

of white crystals: mp 80–84°;  $[\alpha]_D^{25} + 1.4 \pm 0.3^\circ$  (c 1,  $\text{CHCl}_3$ ); uv max (95% EtOH) 282  $m\mu$  ( $\epsilon$  22,000); ir (KBr) 5.88 (ester  $> \text{C}=\text{O}$ ), 6.09 (amide  $> \text{C}=\text{O}$ ), and 6.18  $\mu$  ( $> \text{C}=\text{C}<$ ); nmr ( $\text{CDCl}_3$ )  $\delta$  1.62, 1.70 [s each, 3 each,  $\text{C}(\text{CH}_3)_2$ ], 3.58 (s, 3,  $\text{OCH}_3$ ), 3.33–4.0 (m, 4,  $\text{CH}_2\text{N}$  and aryl- $\text{CH}_2$ ), 5.15 [t, 1,  $J = 7$  Hz,  $\text{CH} = \text{C}(\text{CH}_3)_2$ ], 5.50–6.00 (m, 1,  $\text{C}=\text{NH}$ ), and 6.83–7.66 ppm (m, 7, aryl H,  $=\text{CHN}$ ,  $\text{CONH}$ ). Anal. ( $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_3$ ) C, H, N.

**Hydrolysis of 28 to Methyl Benzylpenaldate (29) and 3-Methyl-2-butenylamine (30).**—To 0.5 g (0.00165 mol) of 28 in 25 ml of warm MeOH was added 0.33 g (0.00165 mol) of 2,4-dinitrophenylhydrazine in 60 ml of warm MeOH and 4 drops of concentrated HCl. The solution was left at 25° overnight. The mixture was cooled to 0°, filtered, and washed with cold MeOH to give 0.5 g (73%) of yellow, matted needles, mp 180–181°; mixture melting point with authentic 2,4-dinitrophenylhydrazone of methyl benzylpenaldate<sup>14</sup> showed no depression.

The MeOH filtrate was evaporated to dryness and the residue partitioned in  $\text{CHCl}_3$ – $\text{H}_2\text{O}$ . The aqueous phase was separated, washed ( $\text{CHCl}_3$ ), and then evaporated *in vacuo* to give a yellowish solid. It was recrystallized from EtOH–Et<sub>2</sub>O to afford 0.15 g of shiny leaflets, mp 194.5–198° dec, identical with authentic 30 (ir spectrum, mixture melting point).<sup>15</sup>

***p*-Methoxybenzyl 4,4-Dimethyl- $\alpha$ -(phenylacetamido)-3-thia-1-azabicyclo[3.1.0]hexane-2-acetate (36).**—Compound 5 (1 g, 0.0021 mol) was heated with 0.34 ml (0.0023 mol) of Et<sub>3</sub>N and 4 ml of *p*-anisyl alcohol on a steam bath for 3 hr. The yellow solution was diluted ( $\text{CHCl}_3$ ) and washed ( $\text{H}_2\text{O}$ , 5%  $\text{H}_3\text{PO}_4$ ,  $\text{H}_2\text{O}$ ) until neutral pH, saturated brine). The dried ( $\text{Na}_2\text{SO}_4$ )

filtrate was evaporated and some of the excess *p*-anisyl alcohol distilled at 65–80° and 0.07 mm (oil bath temperature 95°). The residual viscous oil was purified by preparative tlc (silica plates, benzene–Et<sub>2</sub>O 1:1). Isolation of the band next to the origin afforded 650 mg of a colorless gum: ir ( $\text{CHCl}_3$ ) 5.73 (ester  $> \text{C}=\text{O}$ ) and 5.97  $\mu$  (amide  $> \text{C}=\text{O}$ ); nmr ( $\text{CDCl}_3$ )  $\delta$  1.4, 1.5 [s each, 3 each,  $\text{C}(\text{CH}_3)_2$ ], 1.57–1.83 (m, 2,  $\text{NCH}_2$ ), 2.13–2.38 (m, 1,  $\text{CH}_2\text{CHC}$ ), 3.58 (s, 2, aryl- $\text{CH}_2$ ), 3.73 (s, 3,  $\text{OCH}_3$ ), 4.58–4.75 (m, 2,  $\text{CHCH}$ ), 5.07 (s, 2, aryl- $\text{CH}_2\text{O}$ ), 6.2–6.6 (broad, 1, NH), and 6.7–7.4 ppm (m, 9, aryl H).

