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PYRIDINDENE DERIVATIVES. I

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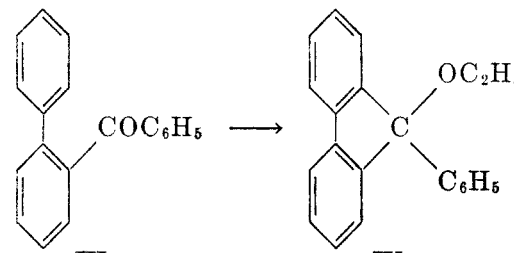
In previous papers (10, 11) we have described convenient methods for the preparation of 1,3,4-trisubstituted piperidine derivatives. The reactions of these amines have since been studied in detail. The present communication deals with an interesting intramolecular cyclodehydration of these piperidine derivatives.

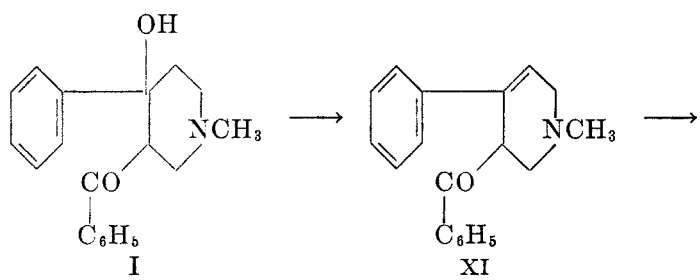
When 1-methyl-3-benzoyl-4-hydroxy-4-phenyl-piperidine, I (6, 10, 12), is subjected to the action of strong hydrobromic acid (40–48%) at temperatures ranging from approximately 100° to reflux temperature, a yellow, well crystallized compound of m.p. 202–203° is formed. It does not contain oxygen. From the complete elementary analysis, the empirical formula $C_{19}H_{17}N \cdot HBr$ can be derived. The identical base $C_{19}H_{17}N$ is obtained when I is treated with strong sulfuric acid at elevated temperatures. Hydrochloric acid, phosphorus oxychloride, and phosphoric acid, however, do not convert I into the new base. The properties and reactions of the base $C_{19}H_{17}N$ lead to the conclusion that it has the formula II and is formed by the removal of two molecules of water from I. One molecule of water is eliminated with the formation of a double bond; the second is lost in a cyclodehydration, a reaction for which numerous examples have been reported in the aromatic series (2).

Our reaction seems to be the first instance of such a cyclodehydration where a hydrogenated heterocyclic ring system is involved. A similar ring closure without dehydration occurs in the case of *o*-phenylbenzophenone, III (3), which is converted into 9-phenyl-9-ethoxy-fluorene (IV) by refluxing with hydrobromic acid and then with alcohol.

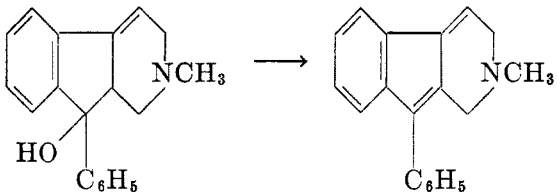


III IV

In our reaction the presence of additional hydrogen makes possible a further loss of water leading to the formation of a double bond. Schematically the sequence of reactions involved in this case may be depicted as follows:

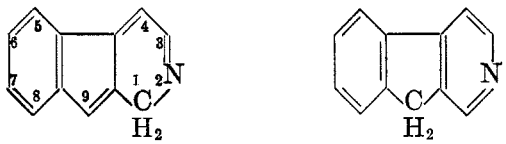


I XI



XII II

The base $C_{19}H_{17}N$ is a derivative of the ring system V. This is isomeric with the

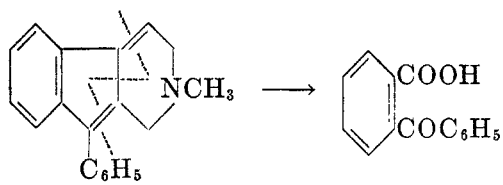


V VI

system VI which is the skeleton present in several aromatic compounds described in the literature (1, 8). This latter system has been called pyridofluorene (8) and 2-azafluorene (1). The official name is 9*H*-indeno[2,1-*c*]pyridine (9). In accordance with this nomenclature, the ring system V should be called 1*H*-indeno[2,1-*c*]pyridine.

