Summary

Sodium reacts with 9-methoxy-10-phenylphenanthrene in ether to give 9-phenylphenanthryl-10-sodium. This can react further with sodium to give a compound which appears to be the disodium addition product of 9-phenylphenanthrene.

1 - Diphenylene - 3 - phenylindene is converted by sodium into 1,2,3,4-dibenzo-9-phenylfluorene-9-sodium.

MINNEAPOLIS, MINN. RECEIVED NOVEMBER 8, 1933

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

The Synthesis of Thiazole Barbituric Acids. XIII

BY FLORENCE E. HOOPER[1] AND TREAT B. JOHNSON

Since Fischer and von Mering's discovery in 1903 of the hypnotic properties of 5,5-diethylbarbituric acid, great interest has been shown in the preparation and study of other 5,5 derivatives of this pyrimidine. With few exceptions,[2] however, little attention has been devoted to such derivatives in which one of the substituent groups in position 5 includes an heterocyclic configuration. In view of the prevalence of such groups in many physiologically active substances the preparation of heterocyclic substituted derivatives of barbituric acid would seem to be of considerable interest. This paper reports the synthesis of 5-ethyl-5-(2-methylthiazole-4-methyl)- and 5-ethyl-5-(2-phenylthiazole-4-methyl)-barbituric acids. A pharmacological investigation of these compounds is now in progress.

Both syntheses were readily accomplished by the condensation of the required substituted malonic esters with urea. The necessary esters were prepared by alkylation of diethyl ethylmalonate with 2-methyl-4-chloromethyl- and 2-phenyl-4-chloromethyl-thiazoles.

Experimental Part

$ClCH_2C{=}CHSC(CH_3){=}N$, **2-Methyl-4-chloromethylthiazole (I),** was prepared according to the method of Hooper and Johnson.[3]

$(C_2H_5OOC)_2C(C_2H_5)CH_2C{=}CHSC(CH_3){=}N$, **Diethyl ethyl-(2-methylthiazole-4-methyl)-malonate (II)** was prepared from diethyl ethylmalonate and I according to the usual procedure for malonic ester syntheses.[4] The product was a colorless odorless liquid, b. p. 168–174° at 4–5 mm.; yield 59%.

Anal. Calcd. for $C_{14}H_{21}O_4NS$: N, 4.68. Found: N, 4.60.

$CONHCONHCOC(C_2H_5)CH_2C{=}CHSC(CH_3){=}N$, **5-Ethyl-5-(2-methylthiazole-4-methyl)-barbituric Acid (III).**—Compound II was condensed with urea according to the method recommended by Dox and Yoder[5] for the preparation of 5-alkyl-5-benzylbarbituric acids. Upon acidification of the reaction mixture with hydrochloric acid, the desired product precipitated with the sodium chloride. The precipitate was extracted with water, dried and recrystallized from alcohol containing a little benzene. The product III was obtained in long slender needles, m. p. 264–265°; yield 63%.

Anal. Calcd. for $C_{11}H_{13}O_3N_3S$: N, 15.73. Found: N, 15.35, 15.45.

$ClCH_2C{=}CHSC(C_6H_5){=}N$, **2-Phenyl-4-chloromethylthiazole (IV).**—Efforts to prepare this thiazole halide by heating equimolecular portions of *sym*-dichloroacetone and thiobenzamide in alcohol resulted in yields far below that reported by Suter and Johnson.[6] The following procedure, however, consistently gave total yields of 75% or more. The hydrochloride, $ClCH_2COCH_2SC(C_6H_5){=}NH\cdot HCl$, was prepared by the reaction of equimolecular portions of *sym*-dichloroacetone and thiobenzamide in acetone solution,[3] 50 g. of the hydrochloride was suspended in a liter of acetone containing 40 cc. of concentrated hydrochloric acid and refluxed on the steam-bath until a clear solution was obtained. On cooling, a copious precipitate of the thiazole hydrochloride, $ClCH_2C{=}CHSC(C_6H_5){=}N\cdot HCl$, crystallized out in lustrous plates. An additional quantity of the hydrochloride was obtained as a sirup on concentration of the filtrate. On decomposition with aqueous sodium bicarbonate the hydrochloride gave a product identical with the 2-phenyl-4-chloromethyl-thiazole reported by Suter and Johnson.

$(C_2H_5OOC)_2C(C_2H_5)CH_2C{=}CHSC(C_6H_5){=}N$, **Diethyl ethyl-(2-phenylthiazole-4-methyl)-malonate (V)** was prepared from diethyl ethylmalonate, and IV according to the usual procedure for malonic ester syntheses.[4] The product was a pale yellow odorless oil, b. p. 208–211° at 4–5 mm.; yield 50%.

Anal. Calcd. for $C_{19}H_{23}O_4NS$: N, 3.88. Found: N, 3.72, 3.90.

(1) Metz Research Fellow in Organic Chemistry, 1932–1933.
(2) Taggart and Richter, THIS JOURNAL, **55**, 1110 (1933).
(3) Hooper and Johnson, *ibid.*, **56**, 470 (1934).
(4) Adams and Kamm, "Organic Syntheses," John Wiley and Sons, New York, 1933, Coll. Vol. 1, p. 245.
(5) Dox and Yoder, THIS JOURNAL, **44**, 1141 (1922).
(6) Suter and Johnson, *Rec. trav. chim.*, **49**, 1066 (1930).

