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IMPROVED SYNTHESES OF QUINALDINES AND 3-ALKYL QUINOLINES

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Although quinaldine and other 2-methylquinolines have been prepared in a number of ways, the only methods in general use at present are modifications of the original Doebner-v. Miller method (1, 2). This method comprises heating aldol, ethylene glycol, paraldehyde, or lactic acid with a primary aromatic amine in the presence of a mineral acid (usually hydrochloric), and of an oxidizing agent, such as nitrobenzene, in some instances. The original method has been somewhat improved by a modification in which paraldehyde, a primary aromatic amine, conc'd hydrochloric acid, and anhydrous zinc chloride are refluxed together (3, 4). All of these methods give relatively large amounts of undesirable by-products (unchanged and N-alkylated amines, tetrahydroquinaldines, etc.) whose removal is tedious and often wasteful.

Of the various quinolines substituted with one alkyl group in the pyridine ring, those with such a group in the 3-position have been studied the least, and only a comparatively few 3-alkyl quinolines have been prepared and described. The classical Friedlaender synthesis, recently reviewed in detail (5), is generally applicable, but depends upon difficultly obtainable aromatic *o*-amino carbonyl compounds, such as *o*-aminobenzaldehyde, as starting materials. 3-Methylquinoline has been obtained in small yield as a by-product in the synthesis of 2-ethyl-3-methylquinoline from a mixture of aniline, propionaldehyde, formaldehyde, and hydrochloric acid (6). Some α-methylacrolein was probably formed as an intermediate in the reaction (7). In more recent times several 3-alkyl quinolines have been prepared by a Skraup type synthesis using α,γ-diethyl ethers of β-alkyl glycerols as the source of the hetero ring carbon chain (8). 3,8-Dimethylquinoline has been prepared in poor yield by application of the Doebner-v.Miller method to a mixture of *o*-toluidine, propionaldehyde, and the dimethyl acetal of formaldehyde (9).

It has been found in this laboratory that crotonaldehyde, α-methylacrolein and α-ethylacrolein, and their diesters may be reacted with equimolar quantities of primary aromatic amines, using a modified Skraup synthesis, to give fairly good yields of the corresponding quinaldines, and 3-methyl- and 3-ethyl-quinolines. Skraup originally employed crotonaldehyde in a quinaldine synthesis but thought that the product obtained was lepidine (10); a similar synthesis employing crotonaldehyde has been disclosed in the patent literature (11). Since the completion of the work in this laboratory, in 1941, some similar reactions employing α-methylacrolein and its dimethyl acetal have been disclosed (4).

Virtually all of the earlier methods reviewed above, especially those relating to 3-alkyl quinolines, have been impractical because of poor yields or relative inaccessibility of the necessary intermediates, or have been tedious due to the

necessity of purifying the product from several chemically similar by-products present in significant amounts.

In the present procedure, the crotonaldehyde or α-alkyl acrolein, or a diester of one of these, was slowly run into a stirred mixture of sulfuric acid, oxidizing agent, and primary aromatic amine at such a temperature and rate that the reaction did not become too violent. Water (and organic acid if a diester had been used) was distilled out through a short stillhead equipped with a variable reflux device. Mixtures containing the aldehyde diesters required higher temperatures and longer times of heating than did mixtures containing the free aldehydes. The reaction mixture was partially cooled, poured onto ice, and made alkaline; the crude alkyl quinoline was then worked up in a customary way, usually by steam distillation and fractionation of the organic layer of the distillate.

In practice it was found that the use of α-methylacrolein diesters was preferable to the use of α-methylacrolein itself, due to apparent polymerization of a part of the latter compound under the conditions of the reaction. This resulted in a lower yield of the 3-methylquinoline. However, crotonaldehyde and α-ethylacrolein gave approximately equal yields of quinolines from given primary aromatic amines as did their diesters. In these cases, the use of the free aldehydes was preferable because of lower cost, shorter reaction time, and lower reaction temperature, compared to reactions utilizing the aldehyde diesters. The α-alkyl acroleins employed were prepared in this laboratory by the vapor-phase reaction of formaldehyde with higher aliphatic aldehydes (12).