Indene and pyridine rings can be fused in several ways leading to different tricyclic ring systems all of which are classified as indenopyridines. They are differentiated by the use of the appropriate figures and letters within the brackets. Three of these fused ring systems are listed in the Ring Index (9) under No. 1760–1762. For the purpose of easy reference and in order to avoid the cumbersome use of letters and figures within the brackets, we decided to assign the simple name "1-pyridindene" to the ring system V. Thus compound II becomes 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene.

The structure of compound II was proved by oxidation. When it was treated with potassium permanganate in alkaline solution, *o*-benzoylbenzoic acid (VII) was formed. The acid VII was identified by a mixed melting point determination with an authentic sample of this acid and by the preparation of the amide (4) and of the anilide (7). The oxidation is illustrated by the scheme:



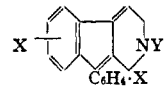
II VII

The dotted line indicates the manner of degradation. The isolation of *o*-benzoylbenzoic acid is conclusive proof that the two phenyl groups, originally separated as shown in formula I, have become attached to the same carbon atom in compound II, and furthermore, the attachment has taken place *ortho* to the substituent in one of the phenyl nuclei. These requirements are met by formula II.

The reaction is not confined to the piperidine derivative I. Other 1,3,4-trisubstituted piperidines of the general formula VIII undergo the ring closure to IX in the same way. The resulting tricyclic compounds are listed in Table I.

TABLE I

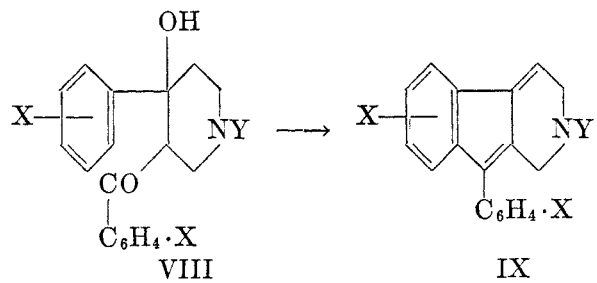
1-PYRIDINDENE DERIVATIVES



FORMULA	X	Y	EMPIRICAL FORMULA	HYDROBROMIDE M.P., °C.
II	H	CH_3	$C_{19}H_{17}N$	201–204
XIII	H	C_2H_5	$C_{20}H_{19}N$	202–204
XIV	H	$CH(CH_3)_2$	$C_{21}H_{21}N$	243–245
XV	H	n-C_4H_9	$C_{22}H_{23}N$	193–195
XVI	CH_3	CH_3	$C_{21}H_{21}N$	200–203[a]
XVII	OCH_3	CH_3	$C_{21}H_{21}NO_2$	209–210

[a] Semi-hydrate.

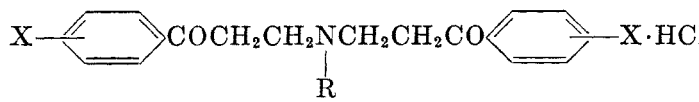
The resulting 1-pyridindene derivatives were isolated as hydrobromides which crystallize readily from the appropriate solvents. The hydrobromides are quite stable in contrast to the free bases which discolor soon on standing.



VIII IX

The ease with which the piperidine bases are converted into 1-pyridindene derivatives prompted an investigation of the behavior of the original Mannich compounds X, from which the piperidine bases are obtained, toward hydrobromic acid.

As discussed in the previous papers (10, 11) the reaction products of the Mannich condensation between acetophenone, alkylamine hydrochlorides, and formaldehyde are hydrochlorides of the formula X.



