[CONTRIBUTION FROM THE NICHOLS LABORATORY, NEW YORK UNIVERSITY]

The Synthesis of 3-Alkyl-4-methylquinolines[1]

BY A. LANGLEY SEARLES AND H. G. LINDWALL

The cyclization of acetoacetanilide (I, R = H) was first carried out by Knorr,[2] who subsequently demonstrated[3] that it was a reaction generally applicable to acetoacetylated aryl amines possessing a vacant ortho position. Although the aryl portion of the molecule has been varied widely, a survey of the literature shows that few attempts have been made to prepare acetoacetanilides carrying alkyl groups in the alpha position. Accordingly, since they promised to be readily convertible into the corresponding 3-alkylquinoline derivatives which are otherwise difficultly accessible, their practical synthesis seemed desirable.

Early attempts followed the work of Knorr, who prepared alpha-methyl-acetoacetanilide (I, R = CH_3) in an unstated yield by the interaction of aniline and alpha-methyl-acetoacetic ester in a sealed tube at an elevated temperature.[4] Later workers showed that this procedure gives very poor results,[5] and their experience finds confirmation in our investigations. Under such conditions the reaction yields mainly *sym*-diphenyl-urea and butanone in place of the desired α-methyl-acetoacetanilide. In an effort to minimize this side-reaction several modifications such as varying the duration and degree of heating, employing a diluent and using an excess of the acetoacetic ester were introduced into the procedure; but since no significant improvement was effected by these means this line of attack was abandoned.

The fact that acetoacetanilide may exist in an enol configuration[6] suggested that its sodio-derivative might be prepared and alkylated directly. It was found that when treated with an equimolecular amount of sodium in anhydrous benzene the compound was transformed smoothly into its insoluble sodium enolate. Removal of the solvent yielded this as a dry, white powder which was alkylated immediately with a slight excess of the calculated quantity of alkyl halide in ethanol; from this reaction mixture the desired alkylacetoacetanilide (I) was obtained in satisfactory yield. Treatment of I with concentrated sulfuric acid effected cyclization to the analogous 2-hydroxy-3-alkyl-4-methylquinoline (II), and conversion of the latter to its 2-chloro-derivative (III) was accomplished by the use of phosphorus oxychloride. The parent 3-alkyl-4-methylquinolines themselves (IV) were obtained by the prolonged action of zinc and acetic acid on III.

(1) Presented before the New York section of the American Chemical Society, June, 1945.

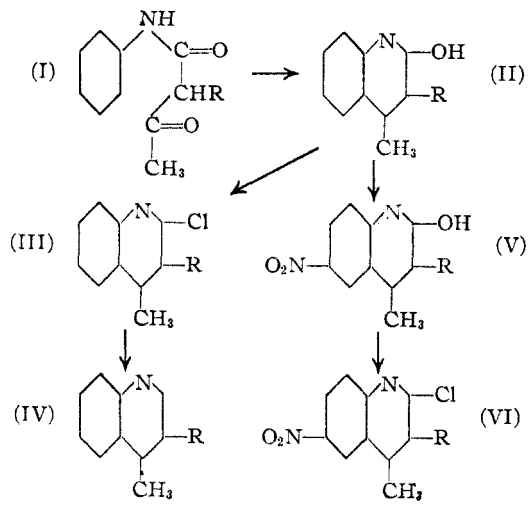
(2) Knorr, *Ber.*, **16**, 2593 (1883).

(3) Knorr, *ibid.*, **17**, 540 (1884); **17**, 2870 (1884); *Ann.*, **236**, 69 (1886).

(4) Knorr, *Ann.*, **245**, 358 (1888).

(5) Hurst and Thorpe, *J. Chem. Soc.*, **107**, 937 (1915).

(6) Meyer, *Ber.*, **45**, 2853 (1912).



