NOTES

2,4,5- and 2,4,7-Trimethylquinolines

By Roger Adams and John Campbell

The use of 8-amino-2,4,7-trimethylquinoline in another investigation required an unequivocal synthesis for this compound. Since it has been demonstrated[1] that 7-methylquinoline nitrates in the 8-position, the nitration of 2,4,7-trimethylquinoline and subsequent reduction of the nitro group appeared to be a suitable route.

The procedures which have thus far been used for the preparation of 2,4,7-trimethylquinoline involve a ring closure which conceivably could have yielded the isomeric 2,4,5-trimethylquinoline. The latter compound has now been synthesized by an unambiguous method and shown to be different in properties from the compound reported as the 2,4,7-analog.

2,4,7-Trimethylquinoline has been formed by the condensation of *m*-toluidine with (1) an acid mixture of acetone and paraldehyde[2]; (2) acetone and acetylene in presence of cupric chloride[3]; and acetone with removal of methane from the resulting 2,2,4,7-tetramethyl-1,2-dihydroquinoline.[4] In the present work, it was obtained very conveniently in excellent yield by ring closure of the anil obtained from *m*-toluidine and acetylacetone. Nitration of 2,4,7-trimethylquinoline gave a 95% yield of the 8-nitro derivative which by catalytic reduction afforded the 8-amino-2,4,7-trimethylquinoline in 75% yield.

The 2,4,5-trimethylquinoline was synthesized by ring closure of the crude anil resulting from the condensation of 3-amino-4-chlorotoluene and acetylacetone. The yield was low in the ring-closure step. Catalytic removal of the chlorine atom gave essentially a quantitative yield of the desired 2,4,5-trimethylquinoline.

Experimental

β-*m*-Toluidinopropenyl Methyl Ketone.—A solution of 72 g. of *m*-toluidine and 74 g. of acetylacetone was gently refluxed for one hour. The water and excess acetylacetone were removed at the water pump and the residue distilled through a 10-inch Vigreux column to yield 98.5 g. (78%) of a pale yellow viscous oil, b. p. 125–126° (2 mm.), $n^{20}D$ 1.6105.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.90; H, 8.30; N, 7.56.

2,4,7-Trimethylquinoline.—To 450 g. of concentrated sulfuric acid cooled to 0° was added dropwise 86 g. of β-*m*-toluidinopropenyl methyl ketone over a period of ten minutes. The resulting solution was heated on the steam cone for ten minutes and then poured onto 2.5 kg. of cracked ice. The mixture was neutralized with 25% sodium hydroxide solution and extracted with three 500-ml. portions of ether. The combined ether extracts were dried over solid potassium hydroxide. After removal of the ether, the residue was distilled through a 10-inch Vigreux column to yield 65 g. (84%) of clear colorless product, b. p. 103–104° (1.5 mm.), $n^{20}D$ 1.5997 (lit.[2] $n^{20}D$ 1.5973).

Anal. Calcd. for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.30; H, 7.44; N, 8.25.

The **picrate** was obtained as small needles from 95% ethanol, m. p. 234–236° (cor.) (lit. m. p. 232°,[2] 230°[3]).

8-Nitro-2,4,7-trimethylquinoline.—To 50 g. of a nitrating mixture consisting of 2 parts by weight of concentrated sulfuric acid and 1 part by weight of fuming nitric acid (d. 1.50) cooled to 0° was added dropwise with stirring 11.7 g. of 2,4,7-trimethylquinoline over a period of five minutes. The resulting solution was allowed to stand at room temperature for one hour and was then poured onto 300 g. of cracked ice. The light yellow product which was the free base separated from the mixture weighed 14.1 g. (95%). Recrystallization from 95% ethanol gave small cream-colored needles, m. p. 131–132° (cor.).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.60; N, 12.96. Found: C, 66.53; H, 5.72; N, 12.77.

