SYNTHESIS OF AZOLO[5,4-c]ISOQUINOLINES

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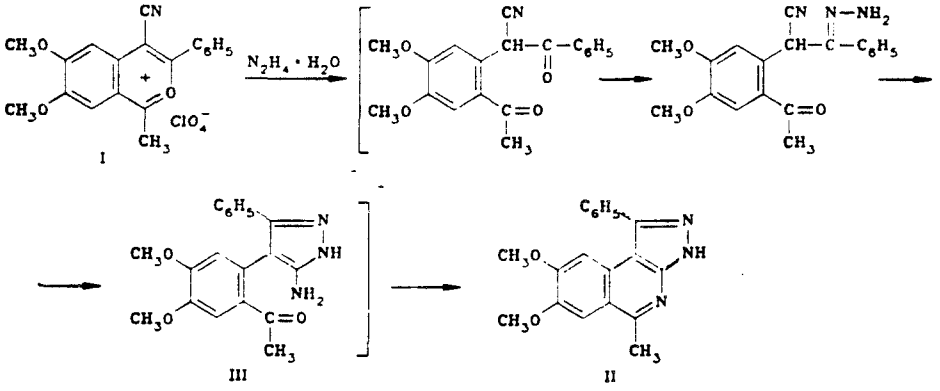
Two pathways are presented for the synthesis of pyrazolo[5,4-c]isoquinoline derivatives: recyclization of 1-methyl-3-phenyl-4-cyano-6,7-dimethoxybenzo[c]pyrylium perchlorate upon treatment with hydrazine, and Bischler–Napieralski cyclization of substituted 5-amino-4-(3,4-dimethoxyphenyl)pyrazoles. A derivative of a new heterocyclic system, isoxazolo[5,4-c]isoquinoline, has also been obtained upon heating 5-amino-3-phenyl-4-(3,4-dimethoxyphenyl)isoxazole in a mixture of acetic anhydride and perchloric acid.

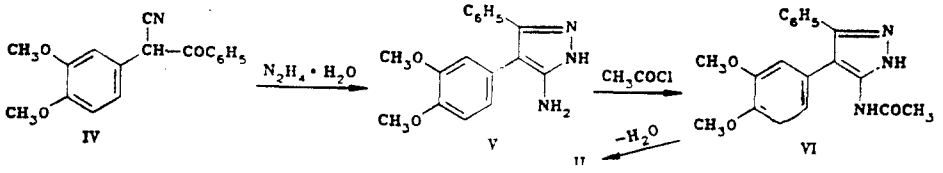
In a preliminary communication [1] we reported an interesting transformation of the 3-phenyl-4-cyanobenzo[c]pyrylium salt I upon treatment with hydrazine hydrate to give a derivative of the tricyclic pyrazolo[5,4-c]isoquinoline system II. In the present paper we describe the experimental course of this reaction in detail, and also report alternative pathways for the preparation of heterocyclic systems of type II.



Conversion of perchlorate I to the pyrazoloisoquinoline II involves, apparently, formation of an intermediate 5-aminopyrazole derivative III arising as a result of reaction of hydrazine with a β-ketonitrile group liberated upon hydrolytic cleavage of the pyrylium ring.

The product of recyclization of salt I has been assigned the pyrazoloisoquinoline structure II based on the following spectral data: the absence in its IR spectrum of nitrile, carbonyl, and amino group absorption bands, as well as the presence in its PMR spectrum (in CF_3COOH solution) of three singlets at 3.20, 3.97, and 4.13 ppm, corresponding to methyl group protons, and the nature of the aromatic proton signals (two singlets with an integrated intensity for one proton unit at 7.67 and 7.80 ppm, and a singlet for the phenyl substituent protons at 7.30 ppm).

Unequivocal evidence for the structure of compound II was obtained, however, by its independent synthesis from β-ketonitrile IV.



