at such a rate that the addition was complete in one hour. The mixture was stirred and heated for three hours longer, the alcohol removed, the oily α-thienylmethyl cyanide dried over fused sodium sulfate and distilled; b. p. 115–120° (22 mm.); yield 23 g. (60%).

Five grams of the cyanide, 5 g. of potassium hydroxide, 25 cc. of alcohol and 25 cc. of water were refluxed for eighteen hours, the alcohol removed and the solution acidified. The oily precipitate was extracted with ether, the solution dried and the ether removed whereupon the residue soon crystallized. The α-thienylacetic acid melted at 75–76° after recrystallization from a mixture of carbon tetrachloride and petroleum ether; yield 2 g.

Diethyl Ethyl-α-thienylmalonate.—Two and three-tenths grams of sodium was added to 100 cc. of absolute alcohol and after the solution had cooled to 55°, it was stirred and 14 g. of diethyl oxalate was added rapidly, followed by the addition of 18 g. of ethyl α-thienylacetate. The alcohol was removed under reduced pressure and the cold residue treated with 18% hydrochloric acid. The oily ethyl ethoxalyl-α-thienylacetate [C_2H_5OOC-CO-CH-(C_4H_3S)-$COOC_2H_5$] was extracted with ether, the solution dried with fused sodium sulfate and the ether removed. After the addition of 1 g. of powdered glass, the material was heated in an oil-bath at 155–160° under 20 mm. pressure; the evolution of gas was complete after two hours. Upon distillation 9 g. (38%) of a pale yellow liquid, diethyl α-thienylmalonate, was obtained; b. p. 145–148° (5 mm.).

A solution of sodium ethylate was prepared from 1 g. of sodium and 50 cc. of absolute alcohol; 9 g. of diethyl α-thienylmalonate was added, the mixture refluxed and 5 g. of ethyl bromide dropped gradually into the solution. The mixture was heated for two hours, 20 cc. of water added and the alcohol removed under reduced pressure. The oily ester layer was separated, dissolved in ether, the solution dried, the solvent removed and the diethyl ethyl-α-thienylmalonate distilled; b. p. 148–150° (5 mm.); yield 7 g. (64%).

5-Ethyl-5-(α-thienyl)-barbituric Acid.—A mixture of 0.5 g. of magnesium ribbon, which had been cleaned with steel wool and cut into small pieces, and 100 cc. of absolute methyl alcohol was heated until all of the magnesium had dissolved; 3.5 g. of diethyl ethyl-α-thienylmalonate and 2.0 g. of urea were added and the material refluxed for twelve hours. After removal of the alcohol, the residue was treated with 18% hydrochloric acid. The barbituric acid was obtained as an oil which soon crystallized; m. p. 179–180° after recrystallization from dilute alcohol; yield 1.7 g. (58%).

Anal. Calcd. for $C_{10}H_{10}O_3N_2S$: N, 11.76; S, 13.44 Found: N, 11.80; S, 13.56.

Summary

The preparation of 5-ethyl-5-(α-thienyl)-barbituric acid has been described. As far as hypnotic activity is concerned, preliminary results indicate that it is as active as phenobarbital.

ANN ARBOR, MICHIGAN RECEIVED JULY 17, 1941

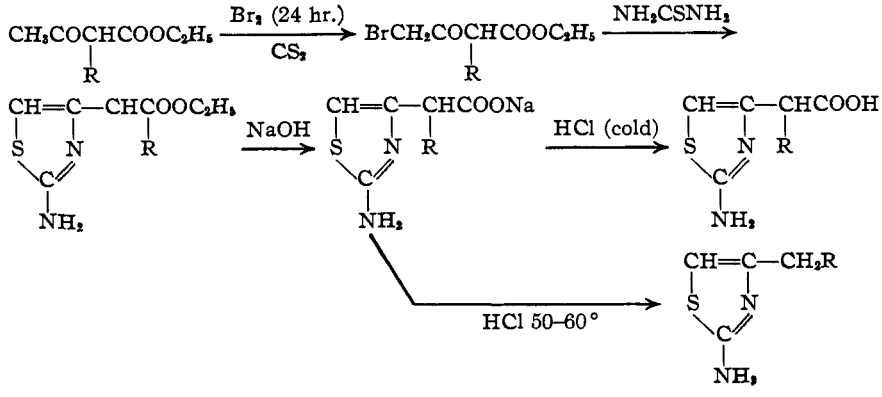
[CONTRIBUTION FROM THE SAMUEL BELL, JR., LABORATORY OF THE PHILADELPHIA INSTITUTE FOR MEDICAL RESEARCH IN THE PHILADELPHIA GENERAL HOSPITAL]

