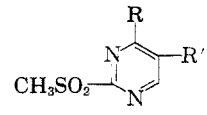
TABLE II

2-METHANESULFONYLPYRIMIDINE



R	R′	Yield, %	M.P.	Molecular Formula	Analyses Calcd.	Found
NH_2	CN	67[a]	211–214	$C_6H_6N_4O_2S$	N 28.3	28.6
NH_2	$CONH_2$	29[b,c]	216–218	$C_6H_8N_4O_3S$	N 25.9	25.4
o-NHC_6H_4Cl	—CO_2Et	87	180–181	$C_{14}H_{14}N_3O_4SCl$	N 11.8	11.6
o-NHC_6H_4Br	—CO_2Et	92	172–174	$C_{14}H_{14}N_3O_4SBr$	N 10.5	11.0
Cl	—CO_2Et	94[b]	129–130	$C_8H_9N_2O_4SCl$	N 10.6	10.1

[a] Oxidation solvent was 60 ml. of 5% hydrochloric acid for 0.5 g. of the pyrimidine. Recrystallization solvent was ethyl acetate. [b] Oxidation solvent was 30 ml. of 1% hydrochloric acid. [c] Recrystallization solvent was 95% ethyl alcohol.

ylsulfonyl-4-*o*-chloroanilino-5-carbethoxypyrimidine (0.5 g.) was heated in 15 ml. of absolute methanol. Ammonia was passed in for 10 min. while the mixture was still warm. After standing at room temperature for 12 hr. the mixture was allowed to cool to 0–5° for 12 hr. and filtered to give 0.3 g. (73%), m.p. 209–213°. The analytical sample, m.p. 215–216°, was recrystallized from methanol.

Anal. Calcd. for $C_{13}H_{13}N_4O_2Cl$: C, 53.3; H, 4.5; N, 19.1. Found: C, 53.5; H, 4.6; N, 19.1.

2-Amino-4-o-bromoanilino-5-carbethoxypyrimidine. This compound was prepared by the method used for the 4-*o*-chloroanilino- analog. The yield was 0.3 g. (71%), m.p. 204–211° of 2-amino-4-*o*-bromoanilino-5-carbethoxypyrimidine from 0.5 g. of sulfone. The analytical sample, m.p. 213–214°, was recrystallized from methanol.

Anal. Calcd. for $C_{13}H_{13}N_4O_2Br$: N, 16.6. Found: N, 16.8.

BUFFALO 14, N. Y.

[CONTRIBUTION FROM HOFFMANN-LA ROCHE, INC.]

Pyridindene Derivatives. IV. Alkylated Pyridindenes

JOHN T. PLATI AND WILHELM WENNER

Received December 14, 1959

The reaction of crotonophenone and methylamine yielded a condensation product which on treatment with alkali gave 1,2,6-trimethyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (III). Dehydration followed by partial reduction gave 1,2,3-trimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (VI). The reaction of methylmagnesium iodide with 1-methyl-3-benzoyl-4-phenyl-4-hydroxypiperidine (VIII) yielded a diol (IX) which on dehydration gave 2,9-dimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (XI).

