SYNTHESIS OF THE ALKALOID DIOXYLINE AND OTHER 6,7-DIMETHOXYISOQUINOLINES IN A MODIFIED RITTER REACTION

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It has been found that aceto- and benzonitriles and 3,4-dimethoxyphenylacetone in the presence of acetylperchlorate or upon heating in polyphosphoric acid or polyphosphoric ester form the corresponding isoquinoline. The data indicate that the reaction proceeds like a typical Ritter reaction and is defined by electrophilic activation of the carbonyl group of the ketone and the nucleophilicity of the nitrile. This methodology gave the alkaloid dioxyline (dimoxyline), obtained in high yield by the use of benzoylhexachloroantimonate.

In 1982 Zelinskii [1] accomplished the synthesis of 1,3-disubstituted isoquinolines by the direct reaction of phenyl acetone with various nitriles in the presence of $POCl_3$. In spite of opinions as to the impossibility of a Ritter reaction between ketones and nitriles [2, 3], the author proposed that the reaction begins with attack of the nitrile on the cation resulting from the addition of $POCl_3$ to the carbonyl group of the ketone.

Thus arose a fundamental new method for the synthesis of isoquinolines, which is of great interest in this traditional region of heterocyclic chemistry [4, 5]. However, the yield of the desired products does not exceed 40%, since this method also gives rise to the formation of substituted pyrimidines.

We discovered that upon maintaining the 3,4-dimethoxyphenylacetone I in acetic anhydride and 70% perchloric acid solution (standard conditions for the synthesis of 2-benzopyrilium salts [6]) with excess aceto- or benzonitrile, isoquinolines IIa, b are formed in 70 and 80% yields, respectively, while the formation of the 2-benzopyrilium salts III was not observed. In the same reaction of ketone I with the above nitriles (or the corresponding amides) heated in polyphosphoric acid (PPA) or polyphosphoric ester (PPE) (prepared according to the method of [7]), the yields of isoquinolines Ia, b are reduced to 40 and 50%, respectively.

The presence of activated donor substituents on the aromatic ring of ketone I under these experimental conditions introduces the possibility that the first step takes place either through the cationic intermediate (IV) of a Ritter reaction (route A, Scheme 1) or a Houben—Hoesch reaction (route B), when the nitrile after N-acylation or protonation is transformed into an electrophilic fragment.

In addition, British authors [8] who brought about the synthesis of 3-isopropyl-6,8-dihydroxyisoquinoline by the reaction of 3,5-dihydroxybenzylisopropyl ketone with hydrogen cyanide in the presence of $ZnCl_2$ interpreted their observed transformation as beginning with the Gattermann reaction, a relative of the Houben—Hoesch reaction.

Thus, since the indicated first step in the formation of isoquinolines with the activated aromatic ring of ketones by this or some other type of interaction is by no means apparent, clarification of this question is undoubtedly needed (see Scheme 1).

With this goal we conducted experiments on the imidoylation of 3,4-dimethoxyphenylacetone I both under traditional conditions for the Houben—Hoesch reaction [RCN, $(C_2H_5)_2O$, $ZnCl_2$ + HCl] and under conditions for the in situ generation of a polyprotonated triazine salt by the action of superacid (CF_3SO_3H) on nitriles, which at the present time is considered to be the most effective method for the introduction of the imidoyl group into an activated aromatic nucleus [9]. However, under both conditions the only product obtained was 1,3-dimethyl-2-veratryl-6,7-dimethoxynaphthalene (V), the result of self-condensation of ketone I.

In addition, as a result of the reaction of ketone I using the more electrophilic dichloroacetonitrile in the acetylated medium, and also with N-phenylbenzimidoyl chloride in the presence of antimony pentachloride, the salt of 10-methyl-2,3,7,8-tetramethoxydibenzo[*a*, d]tropyline (VI) was obtained instead of the corresponding derivative of isoquinoline. Its formation under these conditions (Scheme 2) is possibly connected with the oxidative cleavage of part of the molecule of I through the carboxenium ion (VII) to the benzyl cation (VIII) and its subsequent transformations, as described in [10].

Physical and Organic Chemical Research Institute, Rostov State University, Rostov-on-Don, 344006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 363-368, March, 1992. Original article submitted November 26, 1990.