Good yields in these syntheses, as in other modifications of the Skraup reaction, depend on the use of a suitable oxidizing agent. An especially useful one is nitrobenzenesulfonic acid prepared in sulfuric acid solution. Arsenic acid was an alternative oxidizing agent used in syntheses with nitroanilines. The procedure employing nitrobenzenesulfonic acid possessed several advantages in comparison with previous methods of 2- or 3-alkyl quinoline syntheses. The quinaldine or 3-alkyl quinoline was much less contaminated by by-products than are the products from the usual Skraup or Doebner-v.Miller syntheses, and could be isolated in a satisfactory degree of purity by fractionation alone. Only one steam distillation was necessary. The amounts of unchanged and N-alkylated anilines and of alkyl tetrahydroquinolines which were present were so small that the usual diazotization procedure could be omitted. In addition, yields from this improved method were somewhat better than earlier yields, particularly with substituted anilines.

One run with α-ethylacrolein and aniline was made, using the zinc chloride modification of the Doebner-v.Miller method (3). The yield of 3-ethylquinoline was quite poor, compared with that obtained from the modified Skraup reaction described below.

The various alkyl quinolines prepared are listed according to method of preparation, reactants, and yields in Table I. A number of the 3-alkyl quinolines were characterized by physical properties, picrates, and ethiodides (Table II). Analyses of the ethiodides served to confirm the formulas of the parent quinoline

TABLE I

ALKYL QUINOLINES AND YIELDS

-QUINOLINE	METHOD	AMINE REACTANT	ACROLEIN REACTANT	YIELD, %
2-Methyl	B	Aniline	Crotonaldehyde	43
2-Methyl	A	Aniline	Crotonaldehyde diacetate	49.5
2,7-Dimethyl[a]	A	*m*-Toluidine	Crotonaldehyde diacetate	47
2,7-Dimethyl	B	*m*-Toluidine	Crotonaldehyde	62.5
2-Methyl-7-chloro[a]	B	*m*-Chloroaniline	Crotonaldehyde	60
2-Methyl-6-chloro	A	*p*-Chloroaniline	Crotonaldehyde diacetate	55
2,6-Dimethyl	A	*p*-Toluidine	Crotonaldehyde dipropionate	49
2-Methyl-6-nitro	D	*p*-Nitroaniline	Crotonaldehyde diacetate	30
3-Methyl	A	Aniline	α-Methylacrolein diacetate	49
3-Methyl	A	Aniline	α-Methylacrolein dipropionate	46
3-Methyl	B	Aniline	α-Methylacrolein	30
3-Ethyl	A	Aniline	α-Ethylacrolein diacetate	54
3-Ethyl	B	Aniline	α-Ethylacrolein	42
3-Ethyl	C	Aniline	α-Ethylacrolein	2.5
3,6-Dimethyl	A	*p*-Toluidine	α-Methylacrolein diacetate	54
3,7-Dimethyl[a]	A	*m*-Toluidine	α-Methylacrolein diacetate	65
3,7-Dimethyl	B	*m*-Toluidine	α-Methylacrolein	25
3,8-Dimethyl	A	*o*-Toluidine	α-Methylacrolein diacetate	45
3-Methyl-6-nitro	D	*p*-Nitroaniline	α-Methylacrolein dipropionate	35
3-Methyl-7-chloro[a]	A	*m*-Chloroaniline	α-Methylacrolein diacetate	52
3-Ethyl-6-methyl	A	*p*-Toluidine	α-Ethylacrolein diacetate	32
3-Ethyl-7-methyl[a]	A	*m*-Toluidine	α-Ethylacrolein diacetate	34
3-Ethyl-7-methyl[a]	B	*m*-Toluidine	α-Ethylacrolein	35

[a] Yields given for these products include the small quantities of 3,5-isomers present.

