sium permanganate, in acetone solution, results in the production of 11-(α-pyridyl)-undecanoic and 10-(α-pyridyl)-decanoic acids, the former being a pyridine analog of hydnocarpic acid.

5. By the Arndt–Eistert procedure the decanoic can be converted into the undecanoic acid.

6. The undecanoic acid is being tested at the National Institute of Health, Bethesda, Md., for possible therapeutic properties.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

Researches on Thiazoles. XXVII. A Thiazole Analog of Hydnocarpic Acid

BY FREDERICK BRODY AND MARSTON TAYLOR BOGERT

In a recent paper,[1] we described the synthesis of a pyridine analog of hydnocarpic acid and of a lower homolog. The present communication records experiments carried out in the thiazole field having as their object the synthesis of a similar compound in the thiazole group.

From the therapeutic point of view, thiazole derivatives are of considerable interest, since they have proven useful in the treatment of various diseases. Vitamin B_1 and sulfathiazole (and its derivatives) are beneficent drugs. Some thiazoles possess antimalarial activity. In combatting the tubercle bacillus, Mayer[2] found that sulfathiazole was 6–30 times more potent than sulfanilamide or sulfapyridine, and mercaptobenzothiazole was still more active. And of a large number of organic compounds studied *in vitro* by Smith, Emmart and Westfall,[3] sulfathiazole proved third in order of tuberculostatic effectiveness. Inasmuch as the tubercle bacillus is closely related to *M. leprae*, these observations are at least worthy of note.

The preparation of thiazoles carrying long carbon chains in position 2 with a terminal carboxyl group, should be attainable by oxidation of thiazoles having a suitable hydrocarbon chain in that position, but we failed to find in the literature any satisfactory method for the synthesis of such derivatives.

The reactivity of the 2-methyl group in thiazoles has been tested for aromatic aldehydes,[4,5] but in the pyridine series aliphatic aldehydes or ketones do not condense readily unless activated.[6] An attempt to condense *n*-heptaldehyde with 2,4-dimethylthiazole, in the presence of acetic anhydride, gave such a poor yield of 1-(4-methyl-2-thiazolyl)-octene-1 that further experimentation along that line was discontinued.

The alkylation of the 2-methyl group, therefore, was undertaken with alkyl chlorides, as described by Chichibabin[7] for pyridines and used successfully by us[1] in that series. 2-Methyl- and 2,4-dimethyl-thiazole were used with undecylenyl, lauryl and cetyl chlorides, with or without benzene as diluent, and in the presence of commercial sodamide. The reactions were allowed to proceed at room temperature for several days. The product was mainly a tar, from which a yield of 10–14% of an oil could be distilled giving a crude picrate. But no pure products could be isolated.

The procedure finally adopted is shown by the Flow Sheet. Ethyl undecylenylcyanoacetate (II), from ethyl cyanoacetate and undecylenyl iodide (I) in the presence of potassium carbonate,[8] was converted into the thioamide (III) by the action of hydrogen sulfide. Since hydrogen sulfide does not add easily to higher aliphatic nitriles under ordinary conditions, the method of Ralston, Van der Wal and McCorkle[9] was tried, but the high temperature required led to considerable resinification. Using triethanolamine as catalyst, however, following the experience of Olin and Johnson,[10] a satisfactory yield of thioamide was obtained, provided that the catalyst was used in adequate amount, the stream of hydrogen sulfide was continued long enough, and the temperature was maintained at 25–60°.

