

Summary

The syntheses of 8-(6-allylaminohexylamino)-6-methoxyquinoline and 8-(6-diallylaminohexylamino)-6-methoxyquinoline are reported.

N-Allyl-6-methoxyhexylamine, N,N-diallyl-6-

methoxyhexylamine, N-(6-bromohexyl)-allylammonium bromide, and N-6-(bromohexyl)-diallylammonium bromide were prepared as intermediates in this work.

EVANSTON, ILLINOIS

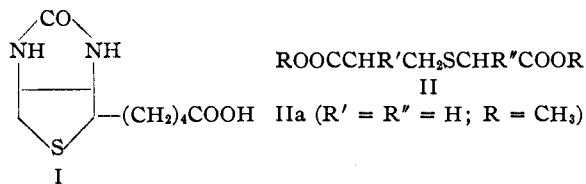
RECEIVED AUGUST 8, 1946

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Tetrahydrothiophene ("Thiophane") Derivatives

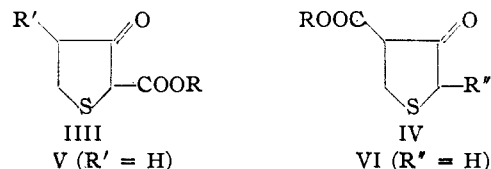
BY R. B. WOODWARD AND R. H. EASTMAN

The elucidation of the structure of biotin (I)¹ has stimulated interest during the past several years in the development of methods useful in the synthesis of tetrahydrothiophene ("thiophane") derivatives. The application of the Dieckmann reaction to compounds of the general structure (II) has received particular attention



and in a specific case² (II, R = CH₃ or C₂H₅, R' = -NHCOC₆H₅, R'' = H) constituted an important step in the brilliant series of reactions which culminated in the total synthesis of natural biotin^{2,3} in this country, while another example⁴ (II, R = C₂H₅, R' = H, R'' = -(CH₂)₄OCH₃) played an equally important role in the total synthesis of *dl*-biotin abroad.⁵

In those cases in which R' or R'' is not a hydrogen atom, cyclization can take place in one direction only, with the formation of (III)^{2,6} or (IV),^{4,7,8} respectively. On the other hand, *a priori* the cyclization of the unsubstituted ester (II, R' = R'' = H) can take place in two ways, with the formation of the cyclic β -keto esters (V) and (VI). Karrer and Schmid,⁹ Buchman and Cohen,¹⁰



Avison, Bergel, Cohen, and Haworth,⁸ and the present authors¹¹ have studied the cyclization in this simplest case. The Swiss workers effected internal condensation of (II, R = C₂H₅, R' = R'' = H) by means of sodium amide in absolute ether, or sodium ethoxide in toluene, in each case at 40–50°. They considered the product to be mainly 4-carbomethoxy-3-ketotetrahydrothiophene (VI, R = C₂H₅), since on methylation, hydrolysis, and decarboxylation, there was obtained 4-methyl-3-ketotetrahydrothiophene, different from the isomeric 2-methyl-3-ketotetrahydrothiophene synthesized by an unambiguous route. On the other hand, the isolation from the cyclized ester of two phenylhydrazones, m.p. 142 and 167°, of which the lower-melting isomer predominated, led to the conclusion that the material was a mixture.^{7a} Buchman and Cohen cyclized the di-ester (II, R = C₂H₅, R' = R'' = H) by means of sodium metal in benzene suspension. The product was described as giving a phenylhydrazone, m.p. 100°, and a semicarbazone, m.p. 176°, and was assigned the structure (VI) on the basis of analogies drawn from work on the Dieckmann condensation of nitrogen-containing esters. Avison, Bergel, Cohen and Haworth, likewise using powdered sodium in benzene, brought forward evidence in support of the view that the major product of the cyclization of esters (II, R' = R'' = H) was always the 2-carbalkoxy derivative (V).

In this communication it is shown that the direction of cyclization may be controlled by the choice of reaction conditions. After some preliminary experiments with the ethyl ester (II, R = C₂H₅, R' = R'' = H), we confined our studies to the methyl ester (IIa), which was obtained smoothly in excellent yield by the piperidine-catalyzed addition of methyl thioglycolate to methyl acrylate.¹² When the ester (IIa) was cyclized by

(11) Our results formed the subject of a preliminary communication, *THIS JOURNAL*, **66**, 849 (1944).

(12) Buchman and Cohen (ref. 10) independently devised a similar method for the preparation of the corresponding ethyl ester.

(1) du Vigneaud, *Science*, **96**, 455 (1942); Hofmann, Kilmer, Melville, du Vigneaud and Darby, *J. Biol. Chem.*, **145**, 503 (1942); du Vigneaud, Melville, Folkers, Wolf, Mozingo, Keresztesy and Harris, *ibid.*, **146**, 475 (1942); Melville, Moyer, Hofmann and du Vigneaud, *ibid.*, **146**, 487 (1942); Hofmann, *Advances in Enzymol.*, **3**, 289 (1943).

(2) Harris, Easton, Heyl, Wilson and Folkers, *THIS JOURNAL*, **66**, 1757 (1944).

(3) Harris, Wolf, Mozingo and Folkers, *Science*, **97**, 447 (1943); Harris, Wolf, Mozingo, Anderson, Arth, Easton, Heyl, Wilson and Folkers, *THIS JOURNAL*, **66**, 1756 (1944); Harris, Wolf, Mozingo, Arth, Anderson, Easton and Folkers, *ibid.*, **67**, 2096 (1945); Wolf, Mozingo, Harris, Anderson and Folkers, *ibid.*, **67**, 2100 (1945).

(4) Schmid, *Helv. chim. acta*, **27**, 127 (1944).

(5) Grüssner, Bourquin and Schneider, *ibid.*, **28**, 517 (1945).

(6) Karrer and Schmid, *ibid.*, **27**, 1280 (1944).

