TABLE I

Reactant: -phenacylidene oxindole	Product: -cinchophen	M. p., °C. (corr.)	Yield (crude), %	Time of heating, hours
p-Methyl-	4'-Methyl-	212–214	95	2
p-Chloro-	4'-Chloro-	243–245	65	12.5
p-Bromo-	4'-Bromo-	242–244	85	6
....	....	210–212	72	2

4'-Chloro-2-phenylcinchoninic acid apparently has not been characterized in the literature, although a study of its physiological activity has been made by Rotter.[6] It was prepared by the Pfitzinger method from isatin, as well as by the rearrangement method described above. The products were identical.

Anal. Calcd. for $C_{16}H_{10}O_2NCl$: Cl, 12.52. Found: Cl, 12.35, 12.32.

Summary

Cinchophen and certain of its 4'-substituted analogs have been prepared by rearrangement, respectively, of 3-phenacylidene oxindole and para-substituted phenacylidene oxindoles under the influence of mineral acid.

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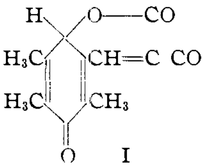
[6] Rotter, *Z. exptl. Path. Ther.*, **19**, 176 (1917).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

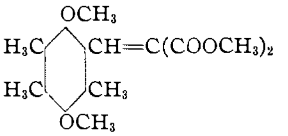
The Reaction between Duroquinone and Sodium Malonic Esters. II. The Synthesis and Reactions of 2,5-Dimethoxy-3,4,6-trimethylbenzaldehyde

BY LEE IRVIN SMITH

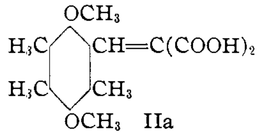
In the first paper of this series[1] the results of an investigation of the reaction between duroquinone and various sodium malonic esters were described. The primary product was a yellow crystalline compound, melting at 184°, to which was assigned the structure I.



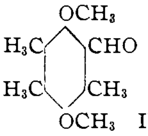
I



II



IIa



III

The substance I was hydrolyzed to an acid, and when this acid was exhaustively methylated, it gave a tetramethyl derivative II, which on careful hydrolysis yielded a dibasic acid, IIa. When this dibasic acid was oxidized, the products were oxalic acid and a substance $C_{12}H_{16}O_3$, to which was assigned the structure III.

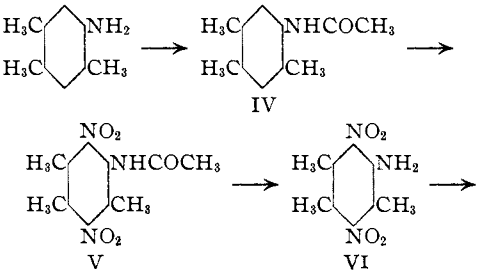
The substance III gave nitrotrimethylquinone with nitric acid, showing the presence of three methyl groups attached to the ring: Zeisel determinations showed two methoxyl groups; and these facts, together with the composition of the substance, left only one C, one H and one O not accounted for. Since the compound formed an oxime, these three atoms were assumed to be part of an aldehyde group, and the structure III written for it. But although III took up two hydrogen atoms on reduction, and the reduction product could be oxidized back to III, the substance could not be oxidized further to give an acid.

Because of the uncertainty regarding the structure of III, the aldehyde has been synthesized in another way. The synthetic product is identical with the compound III; it gives the same oxime, and the acid obtained by hydrolyzing the condensation product of the aldehyde and dimethyl malonate is identical with the dibasic acid, IIa, described in the previous paper. There is, therefore, no further doubt as to the structure of the compounds II, IIa and III.

The work on the reaction between various substituted quinones and substances of the malonic and acetoacetic ester types is being continued in the hope of elucidating the mechanism of the peculiar oxidation reactions involved.

