

RESEARCH IN THE FIELD OF HETEROCYCLIC CHEMISTRY. XL* ORGANIC ACIDS AS INTRAMOLECULAR CONDENSING AGENTS FOR ARYLAMIDE HYDROXY ACIDS

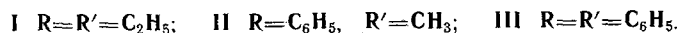
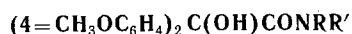
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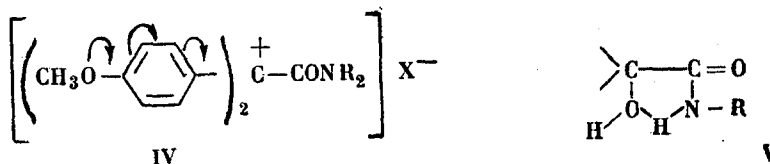
It is shown that the basic properties of arylamides of diarylglycolic acids are determined not only by the nature of the aryl radicals of the acid part of the molecule, but also by the extent to which hydrogen atoms of the amino groups are substituted. Formation of carbonium salts of arylamides is considerably influenced by the nature of the solvent. Intramolecular condensation of tertiary arylamides of 4, 4'-dimethoxy- and 4, 4'-dimethylbenzyllic acids gives a number of new 1-alkyl (aryl)-3, 3-diaryloxindoles. Ethyl N-n-propyl- and N-isobutyloxanilate and N, N-diethylamide-4, 4'-dimethoxybenzylate are described for the first time.

It was previously suggested [2] that organic acids could be used to effect ring closure in tertiary arylamides of diarylglycolic acid. The present work affords support for this view.

The starting compounds chosen were N, N-disubstituted 4, 4'-dimethoxybenzylamides (I-III):



Experiments showed that, irrespective of the nature of the substituent at the nitrogen, tertiary amides I-III have the same basicity and form carbonium (halochromic) salts IV with 2% sulfuric acid. Secondary amides give an acid coloration 21 times stronger [3]. Such a large drop in basicity of secondary as compared with tertiary amines I-III can be explained by intramolecular hydrogen bonding (cf. V) [4]. There is electron displacement from the OH group to the amide hydrogen, giving rise to a decrease in the basicity of the compound.



Hence the basic properties of the arylides of diarylglycolic acids are determined not only by the nature of the radicals of the acid part of the molecule [5], but also by the extent to which the hydrogen atoms of the amido group are substituted.

Similar regularities are observed in the behavior of arylamide towards organic acids (Table 1).

TABLE 1

Reaction of tertiary arylamides I-III with organic acids

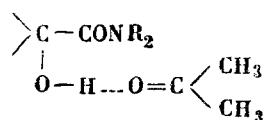
Acid	K	Color	
		CH ₃ COOH	CH ₃ COCH ₃
Picric	4.2 · 10 ⁻¹	+	+
CCl ₃ COOH	2 · 10 ⁻¹	+	+
C ₆ H ₅ SO ₃ H	2 · 10 ⁻¹	+	+
(COOH) ₂	5.9 · 10 ⁻²	+	+
CH ₃ COCOOH	5.6 · 10 ⁻³	+	+
CH ₂ (COOH) ₂	1.49 · 10 ⁻³	—	+
CH ₂ ClCOOH	1.4 · 10 ⁻³	—	+
Citric	8.4 · 10 ⁻⁴	—	+
HCOOH	2.1 · 10 ⁻⁴	+	+

*Colors only on heating (thermochromism).

Acids with K = 5.6 × 10⁻³ or higher give carbonium salts. Formic acid occupies a special position in this series, for though it has a lower dissociation constant, it readily forms carbonium salts. Actually, the OH group of the aryla-

*For part XXXIX see [1].

mides is sterically more accessible to formic acid, which has a smaller molecular volume than other acids. The kind of solvent has an appreciable effect on formation of carbonium salts of arylamides; for example, they form more readily in acetone than in acetic acid. Evidently the basicity of the arylamide increases through intermolecular hydrogen bonding involving solvent VI. The literature [6] describes intermolecular hydrogen bonds of amides derived from benzylic acid and amines [6].



VI

Organic acids were successfully used for converting arylamides II, III to 1-alkyl(aryl)-substituted 3,3-bis-(4'-anisyl)oxindole (VII-XII) (Table 2). The oxindole derivatives VIII-XI were prepared without previously isolating the 4,4'-dimethoxy- and 4,4'-dimethylbenzyl-N-alkyl(aryl)anilides. It is recommended that in the case of weak acids the reaction be carried out in acetone: in the case of formic acid reaction can be effected without a solvent.

Of the organic acids investigated, sulfo acids and formic acid are preferred as condensing agents.