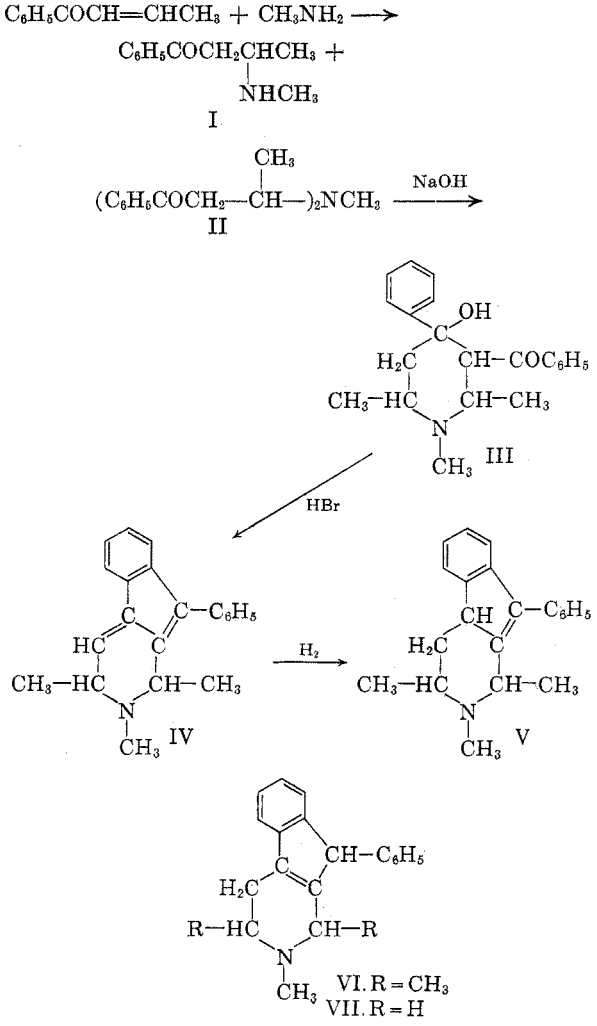
This paper deals with an extension of our earlier work on pyridindene derivatives. Our first concern was the introduction of alkyl groups into the hetero ring in order to ascertain the antihistamine properties of the resulting compound. A type of Mannich reaction between acetophenone, methylamine, and acetaldehyde was briefly considered for the preparation of the starting material, but this scheme was discarded in favor of the reaction between crotonophenone and methylamine.

When the reaction was allowed to proceed for a relatively short period of time, it was possible to isolate the product (I) formed by the addition of one mole of methylamine to one mole of crotonophenone. The bis product (II) may also have been formed, but efforts at isolation were not pursued vigorously, since our primary concern was to obtain the piperidine derivative (III). It was reasoned after our earlier work[1] that this compound could be obtained not only by ring closure of the bis product (II) but also by disproportionation of the mono-addition product (I). The mother liquor from (I) should contain both products, with the bis product predominating after a prolonged reaction time. Accordingly, treatment with alkali should yield the piperidine (III), and actually this expectation was realized. By refluxing with hydrobromic acid, the piperidine (III) underwent dehydration and ring closure to give the pyridindene (IV). On hydrogenation, a mixture of (V) and (VI) was apparently obtained. The (VI) base was obtained by purification through the thiocyanate salt, followed by prolonged treatment with alkali. It is noteworthy that the ultraviolet spectrum (Curve 1) of the VI base is almost identical with that of VII.[2] The treatment with alkali was

(1) J. T. Plati and W. Wenner, *J. Org. Chem.*, **14**, 543 (1949).

(2) J. T. Plati and W. Wenner, *J. Org. Chem.*, **20**, 1413 (1955).

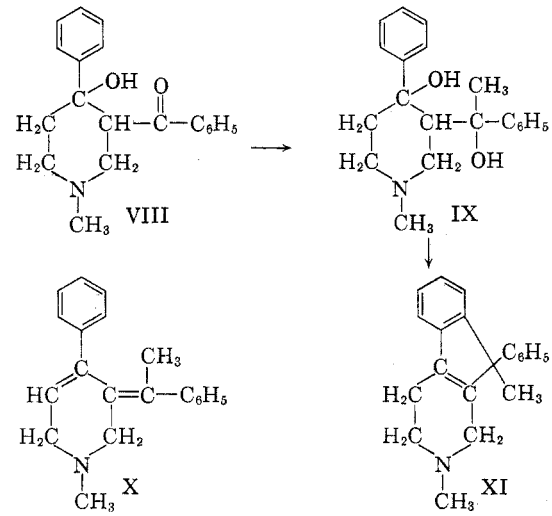
intended to cause isomerization of V into VI just as in the previously described parent series.