Experimental Part

The route to the aldehyde involved the following steps



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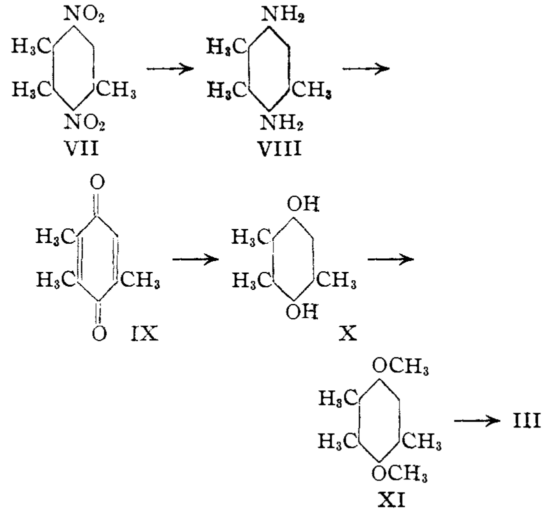
[1] Smith and Dobrovolny, THIS JOURNAL, **48**, 1693 (1926).



Acetylpseudocumidine (IV)[2] was prepared from pseudocumidine in 90% yield by acetylating with acetyl chloride in acetic acid solution; white needles, m. p. 162–163°.

Dinitroacetylpseudocumidine (V).[3]—Acetylpseudocumidine was dissolved in concentrated sulfuric acid and nitrated at −10° with fuming nitric acid. The product was isolated by pouring the reaction mixture onto ice. The precipitate was washed well, and then boiled for half an hour with alcohol containing a little ammonia. After cooling, it was filtered and dried. The yield was 92%; m. p. about 270°. The pure recrystallized product melts at 290–292° (corr.), but the crude product is pure enough for use in the next step.

3,6-Dinitro-5-aminopseudocumene (VI).[4]—The dinitroacetylamine (52 g.) was hydrolyzed by warming it on the steam-bath with concentrated sulfuric acid for thirty minutes after complete solution. After cooling, the product was precipitated by pouring onto cracked ice; yield 97%; m. p. 177–181°; recrystallized from alcohol, m. p. 181–182°.

3,6-Dinitropseudocumene (VII).[5]—The crude dinitropseudocumidine (98 g.) was dissolved in a mixture of 400 cc. of glacial acetic acid and 110 cc. of concentrated sulfuric acid. The cooled solution was stirred and diazotized with 69 g. of sodium nitrite in 100 cc. of water, holding the temperature between 10 and 15°. After diazotization, the reaction mixture was stirred and cooled for thirty minutes longer, and then a liter of cold 95% ethyl alcohol quickly stirred into it. Cooling and stirring were continued until the temperature fell, then the mixture was boiled until the odors of ethyl acetate and acetaldehyde disappeared (volume 600–700 cc.). Water was then added, the red precipitate filtered off, washed and dried; wt. 90 g. To remove the colored impurities, the dry solid was taken up in 600 cc. of pure benzene and this solution extracted (four or five times) with 100 cc. of concentrated sulfuric acid until the benzene solution became light orange. It was washed with water, carbonate, and then with dilute hydrochloric acid, separated, filtered if necessary (but not dried) and the solvent evaporated, leaving a yellow solid, m. p. 86–88°, wt. 64 g. (70%). One recrystallization from alcohol raised the m. p. to 91°. The sulfuric acid extractions were run separately onto ice, the precipitates collected separately, and if they melted above 80°, were combined as "second crops."

3,6-Diaminopseudocumene (Stannichloride) (VIII).[6]—Reduction of dinitropseudocumene by the method developed by Smith and Dobrovolny[7] gave the stannichloride of the diamine. This was filtered and washed with cold alcohol and ether. The compound was not analyzed. The filtrates and washings should be saved, as they contain appreciable amounts of dissolved diamine.

