The Synthesis of Polymethylquinolines and 1,10-Phenanthrolines (1)

Francis H. Case and Harris H. Wisneski

Department of Chemistry, Temple University

Several polymethyl-1,10-phenanthrolines were synthesized by the use of 3-methyl-3-penten-2-one in Skraup reactions. The behavior of this ketone as well as that of 4-hydroxy-2-pentanone and 4-hydroxy-3-methyl-2-butanone with various substituted anilines was studied.

With the object of preparing highly methylated 1,10-phenanthrolines for use as metal-chelating agents, 3-methyl-3-penten-2-one (2) was reacted with *o*-nitroaniline in a modified Skraup reaction (3) yielding 2,3,4-trimethyl-8-nitroquinoline (I). Reduction to the amine followed by another Skraup reaction using the same ketone yielded 2,3,4,7,8,9-hexamethyl-1,10-phenanthroline (II). Treatment of the above amine with glycerol in a Skraup reaction resulted in the formation of 2,3,4-trimethyl-1,10-phenanthroline (III).

Similarly, the reaction of 4-methyl-2-nitroaniline with the above ketone yielded 2,3,4,6-tetramethyl-8-nitroquinoline (IV), which was reduced to the amine and converted in a second Skraup reaction, using glycerol, to 2,3,4,6-tetramethyl-1,10-phenanthroline (V).

In an attempt to prepare the completely methylated, or octamethylphenanthroline, 4,5-dimethyl-2-nitroaniline (4) was treated as before with 3-methyl-3-penten-2-one with the expectation of obtaining 2,3,4,5,6-pentamethyl-8-nitroquinoline. However, the only product isolated from the reaction was found to be 2,5,6-trimethyl-8-nitroquinoline, identical with the compound (5)previously prepared by a Skraup reaction from 4,5-dimethyl-2-nitroaniline and crotonaldehyde diacetate. This deficiency of two methyl groups in the heterocyclic ring led us to try similar Skraup reactions involving the same ketone and other substituted anilines. In all cases yields were low.

With 5-methyl-2-nitroaniline (6) the result was 2,5-dimethyl-8-nitroquinoline, previously prepared by Manske, Marion and Seger (7) from 2-nitro-5-methylaniline and crotonaldehyde in a Doebner-Miller reaction. 3-Amino-4-nitrobiphenyl (8) yielded 2-methyl-8-nitro-5-phenylquinoline, the same product as was obtained from the same amine treated with acetaldehyde in a Doebner-Miller reaction. 2-Bromo-4,5-dimethylaniline (9), similarly treated with 3-methyl-3-penten-2-one, gave a small yield of 8-bromo-2,5,6-trimethylquinoline which was identical with the product obtained from the action of acetaldehyde and the above amine in a Doebner-Miller reaction.

This loss of methyl groups was, however, not observed when methyl was substituted for nitro in the starting amine. Thus, 2,5-dimethyl aniline treated with the above ketone in the modified Skraup reaction yielded 2,3,4,5,8-pentamethylquinoline, which was identical with that prepared from the same amine and methylacetylacetone in a Combs reaction. This compound had been previously reported by Buu-Hoï and Guettier (10) as melting at 54°. We obtained a melting point of 81° for the product of both reactions.

Both the Combs reaction using methylacetylacetone and the Skraup reaction using 3-methyl-3-penten-2-one were tried with 2,4,5-trimethylaniline (pseudocumidine) but neither gave any positive results.

Other unsaturated methyl ketones were then tried to see whether they underwent a similar loss of methyl groups. In the reaction between 4,5-dimethyl-2-nitroaniline and 3-ethyl-3-penten-2-one (11) this was indeed the case as 2,5,6-trimethyl-8-nitroquinoline was formed. However, the reaction of 4-hydroxy-2-pentanone (12) with 5-methyl-2-nitroaniline, 4,5-dimethyl-2-nitroaniline, and 2,5-dimethylaniline yielded, respectively, 2,4,5-trimethyl-8-nitroquinoline, 2,4,5,6-tetramethyl-8-nitroquinoline and 2,4,5,8-tetramethylquinoline, all normal products. Also the reaction of 4-hydroxy-3-methyl-2-butanone (13) with the above amines yielded, respectively, 3,4,5-trimethyl-8-nitroquinoline, 3,4,5,6-tetramethyl-8-nitroquinoline (previously prepared by Badger, *et al.* (14)) and 3,4,5,8-tetramethylquinoline. The same ketol with 3,4-dimethylaniline yielded 3,4,6,7-tetramethylquinoline, and with 2,4,5-trimethylaniline yielded 3,4,5,6,8-pentamethylquinoline,