TABLE 2

Melting points, yields, and analytical data for oxindole derivatives

Compound	1-Alkyl(aryl)-3,3-diaryloxindole	Mp, °C*	Empirical formula	N, %		Yield**, %
				Found	Calc.	
VII	1-Methyl-3,3-bis-(4'-anisyl)oxindole	146-148 [2]	C ₂₃ H ₂₁ NO ₃	—	—	94.7
VIII	1-n-Propyl-3,3-bis-(4'-anisyl)oxindole	127-129	C ₂₅ H ₂₅ NO ₃	3.69 3.42	3.61	65.0
IX	1-n-Butyl-3,3-bis-(4'-anisyl)oxindole	83	C ₂₆ H ₂₇ NO ₃	3.15 3.01	3.49	72.9
X	1-Isobutyl-3,3-bis-(4'-anisyl)oxindole	112-113	C ₂₆ H ₂₇ NO ₃	4.10 3.96	4.39	59.0
XI	1-Phenyl-3,3-bis-(4'-tolyl)oxindole	195 [7]	C ₂₈ H ₂₃ NO	—	—	69.0
XII	1-Phenyl-3,3-bis-(4'-anisyl)oxindole	165 [7]	C ₂₈ H ₂₃ NO ₃	—	—	83.8

*All substances recrystallized from alcohol.

**Yield of VIII-IX calculated on the ester taken for reaction.

EXPERIMENTAL

N,N-Diethylamide-4,4'-dimethoxybenzylate (I). Prepared by reacting 13.8 g (0.08 mole) ethyl N,N-diethyloxamate with p-anisylmagnesium iodide prepared from 46.8 g (0.43 mole) p-iodoanisole and 4.8 g (0.2 mole) magnesium, the reaction product being decomposed with a saturated solution of ammonium chloride. Yield 17 g (62.2%), needles (from alcohol), mp 85°. With mineral and organic acids it gives a stable red-violet color. Found: N 4.20, 4.32%. Calculated for C₂₀H₂₅NO₄: N 4.08%.

Ethyl N-propyloxanilate (XIII). 11.1 g (0.08 mole) monoethyloxalate chloroanhydride is added with cooling and stirring to a solution of 11 g (0.08 mole) n-propylaniline and 8.3 g (0.08 mole) triethylamine, in 50 ml dry ether. The mixture is heated for 30 min, treated with 15 ml water, the ether layer separated off, and dried over sodium sulfate. The solvent is evaporated and the residue distilled. Bp 212-215° (8 mm). Crystallized from petroleum ether, mp 45-46°. Yield 11 g (56.7%). Found: N 6.17, 6.32%. Calculated for C₁₃H₁₇NO₃: N 5.95%.

Ethyl N-isobutyloxanilate (XIV). Yield 49%, bp 130° (2 mm), mp 48° (from petroleum ether). Found: N 6.14, 6.23%. Calculated for C₁₄H₁₉NO₃: N 5.62%.

1-Phenyl-3,3-bis-(4'-anisyl)oxindole (XII).

a) 0.5 ml 85% formic acid (or the corresponding quantity of one of the following acids: picric, CCl₃COOH, CH₃COCO₂H, C₆H₅SO₃H) is added to a solution of 0.2 g (0.8 mmole) III in 1 ml glacial acetic acid. When the red-

violet color has disappeared, the mixture is diluted with 10 ml water, the precipitate filtered off, and crystallized. Yield 0.16 g. A similar experiment was carried out using 2.5 ml 85% formic acid, but without solvent. Yield 0.18 g (94.2%).

b) 0.12 g (1.1 mmole) malonic acid (or monochloroacetic or oxalic acid) is added to 0.2 g (0.8 mmole) III in 0.5 ml acetone. To bring the reaction to completion, the mixture is heated on a water bath till the red-violet color goes, and further worked up in the way described above. Yield 0.17 g (89%).

1-Isobutyl-3,3-bis-(4'-anisyl)oxindole (X). p-Anisylmagnesium iodide is prepared from 10.53 g (0.045 mole) p-iodoanisole and 1.08 g (0.045 mole) magnesium in 50 ml ether, and reacted with 3.74 g (0.015 mole) ester XIV. The Grignard reaction mixture is decomposed with ammonium chloride, the ether layer separated and steam-distilled. The residue of oily liquid is dissolved in 15 ml glacial acetic acid, formic acid added till the transient red-violet color disappears, and the product worked up as in the previous experiment. Yield 3.56 g. Similarly ester XIII and ethyl N-butyloxanilate react with p-anisylmagnesium iodide to give the oxindole derivatives VIII, IX, while ethyl diphenyloxamine and p-tolylmagnesium bromide give XI.

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