Pseudocumoquinone (IX).—The solid stannichloride (118 g.) was stirred into a solution of 500 g. of ferric chloride in 500 cc. of water containing 25 cc. of concentrated hydrochloric acid. After standing for an hour, the reaction mixture was steam distilled. The yield of quinone at this point was 38–40 g. A further 8 g. of quinone was obtained by evaporating to small volume (but not to dryness) the alcohol and ether washings from the stannichloride, combining this with the acid mother liquors, adding a great excess of ferric chloride and steam distilling. The quinone was extracted from the distillate with ether. It usually melted at 25° or slightly above, although if redistilled with steam from a little ferric chloride, the m. p. became 29–30°; yield 92–96%.[8]

Pseudocumohydroquinone (X).—The quinone was dissolved in 60% acetic acid, an excess of 20-mesh zinc added, and the mixture carefully heated. The reaction was very slow until the temperature was near the boiling point, when it suddenly became vigorous. After the reaction subsided, the mixture was refluxed for thirty minutes, 300 cc. of boiling water was added, the hot solution decanted from the zinc, and the zinc boiled with 300 cc. more water, which was decanted and combined with the main solution; white needles, wt. 67–69 g. (90%), m. p. 168–170° (dec.).

Diacetate.—Two grams of hydroquinone, 20 cc. of acetic anhydride, and 5 drops of concentrated sulfuric acid were refluxed for twenty minutes, then poured onto ice and made alkaline with ammonia. The resulting solid, recrystallized twice from 50% alcohol, yielded 2 g. of white needles, m. p. 108.5–110° instead of 112° as stated by Nietzki and Schneider.[8]

Dibenzoate.—Two grams of hydroquinone, 10 cc. of benzoyl chloride and excess 10% sodium hydroxide gave a product which after crystallization from a mixture of chloroform and alcohol weighed 2.3 g.; m. p. 179.5–180.5°; white needles.

Anal. Calcd. for $C_{23}H_{20}O_4$: C, 76.6; H, 5.55. Found: C, 76.0; H, 5.61.

Dimethyl Ether (XI).—In a flask with reflux were placed 7.6 g. of hydroquinone, 50 cc. of dry methyl alcohol and 63 g. of redistilled dimethyl sulfate. The mixture was heated to boiling, then the heating was discontinued and

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(2) Auwers, *Ber.*, **18**, 2661 (1885).

(3) Auwers, *ibid.*, **18**, 2661 (1885); *ibid.* **29**, 1105 (1896).

(4) Auwers, *ibid.*, **18**, 2662 (1885); **29**, 1105 (1896).

(5) Nietzki and Schneider, *ibid.*, **27**, 1429 (1894).

(6) Bamberger, *ibid.*, **24**, 1647 (1891); Nietzki and Schneider, *ibid.*, **27**, 1429 (1894).

(7) Smith and Dobrovolny, THIS JOURNAL, **48**, 1422 (1926).

(8) Nietzki and Schneider, *Ber.*, **27**, 1430 (1894), give the m. p. as 32°, while Noelting and Baumann, *ibid.*, **18**, 1152 (1885), give it as 11°.

there was added, slowly and with vigorous stirring, a hot solution of 60 g. of potassium hydroxide in 300 cc. of dry methyl alcohol. After boiling for half an hour, the mixture was steam distilled, collecting about a liter of distillate. The distillate, diluted with an equal volume of water and extracted with ether, yielded 8 g. of a pale yellow oil (calcd. 9 g.) which was taken up in 5–7 cc. of methyl alcohol and cooled to −15°. The resulting white solid weighed 5.5 g. (61%) and melted at 35.5–36.0°. The product may also be purified by vacuum distillation: b. p. 144° at 30 mm.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.3, H, 8.9. Found: C, 73.0; H, 8.8.