Preparation of 2-Amino-4-alkylthiazoles from Esters of Substituted 2-Aminothiazyl-4-acetic Acids

BY WILLIAM M. ZIEGLER

During a search for new sulfanilamide derivatives several interesting 2-aminothiazoles have been prepared. These contain a fatty acid ester in the 4 position, and lead to 2-amino-4-alkylthiazoles by saponification and decarboxylation.

The steps involved are



The reactions proceed smoothly and good yields of 4-alkylthiazoles are obtained without the usual preparation of the intermediate alkylhaloketones. Since the latter are often hard to obtain and at best unpleasant substances to work with, a method that avoids their use is desirable.

Although 2-amino-4-thiazylacetic acid has been reported to decarboxylate at its melting point,[1] no mention is made of the decarboxylation of this type of compound at a lower temperature. Since the amines turn dark at higher temperatures very

(1) Steude, *Ann.*, **261**, 33 (1891).

rapidly, this method is rather too harsh to be generally applicable. It has been found that much milder conditions can be used to bring about the decarboxylation of the α-thiazyl acids. Heating in a slightly acid aqueous solution at 50–60° is sufficient to accomplish this. This reminds one of the decarboxylation of pyridine-2-acetic acid.[2]

The ease with which these reactions occur and the attendant good yields make this a superior method for the preparation of thiazoles substituted in the 4 position.

Experimental Part

The alkylacetoacetic ester[3] was dissolved in two volumes of carbon disulfide and cooled in ice and water. An equimolecular quantity of bromine was added in such a way that the temperature remained below 20°. The solution was stoppered and allowed to stand at room temperature for eighteen to twenty hours. It was then poured into and washed twice with cold water. After drying with sodium sulfate at 4° for one to two hours, the carbon disulfide was removed under diminished pressure, the bath temperature being kept at 35–40°. Higher temperatures on the bromoesters must be avoided if good yields are to be obtained. To the oily product was added slightly more than an equimolecular quantity of thiourea, and some ice and water. The mixture then was shaken for one to one and one-half hours. Slightly more than the calculated amount of ammonia was then added and the material chilled. The oil that first separated soon crystallized. This was removed by filtration and while moist just covered with methyl alcohol. The mixture was warmed to bring the product into solution, filtered, and chilled. The resulting mass was dissolved in hot benzene and two volumes of petroleum ether were added. The solution was then chilled and the product removed by filtration. The material was recrystallized from aqueous methyl alcohol.

Ethyl α-2-Amino-4-thiazylbutyrate.—The ester from 40 g. (0.25 mole) of ethyl ethylacetoacetate and 13.5 ml. (40 g., 0.25 mole) of bromine was shaken with 100 ml. of water, 50 g. of ice, and 20 g. (0.28 mole) of thiourea. The product resulting from the first crystallization was recrystallized twice from 50% methyl alcohol without treatment of benzene–petroleum ether. The product weighed 22.3 g. (42%) and melted at 104–105° (cor.).

Anal. Calcd. for $C_9H_{14}O_2N_2S$: N, 13.0. Found: N, 13.1, 13.1.

Ethyl α-2-Amino-4-thiazylcaproate.—The ester from 40 g. (0.22 mole) of ethyl butylacetoacetate and 11.5 ml. (34.5 g., 0.22 mole) of bromine was shaken with 70 ml. of water, 30 g. of crushed ice, and 17 g. (0.22 mole) of thiourea. The product was twice recrystallized from 70% methyl alcohol. The yield was 15 g. (33%) of material melting at 79–80.5° (cor.).

Anal. Calcd. for $C_{11}H_{18}O_2N_2S$: N, 11.3. Found: N, 11.4, 11.5.

