[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Isoquinoline Derivatives. III. 3-Isoquinolinecarboxylic Acids

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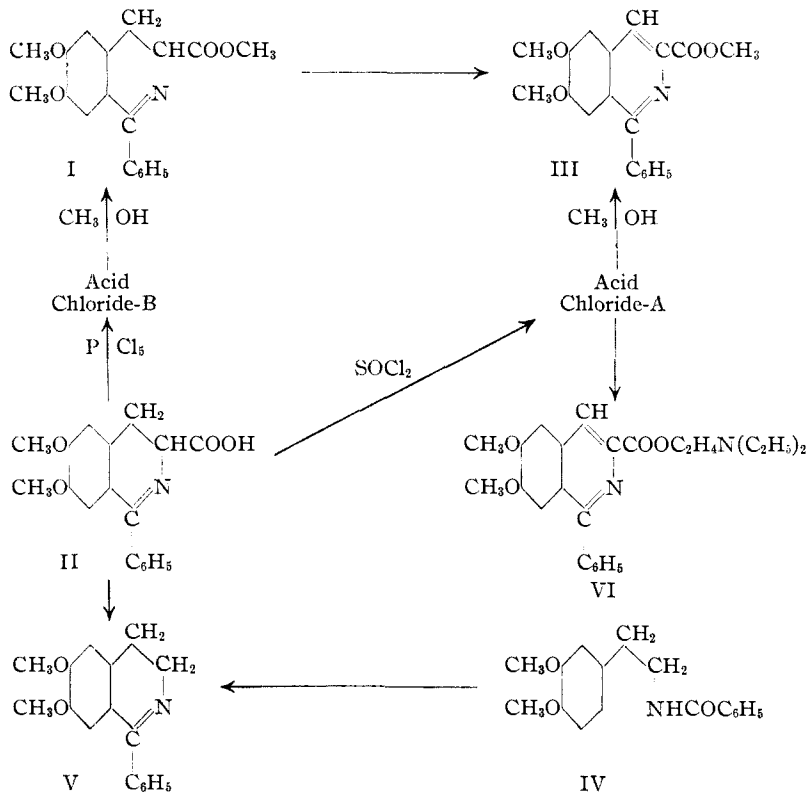
In view of the valuable anesthetic properties possessed by certain aminoalkyl esters and amides of quinolinecarboxylic acids, the preparation of similar compounds in the isoquinoline series seemed to be particularly desirable.

A variety of methods for preparing isoquinolinecarboxylic acids are to be found in the literature. Of these one seemed most applicable to the present work. Hartman and Kagi[2] obtained methyl esters of 3-isoquinoline-carboxylic acids by the ring-closure of N-acylphenylalanine derivatives. These workers, however, did not prepare the free isoquinolinecarboxylic acids.



The procedure of Hartman and Kagi has been applied in our research with certain modifications of technique. The azlactone of α-benzamido-3,4-dimethoxycinnamic acid prepared by the condensation of methylvanillin with hippuric acid was converted into the methyl or ethyl ester. These esters were then hydrogenated catalytically to the esters of N-benzoyl-3,4-dimethoxyphenylalanine. Treatment of the latter compounds with phosphorus pentoxide in boiling xylene resulted in the formation of esters of 1-phenyl-6,7-dimethoxy-3,4-dihydro-3-isoquinolinecarboxylic acid I. Saponification of these esters with dilute alkali yielded the acid II.

The 3-isoquinolinecarboxylic acid II was treated with thionyl chloride to form an acid chloride (A). In order to check the course of the reaction this acid chloride was treated with methyl alcohol. Instead of the original ester I a new compound was obtained which analysis indicated to be the ester I less two hydrogen atoms. Oxidation of the ester I by the method of Pictet and Kay[3] for the preparation of isoquinolines from 3,4-dihydroisoquinoline yielded the same compound. The compound formed here is evidently the ester of 1-phenyl-6,7-dimethoxy-3-isoquinolinecarboxylic acid III. Saponification of this ester III gave the corresponding isoquinolinic acid.

A different acid chloride (B) was obtained when the acid II was treated in benzene solution with phosphorus pentachloride. Treatment of this acid chloride with methyl alcohol regenerated the original ester I. The dehydrogenation brought about by thionyl chloride would, therefore, appear to be an oxidation rather than chlorination followed by loss of hydrogen chloride.

When the acid II was heated in a boiling benzene solution decarboxylation took place with the formation of 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline V. This compound was identical

(1) E. R. Squibb and Sons, Organic Chemistry Research Fellow, 1932–1933.

(2) Hartman and Kagi, U. S. Patent 1,437,802; *C. A.*, **17**, 854 (1923). See also *C. A.* **17**, 3073 (1923), and *Chem. Zentr.*, II, 574 (1923).

(3) Pictet and Kay, *Ber.*, **42**, 1973 (1909).

with that obtained by the ring-closure of N-(3,4-dimethoxyphenylethyl)-benzamide IV.

The synthesis of the desired diethylaminoethyl ester of 1-phenyl-6,7-dimethoxy-3-isoquinolinecarboxylic acid VI was accomplished by interaction of the acid chloride A with diethylaminoethyl alcohol.

