[CONTRIBUTION NO. 419 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LAROCHE INC.]

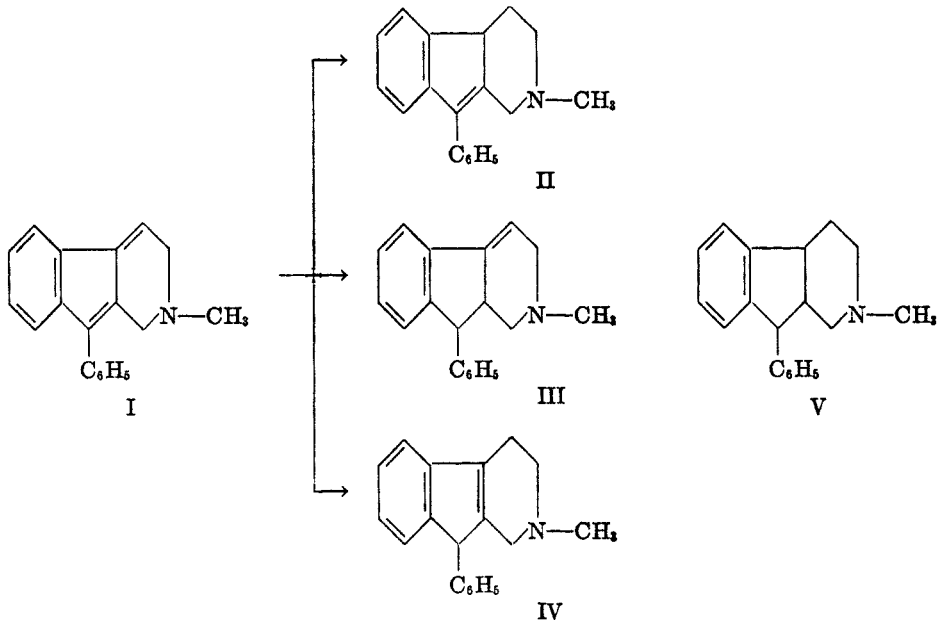
PYRIDINDENE DERIVATIVES. II. THE CHEMISTRY OF 2-METHYL-9-PHENYL-2,3,4,9-TETRAHYDRO-1-PYRIDINDENE

JOHN T. PLATI AND WILHELM WENNER

Received June 9, 1955

The search for compounds with anti-histaminic properties, reported in our earlier publications (1–3), had led to certain dihydropyridindene derivatives which had only weak activity. Subsequent hydrogenation afforded compounds with much greater potency. This paper describes that part of the work dealing with 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene.

The hydrogenation of 2,3-dihydro-1-pyridindene (I) derivatives which contain two non-benzenoid double bonds, should yield tetrahydro- and hexahydro-pyridindenes. In the case of 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene, the hydrogenation may take the following course.



Absorption of one mole of hydrogen could lead to three possible tetrahydro-pyridindene derivatives. Saturation of the double bond in the heterocyclic 6-ring would lead to II, whereas saturation of the double bond in the 5-ring would lead to III. Compound IV could result from 1,4-addition or from rearrangement of either II or III. Absorption of two moles of hydrogen should yield compound V.

The hydrobromide or hydrochloride of I was utilized in the hydrogenation in view of their higher stability as compared to the free base. The absorption of one mole of hydrogen proceeded easily with various catalysts, whereas the further

absorption of a second mole required more energetic conditions. For example, hydrogenation with palladium on charcoal stopped at the tetrahydropyridindene stage, even when the temperature was raised to about 110°. With Raney nickel, the hydrogenation to the same stage proceeded smoothly without external application of heat. Thus, another example is provided of the usefulness of Raney nickel for the hydrogenation of salts in weakly acid solution, an application which one of us has previously reported (10).

With platinum oxide, the absorption of hydrogen proceeded rapidly at room temperature until one mole was absorbed. Further uptake was quite slow and it was necessary to increase the temperature to above 75° to accelerate the absorption of a second mole of hydrogen. In this manner the hexahydropyridindene V could be obtained.

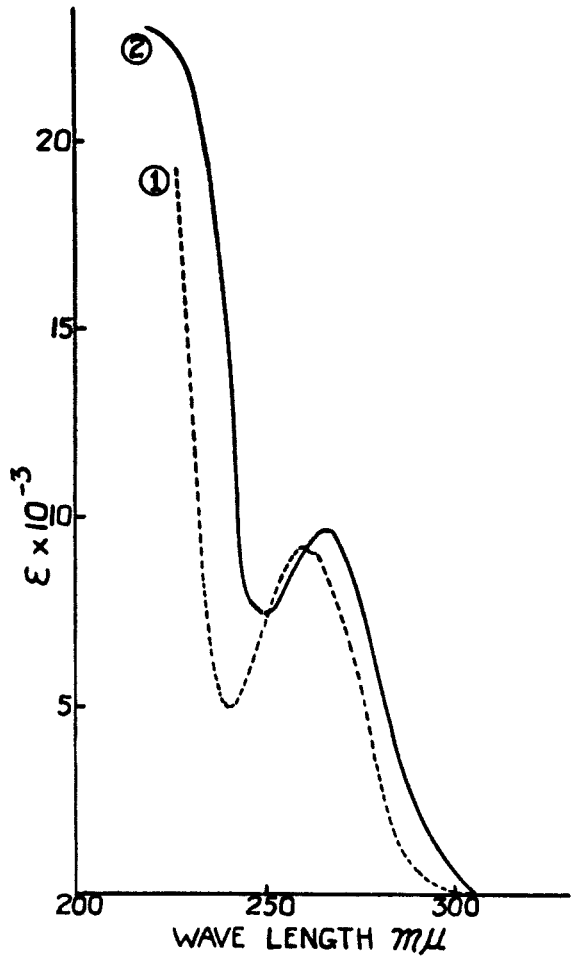


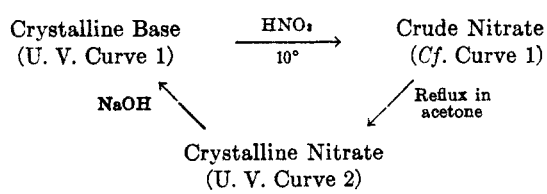
FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA IN 0.1 *N* HCl. Curve 1. 2-Methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (Formula IV). Curve 2. Nitrate of 2-methyl-9-phenyl-2,3,4,4a-tetrahydro-1-pyridindene (Formula II).