X

The corresponding bases are not stable and, when liberated from the salts, they undergo rearrangement into piperidine derivatives of the type I. This reaction

involves an intramolecular aldol condensation. Inasmuch as aldol condensations are frequently brought about in acid as well as in alkaline solution, it was felt that treatment of the Mannich product X with hydrobromic acid should also give initially the piperidine compound II which would then undergo further cyclization to the pyridindene derivative II. This assumption proved to be correct. By treatment with hydrobromic acid, not only *bis*-(β-benzoylethyl)methylamine hydrochloride, but also *bis*-(β-benzoylethyl)ethylamine hydrochloride, and *bis*-(β-*p*-toluylethyl)methylamine hydrochloride are converted into the corresponding pyridindene derivatives.

By the outlined reactions, derivatives of dihydro-1-pyridindenes have become one of the most easily accessible classes of polynuclear heterocyclic compounds.

EXPERIMENTAL

The melting points are uncorrected.

PART I: 1-PYRIDINDENES FROM PIPERIDINE DERIVATIVES

A. *2-Methyl-9-phenyl-2,3-dihydro-1-pyridindene* (II). 1. *With hydrobromic acid.* Seven-hundred-fifty grams of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (5, 6, 12) and 2500 cc. of 48% hydrobromic acid are distilled through a twenty-plate distillation column over a period of about one hour. The temperature rises by this time to 124°. Distillation is discontinued, and the remaining dark yellow solution is poured into 8000 cc. of water with stirring. An oily precipitate forms which soon solidifies. The crystals are recrystallized from 3400 cc. of alcohol to yield 610 g. of yellow crystals, m.p. 201–204°. Additional amounts are obtained from the filtrate. The total yield averages 700–720 g. of 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide. The melting point varies somewhat with the rate of heating.

Anal. Calc'd for $C_{19}H_{17}N \cdot HBr$: C, 67.06; H, 5.33; N, 4.12; Br, 23.49.
Found: C, 66.77; H, 5.26; N, 4.32, Br, 23.99.

The same compound is obtained when the starting material is heated to 90–100° with six times its weight of 48% hydrobromic acid for 10–12 hours.

2. *With 65.6% sulfuric acid.* A mixture of 10 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine and 50 cc. of 65.6% (by weight) sulfuric acid is refluxed for twenty minutes. The solution is poured into 100 cc. of cold water, and the base is liberated by the addition of 10% sodium hydroxide at 20–30°. The base is extracted with ether and treated with hydrogen bromide gas. The hydrobromide separates immediately. It is digested with 75 cc. of hot acetone. On cooling, about 3 g. of 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide of m.p. 202–203° is obtained.

Anal. Calc'd for $C_{19}H_{17}N \cdot HBr$: C, 67.06; H, 5.33.
Found: C, 67.26; H, 5.15.

3. *With 47% sulfuric acid.* A mixture of 20 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine and 80 cc. of 47% sulfuric acid is refluxed for three hours and then treated as in the preceding experiment. Yield, 13.3 g. of 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide, m.p. 202–204°. Recrystallization from methanol gives a product of m.p. 201–203°.

Anal. Calc'd for $C_{19}H_{17}N \cdot HBr$: C, 67.06; H, 5.33.
Found: C, 67.57; H, 5.13.

B. *2-Ethyl-9-phenyl-2,3-dihydro-1-pyridindene* (XIII). A mixture of 46 g. of 1-ethyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (11) and 185 cc. of 48% hydrobromic acid is distilled for thirty minutes through a twelve-plate column. The temperature rises to 122°. The mixture is poured into 370 cc. of water. The oily precipitate is crystallized from 150 cc. of alco-

hol, yielding 40 g. of 2-ethyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide of m.p. 202–204°.

Anal. Calc'd for $C_{20}H_{19}N \cdot HBr$: C, 67.80; H, 5.69.
Found: C, 68.05; H, 5.48.