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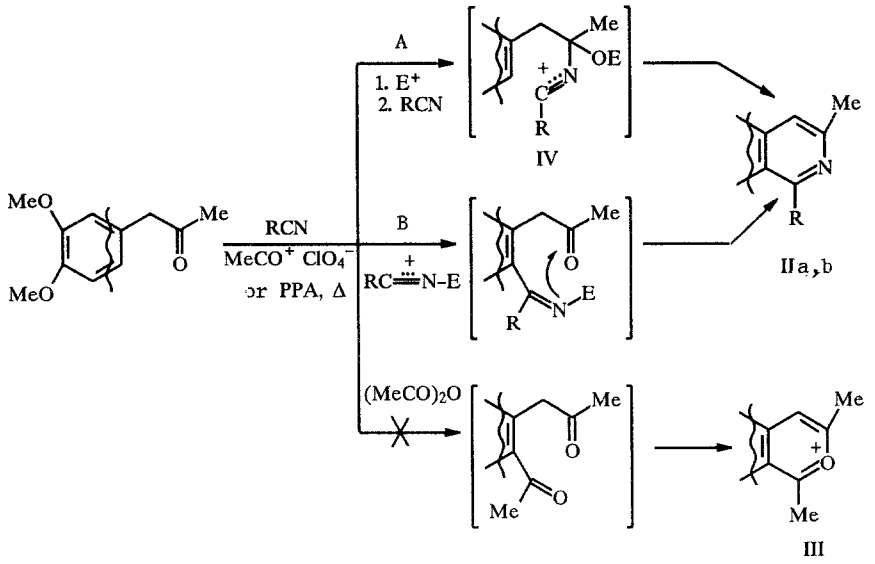
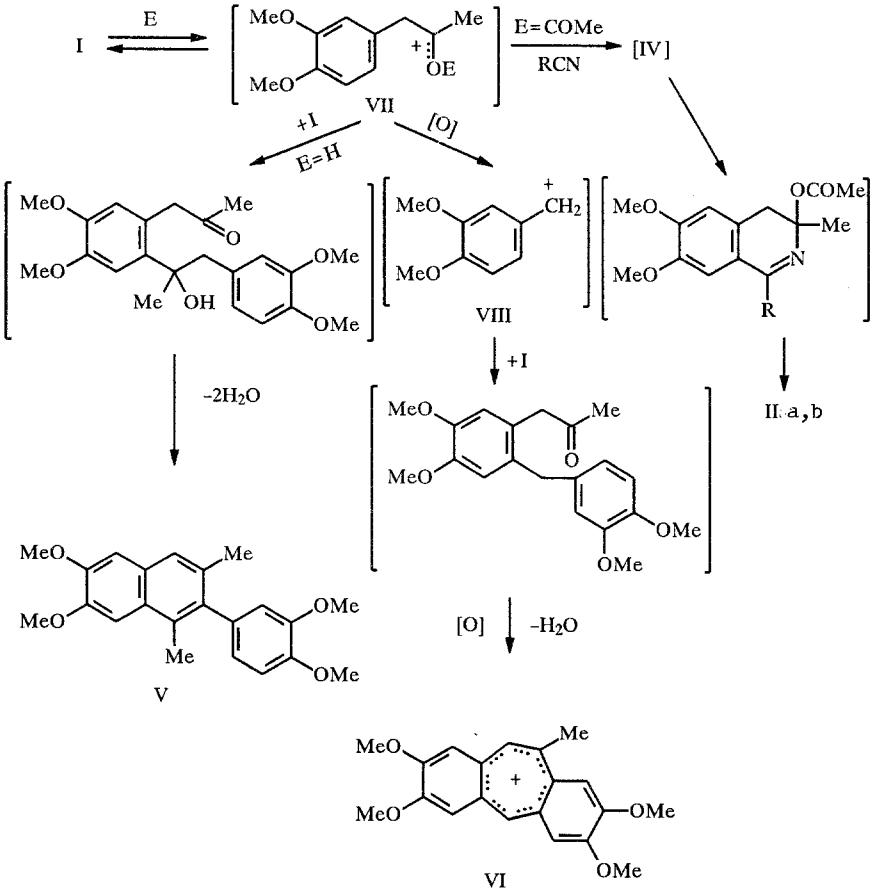
Scheme 1



IIa R=CH_3, b R-C_6H_5; E=CH_3CO, H

Scheme 2

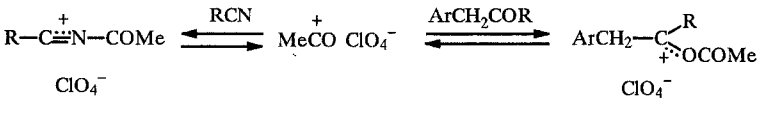


And finally, we did not find products of the imidoylation of the isoquinolines IIa, b (the corresponding imines or aromatic ketones) upon reaction of veratrol with nitriles under conditions for the synthesis of IIa, b.