TABLE I

Quinolines Prepared from 3-Methyl-3-penten-2-one

Substituted quinoline prepared	Substituted aniline used	Yield %	M.P. (°C)	Crystallization solvent	Formula	Analysis Calcd % C	H	N	Found % C	H	N
2,3,4-trimethyl-8-nitro (I)	2-nitro	18.8	199-200	benzene	$C_{12}H_{12}N_2O_2$	66.65	5.59	12.95	66.26	5.74	12.63
2,3,4,6-tetramethyl-8-nitro (IV)	4-methyl-2-nitro	23.0	230-231	benzene	$C_{13}H_{14}N_2O_2$	67.81	6.13	12.17	67.88	6.02	12.51
2,5-dimethyl-8-nitro (a)	5-methyl-2-nitro	7.5	169-170	benzene	$C_{11}H_{10}N_2O_2$						
2,5,6-trimethyl-8-nitro (b)	4,5-dimethyl-2-nitro	16.3	182-183	benzene	$C_{12}H_{12}N_2O_2$						
2,3,4,5.8-pentamethyl	2,5-dimethyl	6.0	82-83	methanol	$C_{14}H_{17}N$	84.37	8.60	7.03	84.19	8.54	6.77
2,3,4,6,7-pentamethyl	3,4-dimethyl	22.1	144-145	benzene	$C_{14}H_{17}N$	84.37	8.60	7.03	84.10	8.26	7.00
2-methyl-5-phenyl-8-nitro	5-phenyl-2-nitro	12.7	140-141	benzene-pet. ether	$C_{16}H_{12}N_2O_2$	72.72	4.58	10.60	72.47	4.53	10.38
8-bromo-2,5,6-trimethyl	2-bromo-4,5-dimethyl	6.7	90-91	pet. ether	$C_{12}H_{12}NB$· (c)	57.60	4.80		57.61	4.84	

(a,b) Previously prepared by another method. See Refs. 7, 5. (c) Calcd: Br, 31.94; Found: Br, 31.79.

TABLE II

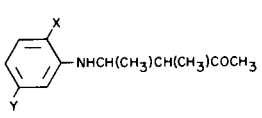
Quinolines Prepared from 4-Hydroxy-2-Pentanone

Substituted quinoline prepared	Substituted aniline used	Yield %	M.P. (°C)	Crystallization solvent	Formula	Analysis Calcd. % C	H	N	Found % C	H	N
2,4,5-trimethyl-8-nitro	5-methyl-2-nitro	7.9	130-131	benzene	$C_{12}H_{12}N_2O_2$	66.65	5.59	12.95	66.82	5.48	12.85
2,4,5,6-tetramethyl-8-nitro	4,5-dimethyl-8-nitro	13.0	168-169	benzene	$C_{13}H_{14}N_2O_2$	67.81	6.13	12.17	67.76	6.08	12.53
2,4,5,8-tetramethyl (a)	2,5-dimethyl	23.1	45-46	pet. ether	$C_{13}H_{15}N$						

(a) Previously prepared by another method. See Ref. 15.

all normal products.

By way of explanation of the abnormal behavior of 3-methyl-3-penten-2-one with anilines substituted in the 2- and 5-positions it is assumed that the first-formed addition compound of the type mentioned by Badger (14),



being unable to cyclize due to hindrance in the 5-position, may slowly revert to the original ingredients, followed by hydration of the 3-methyl-3-penten-2-one to the aldol, $CH_3COCH(CH_3)CH(OH)CH_3$. A retro aldol reaction would then yield butanone and acetaldehyde, which could then condense to form crotonaldehyde, the logical precursor of the 2-methylquinolines obtained. The reaction of cyclization must therefore be much more rapid than the reverse aldol reaction. With such bases as 2-nitroaniline,