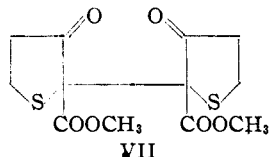
(7) (a) Karrer and Schmid, *ibid.*, **27**, 124 (1944); Karrer and Keller, *ibid.*, **27**, 142 (1944); Karrer, Keller and Usteri, *ibid.*, **27**, 237 (1944); (b) Cheney and Plening, *THIS JOURNAL*, **66**, 1040 (1944).

(8) Avison, Bergel, Cohen and Haworth, *Nature*, **154**, 459 (1944).

(9) Karrer and Schmid, *Helv. Chim. Acta*, **27**, 116 (1944).

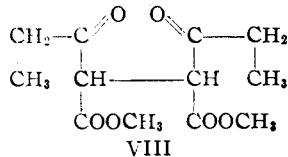
(10) Buchman and Cohen, *THIS JOURNAL*, **66**, 247 (1944).

the action of sodium methoxide in dry ether at room temperature, there was obtained on fractionation an oil, b.p. 114.5° (8 mm.). This material gave, in alcohol solution, a transient red-violet coloration with ferric chloride, and it rapidly decolorized iodine. On titration with ferric chloride, until the color persisted, or with iodine until the reagent was no longer consumed, there was obtained a nicely crystalline solid, C₁₂H₁₄O₆S₂, m.p. 182–184°.¹³ In the manner described below, this oxidation product was shown to have the structure (VII). It was clear that this ma-

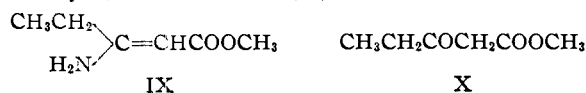


terial had been derived from 2-carbomethoxy-3-ketotetrahydrothiophene (V, R = CH₃), and the amount obtained demonstrated that the initial condensation product had consisted of at least 75–80% of the 2-substituted isomer. From a sample of the condensation product from which the 2-carbomethoxy-3-ketotetrahydrothiophene had been removed by selective oxidation, it was possible to isolate a small quantity of the isomeric 4-carbomethoxy-3-ketotetrahydrothiophene (VI, R = CH₃), which is described in detail below. It is the latter substance which is responsible for the transient ferric reaction described above, which persists only when an excess of ferric ions over that which is reduced by the 2-substituted isomer is added. These circumstances provide a very sensitive test for the presence of 2-carbalkoxy-3-ketotetrahydrothiophene in mixtures containing the 4-substituted isomer.

The oxidation product, C₁₂H₁₄O₆S₂, on treatment with Raney nickel in methanol solution, was desulfurized with the formation of α,β -dipropionyl succinate (VIII), m.p. 125–126°, the structure of which was proven by synthesis.

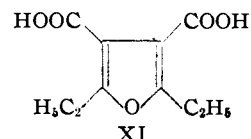


Methyl cyanoacetate, on condensation with ethylmagnesium iodide, gave methyl β -amino- β -ethyl-acrylate (IX), from which, on hydrolysis, methyl β -ketovalerate (X) was obtained. The

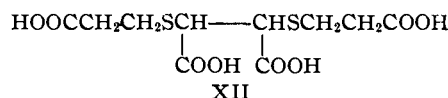


(13) It is worthy of note that the compound C₁₄H₁₈O₆S₂, obtained by Schmid⁴ by treating a material supposed by him to be largely the 4-substituted ester (VI, R = C₂H₅) with sodium nitrite in acetic acid was undoubtedly the diethyl ester corresponding to (VII), and that the formation of this substance furnishes positive evidence of the presence of the 2-carboxy derivative (V, R = C₂H₅) in the cyclization products obtained by the Swiss workers.^{4,14}

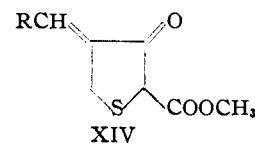
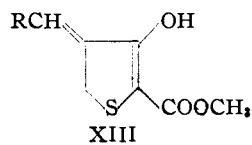
sodium derivative of the latter, on treatment with iodine, gave dimethyl α,β -dipropionyl succinate (VIII), m. p. 125–126°, which was identical in all respects with the product from the desulfurization of (VII). The ester from either source, when boiled with dilute sulfuric acid, was converted to 2,5-diethylfuran-3,4-dicarboxylic acid (XI), m.p. 153–154°.



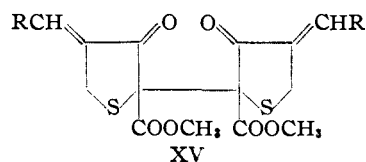
These facts provide unequivocal proof of the structure of the oxidation product (VII). In the course of a correlative line of investigation there was obtained from (VII) by hydrolytic degradation a substance, m.p. 137–140°, which was very probably the dihydrate of the acid (XII), but in view of the successful outcome of the structure proof described above, the acid was not further investigated.



From the low-temperature condensation product, which was shown in the above manner to consist mainly of 2-carbomethoxy-3-ketotetrahydrothiophene (V, R = Me), a number of derivatives of the latter were obtained. The semicarbazone melted at 187–187.5°. By condensation with benzaldehyde, and with furfuraldehyde, in the presence of piperidine, the yellow-orange enolic benzylidene derivative (XIII, R = C₆H₅), m.p. 129–130°, and the orange enolic furfurylidene derivative (XIII, R = C₄H₃O), m.p. 139–140°, were obtained. The definite assignment of the



enolic structures (XIII), rather than the alternative ketonic structures (XIV), to these derivatives was made on the basis of their pronounced colors. Thus, the chromophoric system present in (XIV) is the same as that in the colorless double compounds (XV), one of which (XV, R = C₆H₅), m.p. 236°, was obtained by the condensation of (VII) with benzaldehyde in the presence of piperidine, while another (XV, R = C₄H₃O), m.p.

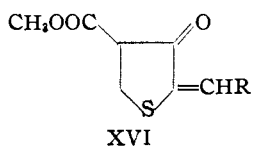


232°, was obtained by the oxidation of (XIII, R = C₄H₃O) by ferric salts [cf. (V, R = CH₃ → VII)].

In accord with their enolic nature, the substances (XIII) dissolved readily in dilute ammonia to give deep red solutions.

