and ordinary C. P., concentrated (68%) nitric acid.

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Summary

The nitroparaffins obtained in the high-temperature, non-catalytic, vapor-phase nitration of 2,3-dimethylbutane were identified as nitromethane, 2-nitropropane, 3-methyl-2-nitrobutane, 2,3-dimethyl-2-nitrobutane and 2,3-dimethyl-1-nitrobutane.

The isolation of these five products and the absence of a dinitroparaffin serve as additional confirmation of the generalizations concerning the vapor-phase nitration of aliphatic hydrocarbons.

LAFAYETTE, INDIANA RECEIVED JULY 14, 1944

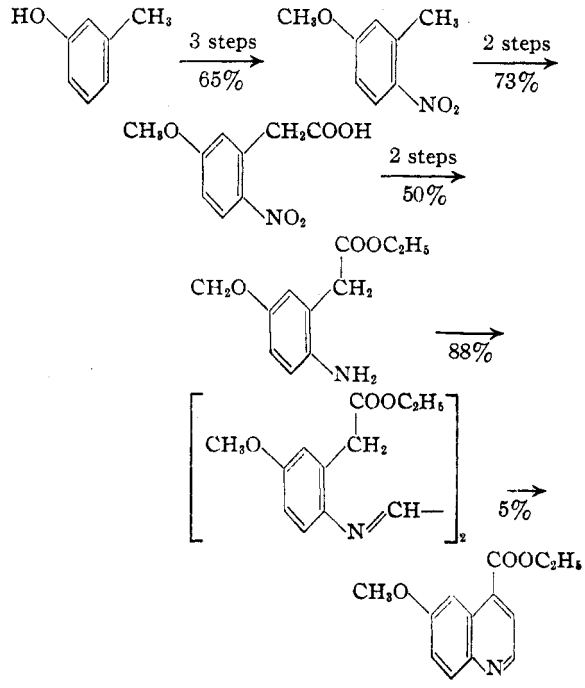
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

A Synthesis of Ethyl Quininate from *m*-Cresol

BY C. F. KOELSCH

Of the several methods which have been used for synthesizing ethyl quininate or quininic acid.[1-6] that of Thielepape and Fulde[6] is the best, but since it requires the isolation and purification of numerous intermediates, a simpler synthesis is desirable.

Analogy with the reaction studied by Kulisch,[7] who obtained quinoline in 35–40% yields from *o*-toluidine and glyoxal, suggested that ethyl quininate might be obtained from ethyl 2-amino-5-methoxy-α-toluate and glyoxal. This has now been realized, but the yield of the desired ester is disappointingly low. The reactions investigated in the present research are summarized in the formulas shown.



Experimental

The direct nitration of *m*-cresol[8,9,10] was unsatisfactory, for even when the conditions described by Schultz and Lehrburger[8] were used, the yield of 4-nitro-3-methylphenol was never better than that (29%) obtained by Blaikie and Perkin,[10] and considerable amounts of the isomeric nitrocresols[9] were obtained. The following procedure, based in part on an old observation of Robertson,[11] furnished 3-methyl-4-nitroanisole simply and in yields of 60–66%.

A stirred mixture of 54 g. of *m*-cresol, 150 ml. of acetic acid and 20 ml. of sulfuric acid was treated at 8–10° with a solution of 35 g. of sodium nitrite in a little water. After a few minutes the mixture was poured into ice-water, and the crystalline nitroso compound was pressed out on a filter. It was then added in portions to a stirred mixture of 50 ml. of nitric acid (d. 1.42) and 150 ml. of water at 40–50°; stirring was continued for a few minutes or as long as nitric oxide was evolved. The resulting crude nitrocresol, isolated by pouring in water and pressing out on a filter, was suspended in 200 ml. of water at 40–45° and stirred while 60 ml. of methyl sulfate and a solution of 35 g. of sodium hydroxide in 90 ml. of water were added alternately and in portions. The crude product was washed with water, dried, and then distilled, giving 50–56 g. of pure 3-methyl-4-nitroanisole, m. p. 55°.