2,5 - Dimethoxy - 3,4,6 - trimethylbenzaldehyde (III).—The dimethyl ether was converted into the aldehyde using the zinc cyanide method developed by Adams and coworkers.[9] Using 40 g. of zinc cyanide, 30 g. of dimethyl ether, 45 g. of aluminum chloride and about 100 cc. of benzene as the solvent, there was obtained, after steam distilling the reaction mixture and extracting the distillate, 30 g. of a yellow oil, about half of which was the aldehyde. To purify it, several runs were made, combining the crude products and then vacuum distilling. The unchanged dimethyl ether distilled first (b. p. 130–132° at 15 mm.), followed by the aldehyde (b. p. 165–167° at 15 mm.). With small amounts of material it was better to distil to about 5° above the boiling point of the ether and then recrystallize the residue. It was extremely difficult to separate the aldehyde and unchanged ether by crystallization alone. The pure aldehyde crystallized from alcohol in white needles of m. p. 83.5–84.5°. This aldehyde had the same melting point as that obtained by Smith and Dobrovolny[10] in the work on the addition of malonic ester to duroquinone. The mixture of the synthetic product and the original specimen melted at 83–85°.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.2; H, 7.69. Found: C, 68.8; H, 7.55.

Although the aldehyde was white when pure and freshly prepared, it quickly turned yellow in the light. This process was reversible: the yellow product, kept in the dark, slowly became colorless. The aldehyde did not undergo auto-oxidation and neither the Cannizzaro reaction nor the benzoin condensation took place, even after prolonged treatment with the usual reagents.

Oxime.—One gram of aldehyde, 1.3 g. of hydroxylamine hydrochloride, 2 g. of sodium acetate and 25 cc. of methyl alcohol were refluxed for a day, allowed to stand for two days and then steam distilled. The liquid in the steam distillation flask was filtered while hot, then cooled and extracted with ether and the ether evaporated. There remained 0.2 g. of white solid, which, when recrystallized from dilute methyl alcohol, melted at 134–135°. This oxime was identical with that prepared in the earlier work and melting at 129–131°. The mixed m. p. was 131–134°.

Condensation with Dimethyl Malonate.—To a solution of 0.2 g. of sodium in 25 cc. of methyl alcohol was added 2 cc. of dimethyl malonate, followed by 1 g. of the aldehyde. The mixture was warmed to dissolve the aldehyde, and then allowed to stand at room temperature for three days, after which it was acidified with dilute hydrochloric acid, diluted with water and extracted twice with ether. On evaporating the ether, there remained 2 g. of thick yellow oil. This was warmed with 4 g. of potassium hydroxide in 50 cc. of methyl alcohol and the resulting solution steam distilled. The distillate yielded 0.2 g. of unchanged aldehyde. The liquid in the distilling flask was filtered while hot, the filtrate cooled, acidified with hydrochloric acid, and extracted twice with ether. The ether on evaporation gave 1 g. of a thick, yellow oil which gradually solidified. This was recrystallized from 15 cc. of 50% alcohol, giving stout needles, m. p. 180–183° (dec.). The material was dissolved in sodium carbonate, the solution extracted with ether, the aqueous layer acidified and the product again crystallized from dilute methyl alcohol, when the melting point became 181–184° (dec.); mixed m. p. with the di-ether diacid (184–186° dec.) obtained in the previous work[11] was 181–184° (dec.). The two products were thus identical, having the structure represented by IIa, which gave II as the structure of the primary condensation product.

Summary

1. A synthesis of 2,5-dimethoxy-3,4,6-trimethylbenzaldehyde has been carried out. This substance is identical with a substance encountered in a previous research as a degradation product of the compound resulting from the reaction between duroquinone and sodium malonic ester.

2. The aldehyde has been condensed with dimethyl malonate and the product hydrolyzed. The resulting dibasic acid is identical with another of the degradation products obtained in the work on duroquinone.

MINNEAPOLIS, MINN. RECEIVED NOVEMBER 2, 1933

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[9] Adams and Levine, THIS JOURNAL, **45**, 2373 (1923); Adams and Montgomery, *ibid.*, **46**, 1518 (1924).

[10] Smith and Dobrovolny, *icid.*, **48**, 1708 (1926).

[11] Ref. 1, p. 1697.