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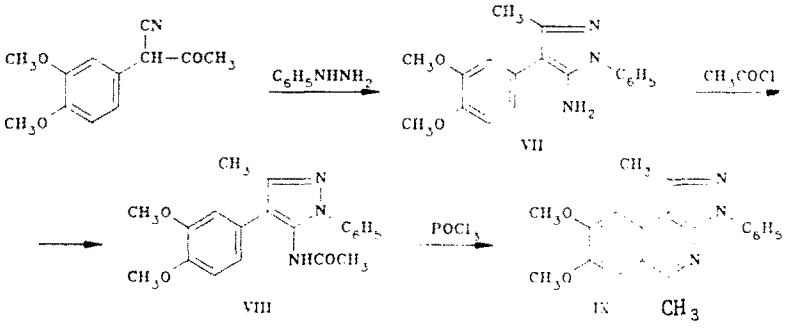
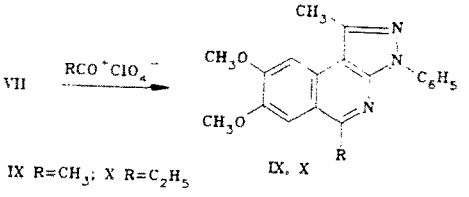
Pyrazole V was prepared via a literature procedure [2], according to which heating α-acetylphenylacetonitrile with hydrazine in acetic acid gave, in addition to the expected 5-aminopyrazole product, another unidentified, high-melting product. We carried out this reaction with α-benzoylhomoveratronitrile IV and also obtained two products. One of the products, which was soluble in dilute hydrochloric acid, consisted of the expected 5-aminopyrazole V. The second product was found to be the 5-acetylaminopyrazole VI; its structure was established based on comparison of its spectral and analytical data with the characteristics of the acetylation product of aminopyrazole V with acetyl chloride. In addition, workup of the 5-acetylaminopyrazole VI with phosphorus oxychloride in refluxing toluene, standard conditions for the Bischler–Napieralski reaction, gave a mixture of low-melting colored compounds which, according to TLC analysis, did not contain the pyrazoloisoquinoline II. The factor responsible for this lack of success is probably the lability of the pyrazole molecule VI associated with the absence of a substituent in the 1-position. And, in fact, if 1-phenylpyrazole VIII, prepared from α-acetylhomoveratronitrile and phenylhydrazine, is used in this reaction sequence, pyrazoloisoquinoline IX is formed without difficulty.

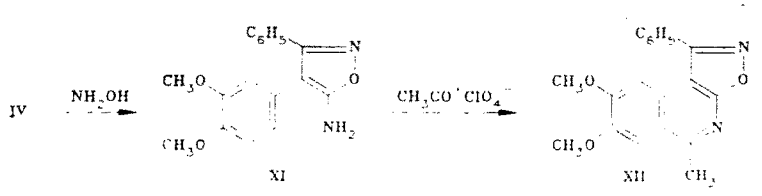


We were able to carry out the last step in the independent synthesis using acetyl perchlorate, which is formed upon mixing acetic anhydride and perchloric acid, as the cyclizing agent. Heating acetylaminopyrazole VI in this mixture led to the formation of pyrazoloisoquinoline II in 73% yield, identical to the product obtained upon reaction of pyrylium salt I with hydrazine. In an analogous manner, acetylaminopyrazole VIII was converted to the corresponding pyrazoloisoquinoline IX upon treatment with acetyl perchlorate.

The use of acyl perchlorates in place of the traditional phosphorus oxychloride in this reaction also enables one to avoid the preliminary acylation step of the starting amino compounds in the reaction sequence, since acylation occurs directly in the reaction mixture.



It is possible that other aminoheterocycles, in which the orientation of an amino group and dimethoxyphenyl ring mirrors the structure of pyrazoles V and VII, may also react in a similar manner. For example, heating 5-amino-3-phenyl-4-(3,4-dimethoxyphenyl)isoxazole (XI) with acetic anhydride and perchloric acid resulted in the formation of isoxazolo[5,4-c]isoquinoline XII, which represents a derivative of a new heterocyclic system.



EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer using Vaseline mulls; PMR spectra were obtained on a Tesla BS-467 (60 MHz) spectrometer versus TMS as internal standard.

TABLE 1. Characteristics of Compounds I, II, V-XII

Compound	Molecular formula	mp, °C	Yield, %	Compound	Molecular formula	mp, °C	Yield, %
I	$C_{19}H_{16}ClNO_7$	210...212	35	VIII	$C_{20}H_{21}N_3O_3$	147...148	74
II	$C_{19}H_{17}N_3O_2$	272...273	73	IX	$C_{20}H_{19}N_3O_2$	191...192	70
V	$C_{17}H_{17}N_3O_2$	145...146	54	X	$C_{21}H_{21}N_3O_2$	157...158	60
VI	$C_{19}H_{19}N_3O_3$	268...269	80	XI	$C_{17}H_{16}N_2O_3$	165...167	60
VII	$C_{18}H_{19}N_3O_2$	169...170	94	XII	$C_{19}H_{16}N_2O_3$	212...213	50

*Compound II was crystallized from xylene, V from benzene, VIII from a mixture of benzene and hexane, XI from aqueous alcohol; the others from alcohol.