We observed further that the keto-ester (V, R = CH₃) was relatively easily cleaved. For example, on boiling the ester for twenty hours with methanol containing a few drops of piperidine, quantitative transformation to α,β' -dicarbomethoxymethyl ethyl sulfide (III) took place, while the 4-substituted ester (VI, R = CH₃) was substantially unchanged by the same treatment. It seems likely that this ready cleavage accounts for the fact that in alkylation experiments on what was undoubtedly a mixture of (V, R = C₂H₅) and (VI, R = C₂H₅) Karrer and Schmid⁹ isolated only derivatives alkylated at the 4-position. In that connection, we did not obtain smooth alkylation of (V, R = CH₃); Avison, Bergel, Cohen and Haworth⁸ indicate, with details, that alkylation is possible, but express preference for the preparation of 2-alkylated derivatives by the direct and unambiguous cyclization of esters of the type (II, R' = H).

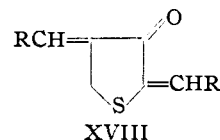
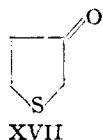
When the ester (IIa) was cyclized by the action of sodium methoxide in dry toluene at 80–120°, the main product of the reaction was the crystalline 4-carbomethoxy-3-ketotetrahydrothiophene (VI, R = CH₃), m.p. 37–38°. Although the oil, b.p. 128.5° (20 mm.), obtained directly from the reaction mixture by fractionation did not crystallize completely,¹⁴ it contained *no* 2-carbomethoxy-3-ketotetrahydrothiophene (V, R = CH₃), since it gave a permanent red-violet coloration with ferric chloride, and did not decolorize iodine. The pure crystalline β -keto-ester (VI, R = CH₃) gave, in alcohol, a permanent red-violet coloration with ferric chloride, and was characterized as the semicarbazone, m.p. 189.5–190°. On condensation with benzaldehyde, and furfuraldehyde, in the presence of piperidine, it gave the pale yellow benzylidene derivative¹⁵ (XVI, R = C₆H₅), m.p. 158–159°, and the deep yellow furfurylidene derivative¹⁶ (XVI, R = C₄H₃O), m.p. 157–158°.



Either of the isomeric β -keto-esters (V, R = CH₃) or (VI, R = CH₃), on hydrolysis with boiling dilute sulfuric acid, gave in good yield 3-ketotetrahydrothiophene (XVII), b.p. 74.5° (15 mm.). The ketone condensed with benzaldehyde, and with furfuraldehyde, in the presence of piperidine, to give the yellow dibenzylidene derivative

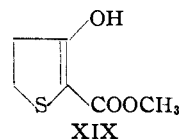
(14) The failure of the oil to crystallize completely may be a consequence of the fact that it was a mixture of the enol and keto forms of (VI, R = CH₃). This was the explanation adduced by Bennett and Scoriah [*J. Chem. Soc.*, 194 (1927)] to explain similar behavior in the closely related case of 3-carbomethoxy-4-ketopenthiene.

(15) We have not established, as we did in the case of the isomeric derivatives (XIII), whether these compounds are enolic or ketonic.

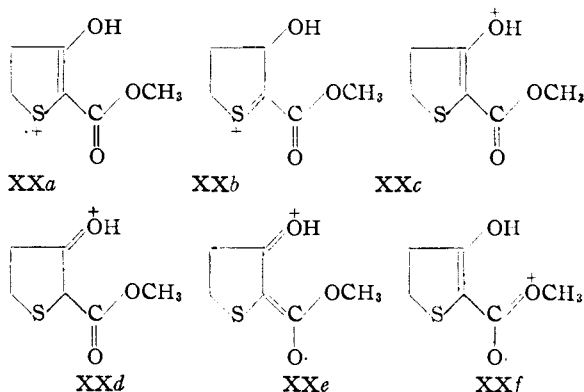


(XVIII, R = C₆H₅), m.p. 187.5°, and the brick red difurfurylidene derivative (XVIII, R = C₄H₃O), m.p. 193°. The ketone gave no color with ferric chloride, nor was it oxidized readily by that reagent, or by iodine.

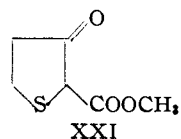
We turn now to a consideration of the circumstances responsible for the remarkably facile oxidation of 2-carbomethoxy-3-ketotetrahydrothiophene (V, R = CH₃). We attribute this behavior to the possibility that the enol (XIX), on loss of an



electron from, say, the sulfur atom, may give a fragment with considerable possibilities for stabilization by electron distribution (*cf.* XXa \leftrightarrow XXb \leftrightarrow



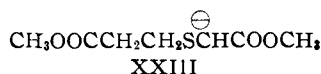
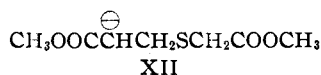
XXc \leftrightarrow XXd \leftrightarrow XXe \leftrightarrow XXf), and that further, the charged fragment (XXa, *etc.*) on loss of a proton, concurrently or stepwise, may give a new species (XXI, and other forms), the dimerization of which to the observed product (VII) needs no further comment. The reaction thus bears a



formal similarity to the facile oxidation of simple sulfhydryl compounds, *viz.*, RSH \rightarrow RSH⁺ \rightarrow RS⁺ \rightarrow RSSR, and it seems probable that, in general, sulfur compounds will be subject to dimeric oxidation in the event that a simple electronic path exists which permits the ready loss of a proton from the positively charged fragment left on removal of one electron by an external oxidizing agent.