The second part of our investigation was aimed at the preparation of a pyridindene molecule containing an alkyl group as well as a phenyl group in the 9-position, as in formula XI. The type of isomerization, represented by a shift of the ethylenic linkage from its position in V to its position in VI, has been shown to be readily reversible, and, in fact, in the case of VII mere salt formation was sufficient to cause a shift in either direction.[2] Maximum antihistamine activity is associated with the double bond in the hetero ring. The shifting of the double bond to the 9- position results in a considerable reduction of antihistamine activity. In XI we have a compound of particular interest, because shifting of the ethylenic linkage to the 9-position is blocked. In addition, the spectrum of such a compound should confirm our earlier assignments of structure.

To obtain the compound XI, the piperidinol (VIII) was utilized as a starting material. Reaction with methylmagnesium iodide gave the diol (IX). Dehydration with the loss of two molecules of water was effected by treatment with hydrobromic acid. Two formulas, (X) and (XI), were considered for the structure of the dehydration product. Its ultraviolet absorption spectrum (Curve 2) strongly resembles that of the pyridindene VI (Curve 1). In any event, the spectrum of the conjugated diene (X) would be expected to be completely different. Accordingly, structure XI was assigned to the dehydration product.

In our earlier work (2), it was shown that deviations from the structure of the parent compound (VII) led to compounds with lower antihistamine activity. In the case of compounds VI and XI, a significant antihistamine activity was found. This finding is quite compatible with the structures assigned.



EXPERIMENTAL[3]

β-Methylaminobutyrophenone hydrochloride (I). To a solution of 6.8 g. of methylamine hydrochloride in 200 cc. of methanol, 6.0 g. of powdered sodium methylate was added with stirring. On addition of 29.2 g. of crotonophenone,[4] the temperature rose to 35°. The mixture was stirred for about 4 hr., 15 cc. of concd. hydrochloric acid was added, and the insoluble material removed by filtration. The solvent was removed by distillation *in vacuo*, and the residue was crystallized from 80 cc. of ethyl acetate. In this manner 10.2 g. of β-methylaminobutyrophenone hydrochloride, m.p. 152–154°, was obtained. Further purification can be effected by crystallization from ethanol.

Anal. Calcd. for $C_{11}H_{15}NO.HCl$: Cl, 16.6. Found: Cl, 16.6.

1,2,6-Trimethyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (III). To a solution of 89.8 g. of methylamine hydrochloride in 2640 cc. of methanol, 79.2 g. of powdered sodium methylate was added with stirring. During 20 min., 383 g. of crotonophenone (3) was added, during which the temperature rose to 36°. After stirring for 3 hr., the mixture was allowed to stand for 13 days and then acidified with 198 cc. of concd.

(3) All melting points are uncorrected.

(4) R. C. Fuson, R. E. Christ, and G. M. Whitman, *J. Am. Chem. Soc.*, **58**, 2450 (1936).

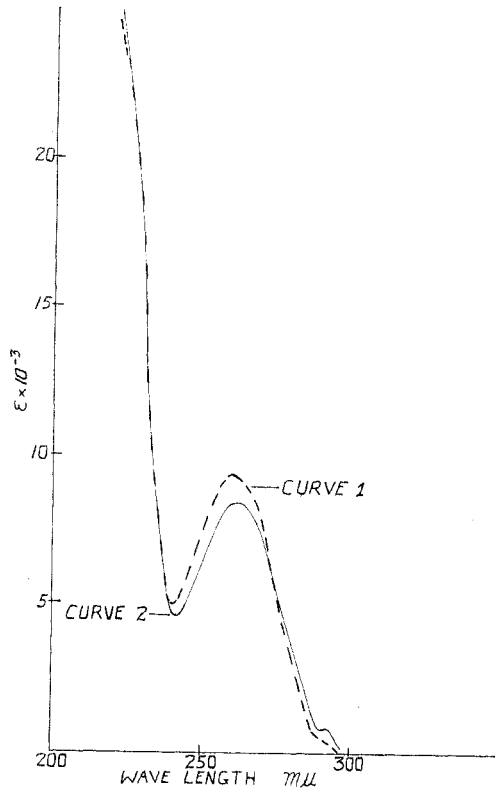


Fig. 1. Ultraviolet absorption spectra in 0.1*N* hydrochloric acid:
Curve 1. 1,2,3,-Trimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (VI)
Curve 2. Hydrobromide of 2,9-dimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (XI)

