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4-HYDROXY-2-QUINOLONES. 37.* SIMPLE SYNTHESIS OF 1-R-2-OXO-3,4-DIHYDROXYQUINOLINES

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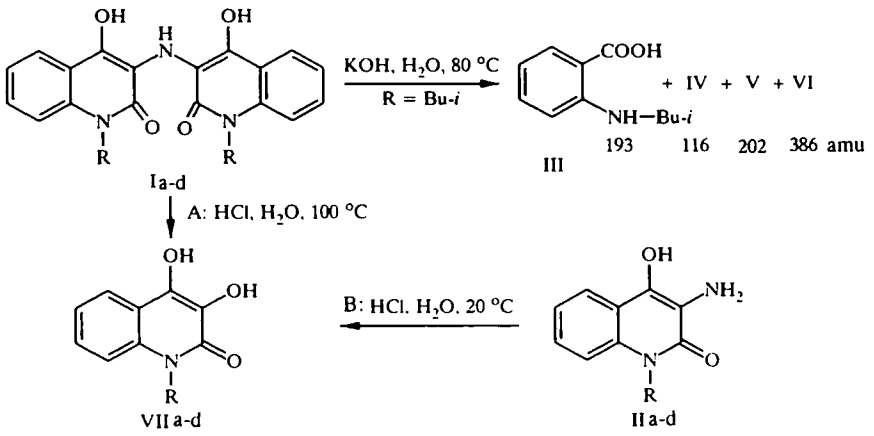
3-Amino-1-R-2-oxo-4-hydroxyquinolines easily undergo acid hydrolysis with formation of the corresponding 1-R-2-oxo-3,4-dihydroxyquinolines.

A rather widely used method for establishing the structure of complicated organic compounds is the now classic method of degradation of the analyte compound under specific conditions followed by identification of the structurally simpler decomposition products, which makes it possible to obtain valuable information about the structure of the starting compound [2, 3] and in a number of cases also leads to interesting synthetic discoveries [4].

One of the steps in the investigation of the structure of di(1-R-2-oxo-4-hydroxyquinolin-3-yl)amines I (the photocondensation products of 3-aminoquinolines II [5]) was the study of the response of these compounds to base and acid hydrolysis. It was found that diquinolylamines I are easily decomposed by aqueous solutions of bases even at room temperature with formation (as shown for the example of the N-isobutyl derivative Id) of a mixture of at least four compounds III-VI; according to TLC and the chromatographic/mass spectrum, the major product is N-isobutylanthranilic acid (III). Formation of N-substituted anthranilic acids was also noted in base hydrolysis of 3-acetylamino-1-R-2-oxo-4-hydroxyquinolines in [6].

The data obtained in acid hydrolysis of diquinolylamines I is no less interesting; as a result of this reaction, 3,4-dihydroxyquinolines VII were unexpectedly isolated (method A).



I, II, VII a R = H; b R = Me; c R = Et; d = *i*-Bu

Being the structural analogs of 3,4-dihydroxypyridines [7-9], these compounds are of interest as potential antithyroid drugs. However, due to the relatively low yields, method A can hardly be of practical importance in synthesis of these compounds.

*For Communication 36, see [1].

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TABLE 1. 1-R-2-Oxo-3,4-dihydroxyquinolines VIIa-d

Compound	Empirical formula	Found, % / Calculated, %			T_{mp}*, °C	Yield by method, %
		C	H	N		
VIIa	$C_9H_7NO_3$	61,07 / 61,02	4,00 / 3,98	7,88 / 7,91	256...258	A 31 B 96
VIIb	$C_{10}H_9NO_3$	62,80 / 62,82	4,71 / 4,74	7,43 / 7,33	210...212	A 25 B 93
VIIc	$C_{11}H_{11}NO_3$	64,40 / 64,38	5,49 / 5,40	6,82 / 6,83	198...200	B 90
VIId	$C_{13}H_{15}NO_3$	66,96 / 66,94	6,52 / 6,48	6,07 / 6,00	192...194	A 22 B 94

*Compounds VIIa,b were crystallized from water; the rest were crystallized from diethyl ether.

TABLE 2. Spectral Characteristics of Synthesized Compounds

Compound	PMR spectra, δ, ppm					Mass spectrum, *m/z* (relative intensity, %)
	4-OH (1H, s)	3-OH (1H, s)	H arom 5-H (1H, d)	H arom 6...8-H (3H, m)	R	
VIIa	10,05	8,72	7,71	7,44...6,98	11,59 (1H, s, NH)	177 (100) $[M]^+$, 148 (10) $[M-CHO]^+$, 103 (44), 93 (38), 76 (27)
VIIb	10,11	8,73	7,84	7,50...7,14	3,64 (3H, s, Me)	191 (100) $[M]^+$, 177 (14), 162 (14) $[M-CHO]^+$, 106 (33), 77 (18)
VIIc	10,11	8,72	7,84	7,53...7,13	4,30 (2H, q, NCH_2); 1,20 (3H, t, Me)	205 (73) $[M]^+$, 177 (100), 148 (15), 130 (20), 103 (32), 77 (19)
VIId	10,59	8,72	7,84	7,50...7,10	4,16 (2H, d, NCH_2); 2,12 (1H, m, CH); 0,88 (6H, d, Me×2)	233 (23) $[M]^+$, 177 (100), 148 (10), 134 (17), 77 (13)

Nevertheless, we have successfully extended the principle itself to the 3-aminoquinolines II, which under mild conditions are hydrolyzed by dilute hydrochloric acid to the corresponding 3-hydroxy derivatives VII in high preparative yields (method B).