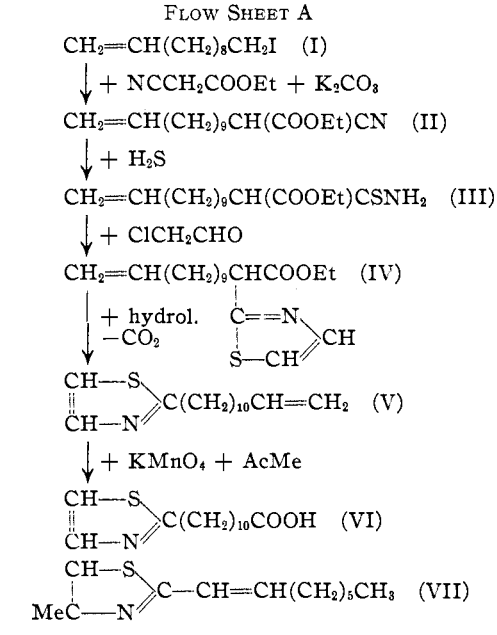
Condensation of the thioamide with chloroacetaldehyde hydrate, in benzene solution, resulted in hydrolysis of the ester and elimination of

(1) Brody and Bogert, THIS JOURNAL, **65**, 1075 (1943).
(2) Mayer, *Rév. Méd. France*, 3 (1941); *C. A.* **36**, 5199 (1942).
(3) Smith, Emmart and Westfall, *J. Pharmacol.*, **74**, 163 (1942).
(4) Kondo and Nagasawa, *J. Pharm. Soc. Japan*, **57**, 909 (1937); *C. A.*, **32**, 1699 (1938).
(5) Mills and Smith, *J. Chem. Soc.*, **121**, 2724 (1922).
(6) McElvain and Johnson, THIS JOURNAL, **63**, 2213 (1941).
(7) Chichibabin, *Bull. soc. chim.*, **3**, 1607 (1936).
(8) Robinson, *J. Chem. Soc.*, **125**, 226 (1924).
(9) Ralston, Van der Wal and McCorkle, *J. Org. Chem.*, **4**, 68 (1939).
(10) Olin and Johnson, *Rec. trav. chim.*, **50**, 72 (1931).

carbon dioxide, with production of the 12-(2-thiazolyl)-dodecene-1 (V). The reactions (I) to (V), inclusive, thus offer a process for preparing thiazoles with long aliphatic side chains in position 2.

Oxidation of the dodecene (V) by potassium permanganate in acetone solution gave the low-melting amphoteric 11-(2-thiazolyl)-undecanoic acid (VI) sought.

FLOW SHEET A



Acknowledgments.—To Mr. Saul Gottlieb of these Laboratories, we are indebted for the analytical results recorded. Through the courtesy of Dr. W. A. Gibbons, the U. S. Rubber Company generously supplied us with five pounds of Captax (commercial 2-mercaptobenzothiazole), for use in this or related lines of thiazole research.

Experimental

All melting points recorded, unless otherwise stated, have been corrected for exposed stem. The thermometers used were calibrated against a set of total-immersion Bureau of Standards thermometers.

Undecylenyl iodide (I) was prepared from the corresponding chloride by the Finkelstein method,[11] as follows.

A solution of 90.5 g. (0.48 mole) of undecylenyl chloride in 550 cc. of dry acetone, mixed with 78.1 g. (0.52 mole) of sodium iodide, was refluxed for twelve hours. The crude product, recovered in the usual way, was distilled at 1 mm. pressure. The first fraction, amounting to 53.6 g., b. p. up to 92°, and $n^{25}D$ 1.4682, contained unchanged undecylenyl chloride. A second fraction was then taken at 92°, amounting to 58.7 g., $n^{25}D$ 1.4937, and was the practically pure iodide. The first fraction, therefore, was refluxed again for nine hours, after adding 300 cc. of dry acetone and 50 g. (0.33 mole) of sodium iodide, and an additional 63.6 g. of the organic iodide was obtained, b. p. 104° (2 mm.), $n^{25}D$ 1.4937, making a total yield of 122 g., or 91%.

Anal. Calcd. for $C_{11}H_{21}I$: C, 47.2; H, 7.6. Found: C, 47.6; H, 7.7.

As a trace of iodine was liberated during the distillation, an analytically pure product was difficult to secure.

Ethyl *alpha*-(11-Undecylenyl)-cyanoacetate (II).—The method of Robinson,[8] which is especially adapted to higher iodides, was followed, except that the cyanoacetate was isolated, instead of being used in the crude state, for further work.