hydrochloric acid. The mixture was filtered, the filtrate was distilled to dryness under reduced pressure, and the residue was digested with 660 cc. of boiling ethyl acetate. The insoluble material was removed by filtration from the hot solvent, and the filtrate allowed to stand in the refrigerator for 2 days. On filtration, 75 g. of a crude crystalline mixture was obtained, which probably consisted of a mixture of the hydrochlorides of β-methylaminobutyrophenone (I), and of the bis product (II). The ethyl acetate was removed *in vacuo*, and the residue was stirred with a solution of 80 g. of sodium hydroxide and 1.2 l. of water. On standing overnight, the oil gradually hardened. After crystallization from a solvent, b.p. 86–100°, consisting essentially of *n*-heptane, 133 g. of 1,2,6-trimethyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (III), m.p. 103–105°, was obtained.

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79. Found: C, 78.35; H, 7.86.

Hydrobromide. The hydrobromide was obtained by dissolving the base in ether and passing in hydrogen bromide. After crystallization from ethanol, it melted at 186–187°.

Anal. Calcd. for $C_{21}H_{25}NO_2.HBr$: C, 62.37; H, 6.48. Found: C, 62.58; H, 6.48.

1,2,3-Trimethyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide (IV). A mixture of 13 g. of the hydroxy ketone (III) and 50 cc. of 48% hydrobromic acid was refluxed for 6 hr. and 40 min. and then poured into 200 cc. of water, where it was allowed to stand for 2 days. The supernatant liquor was removed by decantation, and the insoluble matter was digested with 100 cc. of ethyl acetate. After crystallization from 50 cc. of ethanol, 4.2 g. of the hydrobromide, m.p. 198–201°, was obtained.

Anal. Calcd. for $C_{21}H_{21}N.HBr$: C, 68.48; H, 6.02. Found: C, 68.19; H, 6.19.

Mixture of 1,2,3-trimethyl-9-phenyl-2,3,4,4A-tetrahydro and 1,2,3-trimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene hydrobromides. A mixture of 7.4 g. of the dihydropyridindene hydrobromide (IV), 20 cc. of Raney nickel catalyst, and 160 cc. of ethanol was hydrogenated at room temperature during 3.25 hr. at an initial gauge pressure of 52 lbs. until hydrogen uptake was extremely slow. The catalyst was filtered, the solvent removed *in vacuo*, and the residue crystallized from 15 cc. of acetone. In this manner, 4.6 g. of the tetrahydro compound, m.p. 226–232°, was obtained. Further crystallization from ethanol gave crystals melting at 230–235°.

Anal. Calcd. for $C_{21}H_{23}N.HBr$: C, 68.10; H, 6.53. Found: C, 68.35; H, 6.58.

The ultraviolet spectral curve of the compound was practically parallel to that of the base (VI) but displaced by about 2 mμ towards the higher wave lengths. We have concluded that the hydrobromide is composed preponderantly of the VI species.

1,2,3-Trimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (VI). A mixture of 28 g. of the dihydropyridindene hydrobromide (IV), 25 cc. of Raney nickel catalyst, and 150 cc. of ethanol was hydrogenated at room temperature during a period of 2.5 hr. at an initial gauge pressure of 49 lb. Approximately the theoretical amount of hydrogen was absorbed. The catalyst was filtered, the solvent was removed *in vacuo*, and the residue was dissolved in 200 cc. of warm water. The base was liberated by the addition of 63 cc. of 10% sodium hydroxide, extracted with 200 cc. of ether, washed with water, and dried over sodium sulfate. The ether solution was divided into two portions. One of these portions was extracted with a mixture of 200 cc. of water and 43 cc. of 0.87*N* hydrochloric acid. Addition of 13 g. of potassium thiocyanate in 20 cc. of water to the acid solution gave 9.9 g. of a crude thiocyanate salt. A sample of this salt after crystallization from 50% ethanol melted at 186–189°.