As a first approach to the problem of separating and identifying the possible compounds of the tetrahydropyridindene series (II, III, and IV) salts of various acids were prepared. It soon became apparent from a study of the ultraviolet spectra that these salts were derived from two different isomeric bases. No evidence of a third base could be detected. For example, the thiocyanate, salicylate, and phosphate, as obtained under our experimental conditions, exhibited the spectrum illustrated by Curve 1, whereas the hydrobromide and nitrate exhibited the spectrum illustrated by Curve 2. The hydrobromide was obtained in 61% yield when the solution from the hydrogenation of I in alcohol was allowed to stand. The spectral evidence indicates that approximately the same amount is present when the hydrogenation is effected in water.

Addition of potassium nitrate, sodium salicylate, potassium dihydrogen phosphate, and potassium thiocyanate, respectively, to the aqueous hydrogenation liquor yielded the other salts in yields ranging from 50 to 90%. Of the four salts, only the nitrate belonged to the same spectral series as the above hydrobromide. The conditions of the transformation were mild, involving only a precipitation at room temperature and crystallization from the appropriate solvent (when necessary). When any one of these salts was stirred with alkali, it was eventually converted into the same crystalline base whose ultraviolet spectrum is shown by Curve 1. It was apparent that we were dealing with a facile isomerization between two isomeric bases and that mere combination with an anion and crystallization were sufficient to determine the direction of the isomerization. Thus, the high yields of structurally different salts from the same starting material was due to a rare combination of isomerizability and crystallizability.

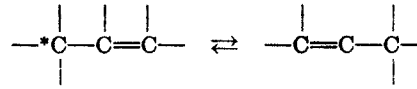
This novel type of behavior justified a more extensive investigation. As stated above, only one base has been isolated in crystalline form from the action of alkali on various salts. The addition of dilute nitric acid to this base under carefully controlled conditions yielded a crude nitrate which belongs predominantly to the same spectral series as the original base (*Cf.* Curve 1). However, mere refluxing with acetone was sufficient to convert the crude nitrate into a material belonging to the other spectral series (*Cf.* Curve 2). Chart 1 summarizes these findings and demonstrates the reversibility of the isomerization.

CHART 1



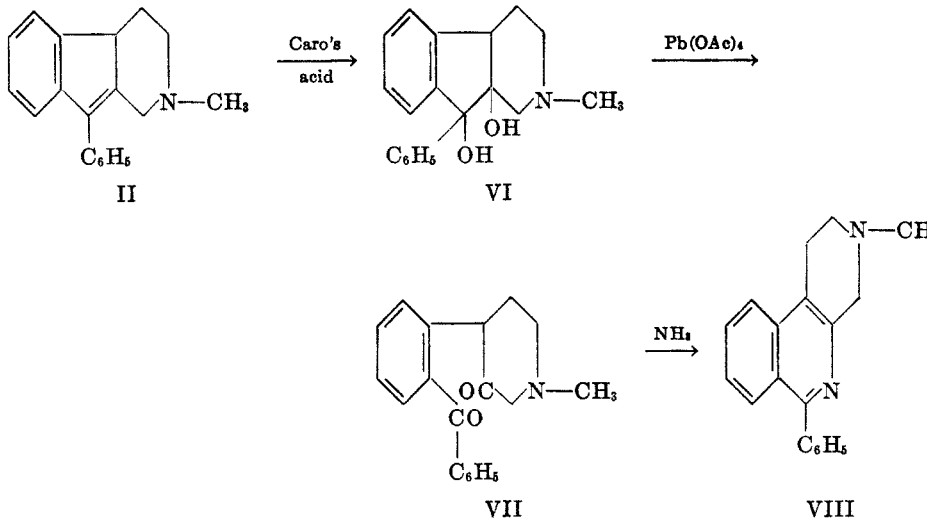
The crystalline base (*Cf.* Curve 1) can be resolved by means of *d*-tartaric acid to yield an optically active base. Crystallization of this optically active base from acetone and water almost completely destroys the optical activity. The shifting of a couble bond to an asymmetric centre provides a ready explanation

for the racemization as well as for the isomerization, as shown in the following expression.



An *a priori* consideration of the products resulting from the absorption of one mole of hydrogen leads to certain assumptions. First of all, the use of a catalyst appears to favor 1,2-addition rather than 1,4-addition (4). Muskat and Knapp (5) adopted this view after their investigation of vinylacrylic acid and phenylbutadiene. They found in the case of phenylbutadiene, which particularly resembles our parent substance I, that the 3,4-ethylenic linkage was almost quantitatively saturated by one mole of hydrogen. The relative stability of the 1,2-ethylenic linkage may be attributed to conjugation with a phenyl ring.

