[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

SYNTHESIS OF TETRAHYDROISOQUINOLINE DERIVATIVES

EUGENE C. WEINBACH[1] AND WALTER H. HARTUNG[2]

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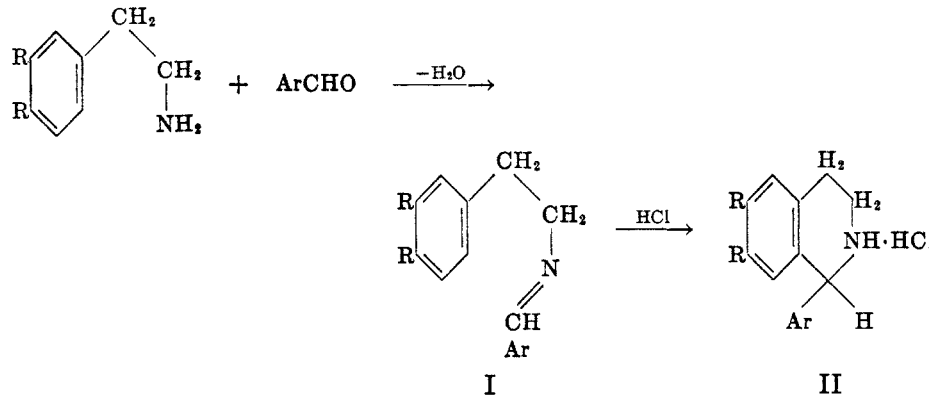
The facility with which β-arethylamines condense with most aldehydes to give the alkylidene derivative (Schiff base) and the cyclization of the resulting Schiff bases into tetrahydroisoquinolines by acidic catalysts led Decker and Becker (1) to synthesize a number of alkaloids of the hydrastinine group:



I II

The intermediate Schiff bases (I) were cyclized to the corresponding tetrahydroisoquinoline (II) by a variety of condensing agents—anhydrous hydrogen chloride, phosphorus oxychloride, zinc chloride, thionyl chloride, and hydrogen bromide (2). Buck (3) prepared a number of tetrahydroisoquinoline hydrochlorides, using formaldehyde, by direct cyclization of the intermediate Schiff base without isolating it. An extension of these earlier studies appears attractive because of the availability of new intermediates which will increase the range of products for pharmacological evaluation.

Table I summarizes the data of the products resulting from the reaction of two β-arethylamines and various aromatic aldehydes. The ease and high degree of purity with which these compounds formed simplified their isolation before the subsequent cyclization reaction.

Biosyntheses of isoquinolines. Schöpf and Bayerle (4) have postulated that isoquinolines can be synthesized under physiological conditions of concentration of reactants, temperature, and *p*H provided that the phenethylamine is activated by a free hydroxyl in the 3-position. This postulate was doubted by Hahn and Schales (5) but their conclusions were shown to be erroneous by Späth, Kuffner, and Kesztler (6). Our own results paralleled those of Späth (6) since, in our hands, homopiperonylamine failed to condense with benzaldehyde at *p*H 5 after standing for 8 days at 25°.

[1] Wm. S. Merrell Company Fellow in Pharmaceutical Chemistry, 1946–1947. Present address: Johns Hopkins School of Medicine, Baltimore, Md.

[2] Present address: University of North Carolina, Chapel Hill, N. C.

It soon became apparent that previously described methods for the cyclization of the Schiff base are not always so dependable or facile as indicated. For example, if the group *para* to the point of ring-closure is hydrogen or unsubstituted phenyl, or if *o*-substituted phenyl or *m*, *p*-dialkoxyphenyl, the cylization proceeds less readily, and hydrolysis of the intermediate rather than cyclization has been observed. After a study of the experimental conditions which promote ring-closure in optimum yields, three variations of a general method were evolved. Method I utilized anhydrous hydrogen chloride, Method II used aqueous hydrogen chloride, and Method III utilized ethanolic hydrogen chloride. Table II presents the data on the substituted tetrahydroisoquinoline hydrochlorides.