In conclusion, we should like to call attention

to the theoretical implications of the results obtained in the study of the cyclization of (IIa). It has been considered that the sulfur atom in the system —S—C— has a considerable proton-releasing effect on the attached carbon atom.^{16,17} The origin of this effect is not entirely clear. Since it appears to be stronger than that exerted by an oxygen atom in a similar position, it is unlikely that the explanation lies simply in the (relatively low) electronegativity of the sulfur atom. The possibility may be considered of anion stabilization through forms such as —S=C— .¹⁷ A decision in the matter must be deferred until a definitive answer is forthcoming to the involved question of the ability of sulfur to accommodate more than eight electrons in its valence shell.¹⁸ In any event our results provide further evidence for the reality of the effect, in that the observed course of the reactions suggests strongly that of the two possible intermediary anions, (XXII) and (XXIII), the latter is the more probable. Con-



sequently, (XXIII) is formed more rapidly, and the cyclization product (V, R = CH₃) derived from it is the one which predominates when the reaction is run at low temperatures, under non-equilibrium conditions. At higher temperatures, however, when the reaction is allowed to proceed to equilibrium, a point ultimately is reached at which the isomer (VI, R = CH₃), formed through the intercession of the relatively improbable anion (XXII), is the sole product.

Experimental

α -Carboxy- β' -carbomethoxymethylethyl Sulfide.—Ethyl β -bromopropionate (10 g.) was added all at once to dry disodium thioglycolate prepared from thioglycolic acid (4.6 g.) and sodium methoxide in methanol (50 cc.) followed by removal of solvent at the water-pump. After the initial vigorous reaction, the pasty reaction mixture was warmed on the steam-bath for one-half hour, then poured into excess 5% aqueous sodium hydroxide. The alkaline solution, after being extracted with ether, was acidified with hydrochloric acid, and the heavy oil which separated taken out in ether. The dried ethereal extract was freed from solvent, and the residual oil on being distilled yielded α -carboxy- β' -carbomethoxymethylethyl sulfide (6.6 g.), a heavy oil of b. p. 168–170° (3 mm.).

Neut. equiv. Calcd. for C₇H₁₂O₄S: 192. Found: 193.

This material was esterified (ethanol-sulfuric acid) to α, β' -dicarbomethoxymethylethyl sulfide, an oil of b. p. 121–123° (3 mm.), and the latter compound was hydrolyzed

with hydrochloric acid in glacial acetic acid (an attempted alkaline hydrolysis was unsuccessful) to β -mercaptopropionic acid-S-acetic acid of m. p. 93.6–94°; reported¹⁹ m. p. 94°.

Neut. equiv. Calcd. for C₆H₈O₄S: 82.1. Found: 82.9.

α, β' -Dicarbomethoxymethylethyl Sulfide (IIa).—To a stirred solution of methyl thioglycolate (53 g.) and piperidine (0.5 cc.), methyl acrylate (45 g.) was added during forty-five minutes, while maintaining the reaction mixture at 40–50° by external cooling. During the reaction more piperidine (total of 1 cc.) was added in portions. After the acrylate had been added, the reaction mixture was warmed to 50° for a few minutes, filtered to remove a small amount of solid, washed with water, and dried over sodium sulfate. The dried oil on being distilled yielded α, β' -dicarbomethoxymethylethyl sulfide (75 g.), a viscous oil of b. p. 111–112° (2 mm.), 141–142° (13 mm.).

For hydrolysis, the diester (1.0 g.) was boiled with glacial acetic acid (10 cc.) containing concentrated hydrochloric acid (ten drops) for twelve hours. After removal of volatile products of hydrolysis at the aspirator, the oily residue crystallized in prisms (0.40 g.) on being cooled. Two crystallizations from methyl acetate-benzene yielded pure β -mercaptopropionic acid-S-acetic acid of m. p. 93.4–94°. The mixed melting point with a sample prepared as described above was 93.6–94°.

4-Carbomethoxy-3-ketotetrahydrothiophene (VI, R = CH₃).—To a stirred solution of sodium methoxide (65 g.) in dry toluene (3.5 liters) heated to 80°, α, β' -dicarbomethoxymethyl ethyl sulfide (96 g.) was added rapidly. The resulting massive, white precipitate dissolved as the reaction mixture was stirred and held at 80° for one hour. Additional diester (96 g.) was added during twenty minutes at this point, and then the reaction mixture was heated to the boiling point and toluene-methanol mixture (200 cc.) was distilled from it during four hours. When cold, the reaction mixture was decomposed with concentrated hydrochloric acid (100 g.) in ice-water (1 liter). The toluene layer was separated and three ether extracts of the aqueous layer were added to it. The combined extracts were dried, the solvents were removed at reduced pressure, and the residue distilled through a 2-ft. Podbielniak column. The main fraction was 4-carbomethoxy-3-ketotetrahydrothiophene (79 g.), b. p. 128.5° (20 mm.), 122° (10 mm.), 109° (4 mm.). When the distillate was cooled, solid 4-carbomethoxy-3-ketotetrahydrothiophene (48 g.) separated.¹⁴ After being twice crystallized from petroleum ether, the material separated as white cubes of m. p. 37.8°.

Anal. Calcd. for C₆H₈O₃S: C, 45.1; H, 5.00; S, 20.0. Found: C, 44.3; H, 5.21; S, 19.8.

Derivatives of 4-Carbomethoxy-3-ketotetrahydrothiophene.—The derivatives described below were prepared in comparable yield from either solid 4-carbomethoxy-3-ketotetrahydrothiophene or from the oil from which the solid separated (see above).

Semicarbazone.—4-Carbomethoxy-3-ketotetrahydrothiophene (0.5 g.) was treated in aqueous (3 cc.) methanol (8 cc.) with semicarbazide hydrochloride (0.33 g.) and sodium acetate (0.25 g.). Within five minutes at room temperature, the semicarbazone (0.5 g.) separated. Two crystallizations from methanol yielded the pure compound as fine white needles, m. p. 189.5–190°.

Anal. Calcd. for C₇H₁₀O₃N₂S: C, 38.7; H, 5.11; N, 19.3. Found: C, 39.1; H, 4.70; N, 19.1.

2-Benzylidene-4-carbomethoxy-3-ketotetrahydrothiophene (XVI, R = C₆H₅).—Two drops of piperidine were added to a solution of 4-carbomethoxy-3-ketotetrahydrothiophene (0.25 g.) and benzaldehyde (0.5 g.) warmed on the steam-bath. After fifteen minutes the clear, red reaction mixture deposited crystals when it was cooled and scratched. Two crystallizations from glacial acetic acid yielded the pure derivative (0.2 g.) as very faintly yellow plates of m. p. 158–159°.