Thus, of the two ethylenic linkages present in I, the one more likely to resist hydrogenation is that of the 5-ring, stabilized not only by conjugation with two aromatic nuclei but also by steric hindrance. Thus, it would be expected that the rate of formation of II would be considerably greater than that of III. Furthermore, since compound IV can result from II by a shift of a double bond to an adjacent position and since this type of allylic shifting can explain the ease of racemization and isomerization, the isolation of compound IV from the hydrogenation mixture can be considered a strong possibility. Thus, the various salts mentioned above are presumably derived from two isomeric bases, II and IV. Actually, only one base has been isolated in crystalline form. The other base can be obtained as an oil from the crystalline nitrate (U. V. Curve 2), provided care is exercised to prevent isomerization.

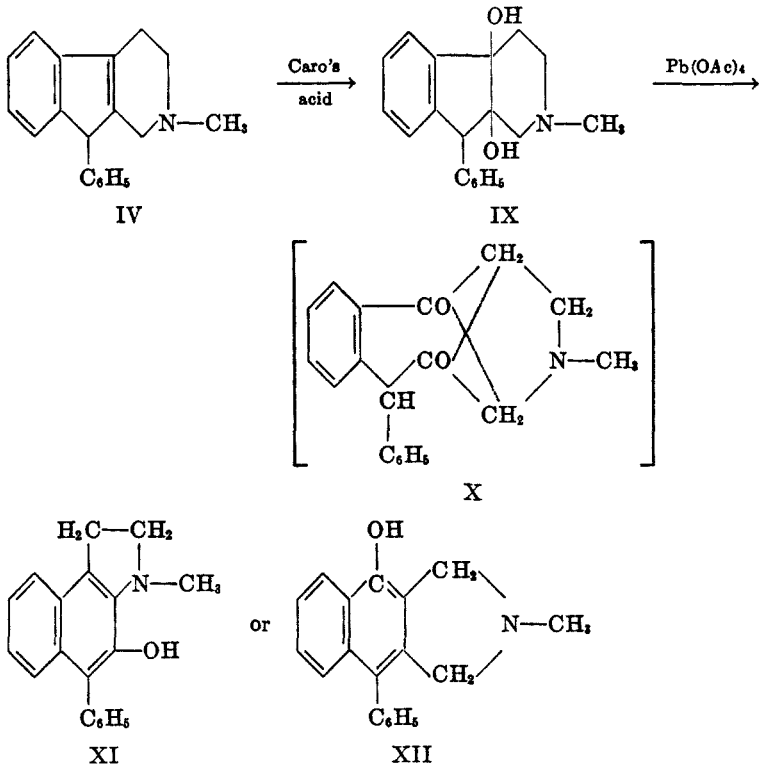


Oxidation experiments next were undertaken to prove our assumptions and to assign definite structures to the individual bases. Both bases gave dihydroxy

compounds when treated with Caro's acid. Each base gave predominantly one characteristic dihydroxy compound, different for each base, so that it can be assumed that the two hydroxyls are attached to the site of the original ethylenic linkage. Caro's acid converted the oily base obtained from the nitrate into a dihydroxy compound (VI). The latter was transformed into a diketone (VII) by lead tetraacetate. Treatment with ammonia gave a non-oxygenated product (VIII). The above behavior is consistent with the equations below, which assign structure II to the oily base.

The isomeric crystalline base was also subjected to the action of Caro's acid under essentially the same conditions to yield the corresponding dihydroxy compound (IX). However, the expected diketone (X) could not be isolated from the reaction with lead tetra-acetate but instead a substance was obtained whose analytical data indicated that it was derived from the diketone by the loss of a molecule of water. Moreover, it was soluble in both acid and alkali and it was easily converted into a benzoate and into a methiodide. A reddish color was developed on treatent with $FeCl_3$.

The most plausible explanation for the above data assigns structure IV to the crystalline base. The sequence of reactions is depicted below.

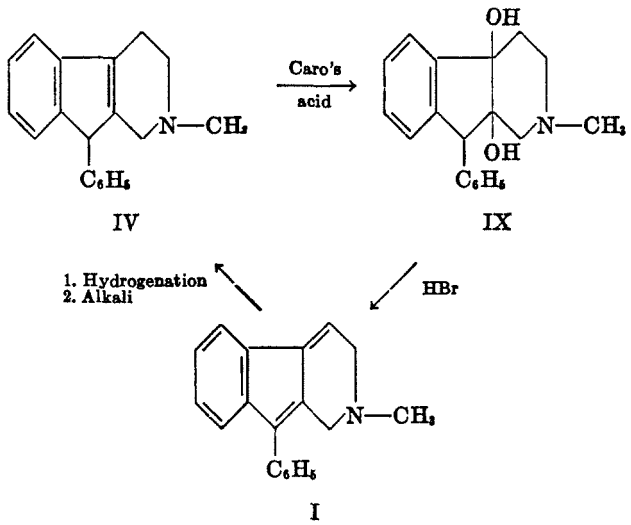


IV IX X XI XII

The intermediate diketone (X) can lose water in either of two different directions, yielding respectively XI or XII. Either of these would explain the am-

photeric nature, the color with ferric chloride, and the formation of a benzoate and methiodide. However, structure XI is favored because of the behavior of the substance on titration with hydrochloric acid. A rough determination of the *p*H at half-neutralization gives a value of 4.3 in 80% aqueous ethanol. The corresponding value in water of *o*-aminophenol is 4.72 (6) and for tyramine, 9.3 (7). Our substance thus resembles *o*-aminophenol in this respect and for this reason XI has been chosen as the most likely structure. However, it is unnecessary to make a choice between XI or XII, since they both can be derived logically from the same starting material (IV), which is thus assigned to the crystalline base.

In further support of the structure which has been assigned, it was found that the dihydroxy compound (IX), derived from the crystalline base (IV), readily loses two molecules of water on refluxing with hydrobromic acid to give the original starting material (I). The other dihydroxy compound derived from the oily base (II) did not yield I but was recovered unchanged. The simplest explanation for these experimental findings is illustrated below. It provides an example of a cyclic process since the crystalline base (IV), as already stated, can be obtained by the partial hydrogenation of I (as the hydrobromide) followed by treatment with alkali.



