

Mannich-type Reactions of an Isobasic Isoquinoline (I).

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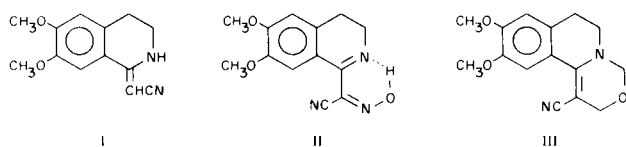
Received May 14, 1973

Base catalyzed reaction of 1-cyanomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (I) with 2 moles of formaldehyde gave rise to the 1,3-oxazino[4,3-*a*]isoquinoline ring system (III). Reaction of I with a primary amine and 2 moles of formaldehyde gave pyrimido[6,1-*a*]isoquinoline (VI).

The Schiff's base $\rightleftharpoons$ enamine type tautomerism of 1-methyl-3,4-dihydroisoquinolines is known. Typical representatives of the enamine form are the 1-cyanomethyl derivatives; the exclusive existence of these as 1-cyanomethylene-1,2,3,4-tetrahydroisoquinolines was proven by Openshaw and Whittaker (2).

Our earlier studies (3) demonstrated that nitrosation of 1-cyanomethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (I) results in the *C*-isonitroso derivative (II) in which, due to the formation of a six-membered chelate ring, the tautomeric equilibrium is shifted to the Schiff's base form.

This paper reports the reaction of I with formaldehyde as the cationic reagent. In the presence of various basic catalysts the reaction of I with two moles of formaldehyde gave 1-cyano-6,7-dihydro-9,10-dimethoxy-2*H*,4*H*-[1,3]oxazino[4,3-*a*]isoquinoline (III).



Structure III was supported by elementary analysis and spectral data; the nmr spectrum showed the appearance of two new methylene singlets, the ir spectrum, a conjugated nitrile band and the disappearance of N-H absorption.

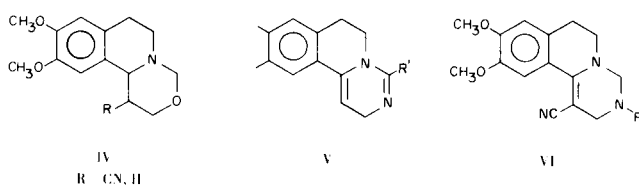
Transformation of isoquinolines to condensed ring systems by reaction with formaldehyde has been reported by other authors (4,5). This either involved reactions of 1,2,3,4-tetrahydroisoquinolines or gave rise to the same;

e.g., by addition of formaldehyde to 3,4-dihydro derivatives.

The yield of III was influenced, apart from the necessary two moles of formaldehyde required by the basicity of the catalyst. Aqueous alkali proved to be optimal.

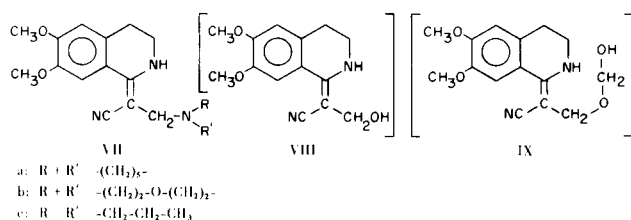
Catalytic hydrogenation of III gave the tetrahydro compound IV (R = CN). Compound IV with R = H has been prepared by Schneider and Schilken (5) from 1-(2-hydroxyethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline who used formaldehyde to form the cyclic *N,O*-acetal moiety. Crabb and Newton (6) established the *cis*-anellation of these heterocyclic rings.

In view of the known (7) double reactivity of primary amines in Mannich-type reactions and the successful preparation of III, it seemed possible to build, from I, formaldehyde and primary amines, the pyrimido[4,3-*a*]isoquinoline ring system. Less saturated representatives of this ring system (V) have been prepared by Kametani (8) by double elimination of water from amides of 2-phenylethylamines with 3-acylaminopropionic acid. We have now prepared compounds of type VI in good yields under the usual conditions of the Mannich-reaction (see Table in the Experimental).