TABLE I

SCHIFF BASES OF HOMOVERATRYLAMINE

SUBSTITUTED BENZALDEHYDES	APPEARANCE	M.P., °C.	YIELD, %	FORMULA	N	
					Calc'd	Found.[c]
3,4-Diethoxy	Colorless flakes	75–75.5	98	$C_{21}H_{27}NO_4$	3.92	4.14
4-Methoxy	Colorless plates	62	82	$C_{18}H_{21}NO_3$	4.68	4.90
2-Hydroxy	Bright yellow needles	74–74.5	90	$C_{17}H_{19}NO_3$	4.91	5.10
3-Methoxy-4-hydroxy[a]	Orange, bulky plates	120	88	$C_{18}H_{21}NO_4$	4.44	4.50
2-Chloro	Colorless plates	70–70.5	86	$C_{17}H_{18}ClNO_2$	4.61	4.93
3-Nitro	Tiny, felted, white needles	98	83	$C_{17}H_{18}N_2O_4$	8.91	9.03
4-Hydroxy	Light buff plates	161–161.5	87	$C_{18}H_{21}NO_3$	4.91	5.05
2-Hydroxy-5-chloro	Scintillating, yellow platelets	69	98	$C_{17}H_{18}ClNO_3$	4.38	4.29
SCHIFF BASES OF HOMOPIPERONYLAMINE						
3,4-Diethoxy	Lemon-yellow fluffy needles	71–72	85	$C_{20}H_{23}NO_4$	4.10	4.06
Cinnamaldehyde	Snow-white fluffy platelets	64–64.5[b]	86	$C_{18}H_{17}NO_2$	5.02	5.13

[a] Recrystallized from isopropanol. [b] Ref. (1) gives m.p. 61–63°. [c] Microanalyses by Oakwold Laboratories, Alexandria, Virginia.

EXPERIMENTAL

Amines. After exploring rather extensively several of the numerous syntheses of β-phenethylamines described in the literature (7, 8, 9, 10, 11), the following method was selected for the preparation of homoveratrylamine and homopiperonylamine: mandelonitrile acetates were prepared according to Albert (12); these were catalytically reduced to the corresponding β-arethylamines as by Kindler (13). The most effective catalyst was obtained by employing a mixture of recovered palladium and platinum chlorides, depositing the metals on charcoal in the presence of sodium acetate (14). The hydrogenations were carried out in the usual Burgess-Parr apparatus.

Preparation of Schiff bases. The aldehydes were freshly distilled *in vacuo*, or, if solid, were recrystallized, before use in the condensation. The β-phenethylamines were also redistilled (*in vacuo*) immediately prior to the condensation reaction; these amines must be carefully protected from the atmosphere as they easily form carbonates.

Method A (for liquid aldehydes): The aldehyde (0.03 mole) was added to 0.03 mole of the amine. Heat was evolved and a yellow to orange color developed. The mixture was stirred manually until it became viscous and finally set into a hard, dry mass, accompanied by the evolution of heat. Heating on a water-bath was not necessary (with freshly

TABLE II

1-PHENYLTETRAHYDROISOQUINOLINE HYDROCHLORIDES

1-PHENYLTETRAHYDROISOQUINOLINE DERIVATIVE	PREPN. METHOD	APPEARANCE	M.P., °C.	YIELD, %	FORMULA	Cl[g]	
						Calc'd	Found
6,7-Dimethoxy-3′,4′-diethoxy	II[a]	Fluffy white needles	222–223	81	$C_{21}H_{28}ClNO_4$	9.00	9.03
4′,6,7-Trimethoxy	I[b]	White, felted needles	151–152	75	$C_{18}H_{22}ClNO_3$	10.56	10.51
6,7-Dimethoxy-2′-hydroxy	II[c]	White, tiny needles	242	78	$C_{17}H_{20}ClNO_3$	11.02	10.80
6,7-Dimethoxy-2′-hydroxy-5′-chloro	II[d]	White platelets	258–260	68	$C_{17}H_{19}Cl_2NO_3$	9.95	10.21
6,7-Dimethoxy-2′-chloro	II[e]	White plates	210–212	74	$C_{17}H_{19}Cl_2NO_2$	10.42	10.24
6,7-Dimethoxy-4′-hydroxy	III[f]	Druse of white needles	237	83	$C_{17}H_{20}ClNO_3$	11.02	10.89
6,7-Dimethoxy-3′-nitro	II	White plates	253–254	80	$C_{17}H_{19}ClN_2O_4$	10.12	9.89