TABLE II

PROPERTIES OF 3-ALKYL QUINOLINES[a,b]

-QUINOLINE	B.P., °C	M.P., °C	n_D^{20}	d_{20}^{20}	PICRATE M.P., °C	ETHIODIDE M.P., °C	IODINE ANALYSES OF ETHIODIDES	
							Calc'd	Fd.
3-Methyl	252–253	—	1.6160	1.0688	187.5	226.5	42.4	41.9
3-Ethyl	265–266	—	1.5988	1.0526	199	215	40.5	40.2
3,6-Dimethyl	270–271.5	56.5	—	—	251	181	40.5	40.3
3,7-Dimethyl	270–271.5	78.5	—	—	240.5	250	40.5	40.2
3,8-Dimethyl	260–262	—	1.6063	1.0524	208.5	192	40.5	40.1
3-Methyl-7-chloro	142–144 at 10 mm.	84.5	—	—	187.5	270	38.1	37.8
3-Methyl-6-nitro[c]	—	151	—	—	200	—	—	—
3-Ethyl-6-methyl	284–285.5	—	1.5955	1.0298	247	204	38.8	38.3
3-Ethyl-7-methyl	282–283	—	1.5947	1.0304	224.5	180	38.8	38.4

[a] Values given for b.p. are not corrected; m.p. values are corrected.

[b] A dash marked in a space indicates the value was not determined (for example, m.p.'s of substances which were liquids at room temperature).

[c] This quinoline was not converted to the ethiodide. Calc'd for $C_{10}H_8N_2O_2$: N, 14.9. Found: N, 14.9.

bases. Physical properties of the various quinaldines prepared were in good agreement with literature values.

In these syntheses of the Skraup type, 2,7- and 3,7-dimethylquinolines were the chief products from the reactions of crotonaldehyde and of *alpha*-methylacrolein, respectively, with *m*-toluidine. This same result, and the proof of structure of the 5- and 7-methylquinolines arising from such syntheses have already been demonstrated in an earlier publication (4). By analogy, it is probable that the reactions of *alpha*-ethylacrolein with *m*-toluidine, and of crotonaldehyde and *alpha*-methylacrolein with *m*-chloroaniline also led chiefly to 7-substituted quinolines, and the products have been so designated in the tables.

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EXPERIMENTAL

Preparation of oxidizing agent. Nitrobenzene (1970 g., 16.0 moles) was sulfonated by running it into 20% oleum (8800 g.) at 20–30°, and then heating the mixture, with stirring, to 60–70° over a period of approximately three hours. The mixture was maintained at this temperature for an additional six to eight hours until a sample was completely soluble in water. This mixture of nitrobenzenesulfonic acid and sulfuric acid is termed the "sulfo mix" in the following descriptions of experiments.

Method A. Aniline and α-ethylacrolein diacetate. Sulfo mix (202 g., containing 0.3 mole of nitrobenzenesulfonic acid) was poured into water (50 ml.) in a one-liter three-neck flask, equipped with a short stillhead and variable length finger condenser, dropping-funnel, thermometer, and stainless steel sweep stirrer. This diluted the sulfuric acid to a concentration of 75%. With stirring, aniline (47 g., 0.5 mole) was added; the aniline sulfate soon dissolved in the acid mixture.

The whole was heated to 125° in an oil-bath, and α-ethylacrolein diacetate (93 g., 0.5 mole) was added dropwise with stirring; the addition was momentarily stopped if the reaction became too violent. Both during and after the addition of the acrolein diester, the mixture was heated and stirred (stirring was momentarily stopped if excessive foaming occurred); meanwhile, the finger condenser was gradually moved up, so that a slow, steady distillation of water and acetic acid took place. In about three hours' time the oil-bath temperature had been allowed to rise to 175°; about 50 ml. of distillate had come over, and distillation had almost ceased. The reaction mixture was partially cooled, poured onto about 500 g. of ice, and neutralized with conc'd sodium hydroxide solution. The crude product was removed by steam distillation, preferably with super-heated steam. The 3-ethylquinoline was separated from the distillate, with the aid of carbon tetrachloride extraction. Fractionation of the solvent-quinoline mixture gave pure 3-ethylquinoline (42.5 g., 54%).