A hot solution of 7.9 g. of the crude thiocyanate in 50 cc. ethanol was cooled, treated with 50 cc. of 6% sodium hydroxide, and allowed to stand with occasional scratching for about 3 days. An oil was first obtained, but on standing it eventually solidified. After washing with 50% ethanol and drying, the substance weighed 5.7 g. and melted at 100–102°. After crystallization from dilute alcohol, it melted at 101–103°.

Anal. Calcd. for $C_{21}H_{23}N$: C, 87.15; H, 8.01. Found: C, 87.13; H, 7.98.

α-Methyl-α-(1-methyl-4-hydroxy-4-phenyl-3-piperidyl)-benzyl alcohol (IX). To a solution of methyl magnesium iodide prepared from 129 g. of methyl iodide and 22.1 g. of magnesium in 500 cc. of dry ether, was added with stirring during 30 min. 128 g. of 1-methyl-3-benzoyl-4-phenyl-4-hydroxy-piperidine (VIII) (1). When the spontaneous refluxing had ceased within a short time after the addition, the mixture was warmed to reflux during about 3 hr., allowed to stand overnight, and then introduced into 1 kg. of cracked ice. The mixture was neutralized with a solution of 25 cc. of concd. sulfuric acid in 100 cc. of water and filtered. The insoluble matter was digested with 1200 cc. of hot acetone and filtered. On cooling, 16.0 g. of the diol, m.p. 194–197°, was obtained. An additional 3.7 g. was obtained from the other fractions. Further crystallization from acetone gave the pure diol, m.p. 197–198°.

Anal. Calcd. for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.05; neut. equiv. 311. Found: C, 77.22; H, 7.88; neut. equiv. 313 (with perchloric acid).

2,9-Dimethyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene hydrobromide (XI). A mixture of 10.4 g. of the diol (IX) and 40 cc. of 48% hydrobromic acid was refluxed in an oil bath at 137–140° during 1 hr. and 16 min., and cooled. On addition of 80 cc. of water, a gum was obtained which gradually

solidified on standing overnight. The solid was filtered and crystallized from 15 cc. of ethanol to give 7.73 g. of the pyridindene (XI), m.p. 245–248°. After recrystallization, it melted at 246–248 .

Anal. Calcd. for $C_{26}H_{22}NBr$: C, 67.41; H, 6.22. Found: C, 67.15; H, 6.29.

Acknowledgment. We are indebted to Dr. Al Steyermark for the microanalyses, to Mr. A. Motchane for the ultraviolet spectra, and to Mr. Pat Bevilacqua for technical assistance.

NUTLEY, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

Synthesis of Compounds in the Pyrrolo[3,4-b]indole Series[1]

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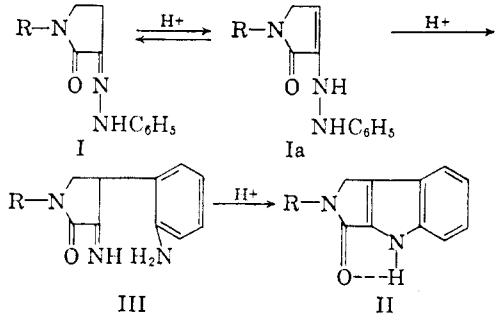
Received December 29, 1959