The formation of III and VI respectively from I is a multistep process and we tried to get some insight into the details of the reaction. We were first of all interested in the steps of the formation of III, since in this case the intermediate can only be formed from I and formaldehyde. Our attempts to isolate an intermediate on the pathway from I to III by modifications of the conditions of the base catalyzed reaction (*e.g.* shorter reaction time, smaller molar ratio of formaldehyde) were without success. Degradation of III in acidic media also failed to lead to the supposed intermediate. This prompted us to gain some information about the details of the process by studying analogous transformations. A possible way of stopping the reaction at the stage of an intermediate is to allow I to react with only one mole of formaldehyde and an amine which would preclude further reactions under the conditions of the Mannich reaction. Reaction with piperidine gave in fact 1-(1-cyano-2-piperidinoethylidene)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIa), the structure of which was proved *inter al.* by conjugated nitrile and NH absorption in the ir spectrum. Reaction of I with other secondary amines gave products of the same type (VIIb, VIIc).

These experiments indicated that the first step in the transformation of I $\rightarrow$ III was a C-alkylation to yield the hydroxymethyl compound VIII which then may be followed by reaction with a second mole of formaldehyde. In order to establish whether in this step the oxygen of the hydroxymethyl group or the ring nitrogen was attacked, further reaction of VIIa with more formaldehyde and piperidine was attempted since this model can only react on the ring nitrogen. Transformation of VIIa under the conditions of this repeated Mannich reaction was not observed which permitted the conclusion that the second step in the sequence leading from I to III was the formation of an O-hemiacetal (IX) and the concluding step was the cyclization between the atoms C₄ and N.



A process through the reactive intermediates VIII and IX is in accord with observations connected with the cyanoethylation of this type of compounds (2) as well as with the synthesis of IV (R = H) (5).

EXPERIMENTAL

1-Cyano-6,7-dihydro-9,10-dimethoxy-2*H*,4*H*-[1,3]oxazino[4,3-*a*]-isoquinoline (III).

To a suspension of I (41.5 g., 0.18 mole) in formaldehyde (35%, 100 ml., 1.17 moles), 2*N* sodium hydroxide (2 ml.) was added dropwise with shaking. The mixture was heated to 65° when a homogenous solution was obtained from which the product precipitated after 5-6 minutes. After cooling this was separated and washed with water, yield 35 g. (71.5%), m.p. 154° (absolute ethanol).

Other basic catalysts gave III with lower yields: sodium bicarbonate, 28%; sodium carbonate, 57%; piperidine, 33%; nmr δ (CDCl₃ + DMSO-*d*₆) ppm: 4.48, 4.75 (each 2H, each s, 2-CH₂, 4-CH₂); ir ν max (potassium bromide) 2170 cm⁻¹ (vs, C $\equiv$ N), no NH absorption.

Anal. Calcd. for C₁₅H₁₆N₂O₃: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.98; H, 6.05; N, 9.97.

1-Cyano-9,10-dimethoxy-1,6,7,11b-tetrahydro-2*H*,4*H*-[1,3]oxazino[4,3-*a*]isoquinoline (IV, R = CN).

Compound III (8.17 g., 0.03 mole) was hydrogenated at atmospheric pressure until the uptake of one molar equivalent of hydrogen in the presence of palladium on carbon (8%, 10 g.) as a suspension in ethyl acetate (350 ml.) at 60°. The usual work up and crystallization from ethanol gave IV (R = CN), 5.7 g. (69.3%), m.p. 203°; nmr δ (CDCl₃ + DMSO-*d*₆) ppm: 3.0 (2H, s, 4-CH₂); 3.7-4.7 (4H, m, 1-CH, 2-CH₂, 11 b CH protons); ir ν max (potassium bromide) 2245 cm⁻¹ (w, C $\equiv$ N).

Anal. Calcd. for C₁₅H₁₈N₂O₃: C, 65.68; H, 6.61; N, 10.22. Found: C, 66.06; H, 6.62; N, 10.42.

General Method for the Preparation of 3-Substituted 1-Cyano-9,10-dimethoxy-2,3,6,7-tetrahydro-4*H*-pyrimido[4,3-*a*]isoquinolines (VI).

To a suspension of III (0.03 mole) in ethanol (125 ml.), the primary amine (0.035 mole) and aqueous formaldehyde (35%, 0.06 mole) were added and the mixture boiled for 10 minutes. Evaporation *in vacuo* and crystallization gave the product.

1-(1-Cyano-2-piperidinoethylidene)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIa).