Ethyl α-2-Amino-4-thiazylcaprylate.—The ester from 64 g. (0.3 mole) of ethyl hexylacetoacetate and 16.0 ml. (48 g., 0.3 mole) of bromine was shaken with 100 ml. of water, 60 g. of crushed ice, and 26 g. (0.35 mole) of thiourea. The product was recrystallized from 70% methyl alcohol. Thirty-five grams (45%) of material melting at 100–101° (cor.) was obtained.

Anal. Calcd. for $C_{13}H_{22}O_2N_2S$: N, 10.3. Found: N, 10.3, 10.4.

2-Amino-4-*n*-heptylthiazole and α-2-Amino-4-thiazylcaprylic Acid.—Twenty grams (0.075 mole) of ethyl α-2-amino-4-thiazylcaprylate was stirred rapidly into a solution of 8.4 g. (0.21 mole) of sodium hydroxide in 95% alcohol on a water-bath. After four minutes the material was cooled rapidly in an ice-water-bath and two volumes of ether added. The salt was removed by filtration, washed with ether and air dried one-half hour. The salt was dissolved in 75 ml. of water and 20 ml. of concd. hydrochloric acid was added. The mixture was warmed on a water-bath to 60°. After cooling the material was removed by filtration and recrystallized from pentane. The yield was 12.5 g. (85%) of material melting at 55–56.5° (cor.).

Anal. Calcd. for $C_{10}H_{18}N_2S$: N, 14.3. Found: N, 14.0, 14.1.

If the salt was dissolved in 50 ml. of water and 20 g. of ice added, then the mixture acidified with ice-cold 6 *N* hydrochloric acid, a sirup was precipitated. The aqueous material was decanted and the sirup mixed with methyl alcohol. The material slowly went into solution and a crystalline product precipitated out. This was removed by filtration and washed with cold methyl alcohol. The product melted, but not sharply, at about 125° with decomposition. The yield was 70%.

Anal. Calcd. for $C_{11}H_{19}O_2N_2S$: N, 11.3. Found: N, 11.6, 11.8.

Dissolving the acid in methyl alcohol at 38° and cooling to recrystallize it did not improve the product. At temperatures higher than 38° in methanol considerable carbon dioxide was evolved.

2-Amino-4-*n*-amylthiazole.—When 5 g. (0.02 mole) of ethyl α-2-amino-4-thiazylcaproate was treated with 2.5 g of sodium hydroxide, decarboxylated and isolated as described for the 2-amino-4-*n*-heptylthiazole, 2.3 g. of product (68%) melting at 45–46° (cor.) was obtained.

Anal. Calcd. for $C_8H_{14}N_2S$: N, 16.5. Found: N, 16.3, 16.4.

2-Amino-4-*n*-propylthiazole.—Ten grams (0.047 mole) of ethyl α-2-amino-4-thiazylbutyrate was treated with 6 g. of sodium hydroxide, and decarboxylated at 60° as described above. The solution was chilled and made ammoniacal, then extracted with ether. After removal of the ether an oil remained which solidified when it was chilled and seeded with a crystal of 2-amino-4-*n*-amylthiazole. The product weighed 5.2 g. (78%) and melted at 25–26°. Recrystallization from pentane containing 10% ether gave a product melting at 27–27.5° (cor.).

Anal. Calcd. for $C_6H_{10}N_2S$: N, 19.7. Found: N 19.3, 19.5.

(2) Oparina, *Khim. Park. Prom.*, No. 2, 98–101 (1936); *C. A.*, **30**, 1789 (1936).

(3) Gilman, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York, N. Y., 1932, p. 243.

Other Reactions.—None of the three esters would react with *p*-acetaminobenzenesulfonyl chloride when treated with that reagent in acetone, in pyridine at 100°, or in quinaldine at 175°. The major part of the ester was recovered in every case.

α-2-Amino-4-thiazylcaprylic acid did not react with *p*-acetaminobenzenesulfonyl chloride in aqueous sodium hydroxide. 2-Amino-4-*n*-heptylthiazole was recovered from this reaction.

With 2-amino-4-*n*-heptylthiazole, 2-amino-4-*n*-amylthiazole and 2-amino-4-*n*-propylthiazole, *p*-acetaminobenzenesulfonyl chloride reacts normally giving products melting at 166–167°, 163–164° and 182–183° (cor.), respectively.