$(HOOC)_2C(C_2H_5)CH_2C{=}CHSC(C_6H_5){=}N$, **Ethyl-(2-phenyl-thiazole-4-methyl)-malonic acid (VI),** was obtained by saponification of the corresponding ester with alcoholic potassium hydroxide. The acid was recrystallized from dilute alcohol, m. p. 145°.

Anal. Calcd. for $C_{15}H_{15}O_4NS$: N, 4.59. Found: N, 4.31, 4.34.

$CONHCONHCOC(C_2H_5)CH_2C{=}CHSC(C_6H_5){=}N$, **5-Ethyl-5-(2-phenyl-thiazole-4-methyl)-barbituric acid (VII),** was prepared by the condensation of the diethyl ester of VI with urea according to the method of Dox and Yoder.[5] The product was obtained by evaporation of the filtrate after acidification of the reaction mixture with hydrochloric acid. It crystallized from 1:3 benzene–alcohol in large colorless prisms of m. p. 210–211°.

Anal. Calcd. for $C_{16}H_{15}O_3N_3S$: N, 12.76. Found: N, 12.70, 12.61.

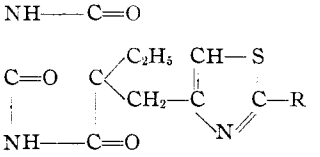
Several new thiazole compounds have also been prepared from IV. The properties of these compounds are shown in Table I.

TABLE I

2-Phenyl-4-( )-thiazole	B. p. or m.p., °C.	Formula	Nitrogen, % Calcd.	Found
Methoxymethyl-	B 116 at 1 mm.	$C_{11}H_{11}ONS$	6.82	6.89 6.71
Phenoxymethyl-	M 67–68	$C_{16}H_{13}ONS$	5.24	5.12
Thiophenoxymethyl-	M 42	$C_{16}H_{13}NS_2$	4.95	4.76 4.8

Summary

The thiazole barbituric acids represented by the formula shown below in which R = CH_3 and C_6H_5 have been prepared. These compounds are being tested pharmacologically.



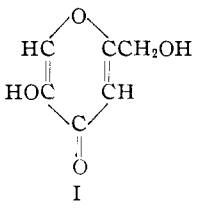
NEW HAVEN, CONN. RECEIVED NOVEMBER 8, 1933

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

The Synthesis of 5-β-d-Glucosidokojic Acid[1]

BY RAYMOND M. HANN

The production of kojic acid (2-hydroxymethyl-5-hydroxy-1,4-pyrone) I from carbohydrates by molds of the Aspergillus group[2] has made the compound readily available. This biological synthesis has been stimulated by the chemical synthesis of the diacetate of this acid from the hydrates of the tetraacetates of glucosone[3] and galactosone.[4] Evidently kojic acid can become the starting material for many syntheses.



I

Kojic acid should be capable of forming many types of glucosides through its possession of both phenolic and aliphatic hydroxyl groups. No glucoside of kojic acid has so far been found in nature.

In the present research a glucoside was prepared synthetically by condensation of the potassium salt of kojic acid with acetobromoglucose following the procedures of Michael and of Königs and Knorr. The operation yielded crystalline 5-(tetraacetyl-β-d-glucosido)-kojic acid (m. p. 201°, $[\alpha]_D^{20}$ −88.3° in $CHCl_3$), from which the crystalline free glucoside (m. p. 198°, $[\alpha]_D^{20}$ −107.3° in H_2O) was obtained by deacetylation with sodium methylate.

This synthetic substance is of the same type as the naturally occurring salicin, arbutin and coniferin, all being β-glucosides in which the sugar is combined with a phenolic hydroxyl group; it is therefore a glucoside of kojic acid which might be expected by analogy to exist in nature.

Experimental

5-β-Tetraacetyl-d-glucosidokojic Acid (2-Hydroxymethyl-5-β-tetraacetyl-d-glucosido-1,4-pyrone).—To a solution of 27.5 g. of glucose pentaacetate in 25 cc. of chloroform was added 75 cc. of glacial acetic acid saturated with dry hydrogen bromide gas and the solution allowed to stand for one hour.

The acid solution was transferred to a separatory funnel with 100 cc. of chloroform and 200 cc. of ice water. The chloroform solution was separated and the aqueous portion extracted successively with 100 cc. of ice water, 200 cc. of ice cold 2% sodium bicarbonate solution and then twice with 100 cc. of water. To this solution was now added a solution of 11 g. of kojic acid (10% excess) dissolved in 81.4 cc. of 0.865 *N* alcoholic potash. An oil which precipitated was carried into solution by addition of 50 cc. of 95% alcohol and the combined solutions refluxed for one-half hour, when potassium bromide precipitated. The solution was cooled, 1 liter of water added and the solution extracted five times with successive por-

(1) Publication authorized by the Surgeon General, U. S. Public Health Service.

(2) May, Moyer, Wells and Herrick, THIS JOURNAL, **53**, 774 (1931).

(3) Maurer, *Ber.*, **63**, 25 (1930).

(4) Maurer and Möller, *ibid.*, **63**, 2069 (1930).