8-Amino-2,4,7-trimethylquinoline.—To a suspension of 52 g. of 8-nitro-2,4,7-trimethylquinoline in 1200 ml. of 95% ethanol was added 5 g. of Raney nickel and the mixture was shaken under 2000 lb. hydrogen pressure for three hours at room temperature, after which time the uptake of hydrogen ceased. The solution was filtered to remove catalyst and the ethanol removed at the water pump. Distillation of the residue gave 34 g. (76%) of a pale yellow viscous oil, b. p. 144–148° (1 mm.), which crystallized upon cooling. Recrystallization from petroleum ether (b. p. 30–60°) gave cream-colored needles, m. p. 45–46° (cor.).

Anal. Calcd. for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.53; H, 7.60; N, 15.04.

8-Chloro-2,4,5-trimethylquinoline.—A solution of 23 g. of 3-amino-4-chlorotoluene and 18 g. of acetylacetone was refluxed for three hours, the condenser being steam heated for the last thirty minutes to remove the water formed. The cooled solution was poured into 200 g. of concentrated sulfuric acid, the resulting mixture heated at 150° for three hours and then poured onto 1 kg. of cracked ice. After filtration to remove dark tarry material, it was neutralized with 30% sodium hydroxide solution. The mixture was extracted with 200 ml. of ether, the ether extract dried over anhydrous sodium sulfate and the ether removed. The dark oily residue, which crystallized upon cooling, was recrystallized twice from petroleum ether (b. p. 80–110°) with the use of Darco to yield 1.89 g. (5.7%) of white needles, m. p. 118–119° (cor.).

Anal. Calcd. for $C_{12}H_{12}NCl$: C, 70.07; H, 5.88; N, 6.81. Found: C, 69.83; H, 5.65; N, 6.65.

2,4,5-Trimethylquinoline.—To a solution of 1.38 g. of 8-chloro-2,4,5-trimethylquinoline and 1.5 g. of potassium hydroxide in 225 ml. of absolute ethanol was added 0.5 g. of Raney nickel and the mixture was shaken under 45 lb. hydrogen pressure for five hours. After filtration to remove the catalyst, the ethanol was distilled off and the residue extracted with 100 ml. of ether. The ether extract was filtered and the ether removed. The residual oil crystallized on cooling. The yield was nearly quantitative. Two recrystallizations from petroleum ether (b. p. 30–60°) gave a product, m. p. 70–71° (cor.), which analyzed approximately for a monoalcoholate. Sublimation gave white needles, m. p. 77°, which were solvent-free.

Anal. Calcd. for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.28; H, 7.76; N, 8.12.

(1) Tomisek, *et al.*, This Journal, **68**, 1587 (1946).

(2) Yamaguchi, *J. Pharm. Soc.* (*Japan*), **503**, 23 (1924).

(3) Koslow and Kantarowitsch, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 366 (1938).

(4) Cliffe, *J. Chem. Soc.*, 1327 (1933).

The picrate was prepared in and recrystallized from 95% ethanol, m. p. 194–195° (cor.).

Anal. Calcd. for $C_{18}H_{16}N_4O_7$: C, 54.00; H, 4.03; N, 14.00. Found: C, 54.15; H, 4.17; N, 13.97.

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The Addition of Malonic Esters to an Acetylenic Ketone

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Recent communications from this Laboratory described some of the reactions of *o*-chlorophenylbenzoylacetylene.[1,2,3,4] The present report further defines the behavior of this unsaturated ketone, outlining the addition of malonic esters and the nature of some of the cyclic products formed from the primary addition compounds.

The addition of malonic ester to phenylbenzoylacetylene was carefully studied by Kohler[5] and the addition of malonic ester to phenyl-*p*-nitrobenzoylacetylene and to phenyl-*p*-methylbenzoylacetylene was used by Barat[6] as a method of identifying these acetylenic ketones.

