QUINALDINE DERIVATIVES

XXVI.* SYNTHESES OF SUBSTITUTED 3,4-DIHYDRO-2H-PYRANO[3,2-c]QUINOLINES

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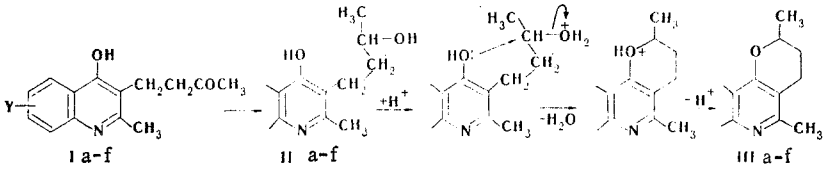
A new synthesis of substituted 2,5-dimethyl-3,4-dihydro-2H-pyrano[3,2-c]quinolines is realized by heating the corresponding 2-methyl-3-(3-hydroxybutyl)-4-hydroxy(methoxy)-quinoline in polyphosphoric acid. The preparation of ketones of the quinoline series is described.

In recent years, there has been growing interest in the synthesis and investigation of pyrano- and pyronoquinolines and their derivatives [2-5], including some natural alkaloids of the pyranoquinoline series [6,7].

We have investigated the possibility of the synthesis of 2,5-dimethyl-3,4-dihydro-2H-pyrano[3,2-c]-quinolines (IIIa-f) from substituted 2-methyl-3-(3-hydroxybutyl)-4-hydroxyquinolines (IIa-f) obtained by the reduction of the corresponding substituted 2-methyl-3-(3-oxobutyl)-4-hydroxyquinolines (Ia-f).

It was found that dihydropyranoquinolines IIId,e are formed only on heating with polyphosphoric acid, while IIIa,b,f are formed on heating the corresponding IIa-f with 17% hydrochloric acid.

The reaction proceeds via the scheme



I a-f II a-f III a-f

a Y=H; b 6-CH_3; c 6-$NHCOCH_3$; d 6-NH_2; e 5,6-benzo; f 7,8-benzo

Thus localization of the charge of the oxygen atom in the 4 position of quinoline is of decisive significance for ring formation. The substituents of the benzene ring, depending on their nature, can also have a definitive effect on this reaction.

Quinolylbutanones (Ib-f) were obtained by hydrolysis of substituted 2-methyl-3-(3-chlorocrotyl)-4-hydroxyquinolines with 85% sulfuric acid as in [8].

Ketones Ia-f are reduced by aluminum isopropoxide in isopropyl alcohol. Compounds IIa-f are formed in low yields because of the low solubility of the ketones in isopropyl alcohol.

In order to obtain alcohols in higher yields, substituted 2-methyl-3-(3-chlorocrotyl)-4-methoxyquinolines (IVa-f) were subjected to sulfuric acid hydrolysis, since the solubility of these compounds in organic solvents increases when the 4-OH group is methylated. The hydrolysis proceeds much more readily than for the corresponding substituted 2-methyl-3-(3-chlorocrotyl)-4-hydroxyquinolines. In order to avoid hydrolysis of the 4-OCH_3 group, the reaction is carried out at low temperatures in concentrated sulfuric acid.

*See [1] for communication XXV.

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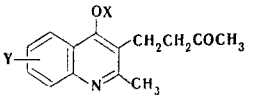
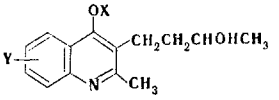
TABLE 1. Substituted 2-Methyl-3-(3-oxobutyl)-4-hydroxy(methoxy)quinolines