Consideration of these results leads to the conclusion that the formation of the heteroring of isoquinolines IIa, b does not begin with the electrophilic reaction of reagents (nitrile salt) with the activated aromatic nucleus substrate (ketone I) but by nucleophilic attack of the nitrile on the carbonyl carbon of I, after preliminary activation by reaction with the electrophilic

agent, i.e., proceeding by route A. In turn, the above modified Ritter reaction results indicate that the possibility of formation of isoquinolines depends upon the nucleophilicity of the nitrile and the nature of the electrophile activating the carbonyl group of the ketone.

It seems that the most effective activating fragment is the acetyl cation formed from acetic anhydride and perchloric acid, giving rise during the associated equilibrium reaction to the intermediate formation of highly reactive salt (IX) [11].



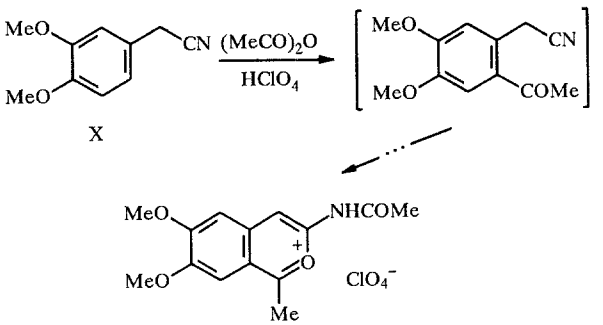
IX

The decreased yields of the isoquinolines IIa, b upon carrying out the reaction in PPA or PPE is apparently explainable by the lower activity (by comparison with the acyloxycarbenium ion) of the polyphosphoryloxycarbocation. Protonation of the same carbonyl group of I under these conditions in the presence of CF_3SO_3H or $ZnCl_2$ + HCl gives rise to the poorly reactive and kinetically unstable oxycarbocation, resulting only in the autocondensation of I.

Thus, the transformations of carboxylic ion VII arising from ketone I can be as presented in Scheme 2.

It has been proposed that the use of 3,4-dimethoxyphenylacetonitrile (X) in the reaction with veratrylacetone (I) may lead to the formation of the natural alkaloid dioxyline (3-methylpapaverine, dimoxyline) (XI), with known antispasmotic activity [4].

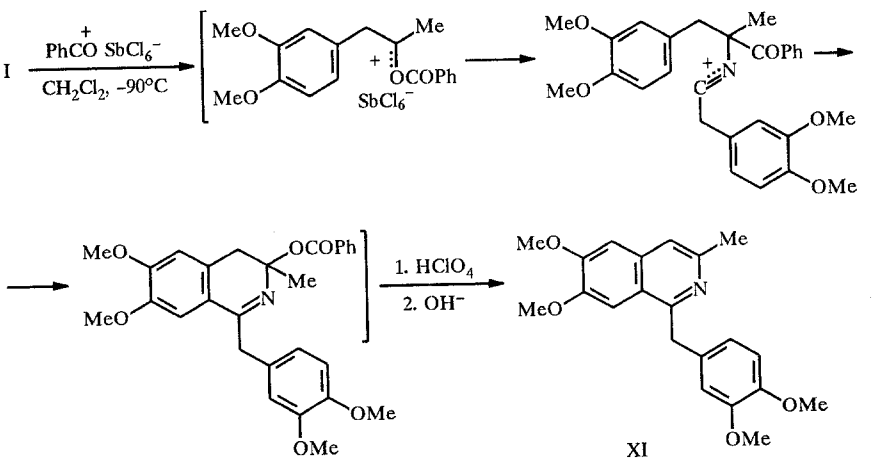
However, upon carrying out the reaction in acetylperchlorate solution only the 2-benzopyrilium salt (XII) was isolated [12], formed, evidently, as a result of the acylation of the activated aromatic ring of the nitrile (X):



XII

To avoid this, the process conditions were modified to allow the stabilization of the acyloxycarbenium ion [11], resulting in the preparation of the desired alkaloid dioxyline XI in 70% yield (see scheme below).

This approach to the synthesis of the alkaloid (XI) is undoubtedly preferable to the traditional method based upon the Bishler—Naperielskii reaction [13], and also to the known two-step synthesis of XI through the corresponding 2-benzopyrilium salt [14].



XI

EXPERIMENTAL

The IR spectra were recorded on a Specord 71-IR spectrometer in Vaseline oil, and the ^1H NMR spectra were determined with a Tesla BS—487 (80 MHz) instrument in $CDCl_3$ and CF_3COOH, using hexamethyldisilane as internal standard.

In the elemental analyses data for C, H, N, and Cl, the found values corresponded with the calculated values.