Anal. Calcd. for $C_{18}H_{25}O_3N_3S_2$: N, 10.7. Found: N, 10.5. Calcd. for $C_{16}H_{21}O_3N_3S_2$: N, 11.4. Found: N, 11.2. Calcd. for $C_{14}H_{17}O_3NS$: N, 12.4. Found: N, 12.4.

Summary

The preparation of some new ethyl α-alkyl-2-amino-thiazyl-4-acetates has been reported.

A method for the conversion of these esters to 2-amino-4-alkythiazoles has been described.

PHILADELPHIA, PENNSYLVANIA RECEIVED APRIL 18, 1941

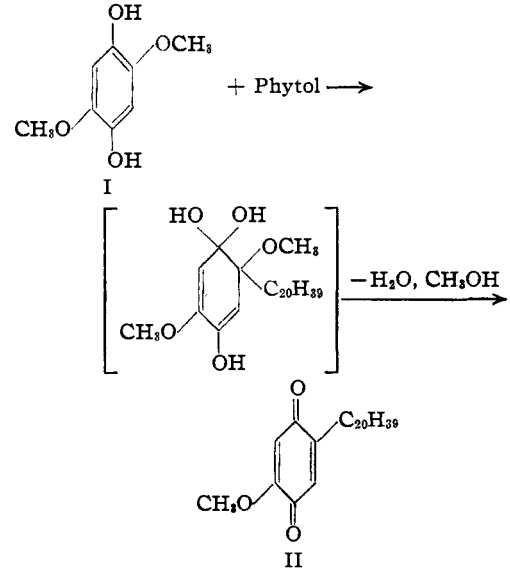
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Condensation of Allylic Alcohols with Hydroxyhydroquinones

BY LOUIS F. FIESER AND MARSHALL D. GATES, JR.

The starting point of this work was an attempt to investigate by synthesis the structure of maesaquinone, a pigment which Hiramoto[1] isolated from the fruit of a Japanese tree and which he characterized as a derivative of 2,5-dihydroxybenzoquinone with an alkenyl side chain of the composition $C_{20}H_{39}$. Since this is the composition of the phytyl radical, and since proof is still lacking of Hiramoto's reasonable postulate that the side chain is normal and not branched, 2,5-dihydroxy-3-phytylquinone would represent at least a possible structure for the pigment.

An attempted synthesis of the phytyl compound by the condensation method developed for the synthesis of vitamin K_1[2] took an unexpected course. The readily oxidizable 1,2,4,5-tetrahydroxybenzene proved to be a less promising starting material than 2,5-dimethoxyhydroquinone (I). When the latter compound was heated with phytol and oxalic acid in dioxane solution, it afforded an evident mixture of substances, but by fractional adsorption of the material in the oxidized condition on magnesium sulfate a chromatographically homogeneous product was isolated as an orange oil. This gives a positive (reddish purple) Dam–Karrer color test with alcoholic alkali, indicative of a β-alkenyl quinone, and it is convertible into a hydroquinone diacetate (liquid). Carbon-hydrogen and methoxyl determinations of the substance as such and in the form of the product of reductive acetylation clearly indicate the formula $C_{26}H_{41}O_2(OCH_3)$, rather than the expected $C_{26}H_{40}O_2(OCH_3)_2$, and therefore one methoxyl group has been eliminated. A plausible interpretation is that the reaction takes a course parallel to the formation, in the vitamin K_1 synthesis, of a by-product in which the phytyl group has affixed itself to a nuclear position already carrying a methyl substituent.[3] Thus a transient addition product or equivalent intermediate may be produced which not only can lose water from the *gem*-diol group, as in the formation of the K_1 by-product, but also suffer elimination of methanol to afford the quinone II.



The reaction may have proceeded in other directions as well, but the properties and analyses of the only substance isolated from the mixture find adequate representation in formula II.

(1) Hiramoto, *Proc. Imp. Acad.* (Tokyo), **15**, 220 (1939).

(2) Fieser, THIS JOURNAL, **61**, 3467 (1939).

(3) Tishler, Fieser and Wendler, *ibid.*, **62**, 1982 (1940).