TABLE 2. Spectral Characteristics of Newly Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm*
I	1100, 1605, 2250	3,20 (3H, s CH_3); 3,97 (3H, s, OCH_3): 4,13 (3H, s OCH_3); 7,30 (5H, s, C_6H_5); 7,67 and 7,80 (each 1H, s 5- and 7-H)
II	1620	3,23 (3H, s, 5-CH_3); 3,80and4,07 (each3H, s 7- and 8-OCH_3); 7,67 (7H, -, H_{arom})
V	1600, 1620, 3160, 3330	3,51and3,73 (each3H, s 3'-and 4'-OCH_3); 6,63...6,73 (3H, m, 4-C_6H_3); 7,20 (5H, s 3-C_6H_5)
VI	1620, 1695, 3250, 3330	2,27 (3H, s $COCH_3$); 3,60and 3,78 (each 3H, s 3'- and 4'-OCH_3); 6,58...6,80 (3H, m, 4-C_6H_3); 7,13 (5H, s, 3-C_6H_5)
VII	1600, 1630, 3310, 3400	2,20 (3H, s 3-CH_3); 3,80 (6H, s 3- & 4-OCH_3); 6,83 (5H, s, 1-C_6H_5); 7,20...8,50 (3H, m 4-C_6H_3)
VIII	1600, 1690, 3140	2,17 (3H, s $COCH_3$); 2,60 (3H, s 3-CH_3); 4,0 (6H, s 3'- and 4'-OCH_3); 7,13 (3H, s 4-C_6H_5); 7,67 (5H, s, 1-C_6H_5)
IX	1600, 1635	3,24 (6H, two run-together singlets 1- and 5-CH_3); 4,23and 4,37 (each3H, s 7-and8-OCH_3); 7,80, 7,90and7,97 (each1H, s 2-, 6-and9-H)
X	1605, 1635	1,60 (3H, t 5-β-CH_3); 3,13 (3H, s, 1-CH_3); 3,60 (2H, q, 5-α-CH_2): 4,23and4,37 (each3H, s 7and 8-OCH_3); 7,77, 7,93 and8,03 (each 1H, s 2-, 6-and 9-H)
XI	1620, 1640, 3350, 3460	3,57and3,77 (each 3H, s 3'-and4'-OCH_3); 4,43 (2H, br.s NH_2); 6,50...6,70 (3H, m 4-C_6H_3); 7,07 ...7,37 (5H, m, 3-C_6H_5)
XII	1580, 1635	3,27 (3H, s, 5-CH_3); 3,75and4,03 (each 3H, s 7-and 8-OCH_3); 7,30 (1H, s H_{arom}; 7,50 (6H, s H_{arom})

*PMR spectra of compounds V, VII, and XI were recorded in $CDCl_3$; the others in CF_3COOH.

The results of C, H, Cl, and N elemental analysis for compounds I, II, V-XII agreed with calculations. The physical characteristics of these newly synthesized compounds are summarized in Tables 1 and 2.

1-Methyl-3-phenyl-4-cyano-6,7-dimethoxybenzo[c]pyrylium Perchlorate (I). To a mixture of 10 ml acetic anhydride and 0.8 ml 70% perchloric acid was added in small portions and with stirring 2.8 g (0.01 mole) α-benzoylhomoveratronitrile. After 5 h the resulting precipitate was removed by filtration and crystallized from acetic acid. Yield 1.4 g (35%).

5-Amino-3-phenyl-4-(3,4-dimethoxyphenyl)pyrazole (V) and 5-Acetylamino-3-phenyl-4-(3,4-dimethoxyphenyl)pyrazole (VI). A mixture of 14 g (0.05 moles) α-benzoylhomoveratronitrile, 6 ml hydrazine hydrate, and 25 ml acetic acid was refluxed for 2 h. The mixture was cooled, poured into 500 ml water, and 17 ml concentrated HCl was added; the mixture was then rapidly heated to boiling. As heating progresses the precipitate dissolved, then was deposited anew. The hot suspension was filtered and washed with water. The cooled filtrate was basified with ammonia to pH 8, and the resulting precipitate of aminopyrazole V was removed by filtration, washed with water, and dried. Yield 8 g (54%).

The precipitate which deposited upon heating the reaction mixture with hydrochloric acid consists of acetylaminopyrazole VI. Yield 6.6 g (39%).