Considerable simplification in the conversion of this substance into 5-methoxy-2-nitro-α-toluic acid has been attained. A suspension of sodium ethoxide from 7 g. of powdered sodium and 15 g. of dry alcohol in 75 ml. of dry ether was treated with 45 g. of ethyl oxalate and then with 50 g. of finely powdered 3-methyl-4-nitro-anisole. After ten minutes the mixture became solid; the sodio derivative is yellow if the starting materials are dry, and not red as described by Blaikie and Perkin.[10] The mixture was heated at 45° for four hours, then treated with 200 ml. of ice-water. Ten per cent. hydrogen peroxide was added until the deep red color was discharged; then small amounts of 30% sodium hydroxide and hydrogen peroxide were added alternately until the alkali no longer restored the red color. About 85% of the calculated amount of oxidant was required. The solution was mixed with "Hyflo,"

(1) Pictet and Misner, *Chem. Zig.*, **35**, 147 (1911); *Ber.*, **45**, 1800 (1912).

(2) Kaufmann, *ibid.*, **45**, 1805 (1912); **51**, 116 (1918); **55**, 614 (1922); *cf.* Cohen and King, *Proc. Roy. Soc.* (London), **B125**, 49 (1938).

(3) Halberkann, *Ber.*, **54**, 3090 (1921).

(4) Rabe, Huntenburg, Schultze and Volger, *ibid.*, **64**, 2487 (1931); *cf.*, Cohen and King, *loc. cit.*

(5) v. Schelven, English Patent 388,087; *Chem. Zentr.*, **104**, II, 3195 (1933); *cf.* Silberg, *Bull. soc. chim.*, [5] **3**, 1767 (1936).

(6) Thielepape and Fulde, *Ber.*, **72**, 1432 (1939).

(7) Kulisch, *Monatsh.*, **15**, 276 (1894).

(8) Schultz and Lehrburger, *Ber.*, **40**, 4322 (1907).

(9) Khotinsky and Jacopson-Jacopmann, *ibid.*, **42**, 3098 (1909).

(10) Blaikie and Perkin, *J. Chem. Soc.*, **125**, 296 (1924).

(11) Robertson, *ibid.*, **81**, 1477 (1902).

filtered, and acidified, giving 45–48 g. (71–76%) of product, m. p. 172–174° without recrystallization (reported[10] m. p. 176°).

Reduction of the potassium salt of 5-methoxy-2-nitro-α-toluic acid in water with Raney nickel and hydrogen at 30 lb. pressure gave the corresponding amino acid, m. p. 122–124° decomp., which was distilled under reduced pressure and analyzed in the form of the resulting lactam, **5-methoxyoxindole,** slightly pink needles from alcohol, m. p. 152–154°.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.3; H, 5.5. Found: C, 66.2; H, 5.5.

Boiling the nitro acid with alcoholic hydrogen chloride gave **ethyl 5-methoxy-2-nitro-α-toluate** in a yield of 55%; the ester boiled at 185° at 1 mm. and formed pale yellow needles from alcohol, m. p. 57–59°.

Anal. Calcd. for $C_{11}H_{13}NO_5$: C, 55.2; H, 5.5. Found: C, 55.0; H, 5.5.

When the nitro ester was reduced in alcohol with Raney nickel and hydrogen at 30 lb. pressure, it yielded ethyl 2-amino-5-methoxy-α-toluate, an oil which was converted into 5-methoxyoxindole when it was heated. The amino ester was analyzed in the form of its **acetyl derivative,** colorless needles from alcohol, m. p. 104–105°.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.2; H, 6.8. Found: C, 62.0; H, 7.2.

A solution obtained by hydrogenating 9.6 g. of the nitro ester in 50 ml. of alcohol was filtered, concentrated under reduced pressure to a volume of 25 ml. and treated at 25° with 15 ml. of a 20% solution of glyoxal (obtained by the action of nitric acid on paraldehyde[12]). The mixture soon solidified when it was scratched or seeded; the product, **glyoxal bis-[2-(carbethoxymethyl)-4-methoxyanil],** crystallized from alcohol in the form of yellow needles (7.3 g., 88%), m. p. 108–109°.