C. *2-Isopropyl-9-phenyl-2,3-dihydro-1-pyridindene* (XIV). A solution of 40 g. of 1-isopropyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (11) in 170 cc. of 48% hydrobromic acid is distilled through a twelve-plate column until the boiling point reaches 122°. The solution is then poured into 350 cc. of water. The precipitate is refluxed with 400 cc. of alcohol to remove impurities. The undissolved crystals are filtered hot and washed with ether. Yield, 41 g. of 2-isopropyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide, m.p. 243–245°.

Anal. Calc'd for $C_{21}H_{21}N \cdot HBr$: C, 68.48; H, 6.02.
Found: C, 68.73; H, 5.99.

D. *2-n-Butyl-9-phenyl-2,3-dihydro-1-pyridindene* (XV). A mixture of 20 g. 1-*n*-butyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (11) and 80 cc. of 48% hydrobromic acid is distilled through a twelve-plate column until the temperature rises to 121–122°. The solution is poured into 160 cc. of water. The precipitate is filtered and recrystallized from about 100 cc. of acetone. Yield, 11.4 g. of 2-*n*-butyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide, m.p. 193–195°.

Anal. Calc'd for $C_{22}H_{23}N \cdot HBr$: C, 69.11; H, 6.33.
Found: C, 69.08; H, 6.40.

E. *2,7-Dimethyl-9-p-tolyl-2,3-dihydro-1-pyridindene* (XVI). A solution of 20 g. of 1-methyl-3-*p*-toluyl-4-hydroxy-4-*p*-tolylpiperidine (11) in 80 cc. of 48% hydrobromic acid is distilled slowly through a twelve-plate column over a period of thirty minutes. The water is thereby removed. The mixture is then poured into 160 cc. of water. The precipitate (18 g.) is crystallized, first from alcohol and then from acetic acid, yielding 2,7-dimethyl-9-*p*-tolyl-2,3-dihydro-1-pyridindene hydrobromide of m.p. 202–203°. It contains one-half molecule of water of crystallization.

Anal. Calc'd for $C_{21}H_{21}N \cdot HBr \cdot \frac{1}{2} H_2O$: C, 66.84; H, 6.14.
Found: C, 67.12; H, 6.42.

F. *2-Methyl-6-methoxy-9-m-methoxyphenyl-2,3-dihydro-1-pyridindene* (XVII). To 12 cc. of conc'd sulfuric acid, maintained at 5–9° by means of an ice-bath, 2 g. of 1-methyl-3-*m*-methoxybenzoyl-4-hydroxy-4-*m*-methoxyphenylpiperidine (11) is slowly added in about twenty minutes. After standing for approximately ten minutes, the solution is poured into cracked ice and treated below 30° with 30% sodium hydroxide solution until distinctly alkaline. The liberated base is extracted with ether, and the ethereal solution is treated with gaseous hydrogen bromide. On standing in the refrigerator, 2-methyl-6-methoxy-9-*m*-methoxy-phenyl-2,3-dihydro-1-pyridindene hydrobromide gradually crystallizes. Recrystallization from alcohol yields the pure product, m.p. 209–210°.

Anal. Calc'd for $C_{21}H_{21}NO_2 \cdot HBr$: C, 63.00; H, 5.54.
Found: C, 62.68; H, 5.35.