A mixture of 29.4 g. (0.26 mole) of cyanoacetic ester, 35.6 g. (0.13 mole) of undecylenyl iodide, and 16.6 g. (0.12 mole) of anhydrous potassium carbonate was refluxed for seven hours at 18–20 mm., in an oil-bath whose temperature was raised from 130 to 150° as rapidly as the ebullition permitted. The b. p. of the mixture rose steadily during this period. The mixture when cold was poured into ice water, extracted with ether, the extract washed with water, dried over magnesium sulfate, and distilled. The product boiled at 142–144° (1 mm.), and showed $n^{25}D$ 1.4493; yield, 28.2 g., or 83%.

Anal. Calcd. for $C_{16}H_{27}O_2N$: C, 72.4; H, 10.3. Found: C, 72.7; H, 10.0.

Ethyl 11-Undecylenyl-thiomalonamate (Undecylenyl-carbethoxythioacetamide) (III).—Into a solution of 85 g. (0.32 mole) of ethyl undecylenylcyanoacetate, 18 g. (0.12 mole) of triethanolamine (4), and 500 cc. commercial absolute alcohol, dry hydrogen sulfide was bubbled for one week, six days at room temperature and the last day at 50°. The reaction mixture was then poured upon ice, the precipitated cake recrystallized from aqueous alcohol, dried and crystallized finally from petroleum ether, giving white needles, m. p. 63.5–64°; yield, 62.8 g. or 66%.

Anal. Calcd. for $C_{16}H_{29}O_2NS$: C, 64.2; H, 9.8. Found: C, 64.3; H, 9.9.

12-(2-Thiazolyl)-dodecene-1 (V).—A mixture of equimolecular amounts of chloroacetal and anhydrous oxalic acid was refluxed for two hours, and from this mixture there was then distilled 11.3 g. (0.13 mole) of chloroacetaldehyde hydrate directly into a reaction flask in which was then placed 24 g. (0.08 mole) of the thioamide (III) and 75 cc. of benzene. The mixture was gently warmed and a vigorous reaction set in when the temperature reached about 70°, accompanied by the evolution of carbon dioxide. Refluxing was continued as long as carbon dioxide was evolved (usually about fifteen hours). Water was then added, the mixture made alkaline, extracted with benzene, and the benzene extract distilled, yielding a fraction b. p. 135–142° (4 mm.), which was purified through its picrate. The thiazole base, regenerated from its picrate by a 10% sodium carbonate solution, yielded 12.7 g. of the dodecene, or a 63% yield based on the amount of thioamide used. It was a colorless liquid, with a faint thiazole-type odor, b. p. 127° (1 mm.), and $n^{25}D$ 1.4924.

Anal. Calcd. for $C_{15}H_{25}NS$: C, 71.7; H, 10.0 Found: C, 71.8; H, 10.2.

Picrate.—Yellow plates from alcohol, m. p. 91–92°,

(11) Finkelstein, *Ber.*, **43**, 1528 (1910).

Anal. Calcd. for $C_{21}H_{28}O_7N_4S$: C, 52.5; H, 5.8. Found: C, 52.8; H, 6.0.

The product is therefore the dodecene (V) sought, the intermediate ester (IV) having suffered hydrolysis and loss of carbon dioxide.

11-(2-Thiazolyl)-undecanoic Acid (VI).—A solution of 2 g. (0.008 mole) of the dodecene (V) in 50 cc. of dry acetone was treated gradually with 4.7 g. (0.03 mole) of potassium permanganate at temperatures below 40°. The precipitate was filtered out, extracted with a 10% sodium carbonate solution, the extract concentrated and carefully acidified to obtain the maximum separation of the desired product. Inasmuch as the product was soluble in excess of acid, it was necessary to test the mother liquor with both dilute acid and dilute alkali, to ensure complete separation of the thiazole acid (VI). The oil so obtained was extracted with ether, the ether extract dried with magnesium sulfate and the ether removed. There remained a yellow viscous oil which congealed to a colorless glass in the refrigerator. Crystallization from a mixture of ethyl acetate and petroleum ether gave 1.5 g. (70% yield) of a crude product which was solid only below room temperature. Further recrystallizations yielded large colorless plates, m. p. 40-41.5°.