The position of the alkyl grouping in these compounds was proved by the preparation of one of them in another way. Using the conditions recommended by Fierz-David and Ziegler,[7] aniline and α-*n*-butyl-acetoacetic ester interacted to give in low yield a substance which, when mixed with the compound obtained by alkylating acetoacetanilide with *n*-butyl bromide according to the procedure just outlined, showed no depression in melting point. This shows that alkylation, as expected, has occurred in the alpha position.

When II was treated in the cold with a mixture of concentrated nitric and sulfuric acids a mononitrated product (V) was obtained in excellent yield. 2-Hydroxy-4-methylquinoline has been nitrated in similar fashion,[8] giving what proved to be the 6-nitro derivative. On the basis of this it is postulated that the derivatives similarly prepared in this research also contain the nitro substituent in the 6 position of the quinoline nucleus. Several of these have been converted into the analogous 2-chloro compounds (VI) by the action of phosphorus oxychloride.

α-Benzyl-acetoacetanilide (I, R = $CH_2C_6H_5$), prepared according to the procedure outlined above, failed to undergo cyclization when treated with sulfuric acid, being recovered unchanged from the reaction mixture.

Experimental

α-*n*-Butyl-acetoacetanilide (Method A).—To 88.6 g. (0.50 mole) of acetoacetanilide dissolved in 500 ml. of warm dry benzene was added 11.5 g. (0.50 mole) of sodium wire,[9] and the resulting mixture refluxed briskly until

(7) Fierz-David and Ziegler, *Helv. Chim. Acta*, **11**, 776 (1928).

(8) Balaban, *J. Chem. Soc.*, 2349 (1930).

(9) Fine sodium sand may be used in place of wire; in this event the heat evolved alone is often sufficient to cause the initial refluxing, and the reaction proceeds to completion more quickly.

separation of the insoluble sodium derivative was complete (about fifteen hours). Most of the benzene was then distilled off on the steam-bath, using reduced pressure in the final stages of the process. The white residue was dissolved immediately in a solution of 82.2 g. (64.5 ml., 0.60 mole) of *n*-butyl bromide in 600 ml. of commercial absolute ethanol.[10] The mixture was brought to a gentle boil, and sodium bromide began to separate. After a half-hour of gentle refluxing the mixture was filtered and then concentrated to a small volume on the steam-bath. The pasty oil remaining was taken up in dilute ethanol, charcoaled, and refrigerated while still warm; on standing the pale orange oil which separated soon solidified. The crude solid was filtered from the solution, washed with cold dilute ethanol, and pressed as dry as possible on the filter-plate. After vacuum-drying above potassium hydroxide it weighed 69.7 g. An additional 3.0 g. of product was obtained by further dilution and refrigeration of the mother liquor, to which the washings of the first crop had been added. The total yield was 72.7 g. (62.4%). After two recrystallizations from ligroin the compound was in the form of rosetted needles of m. p. 88–89°.

Anal. Calcd. for $C_{14}H_{19}O_2N$: N, 6.01. Found: N, 6.21.

α-*n*-Butyl-acetoacetanilide (Method B).—A solution of 4.7 g. (0.050 mole) of aniline, 9.5 g. (0.050 mole) of α-*n*-butyl-acetoacetic ester and a few drops of pyridine in 60 ml. of anhydrous xylene was refluxed gently for five hours and then allowed to stand at room temperature for six days. It was then boiled down to half volume and refrigerated, whereupon 3.0 g. of *sym.*-diphenyl-urea precipitated; this was filtered off and rejected. An additional five ml. of solvent was removed from the filtrate, and the latter again refrigerated. After standing two days an additional amount of solid separated; this was filtered off, washed with cold petroleum ether, and air-dried. The fluffy white needles so obtained weighed 1.6 g. (13.7%); m. p. and mixed m. p. with the compound as prepared by method A above, 87.5–88.5°.

α-*n*-Propyl-acetoacetanilide.—This was prepared from acetoacetanilide and *n*-propyl iodide according to method A; yield, 52.5%. After successive crystallizations from water, ligroin, isopropyl ether and a diethyl ether–petroleum ether mixture, the compound was obtained as fine white needles of m. p. 85–87.5°.