Thus, the structures of the various salts can now be assigned by reference to the spectra illustrated by Curves 1 and 2. Salts whose absorption spectra are essentially identical with Curve 1 belong to the crystalline base, whereas those whose spectra are essentially identical with Curve 2, belong to the oily base.

It is remarkable how the position and number of double bonds influence the pharmacological properties of the new compounds. The compound I, containing two ethylenic linkages, shows only weak antihistaminic properties. The compound V, where these ethylenic linkages have been removed by hydrogenation, has no appreciable anti-histaminic properties. (8, 9). In contrast, salts of com-

pound IV, having one ethylenic link, are powerful histamine antagonists.[1] When the ethylenic link is shifted to yield salts of compound II, again the anti-histaminic activity is decreased.

Acknowledgment. We are indebted to Dr. Al Steyermark for the microanalyses, to Mr. A. Motchane for the ultra-violet spectra and to Mr. Patsy Bevilacqua and Mr. A. Ingberman for technical assistance.

EXPERIMENTAL

All melting points are uncorrected.

1. HYDROGENATION OF 2-METHYL-9-PHENYL-2,3-DIHYDRO-1-PYRIDINDENE (I) WITH ABSORPTION OF ONE MOLE OF HYDROGEN

A. In water with Raney nickel. A mixture of 680 g. (2 moles) of 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide, 6 l. of water, and 200 cc. of Raney nickel catalyst was hydrogenated in a rocking autoclave under a pressure of 1000 lbs. during 3 hours at room temperature. One mole of hydrogen was absorbed and the hydrobromide went completely into solution. The catalyst was filtered and the filtrate used for the preparation of various salts.

B. In alcohol with Raney nickel. A mixture of 400 g. of the pyridindene hydrobromide, 800 cc. of ethanol, and 100 cc. of Raney nickel was hydrogenated at room temperature under a pressure of about 1000 lbs. during 4 hours. About one mole of hydrogen was absorbed. The catalyst was filtered and the filtrate utilized for the preparation of the base and hydrobromide.

C. In alcohol with platinum. A mixture of 3.4 g. of the pyridindene hydrobromide, 150 cc. of ethanol, and 0.100 g. of platinum oxide was hydrogenated under a pressure of 30–50 lbs. during 1¼ hours at room temperature. Approximately one mole of hydrogen was absorbed.

D. In aqueous solution with palladium. A mixture of 14 g. of the pyridindene hydrobromide, 150 cc. of water, 2.0 cc. of constant-boiling hydrochloric acid, and 1.0 g. of 10% palladium on charcoal was hydrogenated under a pressure of 40–50 lbs. during 1½ hours at room temperature. Approximately one mole of hydrogen was absorbed.

2. HYDROGENATION OF 2-METHYL-9-PHENYL-2,3-DIHYDRO-1-PYRIDINDENE (I) WITH ABSORPTION OF TWO MOLES OF HYDROGEN

A. 2-Methyl-9-phenyl-2,3,4,4a,9,9a-hexahydro-1-pyridindene hydrobromide (V). A mixture of 17 g. of dihydropyridindene hydrobromide, 150 cc. of ethanol, and 0.5 g. of platinum oxide catalyst was hydrogenated at about 75° under a pressure of 30–60 lbs. until only a very slow absorption of hydrogen was noted. About two moles of hydrogen was absorbed in 4 hours. The catalyst was filtered off and the filtrate was allowed to stand at room temperature for one day to give 8.9 g. of the hexahydropyridindene hydrobromide, m.p. 243–246°. An additional 2.9 g., m.p. 239–242°, was obtained from the filtrate after concentration to one-half volume and chilling.

Anal. Calc'd for $C_{19}H_{21}N \cdot HBr$.: C, 66.27; H, 6.44; N, 4.07.
Found: C, 66.15; H, 6.45; N, 4.29.

Approximately the same percentage yield was obtained when 1000 g. of the dihydropyridindene hydrobromide, 5500 cc. of ethanol, and 15 g. of platinum oxide was hydrogenated at 130° under a pressure of 1000 lbs.

B. Methiodide. A mixture of 35 g. of the hydrobromide (V), 100 cc. of water, and excess ammonia was extracted with ether. The ether layer was separated and evaporated to dryness. The residue was dissolved in 200 cc. of acetone, 15 g. of methyl iodide was added and

[1] 2-Methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene tartrate is sold by Hoffmann-LaRoche, Inc. as Thephorin® Tartrate.

the whole was refluxed for 2 hours. On standing, 43 g. of the methiodide, m.p. 297–298°, was obtained.

Anal. Calc'd for $C_{20}H_{24}IN$: C, 59.26; H, 5.97; N, 3.46.
Found: C, 59.70; H, 5.65; N, 3.69.

3. SALTS OF 2-METHYL-9-PHENYL-2,3,4,4A-TETRAHYDRO-1-PYRIDINDENE (II)

A. Hydrobromide. A mixture of 68 g. of the dihydropyridindene hydrobromide (I), 125 cc. of ethanol, and 20 cc. of Raney nickel was hydrogenated under a pressure of 35 to 190 cm. of mercury above atmospheric pressure during 3½ hours at room temperature. On standing overnight in the refrigerator, 20.8 g. of the tetrahydropyridindene hydrobromide (II), m.p. 190–193°, was obtained. An additional 12.2 g., m.p. 188–191°, separated after standing another day in the refrigerator. A third crop of 8.0 g., m.p. 190–193°, was obtained after about one week. Only 0.8 g., m.p. 185–188°, separated after more than three weeks. The total yield amounted to 61%. The first three crops exhibited the spectrum illustrated by Curve 2.