Anal. Calcd. for C₁₃H₁₂O₃S: C, 62.9; H, 4.84. Found: C, 62.7; H, 5.2.

(19) Lovén, *Ber.*, **29**, 1140 (1896).

(16) Gilman and Webb, *THIS JOURNAL*, **62**, 987 (1940).

(17) Rothstein, *J. Chem. Soc.*, 1550, 1553, 1558 (1940).

(18) Pauling, "Nature of the Chemical Bond," 2nd ed., Reinhold Publishing Co., New York, N. Y., 1940, p. 239, *et seq.*; Kimball, *J. Chem. Phys.*, **8**, 188 (1940); Arndt and Martius, *Ann.*, **499**, 228 (1943); Kohler and Larsen, *THIS JOURNAL*, **57**, 1448 (1935).

2-Furfurylidene-4-carbomethoxy-3-ketotetrahydrothiophene (XVI, R = C₄H₃O).—4-Carbomethoxy-3-ketothiophane (1.60 g.) upon treatment with furfural and piperidine under the conditions described for the benzylidene derivative, yielded the 2-furfurylidene derivative (1.6 g.) of m. p. 156–158°. Twice crystallized from glacial acetic acid and sublimed *in vacuo* at 100°, the substance was obtained as fine, yellow needles of m. p. 157–158°.

Anal. Calcd. for C₁₁H₁₀O₄S: C, 55.5; H, 4.20. Found: C, 55.6, 55.5; H, 4.56, 4.28.

2-Carbomethoxy-3-ketotetrahydrothiophene (V, R = CH₃).—As pointed out in the theoretical section, 2-carbomethoxy-3-ketotetrahydrothiophene was not isolated in a pure condition, but only as the principal component (ca. 72%) of an oil the remainder of which was, at least in part, the 4-carbomethoxy isomer.

α,β' -Dicarbomethoxymethylethyl sulfide (96 g.) was added during one-half hour to a stirred suspension of sodium methoxide (41 g.) in absolute ether (200 cc.). Gentle reflux during the addition and when one-half of the diester had been added the reaction mixture set to a white paste. The pasty reaction mixture was stirred for five hours,²⁰ and then decomposed with glacial acetic acid (48 g.) in ice-water (200 cc.). The ether layer was separated, dried and freed from solvent. Distillation of the residue at reduced pressure through a 2-ft. Podbielniak column yielded the product, an oil at b. p. 114.5° (8 mm.), 112° (7 mm.).

An alcoholic solution of the product of the reaction gave, with aqueous ferric chloride, a purple color identical with that shown by 4-carbomethoxy-3-ketothiophane under the same conditions; but, in contrast to the behavior of the latter compound, the color in the case of the oil containing the 2-carbomethoxy isomer faded rapidly. The prosecution of this observation is described below under 2,2'-bis-(2-carbomethoxy-3-ketothiophanyl).

Derivatives of 2-Carbomethoxy-3-ketotetrahydrothiophene. Semicarbazone.—Under the conditions described above for the isomeric 4-carbomethoxy compound, the oil (0.5 g.) containing a preponderance of 2-carbomethoxy-3-ketotetrahydrothiophene yielded after two hours the semicarbazone (0.25 g.) as white plates. Two crystallizations from aqueous methanol yielded pure material, m. p. 187–187.5°.

Anal. Calcd. for C₇H₁₁O₃N₃S: C, 38.7; H, 5.11. Found: C, 38.8; H, 4.66.

A mixture of this material with the semicarbazone of 4-carbomethoxy-3-ketotetrahydrothiophene described above had m. p. 176–177°. The substance in sodium carbonate solution gave no color with sodium nitroprusside.

4-Benzylidene-2-carbomethoxy-3-ketotetrahydrothiophene (XIII, R = C₆H₅).—Under the conditions described above for the preparation of 2-benzylidene-4-carbomethoxy-3-ketotetrahydrothiophene, 3.0 g. of the oil containing largely 2-carbomethoxy-3-ketotetrahydrothiophene yielded 1.6 g. of the benzylidene derivative. The pure material was obtained after three crystallizations from methanol as flat, yellow-orange needles of m. p. 129–130°.

Anal. Calcd. for C₁₃H₁₂O₃S: C, 62.9; H, 4.84. Found: C, 62.6; H, 4.99.

4-Furfurylidene-2-carbomethoxy-3-ketotetrahydrothiophene (XIII, R = C₄H₃O).—The derivative (0.5 g.) was obtained by treating the oil (1.6 g.) containing 2-carbomethoxy-3-ketotetrahydrothiophene with furfural and piperidine as described above; orange plates from alcohol, m. p. 139–140°.

Anal. Calcd. for C₁₁H₁₀O₄S: C, 55.5; H, 4.20. Found: C, 55.7; H, 4.30.

This substance dissolved in aqueous ammonia to give a bright red solution and, like the parent β -keto-ester, it reduced ferric ion or iodine instantly. When an alcoholic solution of the material was treated with the calculated

amount of ferric chloride for oxidation, a white substance of m. p. 232° (dec.) was obtained. This material was 4,4'-difurfurylidene-2,2'-bis-(2-carbomethoxy-3-ketothiophanyl) (XV, R = C₄H₃O).

Cleavage of 2-Carbomethoxy-3-ketotetrahydrothiophene (V, R = CH₃) to α,β' -Dicarbomethoxymethylethyl Sulfide (IIa).—The oil containing largely 2-carbomethoxy-3-ketotetrahydrothiophene (10 g.) was heated under reflux with absolute methanol (30 cc.) containing piperidine (5 drops) for twenty-four hours, the solvent was removed, the oily residue taken up in ether, washed with water and dried with sodium sulfate. After the solvent had been removed, distillation yielded material (2 g.) of b. p. 106–120° (6 mm.) which gave a permanent purple ferric chloride test as a result of the presence of 4-carbomethoxy-3-ketotetrahydrothiophene, and, as a main fraction, α,β' -dicarbomethoxymethyl ethyl sulfide (7 g.) of b. p. 126–127° (7 mm.). The identity of the latter material (1 g.) was established by its hydrolysis to β -mercaptopropionic acid-S-acetic acid (0.7 g.) with concentrated hydrochloric acid in acetic acid. The crude acid obtained thus had m. p. 86–87°. One crystallization from benzene ethyl acetate gave material of m. p. 90–92° (alone or mixed with an authentic sample).