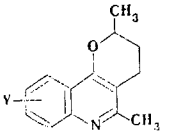
Comp.	Y	X	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
Ia	H	H	243—244	$C_{14}H_{15}NO_2$	73,65	6,67	6,39	73,34	6,59	6,10	82,5
Va		CH_3	66	$C_{15}H_{17}NO_2$	73,82	7,24	5,84	74,07	7,04	5,78	85,6
Ib	6-CH_3	H	262—263	$C_{15}H_{17}NO_2$	73,88	7,21	5,92	74,07	7,04	5,78	80,3
Vb		CH_3	78	$C_{16}H_{19}NO_2$	74,29	7,19	5,21	74,68	7,57	5,44	82,5
Ic	6-HNCO-CH_3	H	268—270	$C_{16}H_{18}N_2O_3$	67,51	6,52	9,48	67,11	6,34	9,79	67,8
Vc		CH_3	166—167	$C_{17}H_{22}N_2O_3$	67,54	6,84	9,51	67,98	7,38	9,33	64,3
Id	6-NH_2	H	183—186	$C_{14}H_{16}N_2O_2$	69,25	6,28	11,25	68,83	6,60	11,47	58,7
Vd		CH_3	92—93	$C_{15}H_{18}N_2O_2$	69,83	7,26	10,67	69,74	7,02	10,84	53,4
Ie	5,6-Benzo-	H	180—182	$C_{18}H_{17}NO_2$	76,7	6,08	5,22	77,38	6,13	5,01	68,5
Ve		CH_3	80—81	$C_{19}H_{19}NO_2$	77,23	6,38	4,63	77,79	6,53	4,77	73,6
If	7,8-Benzo-	H	242—245	$C_{18}H_{17}NO_2$	77,93	6,30	5,18	77,38	6,13	5,01	74,6
Vf		CH_3	125—126	$C_{19}H_{19}NO_2$	78,13	6,65	4,83	77,79	6,53	4,77	81,8

TABLE 2. Substituted 2-Methyl-3-(3-hydroxybutyl)-4-hydroxy-(methoxy)quinolines



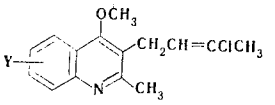
Comp.	Y	X	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
IIa	H	H	218—220	$C_{14}H_{17}NO_2$	73,12	7,38	6,28	72,70	7,25	6,19	45,2
VIa		CH_3	52	$C_{15}H_{19}NO_2$	73,64	8,02	5,92	73,44	7,87	5,79	92,1
IIb	6-CH_3	H	245—246	$C_{15}H_{19}NO_2$	73,18	7,98	5,68	73,44	7,87	5,79	41,5
VIb		CH_3	83—84	$C_{16}H_{21}NO_2$	73,92	8,31	5,65	74,11	8,17	5,40	91,6
IIc	6-$HNCOCH_3$	H	275—276	$C_{16}H_{20}N_2O_3$	66,91	6,78	9,36	66,65	6,99	9,71	12,3
VIc		CH_3	192—193	$C_{17}H_{22}N_2O_3$	67,23	7,52	9,54	67,53	7,33	9,26	84,2
Id	6-NH_2	H	204—206	$C_{14}H_{18}N_2O_2$	68,88	7,12	11,18	68,59	7,36	11,37	14,6
Vd		CH_3	147—149	$C_{15}H_{20}N_2O_2$	69,48	7,68	10,90	69,20	7,74	10,76	85,7
IIe	5,6-Benzo-	H	212—213	$C_{18}H_{19}NO_2$	76,68	7,76	5,12	76,84	6,80	4,97	33,8
VIe		CH_3	87—89	$C_{19}H_{21}NO_2$	77,59	7,32	4,88	77,25	7,16	4,74	90,4
IIf	7,8-Benzo-	H	228—230	$C_{18}H_{19}NO_2$	77,1	6,94	4,82	76,84	6,80	4,97	41,4
VIf		CH_3	94—95	$C_{19}H_{21}NO_2$	77,48	7,04	4,95	77,25	7,16	4,74	94,5