Experimental Part

TABLE I

Ref.	Compound	Analyses, % Calcd.	Found	Calcd.	Found		Yield, %	M. p., °C.
a	Lactone of α-benzamido-3,4-dimethoxycinnamic acid						64–69	148–149
a	Methyl ester of α-benzamido-3,4-dimethoxycinnamic acid						81–84	143–144
b	Ethyl ester of α-benzamido-3,4-dimethoxycinnamic acid			N, 3.94	3.70	3.77	79	118–119
c	Methyl ester of N-benzoyl-3,4-dimethoxyphenylalanine						94	104–105
c	Ethyl ester of N-benzoyl-3,4-dimethoxyphenylalanine			N, 3.92	3.73	3.76	97	100–101
d	Methyl ester of 1-phenyl-6,7-dimethoxy-3,4-dihydro-3-isoquinolinecarboxylic acid I						69	120.5–121.5
e	Ethyl ester of 1-phenyl-6,7-dimethoxy-3,4-dihydro-3-isoquinolinecarboxylic acid						79	
f	1-Phenyl-6,7-dimethoxy-3,4-dihydro-3-isoquinolinecarboxylic acid II						74	
g	Methyl ester of 1-phenyl-6,7-dimethoxy-3-isoquinolinecarboxylic acid III	H, 5.31	5.31	N, 4.34	4.21		...	172–173
		C, 70.56	70.45					
h	1-Phenyl-6,7-dimethoxy-3-isoquinolinecarboxylic acid	C, 69.88	69.68	H, 4.89	4.90		...	216–216.5
i	N-(3,4-Dimethoxyphenylethyl)-benzamide IV			N, 4.91	4.75	4.77	...	90–91
j	1-Phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline V	C, 76.38	76.36	H, 6.42	6.46		...	120.5–121.5
k	Diethylaminoethyl ester of 1-phenyl-6,7-dimethoxy-3-isoquinolinecarboxylic acid VI	C, 70.55	70.26	H, 6.91	6.98		...	158.5–159

[a] Prepared according to the method of Kropp and Decker.[4]

[b] Preparation similar to that of the methyl ester. Crystallized from alcohol.

[c] Obtained by the catalytic hydrogenation of the corresponding cinnamic acid derivative at 3 atmospheres pressure using Adams platinum oxide catalyst.

[d] Prepared by treating a boiling xylene solution of the methyl ester of N-benzoyl-3,4-dimethoxyphenylalanine with phosphorus pentoxide for thirty minutes. The resulting mass was dissolved in water and the isoquinoline precipitated by means of dilute ammonium hydroxide. Crystallized from dilute methyl alcohol.

[e] Preparation similar to that of the methyl ester. This compound was obtained as a viscous oil which failed to crystallize.

[f] Obtained by the saponification of either the methyl or ethyl ester by means of 2% sodium hydroxide solution. The acid was precipitated by the dropwise addition of dilute acetic acid. The compound was not obtained sufficiently pure for analysis probably due to the ease of decarboxylation. This acid was converted into acid chloride A by treatment with thionyl chloride and into acid chloride B by treatment with phosphorus pentachloride in dry benzene. Acid chloride B yielded the original methyl ester I when treated with methyl alcohol.

[g] Acid chloride A was dissolved in absolute methyl alcohol, diluted with water and filtered. The ester was precipitated by means of dilute ammonium hydroxide and crystallized from methyl alcohol. This ester (III) was also obtained by treating 0.5 g. of I in 30 cc. of *N*/2 sulfuric acid with a solution of 0.1 g. of potassium permanganate in 20 cc. of water and warming to 50–60° until clear. The ester was precipitated with dilute ammonium hydroxide and crystallized as before.

[h] Obtained by the saponification of III with 2% sodium hydroxide solution. Upon acidification with dilute hydrochloric acid a white crystalline precipitate separated which effervesced at 207–208° and contained chlorine. After recrystallization from alcohol the product melted to a clear liquid at 216–216.5° and contained no chlorine.

[i] From homoveratrylamine, benzoyl chloride and 10% sodium hydroxide solution. Crystallized from benzene–petroleum ether solution.

[j] By treatment of IV in boiling toluene with phosphorus oxychloride. Toluene diluted with petroleum ether and the precipitated oil dissolved in water and treated with ammonium hydroxide. The isoquinoline was recrystallized from dilute alcohol. V was also obtained by boiling II in benzene for forty-five minutes. After removal of the benzene the residue was dissolved in hot alcohol, the solution made alkaline with ammonium hydroxide and diluted with water. A crystalline precipitate formed which was identical with V obtained above.

[k] Prepared by treating the acid chloride A prepared from 3 g. of II with a cold chloroform solution of 5.5 g. of diethylaminoethyl alcohol. After removal of the chloroform the residue was dissolved in diluted hydrochloric acid. This solution was extracted with ether, filtered and made alkaline with dilute ammonium hydroxide. The ester was purified by repeatedly dissolving in a small amount of hot benzene and diluting with petroleum ether.

Summary

1. 1-Phenyl-6,7-dimethoxy-3,4-dihydro-3-isoquinolinecarboxylic acid has been prepared.

2. This acid reacts normally with phosphorus pentachloride but is dehydrogenated by the action of thionyl chloride giving an isoquinolinic acid chloride. Decarboxylation in boiling benzene leads to the formation of 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline.

3. The methyl and diethylaminoethyl esters of 1-phenyl-6,7-dimethoxy-3-isoquinolinecarboxylic acid have been prepared.

(4) Kropp and Decker, *Ber.*, **42**, 1184 (1909).

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