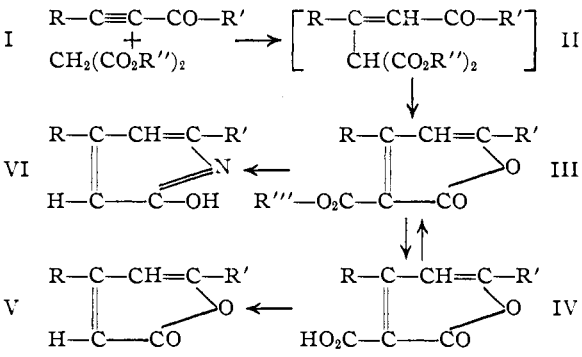
The behavior of *o*-chlorophenylbenzoylacetylene (I) closely parallels that of the unsubstituted analog,[5] the first isolable substance being the cyclized product III, an α-pyrone, formed by the loss of a molecule of alcohol by the primary addition product II. The formation of these pyrone esters constitutes a very interesting example of rapid ester interchange, the alcohol used as the solvent determining the alkyl group of the carboxylate, regardless of the particular malonic ester used. For example, the use of ethyl malonate and methanol gives the methyl ester of the pyrone acid while the use of methyl malonate and butanol gives the butyl ester of the pyrone acid. Moreover, one pyrone ester is converted into another by the action of the appropriate alcohol in the presence of a trace of sodium alcoholate.

Kohler[5] was unable to obtain the pyrone acid corresponding to IV by a simple basic hydrolysis of the pyrone esters, deep-seated decompositions destroying the bulk of the pyrone structure. The method which he finally employed was time-consuming, laborious and gave at best a 70% yield of the acid. In the present study, two simple methods have been developed which give good yields of the pyrone acid IV. Basic hydrolysis, using acetone as the solvent and one equivalent of aqueous sodium hydroxide, converts the esters quantitatively into the acid while acidic hydrolysis, using acetic acid as the solvent and aqueous sulfuric acid, converts the esters into a mixture of the acid and the pyrone V, the extent of decarboxylation of the acid increasing with time. There is no indication that Kohler tried either of these methods. The identity of the acid IV is certain since it is converted quantitatively into the esters from which it is formed either by the use of silver oxide and the appropriate alkyl halide or by the use of sulfuric acid and the appropriate alcohol.

The pyrone V is best prepared by refluxing a solution of the pyrone acid in acetic acid and aqueous sulfuric acid, the conversion being essentially complete. The action of an excess of sodium alcoholate on the pyrone esters, the chemical method of Kohler, gives a large amount of oily products and a low yield of the pyrone.

The *o*-chloropyrone esters, like the unsubstituted compounds, are readily converted into pyridine derivatives by the action of an alcoholic solution of ammonia.

The above reactions are summarized in structural form below, where R represents the *o*-chlorophenyl group, R′ the phenyl group, R″ the alkyl group of the malonic ester and R‴ the alkyl group of the alcohol used as the solvent.



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Experimental

The *o*-chlorophenylbenzoylacetylene was prepared as described previously[1]; the methyl and ethyl malonates were Eastman Kodak Co. products.

The Pyrone Esters, III.—The pyrone esters were prepared by malonic ester synthesis, by interconversion, and also by the esterification of the pyrone acid IV. In the following three paragraphs, each of these methods is illustrated by a general procedure and the particular reactions studied are indicated.

A small amount of an alcoholic solution of sodium alcoholate (the alcohol being the same as that used for the solution of the acetylenic ketone) was added to a warm solution of 5 g. of the acetylenic ketone and a slight excess of malonic ester in 50 ml. of alcohol. After cooling to room temperature, the solution was acidified with glacial acetic acid, the red color of the solution fading to a pale yellow. The solution was then diluted with water to the point of turbidity and left in the refrigerator overnight. The solid product was filtered, washed with water, allowed to dry and finally recrystallized from acetone or ether. The methylpyrone ester was prepared by using methanol and either methyl malonate or ethyl malonate, the ethyl ester by using 95% ethanol and *either* malonic ester, the propyl ester by using propanol-1 and *either* malonic ester, and the

(1) Bickel, THIS JOURNAL, **69**, 73, 2134 (1947).
(2) Bickel, *ibid.*, **70**, 763 (1948).
(3) Bickel, *ibid.*, **71**, 336 (1949).
(4) Bickel and Fabens, *ibid.*, **71**, 1450 (1949).
(5) Kohler, *ibid.*, **44**, 379 (1922).
(6) Barat, *J. Indian Chem. Soc.*, **7**, 851 (1930).