Neut. equiv. Calcd. for C₆H₈O₄S: 82.0. Found: 81.6.

2,2'-bis-(2-Carbomethoxy-3-ketothiophanyl) (VII).—The oil (10 g.) containing mainly 2-carbomethoxy-3-ketotetrahydrothiophene was dissolved in methanol (25 cc.), and to the resulting solution 1.0 M aqueous ferric chloride was added drop by drop until the purple color which appeared with each drop, then faded, became permanent. Toward the end of the oxidation a viscous oil separated, which upon being scratched crystallized. The crude dimeric oxidation product (7.2 g.) obtained in this way had m. p. 182–184°. The pure substance was obtained after four crystallizations from benzene-ligroin (90–120°); hard, white, cubic crystals of m. p. 189–190°.

Anal. Calcd. for C₁₂H₁₄O₆S₂: C, 45.3; H, 4.43; S, 20.1. Found: C, 45.3, 45.6; H, 4.63, 4.43; S, 20.3.

In a quantitative oxidation, using the first permanent purple tint as end-point, 0.210 g. of the oil containing largely 2-carbomethoxy-3-ketotetrahydrothiophene reduced 10.1 ml. of 0.101 N ferric chloride, which corresponded to a one-electron oxidation equivalent of 206 for the oil. The oxidation equivalent determined iodometrically was 204.

On the basis that the oil contained 75% of an oxidizable substance (72% of the oxidation product could be isolated, see above), the molecular weight of the oxidizable material must have been 154. The calculated value for 2-carbomethoxy-3-ketotetrahydrothiophene is 160.

In a subsequent oxidation of the oil (5 g.) the reaction liquor was concentrated *in vacuo* to a small volume after the dimeric oxidation product had been filtered off. The oily residue so obtained partially crystallized. After freeing the solid from oil on porous plate, sublimation *in vacuo* (50°, 4 mm.) yielded white cubic crystals (0.1 g.) that gave a permanent purple color with ferric chloride and had m. p. 37–38.5° when taken alone or in mixture with 4-carbomethoxy-3-ketotetrahydrothiophene.

4,4'-Dibenzylidene-2,2'-bis-(2-carbomethoxy-3-ketothiophanyl) (XV, R = C₆H₅).—2,2'-bis-(2-Carbomethoxy-3-ketothiophanyl) (0.25 g.) was dissolved in benzaldehyde (1.0 g.) by warming, a few drops of piperidine were added, and the mixture was heated on the steam-bath for two hours. During this time a white solid separated which was filtered off, washed with methanol, and purified by crystallization from nitrobenzene-ligroin (90–120°); white micro-crystals, m. p. 236°.

Anal. Calcd. for C₂₈H₂₂O₆S₂: C, 63.0; H, 4.48. Found: C, 63.0; H, 4.59.

Desulfurization of 2,2'-bis-(2-Carbomethoxy-3-ketothiophanyl).—Five grams of analytically pure 2,2'-bis-(2-carbomethoxy-3-ketothiophanyl) was dissolved in 75 cc. of boiling methanol. To the cooled solution, 9 g. of a

(20) In other experiments, the yield was not changed when the reaction product was isolated shortly after the addition of the diester was complete, or alternatively, when the reaction mixture was allowed to stand several days before being decomposed.

slurry of Raney nickel (prepared for hydrogenolysis²¹) was added. The suspension was boiled for ten minutes and filtered through a bed of decolorizing carbon. The catalyst was leached with 100 cc. of hot methanol, and the combined methanol solutions were concentrated to 10 cc. When the concentrate was cooled 0.25 g. of starting material of m. p. 175–179° separated. Further concentration of the methanol solution, after filtration, yielded a thick oil that on standing deposited white plates (0.30 g.). Two crystallizations from methanol yielded white tablets of m. p. 125–126°.

Anal. Calcd. for C₁₂H₁₈O₆: C, 55.8; H, 6.97. Found: C, 56.7; H, 7.32.

The identity of this material was established as dimethyl α,β -dipropionylsuccinate (VIII) by a mixed melting point determination (125–126°) with an authentic specimen, the synthesis of which is described below.

The liquor from which the dimethyl α,β -dipropionylsuccinate separated was freed of solvent *in vacuo* and boiled for eight hours with 8 cc. of 10% sulfuric acid. The hydrolysate, dissolved in ether, was extracted with dilute sodium bicarbonate. Acidification of the bicarbonate layer produced a precipitate of fine needles (0.05 g.). One crystallization from benzene–ligroin (90–120°) yielded fine white needles of m. p. 152–153°.

Anal. Calcd. for C₁₀H₁₂O₈: C, 56.7; H, 5.7. Found: 56.8; H, 6.0.

This material was identified as 2,5-diethylfuran-dicarboxylic acid-3,4 (XI) in a mixed melting point (153–154°) with an authentic sample, prepared as described below.

Synthesis of VIII and XI.—To a stirred solution of the Grignard reagent prepared from ethyl iodide (156 g.) and magnesium (26 g.) in ether (450 g.), methyl cyanoacetate (38 g.) was added during one hour.²² After standing under nitrogen for two days, the reaction-mixture was decomposed with ammonium chloride solution (400 cc. of a 20% solution) during one hour. After separation, the ether layer was dried, freed of solvent, and the product was distilled through a small column. The main fraction (22 g.) was methyl β -amino- β -ethylacrylate (IX), a colorless oil of b. p. 101–104° (13 mm.).

A copious evolution of ammonia occurred when the material was treated with 10% sodium hydroxide solution.