1-Phenyl(methyl)-3-methyl-6,7-dimethoxyisoquinolines (IIa, b). A. A solution of acetylperchlorate was prepared at 0°C by adding dropwise 0.25 ml (3 mmoles) of 70% perchloric acid to 1.2 ml (13 mmoles) of acetic anhydride, followed by 19 mmoles of aceto- or benzonitrile, agitating the mixture until complete homogenization. Then at 20°C 0.58 g (3 mmoles) of 3,4-dimethoxyphenylacetone I was added and the mixture was kept for 3 h, diluted with ether, and triturated to give a precipitate of the corresponding perchlorate of the isoquinoline II which, after isolation, was crystallized from a mixture of acetic acid and ethyl acetate.

B. A mixture of 0.58 g (3 mmoles) of 3,4-dimethoxyphenylacetone I, 6 mmoles of nitrile and 8 g of PPA (or PPE) was kept at 100°C for 1 h. After hydrolysis, the mixture was treated with 70-80 ml of ether and stirred intensively for 10-15 min. The ethereal layer was separated and to the aqueous layer was added 1 ml of 30% $HClO_4$. The resulting precipitate of the isoquinoline salt was separated and recrystallized.

After workup of the isoquinoline perchlorates IIa, b a 10% aqueous solution of sodium acetate gave the free bases, all characteristics of which were identical with those described in the literature [14 15].

1,3-Dimethyl-2-(3,4-dimethoxyphenyl)-6,7-dimethoxynaphthaline (V). Compound V was isolated in 17-30% yield after concentration of the ether extract of the reaction mixture formed, as described above (method **B**) after the reaction of ketone I with nitriles in PPA or PPE. It was also formed in 65% yield upon attempting imidoylation of veratrylacetone I in the presence of $ZnCl_2$ + HCl according to the method of [2], or in a yield of 78% upon attempting the imidoylaton of I using CF_3S_3OH by the known route [9] to give colorless crystals, mp 152°C (from alcohol). IR spectrum: 1600, 1280, 1160 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 2.08 (3H, s, CH_3); 2.25 (3H, s, CH_3); 3.73 (3H, s, OCH_3); 3.85 (9H, s, $3OCH_3$); 6.55-7.48 ppm (6H, m, CH_{arom}).

2,3,7,8-Tetramethoxy-1-methyldibenzo[*a*, d]tropylium Perchlorate (VI). A. To a solution of 1.9 g (10 mmoles) of 3,4-dimethoxyphenylacetone I and 2.15 g (10 mmoles) of N-phenylbenzimidoyl chloride in 35 ml of dry dichloroethane at 0°C was added dropwise 1.27 ml (10 mmoles) of antimony pentachloride. The reaction mixture was kept at room temperature, and the resulting precipitate of antimony tropylium hexachloride was filtered off and recrystallized from acetonitrile containing 70% perchloric acid (0.15 ml in 20 ml of acetonitrile) to give 0.355 g (19%) of VI perchlorate as red-orange crystals, mp >300°C (from acetic acid) [10].

B. Compound VI was isolated in 10% yield from a reaction mixture obtained by the above method upon reacting the ketone I with dichloroacetonitrile in the presence of acetylperchlorate.

1-(3,4-Dimethoxybenzyl-3-methyl-6,7-dimethylhydroxyisoquinoline (Dioxyline) (XI). To a solution of 0.30 ml (2.58 mmoles) of benzoyl chloride in 10 ml of dry CH_2Cl_2 cooled to —10°C was added 0.33 ml (2.58 mmoles) of antimony pentachloride. After 5 min the suspension obtained was cooled with constant stirring to —90°C in a mixture of liquid nitrogen and acetone, and 0.50 g (2.58 mmoles) of 3,4-dimethoxyphenylacetone I in 15 ml of CH_2Cl_2 was added and over 2-3 min at the same temperature was added a solution of 0.68 g (3.85 mmoles) of 3,4-dimethoxyphenylacetonitrile X in 5 ml of CH_2Cl_2. The reaction mixture was stirred until it reached room temperature, diluted with three volumes of dry ether and the precipitated salt was filtered after 2-3 h. It was recrystallized from acetonitrile with added 70% perchloric acid to give 0.82 g (70%) of the perchlorate of XI. IR spectrum: 1630, 1590, 1260, and 1050 cm^{-1}. ^1H NMR spectrum (CF_3COOH): 2.33 (3H, s, CH_3); 3.43 (6H, s, $2CH_3$); 3.62 (3H, s, OCH_3); 3.70 (3H, s, OCH_3); 4.45 (2H, s, CH_2); 6.50 (2H, s, CH_{arom}); 6.55 (1H, s, CH_{arom}); 6.98 (1H, s, CH_{arom}); 7.22 (1H, s, CH_{arom}); 7.40 ppm (1H, s, CH_{arom}).

Dioxydine was obtained by treatment of the salt with a soda solution to give mp 138°C (Lit. mp 138°C [13, 14]).

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