Anal. Calcd. for $C_{14}H_{23}O_2NS$: C, 62.4; H, 8.6. Found: C, 62.1; H, 8.6.

Picrate.—This was prepared in ether solution and was purified by crystallization from ethyl acetate. It formed yellow needles, melting with decomposition at 100–106°.

Anal. Calcd. for $C_{20}H_{26}O_9N_4S$: C, 48.2; H, 5.3. Found: C, 48.4; H, 5.5.

1-(4-Methyl-2-thiazolyl)-octene-1 (VII).—A mixture of 5.7 g. (0.05 mole) of 2,4-dimethylthiazole, 8.7 g. (0.075 mole) of *n*-heptaldehyde and 5.1 g. (0.05 mole) of acetic anhydride was heated in a sealed tube at 240–265° for thirty hours, the product of this reaction was made alkaline, extracted with ether, and the extract dried and distilled. A fraction, b. p. 180–200° (7 mm.), was collected and converted into its picrate, of which 2.4 g. was obtained. Crystallized from alcohol, the picrate formed yellow needles, m. p. 73°.

Anal. Calcd. for $C_{18}H_{22}O_7N_4S$: C, 49.3; H, 5.1. Found: C, 49.6; H, 5.1.

Summary

1. Ethyl undecylenylcyanoacetate has been prepared from undecylenyl iodide and ethyl cyanoacetate.

2. By the addition of hydrogen sulfide to the cyanogen group of this cyanoacetate, the corresponding thioamide of the ester was obtained.

3. Condensation of the thioamide with chloroacetaldehyde hydrate, in benzene solution, resulted in hydrolysis of the ester, elimination of carbon dioxide, and production of 12-(2-thiazolyl)-dodecene-1.

4. Oxidation of this dodecene with potassium permanganate, in acetone solution, gave the desired 11-(2-thiazolyl)-undecanoic acid, a thiazole analog of hydnocarpic acid, which it is hoped to have tested pharmacologically.

5. The reactions covered in items 1, 2 and 3 above, offer a means of preparing thiazoles carrying a long aliphatic chain in position 2.

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Alkylation and Other Reactions of 9-Formylfluorene

BY WELDON G. BROWN AND BEN A. BLUESTEIN[1]

The aldehyde, 9-formylfluorene, obtained by condensing fluorene and ethyl formate,[2] behaves curiously on alkylation in that methyl sulfate reacts with the potassium salt to form the enol ether, whereas methyl iodide reacts to form 9-methylfluorene, the aldehyde group being eliminated as formate. Other alkyl halides, *viz.*, isopropyl bromide, cyclohexyl bromide and benzyl chloride, likewise yield the corresponding alkyl derivatives of fluorene with ease and in good yields.

Derivatives of enolic 9-formylfluorene are not new, the acetate, benzoate and similar compounds having been prepared by Wislicenus and coworkers,[2] but there are no previous examples in which the incoming group is attached to the carbon atom of the triad system. It can be assumed that the alkylation reactions with alkyl halides represent this second mode of reaction, complicated only by the condition that the tertiary aldehydes first formed must be sensitive to alkaline cleavage. In the synthesis of alkyl derivatives of fluorene from fluoreneoxalic ester by the method of Wislicenus,[2a] the intermediate

(1) This paper is taken from a dissertation submitted by Ben A. Bluestein to the Faculty of the Division of Physical Sciences of the University of Chicago in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, December, 1941.

(2) (a) Wislicenus and Densch, *Ber.*, **35**, 759 (1902); Wislicenus and Waldmuller, *ibid.*, **42**, 785 (1909); (c) Wislicenus and Russ, *ibid.*, **43**, 2719 (1910); (d) Wislicenus and Weitmeyer, *Ann.*, **436**, 4 (1924).