Fifteen grams of methyl β -amino- β -ethylacrylate was dissolved all at once in 100 cc. of 3 N hydrochloric acid. From the clear solution an oil separated within one minute. The oil was collected with ether, the extract was dried and the solvent removed. Distillation of the residual oil yielded as the main fraction methyl propionylacetate (X) (8 g.), an oil of b. p. 50–57° (13 mm.).

Anal. Calcd. for C₈H₁₀O₃: C, 55.4; H, 7.77. Found: C, 55.3; H, 7.94.

Two and six-tenths grams of methyl propionylacetate was treated in 30 cc. of dry ether with 0.46 g. of sodium, and when the sodium had reacted completely, 2.5 g. of iodine dissolved in 20 cc. of dry ether was added slowly with stirring.²³ When reaction was complete, the ether solution was washed free of sodium iodide with water, dried and evaporated on the steam-bath. When the residue was cooled, partial crystallization occurred. The crystalline material was filtered off, washed with a small amount of methanol and crystallized from the smallest volume of the same solvent. Pure dimethyl α,β -dipropionylsuccinate (VIII) (0.40 g.) was thus obtained as white tablets of m. p. 125–126°.

Neither the synthetic material nor that obtained in the desulfurization of 2,2'-bis-(2-carbomethoxy-3-ketothiophanyl) gave a color when an alcoholic solution was treated with a few drops of ferric chloride solution.²³

Synthetic dimethyl α,β -dipropionylsuccinate (0.25 g.) was boiled with 3 cc. of 10% sulfuric acid for twelve hours.²⁴

When the hydrolysis mixture was cooled, oily crystals separated which on one crystallization from benzene–ligroin (90–120°) yielded feathery, white needles of pure 2,5-diethylfuran-dicarboxylic acid-3,4 of m. p. 153–154° (0.10 g.).

Hydrolytic Experiments with 2,2'-bis-(2-Carbomethoxy-3-ketothiophanyl) (VII).—The dimeric oxidation product was insoluble in cold aqueous sodium hydroxide but when the compound (0.5 g.) was warmed with 5% sodium hydroxide solution (20 cc.) complete solution occurred within five minutes. Acidification at this point caused a brisk evolution of hydrogen sulfide, and the only organic product isolated from the acidic solution in several experiments was an acidic substance of m. p. 153° which was obtained in very small amount and was not further investigated.

When 2,2'-bis-(2-carbomethoxy-3-ketothiophanyl) was treated in absolute methanol with one mole of sodium methoxide at room temperature, the odor of methyl acrylate was immediately evident. Acidification of the methanol solution caused evolution of hydrogen sulfide. In a similar experiment, the methanol solution of the reactants was refluxed for one and one-half hours before acidification. After removal of the majority of the solvent, the reaction mixture was decomposed with dilute hydrochloric acid, and the oily product so obtained was boiled under reflux with glacial acetic acid containing concentrated hydrochloric acid. The black residue obtained after removal of the hydrolysis medium was dissolved in soda and extracted with ether. Acidification of the soda solution, followed by evaporation to dryness and repeated extractions of the dry residue with benzene yielded a benzene solution that on concentration to a small volume threw down a white crystalline acid of m. p. 115–125°. After three crystallizations from water the material had m. p. 137–140°.

Anal. Calcd. for C₁₀H₁₄O₈S₂·2H₂O: C, 33.2; H, 5.0. Found: C, 32.7; H, 5.0.

The formula C₁₀H₁₄O₈S₂ corresponds to the tetracarboxylic acid (XII) obtained by cleavage of both β -keto-ester groups in 2,2'-bis-(2-carbomethoxy-3-ketothiophanyl) and hydrolysis of the resulting acyclic tetracarboxylic ester.

Attempts to carry out an acidic hydrolysis of 2,2'-bis-(2-carbomethoxy-3-ketothiophanyl) with hydrochloric acid in acetic acid or with aqueous hydrochloric acid led only to intractable dark oils.

3-Ketotetrahydrothiophene (XVII).—Ten grams of crystalline 4-carbomethoxy-3-ketotetrahydrothiophene was heated at 100° with 80 cc. of 10% sulfuric acid for twelve hours during which time a smooth evolution of carbon dioxide occurred. After saturating the cooled reaction mixture with salt it was extracted with ether; and the ether extract after being dried and freed from solvent yielded a residue that on distillation gave 3-ketotetrahydrothiophene (4 g.), a colorless oil of b. p. 74.5° (15 mm.).

Anal. Calcd. for C₄H₆OS: S, 31.4. Found: S, 30.3.

Under the same conditions, the oil (32 g.) containing a preponderance of 2-carbomethoxy-3-ketotetrahydrothiophene yielded 3-ketotetrahydrothiophene (14.9 g.) of b. p. 60.5° (8 mm.).

The cyclic ketone had a foul odor, was quite soluble in water and did not reduce ferric ion or iodine in boiling alcoholic solution.

Derivatives of 3-Ketotetrahydrothiophene.—The derivatives described below were prepared from 3-ketotetrahydrothiophene having as its source crystalline 4-carbonethoxy-3-ketotetrahydrothiophene, oily 4-carbomethoxy-3-ketotetrahydrothiophene, and the oil containing mainly 2-carbonethoxy-3-ketotetrahydrothiophene, and were identical in all cases in mixed melting-point determinations.

2,4-Dibenzylidene-3-ketotetrahydrothiophene (XVIII, R = C₆H₅).—Ten drops of 25% sodium hydroxide solution were added to a mixture of 1.0 g. of benzaldehyde, 0.4 g. of 3-ketotetrahydrothiophene and 5 cc. of alcohol. The deep red solution which resulted promptly deposited yellow crystals that were filtered, washed with alcohol and crystallized from glacial acetic acid to yield the dibenzylidene derivative (0.5 g.), yellow needles, m. p. 187.5°.

(21) Mzingo, Wolf, Harris and Folkers, *THIS JOURNAL*, **65**, 1013 (1943).

(22) Cf. Blaise, *Compt. rend.*, **132**, 978 (1901).

(23) Cf. Willstätter and Clarke, *Ber.*, **47**, 298 (1914).