B. Nitrate. A solution of 100 g. of potassium nitrate in 200 cc. of water was added to 800 cc. of liquor from the hydrogenation of 68 g. of the dihydropyridindene hydrobromide essentially according to part 1 *A*. The oily precipitate was separated by decantation and digested for a few minutes with 100 cc. of hot acetone. After standing for about 3 hours, 42.6 g. (66%) of the crystalline nitrate, m.p. 176–179°, was obtained. Recrystallization from ethanol yielded an analytically pure product melting at 175–177°. The melting point depends on the rate of heating. An additional 19% was obtained by evaporating the acetone mother liquor to dryness and crystallizing the residue from alcohol. The material melted at 170–172°. The spectrum is shown by Curve 2.

Anal. Calc'd for $C_{19}H_{19}N \cdot HNO_3$: C, 70.35; H, 6.22.
Found: C, 70.40; H, 6.25.

4. SALTS OF 2-METHYL-9-PHENYL-2,3,4,9-TETRAHYDRO-1-PYRIDINDENE (IV). SYNTHESIS BY DOUBLE DECOMPOSITION

All these salts exhibit the spectrum illustrated by Curve 1.

A. Thiocyanate. The aqueous hydrogenation liquor from part 1 *A* was treated with a solution of 240 g. of potassium thiocyanate in 400 cc. of water. The mixture was allowed to stand for 30 minutes with occasional stirring to coagulate the precipitate, and the supernatant liquid was separated by decantation. The gummy precipitate was crystallized from 10 l. of ethanol in an atmosphere of nitrogen. The crystals thus obtained weighed 360 g. and melted at 188–189°. Concentration of the filtrate to 2.5 l. under reduced pressure yielded an additional 80 g. of thiocyanate, melting at 184–186°. Thus, the total yield amounted to 440 g. (69%).

Anal. Calc'd for $C_{19}H_{19}N \cdot HSCN$: C, 74.96; H, 6.29.
Found: C, 75.02; H, 6.33.

B. Salicylate. A 2000-cc. portion of the aqueous solution obtained from the hydrogenation of 188 g. (0.55 mole) of the dihydropyridindene hydrobromide essentially according to the procedure of 1 *A* was treated with a solution of 465 g. of sodium salicylate in 500 cc. of water and allowed to stand 30 minutes with occasional stirring. The gummy precipitate was separated by decantation and dissolved in 200 cc. of hot ethanol. On standing 190 g. (86%) of the salicylate, m.p. 159–161°, was obtained. The material can be recrystallized from 85% methanol.

C. Phosphate. A solution of 6.5 g. of potassium dihydrogen phosphate in about 30 cc. of water was added to 165 cc. of liquor from the hydrogenation of 15 g. of the dihydropyridindene hydrobromide essentially according to part 1 *A*. After standing two days at room temperature, 8.8 g. (54%) of the phosphate, m.p. 155–158°, slowly crystallized from the solution as a hemihydrate. The ultraviolet spectrum data conform to Curve 1.

Anal. Calc'd for $C_{19}H_{19}N \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$: C, 61.95; H, 6.29; N, 3.80.
Found: C, 61.87; H, 6.24; N, 3.88.

The substance can also be obtained by direct combination of phosphoric acid with the base in methanol containing a little water.

5. 2-METHYL-9-PHENYL-2,3,4,9-TETRAHYDRO-1-PYRIDINDENE BASE (IV)

A mixture of 400 g. of 2-methyl-2,3-dihydro-9-phenyl-1-pyridindene hydrobromide, 800 cc. of ethanol, and 100 cc. of Raney nickel was hydrogenated at room temperature under a pressure of 1000 lbs. for 4 hours. At the conclusion of the absorption of one mole of hydrogen, the mixture was filtered and the filtrate was stirred overnight with 800 cc. of concentrated ammonium hydroxide in a closed system. The mixture became blue at first but later turned white as crystallization began. The crystals were filtered and dried in a vacuum oven at 45° overnight, yielding 260 g. of the crude base, m.p. 84–85°. An additional 27 g. was obtained on further dilution of the filtrate. The total yield amounted to 93% of the theoretical. Crystallization from dilute acetone or dilute alcohol gave a product melting at 90–91°. The spectrum is shown by Curve 1.

Anal. Calc'd for $C_{13}H_{19}N$: C, 87.31; H, 7.33.
Found: C, 87.18; H, 7.25.

The same product can be obtained in excellent yield by prolonged treatment of thiocyanate, salicylate, or nitrate with alkali.

6. SALTS OF 2-METHYL-9-PHENYL-2,3,4,9-TETRAHYDRO-1-PYRIDINDENE (IV) BY DIRECT COMBINATION WITH BASE

A. Tartrate. A solution of 57.5 g. of *d*-tartaric acid in 290 cc. of ethanol was added to solution of 100 g. of the base in 1 l. of benzene. Crystallization began in a few minutes. After standing overnight, the crystals were filtered. The yield of product, m.p. 160–164°, amounted to 90% of the theoretical, $[\alpha]_D^{24.5}$ 15° (*c*, 2 in water). Apparently partial resolution has occurred since a value of $[\alpha]_D^{26}$ 9.9 (*c*, 2 in water) was obtained when equimolar amounts of base and *d*-tartaric acid were dissolved in water.

Anal. Calc'd for $C_{19}H_{19}N \cdot C_4H_6O_6$: C, 67.14; H, 6.12.
Found: C, 66.72; H, 5.82.