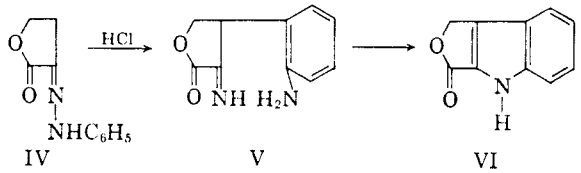
The previously unknown pyrrolo[3,4-b]indole ring system is represented in a series of compounds which were produced when the Fischer indole synthesis was conducted with phenylhydrazones of 1-substituted 2,3-dioxopyrrolidines (I). Seven 2-substituted 1,4-dihydropyrrolo[3,4-b]indol-3(2H)ones (II) have been prepared in this manner; the 2-substituents were *n*-propyl, *n*-butyl, cyclohexyl, phenyl, β-phenylethyl, β-phenylisopropyl, and homoveratryl. The three compounds containing the cyclohexyl, β-phenylethyl, and β-phenylisopropyl groups have been reduced with lithium aluminum hydride and converted into corresponding 2-substituted 1,2,3,4-tetrahydropyrrolo[3,4-b]indoles (VII).

Apparently no compounds containing the relatively simple fused-ring heterocyclic system of pyrrolo[3,4-b]indole have been described in the literature. The report of the preparation of two such compounds by Heller and Wunderlich[3] has been shown by Taylor and Kalenda[4] to be in error. The fact that other compounds containing the indole nucleus have been known to display a variety of interesting types of physiological activity provided the incentive for an attempt to prepare compounds of this class. It seemed possible that the ring system could be created by conducting the



Fischer indole synthesis using phenylhydrazones of 2,3-dioxopyrrolidines (I), a number of which had been prepared in this laboratory.[5]

The result of subjecting the phenylhydrazones I to the conditions of the Fischer indole synthesis was, however, considered subject to uncertainty because of reports in the literature regarding the course of acid-catalyzed reactions of certain similar compounds. Meyer and Vaughan[6] had shown that the phenylhydrazone of 1,5-diphenyl-2,3-dioxopyrrolidine rearranges to 1,5-diphenyl-Δ^2-pyrrazoline-3-carboxanilide when treated with hydrochloric acid, and this type of behavior might have proved general for phenylhydrazones of 2,3-dioxopyrrolidines. On the other hand, the work of Plieninger[7] with the phenylhydrazone of α-keto-γ-butyrolactone (IV) suggested that another interesting departure from the normal course of the Fischer indole synthesis might well be encountered. Compound IV, when treated with hydrogen chloride in acetic acid at 90°,



had yielded the hydrochloride of α-imino-β-*o*-aminophenyl-γ-butyrolactone (V). Compound V required treatment with a boiling mixture of concentrated hydrochloric and glacial acetic acids to undergo cyclization to the indole derivative VI. Whether the failure of compound V to undergo rapid spontaneous ring-closure to VI is the result of a steric or an electronic effect, the close resemblance

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(1) Supported principally by a research grant (RG-4371) from the National Institutes of Health, U. S. Public Health Service.

(2) National Science Foundation Cooperative Predoctoral Fellow, 1959–1960.

(3) G. Heller and P. Wunderlich, *Ber.*, **47**, 1617 (1914).

(4) E. C. Taylor, Jr., and N. W. Kalenda, *J. Org. Chem.* **18**, 1755 (1953).

(5) (a) P. L. Southwick, E. P. Previc, Joseph Casanova, Jr., and E. Herbert Carlson, *J. Org. Chem.* **21**, 1087 (1956); (b) P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.* **75**, 3413 (1953); (c) P. L. Southwick and L. L. Seivard, *J. Am. Chem. Soc.*, **71**, 2532 (1949). The concern expressed in ref. 5a over the possibility that the phenylhydrazine derivatives of the 2,3-dioxopyrrolidines might not represent the expected phenylhydrazone structure (or the related enhydrazine tautomeric form Ia) was evidently unwarranted. *Cf.* discussion by Meyer and Vaughan, ref. 6.

(6) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.* **22**, 1565 (1957).

(7)(a) H. Plieninger, *Ber.* **83**, 273 (1950); (b) H. Plieninger and I. Nógrádi, *Ber.*, **88**, 1965 (1955).