(24) Cf. Harrow, *Ann.*, **201**, 157 (1880).

Anal. Calcd. for $C_{18}H_{14}OS$: C, 77.8; H, 5.08; S, 11.5. Found: C, 77.9; H, 5.27; S, 11.7.

2,4-Difurfurylidene-3-ketotetrahydrothiophene (XVIII, R = C_4H_3O).—Under the conditions described above for the analogous dibenzylidene derivative, 0.3 g. of 3-ketotetrahydrothiophene yielded on treatment with furfural (1.0 g.) the difurfurylidene derivative (0.75 g.); the brick red needles from glacial acetic acid gave a m. p. 193°.

Anal. Calcd. for $C_{14}H_{10}O_3S$: C, 65.1; H, 3.88. Found: C, 65.1; H, 4.16.

Summary

The Dieckmann cyclization of α,β' -dicarbomethoxymethylethyl sulfide under two different sets of experimental conditions has been shown to result in the formation of two different cyclic β -keto-esters, namely, 4-carbomethoxy-3-ketotetrahydrothiophene and 2-carbomethoxy-3-ketotetrahydrothiophene.

CAMBRIDGE, MASS.

RECEIVED JUNE 17, 1946

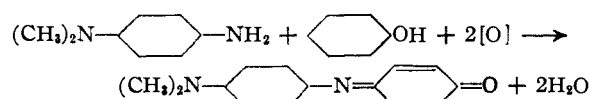
[COMMUNICATION NO. 1091 FROM THE KODAK RESEARCH LABORATORIES]

Indoaniline Dyes. I. Some Phenol Blue Derivatives with Substituents in the Phenol Ring

BY PAUL W. VITTMUM AND GORDON H. BROWN

The indoaniline dyes have received little attention in recent years because their usefulness is limited by a general instability.¹ With their increasing use² as cyan dye images in color photography, however, a more complete examination of these and related dyes is now of interest. This paper describes the preparation and properties of a selected group of indoaniline dyes related to the simple dye, Phenol Blue, but having substituents in the phenol ring.

Phenol Blue has been prepared most conveniently by oxidizing an alkaline solution of *p*-aminodimethylaniline and phenol. The reaction has been reported to be effected by various oxidizing



hypochlorite.^{5,6,7} Of these, the last reagent, as used in the procedure of Fieser and Thompson,⁷ proved the most satisfactory for the preparation of the substituted dyes, but in some cases the phenol was attacked by the hypochlorite, leading to side products which made the isolation of the pure dye very difficult or impossible. The search for a more satisfactory procedure led to an adaptation of the photographic process of color development² which could be used to great advantage.

TABLE I
PHYSICAL PROPERTIES OF DYES: $(CH_3)_2N-C_6H_4-N=C_6H_3(X)=O$

Substituent, X	M. p., °C. ^a	Crystallized from	Appearance of crystals	Carbon, %		Hydrogen, %		Nitrogen, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
-H	161-162 ^b	Ethanol	Dark purple needles	74.34	74.29	6.19	6.21	12.39	12.54
2-CH ₃	123-124 ^c	Ligroin	Dark purple crystals, green reflection	75.00	74.83	6.67	6.78	11.67	11.86
3-CH ₃	118-119 ^d	Ligroin	Black metallic crystals, gold reflection	75.00	74.84	6.67	6.54	11.67	11.85
2-Cl	125 (dec.) ^e	<i>n</i> -Butanol	Lustrous dark green needles	64.49	64.58	4.99	5.10	10.75	10.87
3-Cl	144-145 ^f	Carbon tetrachloride	Dark purple metallic needles	64.49	64.28	4.99	4.64	10.75	10.67
2-Br	119-120 (dec.)	<i>n</i> -Butanol	Fine dark blue needles, green reflection	55.10	55.29	4.26	4.10	9.18	9.25
2-OCH ₃	167-168	Ethanol	Dark purple crystals	70.31	70.02	6.25	6.38	10.94	10.74
3-OCH ₃	141-142 ^f	Ligroin	Purple-black crystals	70.31	70.25	6.25	6.16	10.94	10.86
2-NHCOCH ₃	184-185	Ethanol	Dark golden needles	67.84	67.72	6.01	6.08	14.84	14.91
3-NHCOCH ₃	150-151	Ethanol	Gold crystals	67.84	67.85	6.01	5.65	14.84	14.80
2-CH ₂ OH	157-158	<i>n</i> -Butanol	Dark purple crystals	70.31	70.29	6.25	6.40	10.94	10.91
2-CH=CHCO ₂ C ₂ H ₅	158-159	Ethyl acetate	Fine green needles	77.53	77.24	5.62	5.41	7.87	7.93

^a Melting points determined with Fisher-Johns apparatus. ^b Fieser⁷ gives 161° from ethyl acetate; Heller,⁶ 167° from alcohol; and Gnehm,⁵ 160° from ethyl acetate. ^c Fieser⁷ gives 127°; Bayrac⁴ gives 123°. ^d Fieser⁷ gives 121°; Bayrac⁴ gives 117-118°. ^e Bayrac⁴ gives 125-126°. ^f Fieser⁷ was unable to crystallize. Isolated as leuco form.

agents: potassium dichromate,^{3,4} potassium ferricyanide,³ potassium permanganate³ and sodium

In this procedure, the oxidizing agent was *silver chloride*, which was found to react readily with the *p*-phenylenediamine without attacking the phenols. The dyes prepared from *p*-aminodimethylaniline and the substituted phenols are listed in Table I.

(1) See, for example, Bucherer, "Lehrbuch der Farbenchemie," O. Spamer, Leipzig, 1914, p. 293.

(2) R. Fischer, U. S. Patent 1,102,028 (1914), and many more recent patents.

(3) Koechlin and Witt, German Patent 15,915 (1881).

(4) Bayrac, *Ann. chim.*, [7] 10, 18 (1897).

(5) Gnehm, *J. prakt. Chem.*, 69, 162 (1904).

(6) Heller, *Ann.*, 392, 16 (1912).

(7) Fieser and Thompson, *This Journal*, 61, 376 (1939).