Anal. Calcd. for $C_{13}H_{17}O_2N$: N, 6.39. Found: N, 6.54.

α-Ethyl-acetoacetanilide.—This was prepared in 66.6% yield from acetoacetanilide and ethyl bromide according to method A. After three crystallizations from dilute ethanol the compound formed transparent needles, m. p. 106–108°.

Anal. Calcd. for $C_{12}H_{15}O_2N$: N, 6.83. Found: N, 6.86.

α-Methyl-acetoacetanilide.—This was prepared from acetoacetanilide and methyl iodide by method A; yield, 66.5%. After two recrystallizations from benzene and two from water, the compound was obtained as squat transparent needles, m. p. 137–139°.[11]

2-Methyl-α-ethyl-acetoacetanilide.—To 19.1 g. (0.10 mole) of 2-methyl-acetoacetanilide dissolved in 250 ml. of warm dry benzene was added 2.3 g. (0.10 mole) of sodium wire, and the mixture refluxed gently until the metal dissolved completely (2.5 hours). The benzene was distilled off on the steam-bath, and to the solid residue remaining was added 16.4 g. (11.4 ml., 0.150 mole) of ethyl bromide in 150 ml. of commercial absolute ethanol. After a few minutes of refluxing sodium bromide began to precipitate, and the reaction was completed by an additional half-hour of gentle boiling. Following this, the mixture was filtered and concentrated to a volume of about 75 ml. It was then diluted with warm water to 300 ml. and finally refrigerated. The pale orange liquid which separated on standing was removed, freed of traces of mother liquor, and vacuum distilled. This latter process entailed a reduction in yield, as some of the product decomposed into *sym*-diphenyl-urea, which sublimed into the receiver. A small amount of forerun was discarded, and the fraction boiling at 170–180° (4 mm.) was collected; weight, 7.5 g. (34.2%). The product redistilled as a viscous, straw-colored oil, b. p. 178.5–181° (3 mm.), which became semisolid on long standing at room temperature.

Anal. Calcd. for $C_{13}H_{17}O_2N$: C, 71.3; H, 7.82. Found: C, 71.1; H, 7.88.

α-Benzyl-acetoacetanilide.—This compound was prepared according to method A from acetoacetanilide and benzyl chloride in 75% yield. Crystallization from dilute ethanol and then ligroin yielded it as rosetted needles of m. p. 111.5–113°.

Anal. Calcd. for $C_{17}H_{17}O_2N$: N, 5.24. Found: N, 5.16.

2-Hydroxy-3-*n*-butyl-4-methylquinoline.—To 25 ml. of precooled sulfuric acid (98%, sp. gr. 1.84) was added 21.6 g. (0.092 mole) of α-*n*-butyl-acetoacetanilide. The mixture warmed slightly, and was stirred until solution was complete. After remaining at room temperature for twenty hours, it was warmed for a few minutes on the steam-bath, and finally poured into a mixture of sodium carbonate solution and crushed ice. The resulting mixture was allowed to stand with occasional stirring until the ice had melted, whereupon it was filtered, and the precipitate washed with several portions of water. After vacuum-drying above potassium hydroxide the product weighed 18.6 g. (89.4%). Crystallization from dilute ethanol yielded the compound in the form of long, silky, transparent needles, m. p. 170–171°.

Anal. Calcd. for $C_{14}H_{17}ON$: N, 6.51. Found: N, 6.48.

2-Hydroxy-3-*n*-propyl-4-methylquinoline.—This compound was prepared from α-*n*-propyl-acetoacetanilide as above; yield, 76%. Fine, transparent needles of m. p. 175.5–177° were obtained after crystallization from dilute ethanol.

Anal. Calcd. for $C_{13}H_{15}ON$: C, 77.6; H, 7.46; N, 6.96. Found: C, 77.9; H, 7.65; N, 6.88.

2-Hydroxy-3-ethyl-4-methylquinoline.—This compound was prepared from α-ethyl-acetoacetanilide in the same way; yield, 82%. After crystallization from dilute ethanol and then twice from an ethanol–benzene mixture it formed fine, transparent needles, m. p. 228.5–229°.