TABLE 3. Substituted 2,5-Dimethyl-3,4-dihydro-2H-pyrano[3,2-c]-quinolines



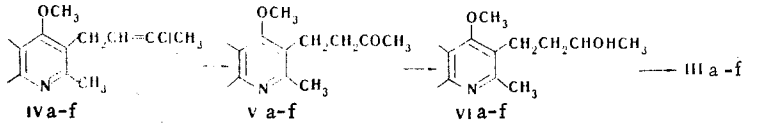
Comp.	Y	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
IIIa	H	76—77	$C_{16}H_{15}NO$	79,12	7,24	6,25	78,56	7,08	6,56	87,1
IIIb	6-CH_3	82	$C_{15}H_{17}NO$	78,90	7,46	6,73	79,26	7,53	6,53	90,5
IIIc	6-NH_2	104—105	$C_{14}H_{16}N_2O$	74,13	6,91	12,32	73,65	7,06	12,28	63,4
IIIe	5,6-Benzo-	125—126	$C_{18}H_{17}NO$	81,50	6,72	5,15	82,11	6,50	5,31	78,3
IIIf	7,8-Benzo-	167—169	$C_{18}H_{17}NO$	82,81	6,64	5,18	82,11	6,50	5,31	93,4

TABLE 4. Substituted 2-Methyl-3-(3-chlorocrotyl)-4-methoxyquinolines

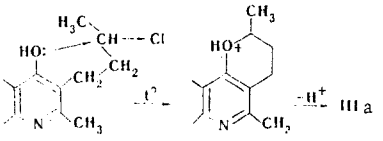


Comp.	Y	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	N	Cl	C	H	N	Cl	
IVa	H	56	$C_{15}H_{16}ClNO$	69,10	6,26	5,56	13,98	68,83	6,16	5,35	13,54	78,5
IVb	6-CH_3	68	$C_{16}H_{18}ClNO$	76,48	6,72	5,38	13,12	76,97	6,58	5,08	12,85	68,4
IVc	6-$HNCOCH_3$	188—190	$C_{17}H_{19}ClN_2O_2$	64,60	5,89	9,54	11,36	64,05	6,01	9,88	11,12	52,8
IVd	6-NH_2	167	$C_{15}H_{17}ClN_2O$	65,31	6,33	9,85	12,48	65,09	6,19	10,12	12,81	54,4
IVe	5,6-Benzo-	82—83	$C_{19}H_{18}ClNO$	72,85	5,96	4,72	11,16	73,19	5,81	4,49	11,36	65,3
IVf	7,8-Benzo-	79—80	$C_{19}H_{18}ClNO$	73,43	5,88	4,68	11,54	73,19	5,81	4,49	11,36	72,6

The resulting substituted 2-methyl-3-(3-oxobutyl)-4-methoxyquinolines (Va-f) are reduced to VIa-f with lithium isopropoxide. Like IIa-f, the latter undergo cyclization to form pyranoquinolines IIIa-f.



The action of thionyl chloride on IIa gives 2-methyl-3-(3-chlorobutyl)-4-hydroxylquinoline (VII), which, on heating to 150°, is converted to the hydrochloride of IIIa. The latter forms free base IIIa on treatment with alkali.



EXPERIMENTAL

Substituted 2-Methyl-4-hydroxy-3-(3-oxobutyl)quinolines (Ia-f). A mixture of 0.05 mole of the corresponding substituted 2-methyl-3-(3-chlorocrotyl)-4-hydroxyquinoline and 20 ml of 85% sulfuric acid was heated with stirring at 60-70° for 5-10 min. The mixture was then cooled and poured over 200 g of ice and filtered. The mother liquor was neutralized with sodium carbonate, and the resulting precipitate was removed by filtration and crystallized from alcohol. Data for the resulting ketones (Ia-f) are presented in Table 1.