Considering the instability of 3-aminoquinolines II, earlier it was suggested that they be converted to hydrochlorides as needed for storage [10]. We consider it advisable to revise this statement to say that such a recommendation may concern only 1-substituted derivatives, since as shown by further investigations, the hydrochloride of 3-amino-1-H-2-oxo-4-hydroxyquinoline during storage without any treatment is quantitatively converted to the diquinolylamine Ia. The hydrochlorides of 1-alkyl-substituted analogs under the same conditions do not undergo appreciable chemical conversions, so the likely reason for the lability of the 1H-derivative may be its ability to form the 2,4-dihydroxy form.

EXPERIMENTAL

The PMR spectra of the synthesized compounds were recorded on a Bruker WP-100 SY instrument in DMSO-D_6, internal standard TMS. The mass spectra were recorded on a Finnigan MAT Incos 50 quadrupole spectrometer with full scanning in the 33-700 *m/z* range, electron-impact ionization at 70 eV, direct injection, heating rate ~5°C.

Di(1H-2-oxo-4-hydroxyquinolin-3-yl)amine (Ia). The hydrochloride of 3-amino-1H-2-oxo-4-hydroxyquinoline [10] was stored under usual conditions for one month, after which it was subjected to chromatographic/mass spectrometric analysis. There was none of the starting amine in the sample. The material obtained was treated with a 5% aqueous HCl solution, filtered, washed with water, and dried. Diquinolylamine Ia was obtained in quantitative yield, mp > 300°C. Mass spectrum,

m/z (relative intensity, %): 335 (20) $[M]^+$, 161 (30), 103 (22), 92 (28), 40 (100). Found, %: C 64.40; H 3.97; N 12.62. $C_{18}H_{13}N_3O_4$. Calculated, %: C 64.48; H 3.91; N 12.53.

Base Hydrolysis of Diamines Ia-d. 1 g of the corresponding diamine I in 20 in 20 ml 10% aqueous KOH solution was allowed to stand for 4-5 days. Then the intense blue color present at the beginning disappeared. The reaction mixture was acidified with dilute (1:1) HCl down to pH ~4 and extracted with ether (3 × 20 ml). The ether extract was evaporated and the mixture obtained was subjected to chromatographic/mass spectrometric analysis, the results of which for the N-isobutyl derivative Id are given on the scheme shown earlier in the text. TLC was done on a Silufol UV-254 plate in the hexane–ether system, 5:3. N-Isobutylanthranilic acid (III), as the product of base hydrolysis of the diamine Id, was identified from the R_f value (0.50) compared with a known sample.

1H-2-Oxo-3,4-dihydroxyquinoline (VIIa). A. A solution of 3.35 g (0.01 moles) diquinolylamine Ia in 50 ml dilute (1:1) HCl was boiled for 30 min and filtered hot. As the filtrate cooled, 3,4-dihydroxyquinoline VIIa crystallized out of solution. It was filtered off, washed with water, and dried.

B. 2 ml conc. HCl was added to a suspension of 1.76 g (0.01 moles) 3-aminoquinoline IIa in 30 ml water (in this case, the hydrochloride of the aminoquinoline should not precipitate) and the solution obtained was allowed to stand for 10-12 h at room temperature. The crystalline precipitate of the 3-hydroxy derivative falling out of solution over this time period was filtered off, washed with water, and dried.

A mixture with a sample of 3,4-dihydroxyquinoline VIIa obtained by method A did not give a depression of the melting point; the PMR and mass spectra of these compounds were identical.

REFERENCES

1. I. V. Ukrainets, S. G. Taran, S. V. Sidorenko, O. V. Gorokhova, and A. V. Turov, Khim. Geterotsikl. Soedin., No. 11, 1536 (1997) [this issue].
2. K. W. Bentley (ed.), Elucidation of Structures by Physical and Chemical Methods, Vol. 2 [Technique of Organic Chemistry, Vol. 11, A. Weissberger (ed.)], [Russian translation], Khimiya, Moscow (1967).
3. R. C. Elderfield (ed.), Heterocyclic Compounds, Vol. 5 [Russian translation], Inostr. Lit., Moscow (1961), p. 548.
4. D. Gröger, in: Abstracts of Proceedings, Bioorganic Heterocyclic Synthesis, Physical Organic and Pharmacological Aspects, 1984: Third Fechem Conference on Heterocyclic Bioorganic Chemistry, Balaton, Budapest (1984), p. 165.
5. I. V. Ukrainets, S. G. Taran, L. V. Sidorenko, O. V. Gorokhova, A. V. Turov, and A. A. Ogirenko, Khim. Geterotsikl. Soedin., No. 7, 933 (1997).
6. S. M. Sami, A. A. Sayed, S. S. Ibrahim, and S. Z. Ahmed, Egypt. J. Chem., **27**, 11 (1984).
7. B. Hallengren, M. P. Hegarty, and A. Forsgren, Acta Endocrinol., **114**, 305 (1987).
8. Masahiro Sugawaga, D. L. Park, and J. Hershman, Proc. Soc. Exp. Biol. Med., **110**, 431 (1982).
9. G. S. Christie, C. P. Lee, and M. P. Hegarty, Endocrinology, **105**, 342 (1979).
10. I. V. Ukrainets, S. G. Taran, L. V. Sidorenko, O. V. Gorokhova, A. A. Ogirenko, A. V. Turov, and N. I. Filimonova, Khim. Geterotsikl. Soedin., No. 8, 1113 (1996).