B. Hydrochloride. An ether solution of the base was treated with an equivalent amount of 1 *N* hydrochloric acid and the entire mixture was evaporated to dryness under reduced pressure. The residue was crystallized from acetone. The hydrochloride melts at 151–154°.

C. Maleate. This compound was obtained by addition of maleic acid to an ether solution of the base. On crystallization from alcohol, it melted at 169–171°.

7. QUATERNARY SALTS OF 2-METHYL-9-PHENYL-2,3,4,9-TETRAHYDRO-1-PYRIDINDENE (IV)

A. Methiodide. A solution of 13.5 g. of 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (IV) in 500 cc. of ethyl acetate was treated with 8 g. of methyl iodide. On standing, a quantitative yield of crystals, m.p. 133–135°, was obtained.

Anal. Calc'd for $C_{20}H_{22}IN$: C, 59.56; H, 5.50; N, 3.47.
Found: C, 59.21; H, 5.45; N, 3.28.

B. The methochloride was obtained by shaking a mixture of the methiodide, freshly precipitated silver chloride, and dilute alcohol. The pure substance, m.p. 257°, can be obtained by crystallization from ethanol-ether.

Anal. Calc'd for $C_{20}H_{22}ClN \cdot H_2O$: C, 72.82; H, 7.33; N, 4.25.
Found: C, 72.71; H, 6.95; N, 4.24.

C. The quaternary salt with *methyl p-toluenesulfonate* was obtained after refluxing a solution of 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (IV), methyl *p*-toluenesulfonate, and benzene. The crude substance was crystallized from isopropyl alcohol. The crystals are solvated and melt in the range 82–90°.

Anal. Calc'd for $C_{27}H_{29}NO_3S \cdot C_3H_8O$: C, 70.97; H, 7.35.
Found, C, 70.78; H, 7.22.

8. MISCELLANEOUS SALTS

A. Acid sulfate. A mixture of 20 g. of 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (IV) and 100 cc. of 50% (by weight) sulfuric acid was warmed to solution on the steam-bath. On cooling, 22 g. of the acid sulfate was obtained. The pure substance, m.p. 104–106°, was obtained by crystallization from ethanol or isopropyl alcohol.

Anal. Calc'd for $C_{19}H_{19}N \cdot H_2SO_4H_2O$: C, 60.46; H, 6.14; N, 3.71.
Found: C, 60.41; H, 6.05; N, 3.77.

B. The *neutral sulfate*, m.p. 85–86°, crystallized from a solution of 20 g. of the acid sulfate in 300 cc. of water at room temperature on standing for 12 hours.

Anal. Calc'd for $(C_{19}H_{19}N)_2 \cdot H_2SO_4 \cdot H_2O$: C, 71.44; H, 6.62; N, 4.38.
Found: C, 70.87; H, 6.32; N, 4.40.

C. Picrate. A solution of 18.5 g. of the phosphate in 100 cc. of water was added to a solution of 11.5 g. of picric acid in 200 cc. of ethanol. The precipitate was crystallized from acetone, m.p. 169–170°.

Anal. Calc'd for $C_{19}H_{19}N \cdot C_6H_3N_3O_7$: C, 61.22; H, 4.52; N, 11.42.
Found: C, 61.64; H, 4.70; N, 11.37.

D. p-Aminosalicylate. The *p*-aminosalicylate was obtained by shaking a solution of 26 g. of 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (IV) in 200 cc. of ether with 16 g. of *p*-aminosalicylic acid. After 24 hours the crystals were recrystallized from 500 cc. of ethanol, m.p. 155°.

Anal. Calc'd for $C_{19}H_{19}N \cdot C_7H_7NO_3$: C, 75.34; H, 6.32; H, 6.76.
Found: C, 75.11; H, 6.41; H, 6.85.

9. ISOMERIZATION STUDIES

A. Nitrate of 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (IV). A mixture of 52 g. of 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (part 5) and 200 cc. of water was surrounded with an ice-bath and 130 cc. of 10% (by weight) nitric acid was added so that the temperature was maintained just below 10°. When about one-quarter of this amount had been added, 200 cc. of ethanol was introduced and the addition of the nitric acid was continued. This process required about 25 minutes. Only a few particles remained undissolved at 10°. On continued stirring, 43 g. of a crystalline nitrate was obtained. On heating, it softened at 147° and melted at 165–167°. The ultraviolet data indicated that approximately 70% of the precipitate belonged to the same spectral series as the base (*Cf.* Curve 1).

B. Conversion into nitrate of 2-methyl-9-phenyl-2,3,4,4a-tetrahydro-1-pyridindene (II). A mixture of 10 g. of the above precipitate and 100 cc. of acetone was refluxed for about three hours. Most of the precipitate went into solution during the first five minutes. On standing overnight, 7.0 g. of a nitrate, m.p. 169–171°, was obtained. An additional 1.4 g. was obtained from the filtrate. The data indicated that the first crop belonged to the opposite spectral series (*Cf.* Curve 2).

C. Racemization studies. In the following work no claim is made that the described substances are pure optical species and that maximum resolution has been effected. The optically active base was obtained by resolution through the tartrate. The latter was obtained with enhanced optical activity by adding a half mole of *d*-tartaric acid to one mole of the base in benzene as follows:

A solution of 313 g. (2.1 moles) of *d*-tartaric acid in 1577 cc. of ethanol was added to a solution of 1088 g. (4.2 moles) of the base IV in 10,880 cc. of benzene. After standing for 3.75 hours, the mixture was filtered and the precipitate dried at 45–50°. Weight, 500 g. In general, $[\alpha]_D^{25}$ *ca* 30° (*c*, 2 in water), as compared to a value of about 9.9° for the tartrate prepared from equimolar amounts of base and *d*-tartaric acid in water. A considerable amount of resolution thus has been obtained.