**4,4-Dimethyl- $\alpha$ -(phenylacetamido)-3-thia-1-azabicyclo[3.1.0]hexane-2-acetic Acid (37).**—A sample of 36 was treated in the cold with TFAA to give a deep red solution. After 5 min the excess acid was evaporated *in vacuo* at 25°. The residual red mush was dissolved in  $\text{CHCl}_3$  and washed in the cold with saturated  $\text{NaHCO}_3$ . The basic extracts were combined and acidified in the cold with 10% aqueous  $\text{H}_3\text{PO}_4$  to pH 3. The gum was extracted with cold  $\text{CHCl}_3$  and the combined organic fractions washed ( $\text{H}_2\text{O}$ , brine). The dried ( $\text{Na}_2\text{SO}_4$ ) filtrate was evaporated *in vacuo* at 25° to afford a colorless, amorphous solid: ir ( $\text{CHCl}_3$ ) 3.8–4.1 (broad OH), 5.79 (acid  $> \text{C}=\text{O}$ ), and 5.98  $\mu$  (amide  $> \text{C}=\text{O}$ ); nmr ( $\text{CDCl}_3$ )  $\delta$  1.4, 1.5 [s each, 3 each,  $\text{C}(\text{CH}_3)_2$ ], 1.67–2.0 (m, 2,  $\text{NCH}_2$ ), 2.33–2.67 (m, 1,  $\text{CH}_2\text{CHC}$ ), 3.6 (s, 2, aryl- $\text{CH}_2$ ), 4.42–5.08 (m, 2,  $\text{CHCH}$ ), 7.0–7.42 (m, 6, aryl H, NH), and 10.6 ppm (s, 1, COOH). The carboxylic acid was unstable at room temperature in the amorphous state or in chloroform solution. The change was apparent from the nmr spectra which became diffuse and uninterpretable.

## 2-Tetrahydropyridylindoles as Histamine and Serotonin Antagonists

ROBERT N. SCHUT, FREDERICK E. WARD, O. J. LORENZETTI,

*Therapeutics Research Division, Miles Laboratories, Inc., Elkhart, Indiana*

AND ENRIQUE HONG

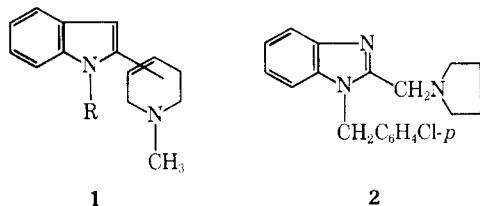
*Instituto Miles de Terapeutica Experimental, Mexico 22, D.F., Mexico*

Received July 9, 1969

A series of 2-(1-methyl-1,2,5,6-tetrahydro-3( and 4)-pyridyl)indoles was synthesized by borohydride reduction of the corresponding pyridinium compounds. The compounds were tested for antihistaminic and antiserotonin activity.

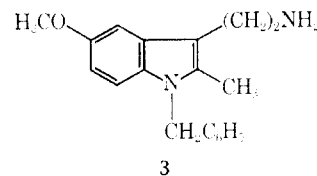
During an investigation of 2-tetrahydropyridylindoles 1 as intermediates in the synthesis of certain model indole alkaloid systems, it was found that a few of these compounds exhibited antihistaminic and antiserotonin activity. We noticed that those compounds with an indole-*N*-benzyl moiety bore structural resemblance to clemizole (2);<sup>1</sup> structural features of the serotonin antagonist benanserine (3)<sup>2</sup> are also present.

This paper describes the synthesis and pharmacological action of a small series of such compounds (Table I). Our objective was to obtain a compound which possessed both good antihistaminic and antiserotonin activity.



(1) (a) D. Jerchel, H. Fischer, and M. Kracht, *Justus Liebig's Ann. Chem.*, **575**, 173 (1952); (b) H. Muckter, *et al.*, *Arzneim. Forsch.*, **4**, 487 (1954).

(2) (a) E. Shaw, *J. Amer. Chem. Soc.*, **77**, 4319 (1955); (b) D. W. Woolley and E. Shaw, U.S. Patent 2,890,223 (1959).



The general synthetic method involves Fischer cyclization of the appropriate hydrazone 4 followed by quaternization and  $\text{BH}_4^-$  reduction of the pyridylindoles 5. When R was benzyl or Me thermal indolization was preferred over the usual acid-catalyzed procedure.

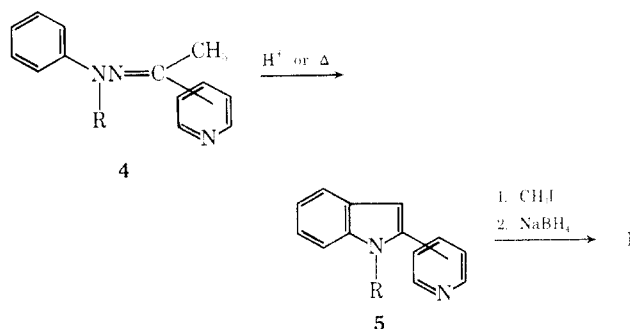
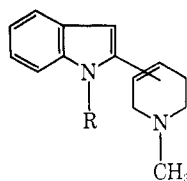