Anal. Calcd. for $C_{12}H_{13}ON$: N, 7.48. Found: N, 7.71.

2-Hydroxy-3,4-dimethylquinoline.—This was prepared similarly from α-methyl-acetoacetanilide in quantitative yield. On crystallization from 95% ethanol the compound was obtained as fine needles of m. p. 269–271°.[12]

2-Chloro-3-*n*-butyl-4-methylquinoline.—To 2.15 g. (0.010 mole) of 2-hydroxy-3-*n*-butyl-4-methylquinoline was added 6.0 ml. of phosphorus oxychloride, and the mixture immersed in an oil-bath previously heated to 110°, at which temperature it was held for fifteen minutes. After cooling briefly, the resulting solution was poured onto finely crushed ice, and allowed to stand for an hour with occasional stirring. The aqueous layer was decanted from the light-brown semisolid material which had settled, and the latter was vacuum distilled; 1.6 g. (68%) of product boiling at 192–195° (11 mm.) was thus obtained. On redistillation it was collected at 183–183.5° (5 mm.) in the form of a pale yellow oil; $n^{20}D$ 1.5957.

Anal. Calcd. for $C_{14}H_{16}NCl$: C, 71.8; H, 6.89. Found: C, 71.9; H, 7.00.

2-Chloro-3-*n*-propyl-4-methylquinoline.—A mixture of 0.70 g. (0.0035 mole) of 2-hydroxy-3-*n*-propyl-4-methylquinoline and 3.0 ml. of phosphorus oxychloride was refluxed for a half-hour. After cooling, it was poured into a

(10) The use of anhydrous ethanol does not improve the yield significantly.

(11) Knorr, ref. 1, prepared this compound in another way, reporting a m. p. of 138–140°.

(12) Knorr, *ibid.*, reports a m. p. of 262°.

mixture of sodium carbonate solution and finely crushed ice. On standing overnight the brown oil which separated became solid. This was filtered from the solution and vacuum-dried; weight, 0.75 g. (96%). After two crystallizations from dilute ethanol, using Norite, the compound was obtained as flat white needles, m. p. 79–80°.

Anal. Calcd. for $C_{13}H_{14}NCl$: N, 6.38. Found: N, 6.41.

2-Chloro-3-ethyl-4-methylquinoline.—This was prepared in the same manner as the above propyl derivative; yield, 88%; m. p., 83.5–85.5° after two crystallizations from dilute ethanol. The compound was in the form of stubby, transparent needles.

Anal. Calcd. for $C_{12}H_{12}NCl$: N, 6.82. Found: N, 6.84.

3-*n*-Butyl-4-methylquinoline.—2-Chloro-3-*n*-butyl-4-methylquinoline (4.2 g., 0.0205 mole) was dissolved in 50 ml. of 90% acetic acid. After warming the solution to 40°, 4.5 g. of zinc dust was added in small portions over an eight-hour period, during which time vigorous mechanical stirring was employed. The resulting solution was rendered alkaline with concentrated sodium hydroxide solution, and then extracted several times with ether. Concentration and distillation of these combined extracts yielded a pale yellow oil of b. p. 134–142° (2 mm.). On redistillation 1.8 g. (50%) was collected at 142–143.5° (1 mm.); $n^{20}D$ 1.5803.

Anal. Calcd. for $C_{14}H_{17}N$: C, 84.4; H, 8.34. Found: C, 84.2; H, 8.43.

The picrate of this base was prepared in the usual way; after two recrystallizations from dilute ethanol it was obtained as bright yellow needles of m. p. 162.5–164°, with softening at 156°.

3-Ethyl-4-methylquinoline.—This compound was prepared in the same way as the analogous butyl derivative. The yield of redistilled product boiling at 177–180° (29 mm.) was 72.4%; $n^{20}D$ 1.6033.

Anal. Calcd. for $C_{12}H_{13}N$: N, 8.18. Found: N, 8.07.

