in a brown bottle.

γ-Di-*n*-butylaminopropyl 5-Methyl-4-nitro-2-thenoate Hydrochloride.—A solution of 9.4 g. (0.05 mole) of γ-di-*n*-butylaminopropyl alcohol in 100 ml. of dry benzene was added dropwise to a solution of 10 g. (0.049 mole) of 5-methyl-4-nitro-2-thenoyl chloride in 50 ml. of dry benzene. After the addition was complete, the mixture was refluxed four hours, and the benzene then removed by distillation. The residual dark oil was recrystallized several times from an ethanol–ether mixture, giving 11.9 g. (62%) of grayish-white crystals melting at 93–95° (cor.).

Anal. Calcd. for $C_{17}H_{29}O_4N_2SCl$: N, 7.13. Found: N, 7.18.

The free base could not be distilled, decomposing quite rapidly on heating, even at 1 mm.

β-Diethylaminoethyl 5-Methyl-4-amino-2-thenoate Hydrochloride.—Two grams (0.0062 mole) of β-diethylaminoethyl 5-methyl-4-nitro-2-thenoate hydrochloride was reduced over 6 g. of palladium on "Darco" catalyst in 120

(3) M. P. de Lange, *ibid.*, **45**, 27 (1926).
(4) O. V. Nightingale, *Chem. Revs.*, **40**, 134 (1947).
(5) M. P. de Lange, *Rec. trav. chim.*, **45**, 45 (1926).
(6) H. G. Hartough and L. G. Conley, THIS JOURNAL, **69**, 3096 (1947).

ml. of absolute ethanol, at 44 lb. pressure of hydrogen. The theoretical drop in pressure, 1.4 lb., occurred within 15 minutes. The alcohol solution was filtered and diluted with 200 ml. of anhydrous ether, and stored in a refrigerator. The brown crystals which formed were recrystallized from ethanol–ether mixture to yield 1.3 g. (72%) of tan crystals, melting at 159.5–161° (cor.). Further recrystallizations did not lighten the color or improve the melting point.

Anal. Calcd. for $C_{12}H_{21}O_2N_2SCl$: N, 9.57. Found: N, 9.59.

The free base was quite unstable to heat, and could not be purified.

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2,5,5-Trialkyl-1,4,5,6-tetrahydropyrimidines

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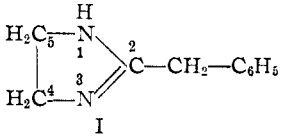
The synthesis of these tetrahydropyrimidine derivatives was undertaken in order to compare them with similar imidazolines which have shown sympathomimetic action. The presence of two alkyl groups at position 5 was desired for the further purpose of simulating physiologically active barbiturates. The radical at position 2 was varied in a homologous manner. Pharmacological screening tests indicate that they are not effective.

Some of the sympathomimetic amines such as epinephrine, ephedrine, benzedrine and propadrine contain the characteristic structure of β-phenylethylamine. 2-Alkylimidazolines[2] also show sympathomimetic action, the most effective being 2-benzylimidazoline (I) which likewise contains the β-phenylethylamine skeleton. The similar 2-benzyl-1,4,5,6-tetrahydropyrimidine (II) has not been reported. Although some other 2-alkyl-1,4,5,6-tetrahydropyrimidines have been described, the parent compound has not. Neither have any derivatives with two alkyl groups at position 5 been reported. The fact that two alkyl groups are located at position 5 in the physiologically active barbituric acids seemed to afford additional reason for making compounds of this type.



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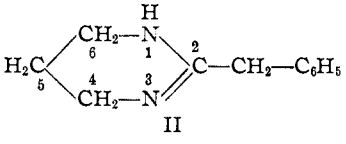

II

A number of methods of preparing the simpler 2-alkyl-1,4,5,6-tetrahydropyrimidines have been reported but the most generally satisfactory method appeared to be that used by Aspinall[3] in which an ester and trimethylenediamine are heated in a sealed tube with lime. We have modified the method to avoid the use of lime and the sealed tube.

Because the 2,2-dialkyl-1,3-propanediamines are of the neopentyl type and not available, their synthesis provided the difficult part of the problem. The needed 2,2-dialkyl-1,3-propanediols[4] were obtained in yields of 48–77%. The yields of dibromides were not above 37% and the yield of diphthalimido compound was almost nil if the alkyls are ethyl radicals. The method of Komppa and Sevon[5] is therefore impractical. The dibenzenesulfonates were obtained in practical yields but the route through the phthalimido compounds failed.

In our hands the best route to the needed 2,2-dialkyl-1,3-propanediamines[6a,b] involved the condensation of the corresponding ketones with nitromethane to give the 2,2-dialkyl-1,3-dinitropropanes which were reduced to the diamines with the aid of Raney nickel. These then gave the desired tetrahydropyrimidines (Table I). The compounds derived from 1,3-diaminobutane were mixtures as expected.

The pharmacological screening tests were made by Eli Lilly and Co. The determinations of the pressor value by vein in anesthetized cats indicate that the tetrahydropyrimidines produce a slight fall in blood pressure. Therefore, no attempt was made to separate the mixture of isomers derived from 1,3-diaminobutane. The 1,3-propanediamides (Table II) in rats by mouth gave no hypnotic action.

Experimental

2,2-Dialkyl-1,3-propanedibenzenesulfonates.—These compounds were made from the diol and benzenesulfonyl chloride in pyridine.[7] By treating the residue from the filtrate with more benzenesulfonyl chloride and pyridine the yield of the diethyl compound was increased from 69 to 86%.

Alkyls		Diol, mole	Chloride, mole	Pyridine, moles	Yield, %	M.p., °C.	Sulfur, % Calcd.	Found
CH_3–	CH_3–	0.050	0.105	0.20	62	65.5	17.58	17.63
C_2H_5–	C_2H_5–	.30	.70	1.20	69	55.5	15.53	15.47
C_2H_5–	*n*-C_4H_9–	.30	.90	1.20	81	67–68	14.55	14.86

2,2-Dialkylphthalimidopropanes.—In a typical experiment a mixture of 19.2 g. (0.050 mole) of 2,2-dimethyl-1,3-propanedibenzenesulfonate, 27.8 g. (0.15 mole) of potassium phthalimide and 100 cc. of kerosene was stirred for six hours at 210–215° and then heated at this temperature for 14 hours longer. The solid product was filtered, washed with petroleum ether, digested with dilute alkali to remove phthalimide, washed with water and ether. By recrystallization from a 1:1 mixture of alcohol and chloroform 4.7 g. (26%) of 2,2-dimethylphthalimidopropane (235–237°) was obtained. The yield from the dibromide was 11%. Neither the disulfonate nor the dibromide of the diethyl compound gave the desired phthalimido derivative.

(1) du Pont Fellow, 1949. Augsburg College, Minneapolis, Minnesota.

(2) M. Hartmann and H. Isler, *Arch. exptl. Path. Pharmakol.*, **192**, 141 (1939).

(3) S. R. Aspinall, THIS JOURNAL, **62**, 2160 (1940).

(4) A. Franke, *Monatsh.*, **34**, 1893 (1913).

(5) G. Komppa and J. Sevon, *Ann. Acad. Sci. Fennicae*, **37A**, No. 7, 8 (1933).

(6) (a) H. B. Hass and J. F. Bourland, U. S. Patent 2,343,256 (1944); (b) H. B. Hass and M. S. Larrison, U. S. Patent 2,383,603 (1946).

(7) V. C. Sekera and C. S. Marvel, THIS JOURNAL, **55**, 345 (1933).