Acetylaminopyrazole VI could also be prepared by acylation of aminopyrazole V with acetyl chloride: To a suspension of 1.5 g (5 mmoles) aminopyrazole V in 15 ml absolute benzene was added 1 ml triethylamine, followed by dropwise a solution of 0.4 ml (5.6 mmoles) acetyl chloride in 5 ml benzene. The mixture was heated to boiling and allowed to stand overnight. The resulting precipitate was removed by filtration, washed with water, and dried. Yield 1.4 g (80%). A mixed melting point analysis with a sample prepared as in the preceding method did not exhibit melting point depression.

5-(Amino-3-methyl-1-phenyl-4-(3,4-dimethoxyphenyl)pyrazole (VII). A mixture of 11 g (0.05 moles) α-acetylhomoveratronitrile, 8.7 g (0.06 moles) phenylhydrazine hydrochloride, and 50 ml acetic acid was refluxed for 2 h. The mixture was cooled and poured into 300 ml water. The solution was basified with aqueous ammonia to pH 8, and the resulting precipitate was filtered, washed with water, and dried. Yield 14.5 g (94%).

5-Acetylamino-3-methyl-4-(3,4-dimethoxyphenyl)pyrazole (VIII). This was prepared in an analogous manner to acetylaminopyrazole VI from aminopyrazole VII and acetyl chloride.

5-Amino-3-phenyl-4-(3,4-dimethoxyphenyl)isoxazole (XI). A mixture of 8.4 g (0.03 moles) β-ketonitrile IV, 6.3 g (0.09 mole) hydroxylamine hydrochloride, 12.3 g sodium acetate, 135 ml ethanol, and 45 ml water was refluxed for 4 h. The mixture was cooled, diluted threefold with water, and allowed to stand overnight at 0°C. The resulting precipitate was removed by filtration, washed with water, and dried. Yield 5.3 g (60%).

5-Methyl-1-phenyl-7,6-dimethoxypyrazolo[5,4-c]isoquinoline (II). A. To a suspension of 1.2 g (3 mmoles) perchlorate I in 5 ml acetonitrile was added 1.5 ml (30 mmoles) hydrazine hydrate. The solution was refluxed for 10 min, cooled, and the resulting precipitate was filtered. Yield 0.3 g (30%).

B. To a solution of 0.6 ml 70% perchloric acid in 5 ml acetic anhydride was added 1 g (3 mmoles) acetylaminopyrazole VI, 5 ml nitromethane, and the mixture was heated to boiling. The mixture was allowed to stand overnight t 20°C, and was then diluted threefold with ether; the resulting sticky precipitate was triturated with a fresh portion of ether and then filtered. The precipitate was triturated with aqueous ammonia, removed by filtration, washed with water, and dried. Yield 0.7 g (73%).

1,5-Dimethyl-3-phenyl-7,8-dimethoxypyrazolo[5,4-c]isoquinoline (IX). A. A mixture of 0.35 g (1 mmole) acetylaminopyrazole VIII, 0.5 ml phosphorus oxychloride, and 4 ml absolute toluene was refluxed for 2 h. The mixture was cooled, 25 ml heptane was added, and the resulting precipitate was removed by filtration. It was dissolved in 5 ml concentrated HCl, filtered, and basified with aqueous ammonia to pH 8. The resulting precipitate was filtered, washed with water, and dried. Yield 0.2 g (61%).

B. To a suspension of 1.5 g (5 mmoles) aminopyrazole VII in 9 ml (0.1 mole) acetic anhydride was added 0.8 ml 70% perchloric acid dropwise and with caution. The solution was then heated for 30 min on a steam bath, at which point a precipitate was deposited in solution. The mixture was cooled, the precipitate was removed by filtration and washed with ether. The dry precipitate was then triturated with concentrated NH_4OH, filtered, and washed with water and dried. Yield 0.5 g (70%).

1-Methyl-5-ethyl-3-phenyl-7,8-dimethoxypyrazolo[5,4-c]isoquinoline (X). Prepared analogously to pyrazoloisoquinoline IX using method B and starting from aminopyrazole VII and propionic anhydride; yield 60%.

5-Methyl-1-phenyl-7,8-dimethoxyisoxazolo[5,4-c]isoquinoline (XII). Prepared in an analogous manner from aminoisoxazole XI and acetic anhydride; yield 50%.

LITERATURE CITED

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2. C. Alberti, *Gazz. Chim. Ital.*, **89**, 1017 (1959).