The partially resolved tartrate (100 g.), $[\alpha]_D^{25}$ *ca* 30°, was stirred with 5 l. of water and then was filtered to remove 13 g. of undissolved material. The filtrate was cooled below

10° and 200 cc. of 10% sodium hydroxide was added. A gummy ball was obtained. After standing for about 2 hours, it was withdrawn and digested at room temperature in about 400 cc. of methanol; 300 cc. of water was added slowly and the whole was recombined with the aqueous alkaline solution. After standing for an additional hour below 12°, the precipitate was filtered and dried in a desiccator over KOH. In this manner, 50 g. of crude base was obtained. Specific rotation $[\alpha]_D^{23}$ 59° (*c*, 2 in benzene). Crystallization of 48 g. of the crude base from 205 cc. of acetone and 100 cc. of water gave 29.3 g. of crystals, melting at 84–86°. The optical activity value had decreased to $[\alpha]_D^{27.5}$ 7–9° (*c*, 2 in benzene). An additional 5.6 g. of crystalline base was obtained by dilution of the mother liquor. This material had an even lower rotation with $[\alpha]_D^{26.5}$ *ca* 0.9° (*c*, 2 in benzene).

10. OXIDATION IN THE 2-METHYL-9-PHENYL-2,3,4,4A-TETRAHYDRO PYRIDINDENE SERIES (II)

A. Dihydroxy derivative (VI). A mixture of 150 g. of the nitrate, 500 cc. of ice-water, and 210 cc. of 10% sodium hydroxide was extracted with 800 cc. of ether. The ether extract was washed twice with 100 cc. of ice-water and was evaporated under reduced pressure in a bath maintained below 23°. The residue was surrounded with an ice-bath and treated at 10° with 600 cc. of water and 360 cc. of 1.3 *N* sulfuric acid. A vacuum was applied to remove traces of ether and then a slurry of 175 g. of potassium persulfate, 362 cc. of concentrated sulfuric acid, and 94 cc. of water was added with stirring during about 20 minutes at 21°. The mixture was surrounded with a bath of water maintained at 26°, stirred for 3½ hours, and then was poured into 4.5 kg. of ice. The whole then was made alkaline with 90 cc. of 50% (by wt.) of sodium hydroxide and the precipitate was filtered, digested with 1.5 l. of water, and filtered again. The solid cake next was shaken with 500 cc. of water and 500 cc. of ether and the undissolved material was removed by filtration. In carefully run experiments, this amount was less than 4 g. It melted at 200° and represents the crude dihydroxy derivative of the isomeric 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene.

Evaporation of the ether yielded a residue which was allowed to crystallize slowly from methanol to yield 52 g. of crystals containing methanol of crystallization. Recrystallization from ethanol yielded 36 g. of anhydrous 9,9a-dihydroxy-2-methyl-9-phenyl-2,3,4,4a,9,9a-hexahydro-1-pyridindene (VI), m.p. 129–131°.

Anal. Calc'd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17.

Found: C, 77.52; H, 7.18.

B. Diketone (VII). A solution of 31 g. of the above dihydroxy compound (VI) in 775 cc. of ethanol was shaken for about 10 minutes with 46.5 g. of lead tetraacetate. The mixture was allowed to stand for 45 minutes and filtered. The filtrate was evaporated under reduced pressure and the residue was dissolved in water with the aid of a little acetic acid. After passing in hydrogen sulfide to remove the lead as the insoluble sulfide, the solution was made basic and the precipitate was digested with 80 cc. of hot ethanol. The hot mixture was filtered and on standing in the refrigerator for 2 days, 5.3 g. of 2-(1-methyl-3-keto-4-piperidyl)benzophenone (VII), m.p. 134–137° d., was obtained.

Anal. Calc'd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53.

Found: C, 77.50; H, 6.36.

C. 1,2,3,4-Tetrahydro-3-methyl-6-phenyl-pyrido[3,4-c]*isoquinoline* (VIII). A mixture of 10.2 g. of the diketone (VII) (part *B* above) and 500 cc. of methanol was surrounded with an ice-bath and ammonia gas was introduced during 20 minutes. The diketone went into solution. After standing 22 hours the solution was evaporated under reduced pressure and the residue was dissolved in ether. Addition of oxalic acid gave a crude oxalate, which after crystallization from water, weighed 6.83 g. and melted at 230–232°. Titration of this oxalate with perchloric acid in acetic acid (*ca* 100 cc.) gave a neutral equivalent of 184, agreeing with the calculated value of 182. The base obtained from the oxalate melted at 92–93° after crystallization from acetonitrile. An additional 2.53 g. of base could be obtained from the aqueous mother liquor from the crystallization of the oxalate.

Anal. Calc'd for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61.

Found: C, 82.95; H, 6.79.

The *methiodide* obtained with methyl iodide in benzene melted at 252–254° after crystallization from methanol and water.

Anal. Calc'd for $C_{20}H_{21}IN_2$: C, 57.70; H, 5.09.
Found: C, 57.65; H, 5.28.

11. OXIDATION IN THE 2-METHYL-9-PHENYL-2,3,4,9-TETRAHYDRO-1-PYRIDINDENE SERIES (IV)

A. Dihydroxy derivative (IX). A mixture of 120 g. of 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (IV) and 600 cc. of water was surrounded with an ice-bath and treated with 360 cc. of 1.3 *N* sulfuric acid below 15°. A mixture of 175 g. of potassium persulfate, 362 cc. of concentrated sulfuric acid, and 94 cc. of water was added, below 24°, during about 20 minutes. The mixture was surrounded with a bath of water maintained at 26°, stirred during 3½ hours, and poured into 4.5 kg. of ice. Addition of 90 cc. of 50% (by weight) sodium hydroxide gave a precipitate which was digested with 2 l. of water and with 500 cc. of hot ethanol. The crude dihydroxy derivative (IX) weighed 112 g. and melted at 239–241° d. The substance can be crystallized from pyridine with about 85% recovery but the melting point is not appreciably changed.