To a suspension of I (6.9 g., 0.03 mole) in water (50 ml.) piperidine (2.98 g., 0.035 mole), aqueous formaldehyde (35%, 3 ml., 0.035 mole) and with shaking sodium hydroxide solution (2*N*, 1 ml.) was added. After boiling for 3 minutes, the product separated as an oil. After cooling, the mother liquor was decanted and the oily portion crystallized from ethanol; yield, 3.63 g. (37%), m.p. 125-126°; nmr δ (CDCl₃ + DMSO-*d*₆) ppm: 3.23 (1- β -CH₂); ir ν max (potassium bromide) 2167 cm⁻¹ (vs, C $\equiv$ N), 3280 cm⁻¹ (NH).

Anal. Calcd. for C₁₉H₂₅N₃O₂: C, 69.61; H, 7.69; N, 12.83. Found: C, 69.74; H, 7.56; N, 13.30.

The morpholinoethylidene (VIIb) and the di-*n*-propylaminoethylidene derivative (VIIc) were prepared similarly.

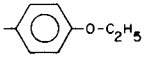
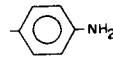
Compound VIIb, yield, 17%, m.p. 144-145° (from ethanol). *Anal.* Calcd. for C₁₈H₂₃N₃O₃: C, 65.63; H, 7.03; N, 12.75. Found: C, 65.74; H, 7.24; N, 12.51.

Compound VIIc, yield, 18.5%, m.p. 104-105° (ethanol-water 1:1).

Anal. Calcd. for C₂₀H₂₉N₃O₂: C, 69.94; H, 8.51; N, 12.23. Found: C, 70.15; H, 8.46; N, 12.36.

Attempted Reaction of VIIa with Formaldehyde and Secondary Amines.

TABLE

	R	M.p.	Solvent	Yield, %	Formula	Analysis		
						Calcd.	(Found)	
1.		140°	methanol	61	C ₂₁ H ₂₇ N ₃ O ₂	C, 71.36; (C, 71.56;	H, 7.70; H, 7.70;	N, 11.88. N, 12.08).
2.*		136°	ethanol	72	C ₂₁ H ₂₁ N ₃ O ₂	C, 72.59; (C, 72.22;	H, 6.09; H, 6.16;	N, 12.09. N, 12.08).
3.		156-157°	acetonitrile	76	C ₂₃ H ₂₅ N ₃ O ₃	C, 70.56; (C, 70.48;	H, 6.43; H, 6.38;	N, 10.82. N, 11.01).
4.		120-122° dec.	dioxane-water	69	C ₂₁ H ₂₂ N ₄ O ₂	C, 69.59; (C, 69.37;	H, 6.12; H, 6.32;	N, 15.46. N, 15.16).
5.**		99-101°	methanol	31	C ₁₈ H ₂₃ N ₃ O ₂	C, 68.98; (C, 68.87;	H, 7.39; H, 7.27;	N, 13.40. N, 13.32).
6.		123-124°	ethanol	44	C ₁₉ H ₂₅ N ₃ O ₂	C, 69.69; (C, 69.99;	H, 7.70; H, 8.00;	N, 12.83. N, 12.97).

* nmr δ (CDCl₃ + DMSO-d₆) ppm: 4.25, 4.72 (each 2H, each s, 2-CH₂, 4-CH₂); ir ν max (potassium bromide) 2186 cm⁻¹ (s, C $\equiv$ N).

** nmr δ (CDCl₃ + DMSO-d₆) ppm: 3.70, 4.23 (each 2H, each s, 2-CH₂, 4-CH₂); ir ν max (potassium bromide) 2162 cm⁻¹ (vs, C $\equiv$ N).

To a suspension of VIIa (1.64 g., 0.005 mole) in water (10 ml.) piperidine (0.43 g., 0.005 mole) and aqueous formaldehyde (35%, 0.5 ml., 0.006 mole) and with shaking sodium hydroxide (2N, 0.2 ml.) were added. The mixture was boiled for 10 minutes. On cooling an oil separated which, after decantation of the mother liquor, was crystallized from ethanol to give VIIa (1.05 g., 63%, m.p. 125°). More VIIa (0.12 g., 7%) could be obtained from the mother liquor.

Acknowledgment.

We are indebted to Dr. S. Holly and Dr. A. Neszmelyi for spectra, to Mr. I. Remport for microanalyses and to Miss A. Baróti and Miss A. Sárvári for technical assistance.

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