Method B. Aniline and α-ethylacrolein. Sulfo mix (202 g.), water (50 ml.), and aniline (47 g.) were mixed as in method A above. The mixture was heated with stirring to about 100°. α-Ethylacrolein (40 g., 0.475 mole) was run in dropwise, the addition being regulated to prevent too violent a reaction, and the temperature being held at 105–110°. After all of the α-ethylacrolein was added, the whole was stirred and heated for 30–40 minutes, during which time water distilled off. The maximum temperature reached was 135°. The mixture was worked up as before to give pure 3-ethylquinoline (31 g., 42%).

Method C. Aniline and α-ethylacrolein, Doebner-v. Miller method. To a well stirred mixture of aniline (186 g.) and conc'd hydrochloric acid (600 ml.), set in an ice-salt bath, α-ethylacrolein (170 g.) was added dropwise. Anhydrous zinc chloride (150 g.) was added, and the mixture was refluxed in an oil-bath (130°) for five hours. It was then neutralized

with conc'd sodium hydroxide solution and steam distilled. Most of the organic material present was a heavy tar which was not volatile with steam. The organic layer in the distillate was separated and taken through a diazotization procedure to remove the primary and secondary amines present. Steam distillation of the suspension resulting from treatment of the diazotized mixture with excess alkali gave only a small amount of organic layer. This upon separation and distillation gave 3-ethylquinoline (8 g., 2.5%).

Method D. p-*Nitroaniline and α-methylacrolein dipropionate.* α-Methylacrolein dipropionate (200 g., 1.15 mole) was added slowly, using the same apparatus as described in method A, to a hot stirred mixture of arsenic pentoxide (138 g., 0.6 mole), water (50 ml.), *p*-nitroaniline (138 g., 1.0 mole), and conc'd sulfuric acid (280 g.). The reaction was carried out as in previous examples. Neutralization of the reaction mixture gave a dark granular precipitate. The latter was dissolved in dilute hydrochloric acid, warmed with charcoal, filtered and chilled, and taken through a diazotization procedure to remove unreacted *p*-nitroaniline. The filtrate from this treatment, upon neutralization with ammonium hydroxide solution, gave crude 3-methyl-6-nitroquinoline (132 g., 70%) as a dull brown colored solid. Recrystallization from methanol and then from ethanol with aid of charcoal gave the product as light cream colored needles in about half the yield of crude material (35% over-all).

Other alkyl quinoline syntheses. Using methods A, B, and D, some other 3-alkyl quinolines and a number of quinaldines were prepared from primary aromatic amines and α-alkyl acroleins, crotonaldehyde, or their diesters. In all cases, the same relative amounts of reactants were employed as given in the above methods. These reactions are summarized in Table I. Physical properties and analyses of the 3-alkyl quinolines are listed in Table II.

These alkyl quinolines were colorless when freshly distilled, but on standing, especially if exposed to light, quickly became yellow or brown in color, and absorbed moisture from the air. The picrates were bright yellow crystalline solids when recrystallized from alcohol. The ethiodides were dull yellow to bright yellow crystalline solids.

SUMMARY

1. Various 2-methyl-, 3-methyl-, and 3-ethyl-quinolines have been prepared by the reaction of crotonaldehyde, α-methylacrolein, and α-ethylacrolein, respectively, with primary aromatic amines in the presence of sulfuric acid and nitrobenzene sulfonic acid. The diesters of the unsaturated aldehydes may be employed in place of the free aldehydes.

2. These reactions appear suitable for practical syntheses because of their simplicity, improved yields, and ease of isolation of product, compared with most of the preparations of corresponding quinolines described in the previous literature.

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