TABLE III

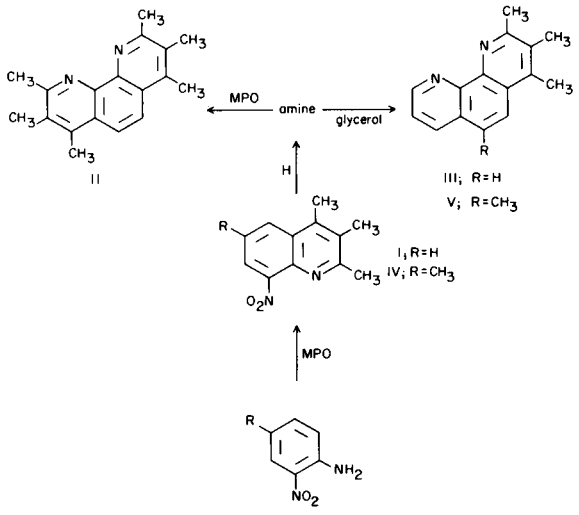
Quinolines Prepared from 4-Hydroxy-3-methyl-2-butanone

Substituted quinoline prepared	Substituted sniline used	Yield %	M.P. (°C)	Crystal-lization solvent	Formula	Analysis Calcd. % C	H	N	Found % C	H	N
3,4,5-tri-methyl-8-nitro	5-methyl-2-nitro	24.6	177-178	benzene	$C_{12}H_{12}N_2O_2$	66.65	5.59	12.95	66.87	5.61	12.81
3,4,5,8-tetra-methyl	2,5-dimethyl	7.2	81-82	pet. ether	$C_{13}H_{15}N$	84.28	8.16	7.56	84.37	8.39	7.55
3,4,6,7-tetra-methyl	3,4-dimethyl	14.6	124-125	benzene	$C_{13}H_{15}N$	84.28	8.16	7.56	84.35	8.18	7.71
3,4,5,6,8-tenta-methyl	2,4,5-tri-methyl	13.9	101-102	pet. ether	$C_{14}H_{17}N$	84.37	8.60	7.03	84.55	8.65	6.98

4-methyl-2-nitroaniline and 3,4-dimethylaniline, where there is no hindering group in the 5-position, three methyl groups were introduced into the heterocyclic ring. In the case of 2,5-dimethylaniline this is also true, but a very low yield resulted.

When 4-hydroxy-3-methyl-2-butanone was substituted for 3-methyl-3-penten-2-one, methyl groups were found in the 3 and 4 positions of the heterocyclic ring even when the original anilines were substituted in the 2- and 5-positions. In this case a retro aldol reaction would yield formaldehyde, which could not form a new unsaturated aldehyde.

4-Hydroxy-2-pentanone with similarly substituted anilines also yielded the expected 2,4-dimethylquinoline derivatives. Apparently here the retro aldol reaction which would yield acetaldehyde did not occur so readily.



MPO = 3-methyl-3-penten-2-one

In the reaction of 3,4-dimethylaniline with 3-methyl-3-penten-2-one and with 4-hydroxy-3-methyl-2-butanone, where ring closure in either of two positions is possible, it was shown to occur as expected, in the unhindered position by nmr measurements.

EXPERIMENTAL

General Procedure for the Preparation of Polymethyl and 8-Nitro-polymethylquinolines.

A mixture of one molar proportion of the appropriately substituted aniline, two molar proportions of arsenic acid hemihydrate and 85% phosphoric acid (100 ml. per 0.1 mole of amine) was heated to 105-110° in a three-neck flask equipped with reflux condenser, stirrer and thermometer, and treated dropwise with two molar proportions of the suitable α,β-unsaturated ketone. After addition was completed, the temperature of the reaction mixture was maintained at 120-130° for 3 hours. It was then poured on ice, and made alkaline with concentrated potassium hydroxide solution. If a precipitate formed, it was removed by filtration, dried, extracted with benzene, the solvent removed, and the residue crystallized from the solvent indicated in the tables. If a liquid remained after making alkaline, it was extracted with benzene, the solvent removed, and the liquid distilled *in vacuo*. The distillate, on solidification, was crystallized from the solvent shown in the tables.

2,3,4-Trimethyl-8-aminoquinoline.