Anal. Calcd. for $C_{24}H_{28}N_2O_6$: C, 65.4; H, 6.4. Found: C, 65.5; H, 6.4.

Seven grams of the anil was added to a solution of 1 g. of sodium in 20 ml. of dry alcohol. The mixture was boiled for five minutes, then acidified with 3 ml. of acetic acid and filtered. Most of the anil was converted into a black insoluble material, but from the filtrate there was isolated ethyl quininate which weighed 0.3 g. after it had been distilled and crystallized, and melted at 65–67° alone or mixed with an authentic sample. The action of pyridine, piperidine, or potassium carbonate in hot quinoline on the anil yielded no ethyl quininate.

(12) Behrend and Kölln, *Ann.*, **416**, 230 (1918).

Summary

Kulisch's quinoline synthesis can be used for the preparation of ethyl quininate. The starting material is *m*-cresol, and the intermediate steps, involving nitrosation, oxidation and methylation to 3-methyl-4-nitroanisole, then condensation with ethyl oxalate, oxidation, esterification and reduction to ethyl 2-amino-5-methoxy-α-toluate, can be carried out with good yields. The final step, condensation with glyoxal, however, gives the desired substance in very small amount.

MINNEAPOLIS, MINNESOTA RECEIVED AUGUST 28, 1944

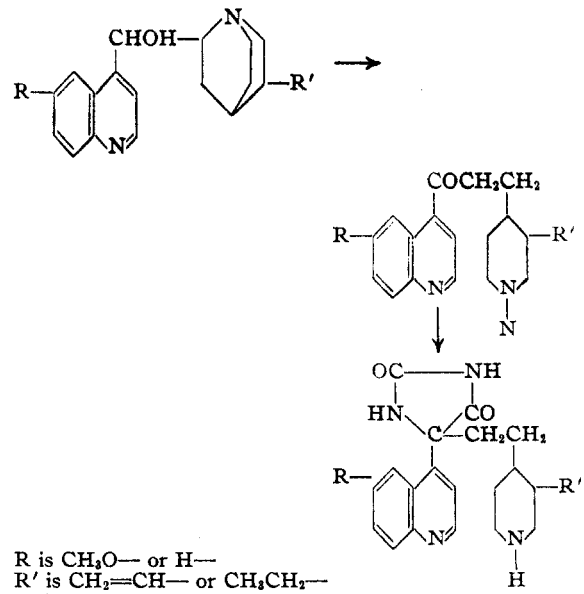
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Preparation of 5-Substituted Hydantoins Related to Certain Cinchona Alkaloids[1]

BY ROBERT LAMBERT McKEE[2] WITH HENRY R. HENZE

For several years past, a considerable amount of effort in this Laboratory has been directed toward the production of synthetic compounds having usefulness as anticonvulsants. To date the most satisfactory substances have been 5,5-disubstituted hydantoins; the latter have been prepared from ketones containing at least one cyclic (usually phenyl) substituent. In order to broaden our investigation, it was decided to prepare samples of 5-substituted hydantoins in which the different groups should be derived from nitrogen heterocycles related to certain cinchona alkaloids.

Molecular rearrangement of certain of the cinchona alkaloids to form ketones has been recognized for a long time; thus, quinine and its isomer quinidine have been converted to the same product, quinotoxine[3] (I). Likewise, both cinchonidine and cinchonine yield cinchotoxine (II). Moreover, the dihydro derivatives[4] of these four cinchona bases undergo the same "hydramine



R is CH_3O— or H—
R′ is CH_2=CH— or CH_3CH_2—

through use of Raney nickel at a hydrogen pressure of 70–100 m and at room temperature.

(1) From the Ph.D. dissertation of R. L. McKee, June, 1943.

(2) Research Assistant, University of Texas Research Institute, Fall Semester, 1942–1943. Present address: Department of Chemistry, University of North Carolina.

(3) (a) Pasteur, *Compt. rend.*, **37**, 111 (1853); (b) Biddle, THIS JOURNAL, **38**, 906 (1916).

(4) Reduction of the vinyl group in ths cinchona bases has been accomplished by Paul and Cottin [*Bull. soc. chim.*, [5] **7**, 370 (1940)]