Substituted 2-Methyl-3-(3-oxobutyl)-4-hydroxyquinolines (IIa-f). A mixture of 0.03 mole of Ia-f, 45 ml of a 1 M solution of aluminum isopropoxide in isopropyl alcohol (0.045 mole), and 50 ml of isopropyl alcohol was refluxed moderately on a water bath in such a way that the isopropyl alcohol slowly distilled off. Reduction of Ia,b,e,f was complete after 1 h, after which the isopropyl alcohol was completely removed by distillation, and water was added to the residue. After 10-15 min of vigorous stirring at 70-80°, the precipitate was removed by filtration and refluxed with alcohol. The resulting alcohol solution was evaporated, and the residue was crystallized from 50% aqueous alcohol.

In the preparation of IIc, d the initial mixture was refluxed for 6 h. The undissolved starting substance was then removed by filtration, and the solution was worked up as described above. Data for the alcohols obtained are presented in Table 2.

Substituted 2,5-Dimethyl-3,4-dihydro-2H-pyrano[3,2-c]quinolines (IIIa-f). A) A mixture of 0.01 mole of IIa-f and 25 g of polyphosphoric acid was heated at 100-110° for 3 h. The mixture was then cooled and poured over ice, and the ice mixture was filtered and neutralized with sodium carbonate. The resulting precipitate was removed by filtration and crystallized from 50% alcohol. Data for IIIa-f are presented in Table 3.

B) A mixture of 0.01 mole of VIa-f and 25 g of polyphosphoric acid was heated at 100-110° for 1-2 h. The mixture was then worked up as in the preceding experiment to give the corresponding IIIa-f.

C) A mixture of 0.01 mole of IIa,b,f and 50 ml of 6 N hydrochloric acid was refluxed for 5-6 h. The mixture was cooled and diluted with water to twice the original volume and neutralized with sodium carbonate to give 55-64% yields of IIIa,b,f.

D) A 1-g sample of VII was heated at 150° for about 1 h. It was then dissolved in water, and the solution was neutralized with alkali to give 0.84 g (98%) of a product that was identical to IIIa.

Substituted 2-Methyl-3-(3-chlorocrotyl)-4-methoxyquinolines (IVa-f). A mixture of 0.1 mole of substituted 2-methyl-3-(3-chlorocrotyl)-4-hydroxyquinoline, 100 ml of dry toluene, and 0.1 mole of dimethyl sulfate was refluxed for 12 h. The mixture was cooled, the toluene was decanted, and 10% sodium carbonate solution was added to the residual viscous mass. The mass began to crystallize after thorough stirring. The decanted toluene solution was distilled, the residue was dissolved in water, and the solution was neutralized with sodium carbonate. The resulting crystalline substances were mixed and recrystallized from 50% aqueous alcohol. Data for IVa-f are presented in Table 4.

Substituted 2-Methyl-3-(3-oxobutyl)-4-methoxyquinolines (Va-f). A mixture of 0.01 mole of IVa-f and 20 ml of sulfuric acid (sp. gr. 1.84) was shaken for 15-20 min at room temperature and poured into 200 g of crushed ice. The mixture was filtered, and the filtrate was neutralized with ammonia. The precipitate was separated and crystallized from water. Data for Va-f are presented in Table 1.

Substituted 2-Methyl-3-(3-hydroxybutyl)-4-methoxyquinolines (VIa-f). Compounds Va-f were reduced in the same way as IIa-f. At the end of the reaction, the isopropyl alcohol was removed completely by distillation, and the residue was dissolved in 10% sulfuric acid. The resulting solution was filtered and made alkaline with NaOH. The 4-methoxyquinolylbutanols were separated by filtration and crystallized from water. Data for VIa-f are presented in Table 2.

2-Methyl-3-(3-chlorobutyl)-4-hydroxyquinoline (VII). A mixture of 1.3 g (5 mmole) of Ia and 20 ml of thionyl chloride was refluxed for 1.5 h. The thionyl chloride was removed by distillation, and the residue was treated with cold water, filtered, and crystallized from alcohol to give 1.1 g (89.5%) of a product with mp 138°. Found: Cl 14.62; N 5.62%. $C_{14}H_{16}ClNO$. Calculated: Cl 14.45; N 5.70%.

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