Anal. Calc'd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74.
Found: C, 77.00; H, 7.04; N, 4.74.

B. Oxidation with lead tetraacetate to 3-methyl-4-hydroxy-5-phenylbenz[e]indoline (XI). A mixture of 60 g. of dihydroxy compound (part 11 *A* above) and 1500 cc. of benzene was cooled to 16°, shaken vigorously for 20 minutes with 90 g. of lead tetraacetate, filtered, and distilled to dryness under reduced pressure in a bath maintained below 50°. The residue was macerated in 300 cc. of water and the insoluble material was filtered and crystallized from 450 cc. of ethanol. The yield of the benzindoline in several experiments amounted to 30–34 g. The pure product melted at 135–137°. A red color was developed on standing in the presence of ferric chloride for five minutes. The compound is soluble in both acid and alkali. Addition of 10.00 cc. of 0.1 *N* hydrochloric acid to 0.550 g. (0.002 mole) in 100 cc. of ethanol and 10 cc. of water gave a *p*H of 4.29.

Anal. Calc'd for $C_{19}H_{17}NO$: C, 82.88; H, 6.23; N, 5.09.
Found: C, 82.88; H, 6.17; N, 4.95.

Benzoyl derivative. To a suspension of 0.50 g. of the lead tetraacetate oxidation product in 5 cc. of water, 1.0 cc. of benzoyl chloride and 5 cc. of 10% sodium hydroxide were added alternately in small portions to maintain a slight alkalinity. Another 5 cc. of alkali then was added and the mixture was stirred until the gummy solid became quite hard. The yield of crude benzoyl derivative, m.p. 166–169°, amounted to 0.67 g. Crystallization from ethyl acetate gave the pure substance melting at 173–174°.

Anal. Calc'd for $C_{26}H_{21}NO_2$: C, 82.30, H, 5.58; N, 3.69.
Found: C, 82.15; H, 5.39; N, 3.90.

Methiodide. This compound was prepared with methyl iodide in benzene. The pure substance, m.p. 239–242°, was obtained by crystallization from ethyl acetate.

Anal. Calc'd for $C_{20}H_{20}INO$: C, 57.56; H, 4.83; N, 3.36.
Found: C, 57.29; H, 4.99; N, 3.55.

Methochloride. This compound was obtained by the interaction of the methiodide with silver chloride and crystallization from dilute hydrochloric acid; m.p. 225–226° d.

Anal. Calc'd for $C_{20}H_{20}ClNO$: C, 73.72; H, 6.19.
Found: C, 73.64; H, 6.29.

12. DEHYDRATION OF DIHYDROXY DERIVATIVES

A. A mixture of the dihydroxy derivative (IX) (part 11*A*) from 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene and 50 cc. of 48% hydrobromic acid was distilled slowly through a 12-plate column, so that 10 cc. of distillate was collected and the temperature rose to 122°. The mixture was poured into 100 cc. of water and the resulting precipitate was crystallized from 25 cc. of ethanol. Yield, 6.9 g. of 2-methyl-2,3-dihydro-9-phenyl-1-

pyridindene hydrobromide (I), m.p. 203–206°, identified further by its absorption spectrum and analysis.

Anal. Calc'd for $C_{19}H_{17}N \cdot HBr$: C, 67.06; H, 5.33.
Found: C, 66.72; H, 5.58.

B. A mixture of 5.0 g. of the dihydroxy derivative (VI) from 2-methyl-9-phenyl-2,3,4,4a-tetrahydro-1-pyridindene and 25 cc. of 48% hydrobromic acid was distilled slowly during 30 minutes. The distillation temperature rose to 124°. On pouring into 50 cc. of water and cooling in an ice-bath, a gum was obtained. On being treated with alkali, a blue-white precipitate was obtained. Crystallization from methanol and ethanol gave the starting material (VI), m.p. 129–131°. No depression was noted in a mixture melting point determination.

SUMMARY

The chemistry of 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (Thephorin®) and some of its closely related derivatives is described. The assignment of structure was rather difficult since it involved a novel type of reversible isomerism between two compounds, distinguished by the position of a double bond. The formation of either isomer was extraordinarily sensitive to the choice of anion, used for salt formation. The structures were assigned on the basis of oxidative studies, where the pertinent dihydroxy compounds were subjected to the action of lead tetraacetate.

NUTLEY, NEW JERSEY

REFERENCES

(1) PLATI AND WENNER, *J. Org. Chem.*, **15**, 209 (1950).
(2) PLATI, SCHMIDT, AND WENNER, *J. Org. Chem.*, **15**, 873 (1949).
(3) PLATI AND WENNER, *J. Org. Chem.*, **15**, 543 (1949).
(4) BERGMANN, *Isomerism and Isomerization of Organic Compounds*, Interscience Publishers, Inc., New York, 1948, p. 56.
(5) MUSKAT AND KNAPP, *Ber.*, **64**, 779 (1931).
(6) KUHN AND WASSERMAN, *Helv. Chim. Acta*, **11**, 25 (1928).
(7) OGSTON, *J. Chem. Soc.*, **1936**, 1713 (1936).
(8) LEHMANN, *J. Pharmacol. Exptl. Therap.*, **92**, 249 (1948).
(9) LEHMANN, RANDALL, AND HAGAN, *Arch. intern. pharmacodynamie*, **78**, 253 (1945).
(10) WENNER, *J. Org. Chem.*, **15**, 301 (1950).