[a] Method I gave homoveratrylamine hydrochloride. Method III gave negligible yields of the isoquinoline. [b] Method II caused hydrolysis instead of cyclization. Method III gave a 20% yield of the isoquinoline. [c] Method I yielded the Schiff base hydrochloride. Method III gave a 35% yield of the isoquinoline. [d] Method I gave a negligible yield and Method III gave a 34% yield of the isoquinoline. [e] Method I gave a gummy, unidentified product. Method III caused hydrolysis instead of cyclization. [f] Method II gave a 75% yield of the isoquinoline. Method I gave a gummy, unidentified product. [g] Volhard analysis.

distilled reactants) to complete the reaction. The products were recrystallized from dilute ethanol, usually in quantitative yields.

Method B (for solid aldehydes): The aldehyde (0.03 mole) was dissolved in 30 ml. of commercial absolute ethanol (in some instances more ethanol and a gentle warming was required for complete solution). To this alcoholic solution, 0.03 mole of the amine was added, accompanied by the development of color. After gentle heating on a water-bath to drive off most of the alcohol, the mixture was set aside to cool. On cooling, the entire mixture set to a druse of crystals. The product was recrystallized from dilute ethanol.

Cyclization of the Schiff bases. Numerous attempts to effect cyclization (including variations of solvent and temperature) with condensing agents such as boron trifluoride and

thionyl chloride were without success. Hydrogen chloride was the agent of choice and three methods for its use were developed.

Method I: In a 200-ml., three-necked flask, equipped with stirrer, drying-tube, and a glass tube which ended 2 cm. above the surface of the reaction mixture, was placed a solution of 0.02 mole of the Schiff base in 25 ml. of anhydrous benzene. During vigorous stirring of the solution, anhydrous hydrogen chloride was blown over the surface of the reaction mixture. Separation of a yellow precipitate (Schiff base hydrochloride) immediately ensued. After the reaction flask was saturated with hydrogen chloride, the flow of the gas was stopped; upon gentle heating the yellow color disappeared (indicative of cyclization) and the clear solution was allowed to cool in a refrigerator. The precipitated isoquinoline hydrochloride was recrystallized from anhydrous alcohol-ether.

Method II: In a 200-ml., three-necked flask, fitted with a stirrer and reflux condenser, was placed 0.03 mole of the Schiff base and during vigorous stirring, 40-ml. of 24% hydrochloric acid was added. The flask was heated on a water-bath and stirring was continued for 40–60 minutes. If, after cooling, the product separated it was collected and recrystallized. Frequently the product did not separate upon cooling; if this occurred, the reaction mixture was evaporated to dryness *in vacuo*, and the residue was dissolved in the minimum amount of hot absolute ethanol, cooled, and anhydrous ether added to initiate precipitation of the isoquinoline hydrochloride.

Method III: To a solution of 0.02 mole of the Schiff base and 20-ml. of 95% ethanol was added 25-ml. of a saturated ether solution of hydrogen chloride and the whole was concentrated to approximately one-eighth its volume on a water-bath. After cooling, anhydrous ether was added to initiate precipitation. The tetrahydroisoquinoline hydrochloride was recrystallized from anhydrous alcohol-ether.

The hydrochlorides are white and well-crystallized. They are soluble in water, moderately soluble in alcohol, and sparingly soluble in ethyl acetate. They are insoluble in anhydrous ether.

SUMMARY

A study is reported of the synthesis of 1-phenyltetrahydroisoquinoline hydrochlorides *via* the formation and isolation of Schiff bases, from substituted β-arethylamines and aromatic aldehydes, and of their subsequent cyclization.

BALTIMORE, MARYLAND

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