To a cooled, stirred solution of 94.8 g. of tin (II) chloride dihydrate in 275 ml. of concentrated hydrochloric acid was added a suspension of 22.6 g. of 2,3,4-trimethyl-8-nitroquinoline (I) (see (Table I) in 96 ml. of hydrochloric acid at such a rate that the temperature did not exceed 10°. The reaction mixture was stirred for one hour at this temperature and for 3 hours at room temperature. It was then made alkaline with concentrated sodium hydroxide solution, extracted with ether and dried over sodium sulfate. The solid remaining after removal of the ether was crystallized from petroleum ether, yielding 16.8 g. (86.6%) of pure product, m.p. 90-91°.

Anal. Calcd. for $C_{12}H_{14}N_2$: C, 77.39; H, 7.58; N, 15.04. Found: C, 77.26; H, 7.46; N, 14.96.

2,3,4,6-Tetramethyl-8-aminoquinoline.

A solution of 11.1 g. of 2,3,4,6-tetramethyl-8-nitroquinoline (IV) (see Table I) in 43 ml. of concentrated hydrochloric acid was added to a cooled, stirred solution of 43 g. of tin (II) chloride dihydrate in 121 ml. of concentrated hydrochloric acid while keeping the temperature below 10°. The further procedure was the same as in the preparation of 2,3,4-trimethyl-8-aminoquinoline. The yield of pure product, crystallized from petroleum ether, and melting at 122°, was 6.6 g. (70.2%).

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 78.29; H, 8.15; N, 14.18.

2,3,4-Trimethyl-1,10-phenanthroline (III).

To a stirred mixture of 16.8 g. of 2,3,4-trimethyl-8-aminoquinoline, 90 ml. of water, 27 ml. of concentrated sulfuric acid and 12 g. of arsenic acid hemihydrate heated to 100°, was added 33 g. of glycerol while keeping the temperature below 110°. Heating was then continued for 2 hours at 135-140°. The mixture was then poured into ice water and neutralized with concentrated potassium hydroxide solution. The resulting precipitate and filtrate were extracted with hot benzene. The benzene was removed, and the residue was recrystallized from benzene. The yield of pure product, m.p. 173-174° (after drying at 100°), was 2.7 g. (13.5%).

Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.55; H, 6.24; N,12.31.

2,3,4,7,8,9-Hexamethyl-1,10-phenanthroline (II).

A stirred mixture of 11.0 g. of 2,3,4-trimethyl-8-aminoquinoline, 16.7 g. of arsenic acid hemihydrate and 60 ml. of 85% phosphoric acid was heated to 100°. While maintaining this temperature there was added 11.6 g. of 3-methyl-3-penten-2-one. The temperature was gradually raised to 135-140° over a period of 2 hours. The contents of the flask were then poured on ice and neutralized with concentrated potassium hydroxide solution. The resulting precipitate, after drying overnight, was extracted with benzene, the benzene was removed and the residue was crystallized from the same solvent. The yield of pure product, m.p. 247-248°, was 1.9 g. (12.4%).

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.75; H, 7.55; N, 10.66.

2,3,4,6-Tetramethyl-1,10-phenanthroline (V).

To a stirred mixture of 6.6 g. of 2,3,4,6-tetramethyl-8-aminoquinoline, 5 ml. of water, 6.7 ml. of concentrated sulfuric acid and 9.9 g. of arsenic acid, preheated to 100°, was gradually added 11 g. of glycerol. The further procedure was the same as for the preparation of 2,3,4-trimethyl-1,10-phenanthroline. The yield of pure product, crystallized from benzene, and melting at 205°, was 1.6 g. (20.5%).

Anal. Calcd. for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.54; H, 6.88; N, 11.55.

2,5,6-Trimethyl-8-nitroquinoline (alternate method).

A mixture of 10 g. of 2-nitro-4,5-dimethylaniline, 17.1 g. of arsenic acid and 100 ml. of 85% phosphoric acid was treated with 13.4 g. of 3-ethyl-3-penten-2-one according to the general directions. The yield of pure product, m.p. 182-183°, was 0.9 g. (7.0%). This was identical with that obtained from 3-methyl-3-pentene-2-one and the same base.

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