The picrate of this substance, prepared in the usual way, separated as yellow needles after two recrystallizations from 95% ethanol; m. p. 209–210°, with softening at 201°.[13]

2-Hydroxy-3-*n*-butyl-4-methyl-6-nitroquinoline.—A solution of 2.15 g. (0.010 mole) of 2-hydroxy-3-*n*-butyl-4-methylquinoline in 5 ml. of sulfuric acid (98%, sp. gr. 1.84) was chilled to 0°. To it was then added, in dropwise fashion, a mixture of 0.8 ml. of nitric acid (sp. gr. 1.42) and 1.0 ml. of sulfuric acid (98%, sp. gr. 1.84). After standing at room temperature for a half-hour the resulting solution was poured slowly into a mixture of sodium carbonate solution and finely crushed ice. Filtration and vacuum-drying gave the crude product in quantitative yield. After two crystallizations from ethyl acetate fine, fluffy, cream-colored needles were obtained; m. p. 259–260°, with softening at 243°.

(13) Byvanck, *Ber.*, **31**, 2150 (1898), prepared the parent quinoline in another way, but reported none of its constants; he assigned a m. p. of 202° to its picrate.

Anal. Calcd. for $C_{14}H_{16}O_3N_2$: N, 10.77. Found: N, 11.00.

2-Hydroxy-3-ethyl-4-methyl-6-nitroquinoline.—This compound was prepared in the same way as its analogous butyl derivative in a 94% yield. After two crystallizations from *o*-dichlorobenzene it was obtained as a cream-colored microcrystalline powder, m. p. 308.5–309.5°.

Anal. Calcd. for $C_{12}H_{12}O_3N_2$: C, 62.1; H, 5.21; N, 12.06. Found: C, 62.3; H, 5.16; N, 11.80.

2-Hydroxy-3,4-dimethyl-6-nitroquinoline.—This nitration was accomplished in the same way as described above; yield, 93%. After successive crystallization from nitrobenzene and *o*-dichlorobenzene it was in the form of fine yellow needles, m. p. 368–369° with decomposition.

Anal. Calcd. for $C_{11}H_{10}O_3N_2$: N, 12.85. Found: N, 12.72.

2-Chloro-3-*n*-butyl-4-methyl-6-nitroquinoline.—2-Hydroxy-3-*n*-butyl-4-methyl-6-nitroquinoline (0.8 g.) was mixed with 2.0 ml. of phosphorus oxychloride, and immediately immersed in an an oil-bath held at 120°, where it was allowed to remain for ten minutes. The resulting solution was then poured into a mixture of crushed ice and sodium carbonate solution; a pink oil separated which solidified on stirring. Filtration and vacuum-drying yielded 0.7 g. (82%) of product. The compound was twice crystallized from dilute ethanol, whence it was obtained as pale rose needles, m. p. 124–124.5°.

Anal. Calcd. for $C_{14}H_{15}O_2N_2Cl$: N, 10.06. Found: N, 9.85.

2-Chloro-3,4-dimethyl-6-nitroquinoline.—This compound was obtained by treatment of 2-hydroxy-3,4-dimethyl-6-nitroquinoline with phosphorus oxychloride as above. The yield was quantitative. Purification was effected by its successive crystallization from ethanol and benzene, whence it separated in pale yellow needles of m. p. 191–194°.

Anal. Calcd. for $C_{11}H_9O_2N_2Cl$: N, 11.83. Found: 11.74.

Summary

Acetoacetanilide has been converted into its sodium derivative, and this, on treatment with alkyl halides, has been shown to yield α-alkylated products. These have been cyclized to the corresponding 2-hydroxy-3-alkyl-4-methylquinolines by means of sulfuric acid, and the respective interaction of the latter compounds with phosphorus oxychloride and nitric acid has been studied. Their 2-chloro derivatives have been dechlorinated, and the resulting bases characterized by means of their picrates.

UNIVERSITY HEIGHTS
NEW YORK 53, N. Y. RECEIVED FEBRUARY 11, 1946