PART II: 1-PYRIDINDENES FROM "MANNICH BASES"

A. *2-Methyl-9-phenyl-2,3-dihydro-1-pyridindene* (II). A mixture of 250 g. of *bis*-(β-benzoylethyl)methylamine hydrochloride and 1000 ml. of hydrobromic acid 48% is refluxed with stirring for one hour. The hydrochloride dissolves slowly. Hydrogen chloride is formed and escapes through the condenser. After standing overnight, 1000 cc. of water is added with stirring. Crystallization starts slowly but proceeds rapidly as soon as crystals are present. After stirring for two hours, the mixture is filtered, washed with 50 cc. of water, and dried. The crude hydrobromide (250–255 g.) is recrystallized from 2000 cc. of boiling alcohol, yielding 200–220 g. of pure 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide of m.p. 202–204°. The synthesis of the 1-pyridindene compounds proceeds in the same manner if *bis*-(β-benzoylethyl)methylamine hydrobromide of m.p. 182° is used in place of the hydrochloride. This hydrobromide is obtained directly when the Mannich reaction is carried

out with methylamine hydrobromide instead of methylamine hydrochloride as found by Mr. Weinhagen.

B. *2-Ethyl-9-phenyl-2,3-dihydro-1-pyridindene* (XIII). Twenty-five grams of *bis*-(β-benzoylethyl)ethylamine hydrochloride (11) is refluxed in 100 cc. of 48% hydrobromic acid. After cooling, 200 cc. of water is added with stirring; an oil separates. The supernatant liquid is poured off, and the oil is dissolved in about 50 cc. of alcohol. On standing in the refrigerator, 2-ethyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide crystallizes slowly. Recrystallization from alcohol yields the pure compound, m.p. 201–203°.

C. *2,7-Dimethyl-9-p-tolyl-2,3-dihydro-1-pyridindene* (XVI). Twenty grams of *bis*-(β-*p*-toluylethyl)methylamine hydrochloride is suspended in 80 cc. of 48% hydrobromic acid. The mixture is distilled through a twelve-plate column until the vapor temperature reaches 122–123°. The remaining solution is then poured into 160 cc. of water. A gummy precipitate appears from which the supernatant liquid is poured off. The material is dissolved in 60 cc. of boiling alcohol. On cooling, 14 g. of crystals of m.p. 174–190° is obtained. Recrystallization from about 200 cc. of glacial acetic acid yields pure 2,7-dimethyl-9-*p*-tolyl-2,3-dihydro-1-pyridindene hydrobromide, m.p. 200–203°.

PART III: OXIDATION OF 2-METHYL-9-PHENYL-2,3-DIHYDRO-1-PYRIDINDENE

A mixture of 3 g. of 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide, 12 g. of potassium permanganate, and 15 cc. of 10% sodium hydroxide was heated on the steam-bath with occasional shaking for about 5 hours. Sulfur dioxide was then passed into the mixture until only a gummy precipitate remained. This material was separated and digested with 50 cc. of 5% sodium hydroxide. The solution was filtered. The filtrate was acidified with conc'd hydrochloric acid, and the gummy precipitate was digested with 50-cc. portions of boiling water. Each time the hot supernatant solution was decanted and filtered with a little charcoal. On cooling the first portion gave crystals which, after drying at 70°, melted at 126–127° and weighed 0.07 g. The second portion yielded 0.1 g. of m.p. 128–129°. Recrystallization of the combined crops of crystals from water gave a product of m.p. 128–129°. It showed no depression in melting point when mixed with an authentic sample of *o*-benzoylbenzoic acid. The melting points of the amide and of the anilide, prepared by conventional methods, were substantially identical with those reported in the literature; the amide melting at 161–163° (4) and the anilide at 192–194° (7). The anilide was analyzed to establish its structure.

Anal. Calc'd for $C_{20}H_{16}NO_2$: C, 79.45; H, 5.34.
Found: C, 79.40; H, 5.29.

Acknowledgment. We thank Dr. A. Steyermark for the microanalyses and Mr. P. Bevilacqua for technical assistance.

SUMMARY

1-Alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidines and their ring-substituted derivatives are converted by cyclodehydration into derivatives of 1-pyridindene (1*H*-indeno[2,1-*c*]pyridine). The same compounds are formed when diketone-amine hydrochlorides, obtained by Mannich reactions from acetophenone, are refluxed with strong hydrobromic acid.

NUTLEY, N. J.

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