4-HYDROXY-2-QUINOLONES.

2.* SIMPLE SYNTHESIS OF ARBORICINE

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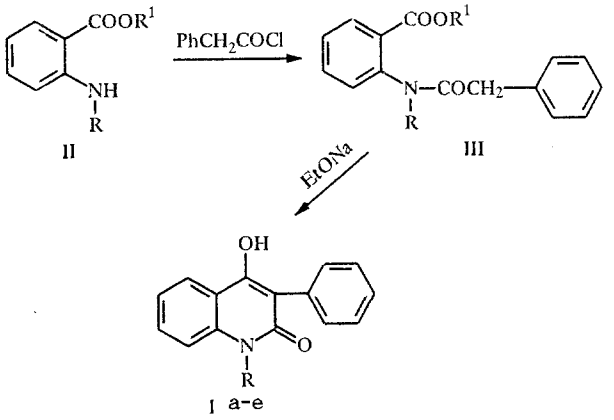
Acylation of methyl N-methylanthranilate with phenylacetyl chloride with subsequent intramolecular cyclization of the resulting anilide was used to synthesize 1-methyl-3-phenyl-4-hydroxy-2-quinolone (arboricine).

Arboricine (Ib) was obtained as a minor product after alkaline destruction in an attempt to prove the structure of the alkaloid arbornine, which is isolated from the leaves of the plant *Glycosmis arborea* (India) [2]. Since that time, the rarely encountered and little-studied 3-phenyl-substituted quinolones — analogs of 4-aryl-3-hydroxy-2-quinolones that are produced by some species of mold fungi of the genus *Penicillium* [3] — have become the subjects of the great attention of synthetic chemists as potential antimicrobial and antifungal agents [4, 5].

Thus arboricine was synthesized by the reaction of N-methylisatoic anhydride with the enolate generated from ethyl phenylacetate with subsequent cyclization of the product by refluxing in toluene [6]. However, despite the high yield (80%) of the desired quinolone Ib, this method has more theoretical than practical value. The low temperature (−78°C) at which the synthesis is accomplished and the use of a difficult-to-obtain base (potassium hexamethyldisilazide), which is necessary to generate the enolate, are not acceptable for wide application.



I-III a R=H, b R=Me, c R=Et, d R=Pr, e R=Bu; II-III R^1=Me or Et

In this connection, we set out to develop a simpler and more accessible method for the synthesis of 3-phenyl-substituted quinolones. To solve this problem it was of interest to use the method for obtaining 3-alkyl-4-hydroxy-2-quinolones that we previously proposed in [1]. However, the syntheses of the arylmalonic acid monoesters that are necessary for realizing this method are extremely laborious. We therefore attempted to obtain arboricine and its analogs by another method.

The results of our studies showed that 1-R-3-phenyl-4-hydroxy-2-quinolones Ia-e can be synthesized in good yields by acylation of N-R-anthranilic acid esters II with phenylacetyl chloride with subsequent cyclization of the resulting anilides III without isolating them from the reaction mixtures.

The characteristics of the synthesized Ia-e are presented in Table 1. Their structures were confirmed by the PMR spectral data in Table 1.

*See [1] for Communication 1.

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TABLE 1. Characteristics of 1-R-3-Phenyl-4-hydroxy-2-quinolones Ia-e

Compound	Empirical formula	Mp, °C	PMR spectrum, δ, ppm* (SSCC, ^3J and ^4J, Hz)				Yield, %
			Harom			R	
			5-H, dd	7-H, td	Ph, 6-H, 8-H (7H, m)		
Ia	$C_{15}H_{11}NO_2$	325...327	7,95 (8,0 and 1.5)	7,52 (7,0 and 1.9)	7,42...7,08	11,48 (1H, s, NH)	96
I6	$C_{16}H_{13}NO_2$	220...222, (221...223 [6])	8,08 (7,9 and (1.8)	7,67 (7,2 and 1.8)	7,51...7,19	3,61 (3H, s, CH_3)	88
Ic	$C_{17}H_{15}NO_2$	146...147	8,08 (8,0 and (1.5)	7,59 (7,0 and 1.8)	7,46...7,17	4,27 (2H, q, CH_2); 1,21 (3H, t, CH_3)	91
Ir	$C_{18}H_{17}NO_2$	185...186	8,09 (8,0 and 1.8)	7,58 (7,0 and 1.8)	7,48...7,07	4,18 (2H, t, NCH_2); 1,64 (2H, m CH_2—CH_3); 0,95 (3H, t, CH_3)	89
Ie	$C_{19}H_{19}NO_2$	168...169	8,07 (7,9 and 1.8)	7,59 (7,0 and 1.8)	7,43...7,13	4,23 (2H, t NCH_2); 1,50 (4H, m $(CH_2)_2$); 0,93 (3H, t CH_3)	92

*The signals of the protons of the 4-OH groups have the form of a singlet at 10.09-10.3 ppm.

Thus the results demonstrate the possibility of the use of N-(arylacetyl) anthranilic esters for the construction of new cyclic structures.

EXPERIMENTAL

The PMR spectra of solutions of the synthesized compounds in d_6-DMSO were recorded with a Bruker WP-100 SY spectrometer (100 MHz) with tetramethylsilane (TMS) as the internal standard.

The results of elementary analysis for C, H, and N for Ia-e were in agreement with the calculated values.

General Method for the Synthesis of 1-R-3-Phenyl-4-hydroxy-2-quinolones Ia-e. A 3.25-g (0.21 mole) sample of phenylacetyl chloride was added to a solution of 0.02 mole of the N-R-anthranilic acid ester and 2.94 ml (0.021 mole) of triethylamine in 15 ml of acetone, and the reaction mixture was stirred for 4-5 h at room temperature. The acetone was then removed by distillation, an alcohol solution of sodium ethoxide [from 2.3 g (0.1 mole) of sodium metal and 30 ml of ethanol] was added, and the mixture was refluxed for 5 h. It was then cooled and poured into 100 ml of water, and the aqueous mixture was acidified to pH 3-4 with concentrated HCl. The precipitated hydroxyquinolone was removed by filtration, washed with water, and dried. Compound Ia was crystallized from DMF, and the remaining compounds were crystallized from ethanol.

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