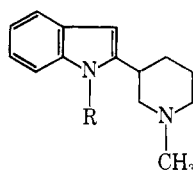
TABLE I



| No.             | R   | Position of substitution | Mp, °C             | Formula   | Anal                                       |
|-----------------|---|--------------------------|--------------------|---|--|
| 10 <sup>a</sup> | H   | 4                        | 178-179<br>164-166 | C <sub>14</sub> H <sub>16</sub> N <sub>2</sub><br>C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> · (CHCO <sub>2</sub> H) <sub>2</sub> | C, H, N<br>N(total), N(basic) <sup>a</sup> |
| 11              | H   | 3                        | 154-155<br>185-186 | C <sub>14</sub> H <sub>16</sub> N <sub>2</sub><br>C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> · (CHCO <sub>2</sub> H) <sub>2</sub> | C, <sup>b</sup> H, N<br>N(total), N(basic) |
| 12              | CH <sub>3</sub>                                   | 3                        | 240-241            | C <sub>15</sub> H <sub>18</sub> N <sub>2</sub> · HCl  | HCl, <sup>c</sup> N                        |
| 13              | CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>     | 3                        | 106-107<br>161-163 | C <sub>21</sub> H <sub>22</sub> N <sub>2</sub><br>C <sub>21</sub> H <sub>22</sub> N <sub>2</sub> · (CHCO <sub>2</sub> H) <sub>2</sub> | C, H, N<br>N(basic, total)                 |
| 14              | COC <sub>6</sub> H <sub>5</sub>                   | 3                        | 242-244            | C <sub>21</sub> H <sub>20</sub> N <sub>2</sub> O · HCl  | HCl, N                                     |
| 15              | 4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> | 3                        | 172-173            | C <sub>21</sub> H <sub>24</sub> ClN <sub>2</sub> · (CHCO <sub>2</sub> H) <sub>2</sub>   | C, H, N(basic, total)                      |
| 16              | CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>     | 4                        | 147-148            | C <sub>21</sub> H <sub>22</sub> N <sub>2</sub> · (CHCO <sub>2</sub> H) <sub>2</sub>   | C, H, N(basic, total)                      |
| 17              | CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>     | 2 <sup>d</sup>           | 192-193            | C <sub>21</sub> H <sub>22</sub> N <sub>2</sub> · (CHCO <sub>2</sub> H) <sub>2</sub>   | C, H, N(basic, total)                      |

<sup>a</sup> Nonaqueous titration in HOAc using standard HClO<sub>4</sub> as titrant. <sup>b</sup> Calcd: C, 79.25; found, 78.66. <sup>c</sup> Aqueous titration. <sup>d</sup> 1,2,3,6-Tetrahydro isomer.

The BH<sub>4</sub><sup>-</sup> reduction of pyridinium compounds has been extensively investigated by Lyle and coworkers.<sup>3</sup> In the case of the 3- and 4-(2-indolyl)pyridinium salts the reduction proceeded as expected to give tetrahydro derivatives wherein the double bond was conjugated with the indole ring.<sup>4</sup> Conclusive evidence of structure was obtained from nmr and uv spectral data and also by catalytic hydrogenation (1 mol equiv uptake) of **11** and **13** to the 2-(1-methyl-3-piperidyl)-indoles (**6** and **7**).



6, R = H

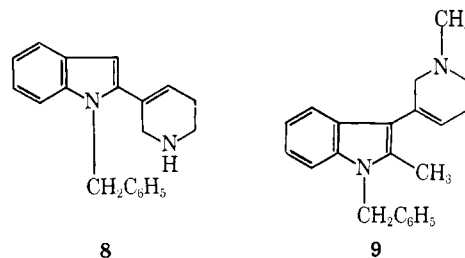
7, R = CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>

Borohydride reduction of 1-benzyl-2-(1-methyl-2-pyridinium)indole iodide gave as the only isolable product the 1,2,3,6-tetrahydro derivative **17**. The assignment of structure was based on the fact that the 2-proton signal of the tetrahydropyridine ring was split into a quartet by the 2 nonequivalent hydrogens at position 3.<sup>5</sup>

For further structure-activity relationships, **13** was demethylated by the von Braun CNBr method to give **8**. To determine the effect of shifting the tetrahydropyridyl ring to the 3 position of indole, **9** was prepared by Fischer cyclization of the 1-benzyl-1-phenylhydrazine of 3-acetonylpyridine and subsequent BH<sub>4</sub><sup>-</sup> reduction of the methiodide.

TABLE II  
ANTIHISTAMINIC AND ANTISEROTONIN  
ACTION OF 2-TETRAHYDROPYRIDYLINDOLES

| Compd | —Histamine antagonism—                    |  | —Serotonin antagonism—                       |  |
|-------|---|--|--|--|
|       | Guinea pig ileum ED <sub>50</sub> (μg/ml) | Konzett-Rössler preparation ED <sub>50</sub> (mg/kg) | Rat uterine segment EC <sub>50</sub> (μg/ml) | Konzett-Rössler preparation ED <sub>50</sub> (mg/kg) |
| 7     | 0.46                                      | 0.295  | 0.126  | >1.0   |
| 8     | 0.05                                      | >1.0   | 0.114  | >1.0   |
| 9     | 1.99                                      | >1.0   | 0.118  | >1.0   |
| 10    | 0.03                                      | >1.0   | 0.140  | 0.355  |
| 11    | 0.21                                      | >1.0   | 0.017  | >1.0   |
| 12    | 0.13                                      | >1.0   | 1.95   | >1.0   |
| 13    | 0.0085                                    | 0.1  | 0.0057                                       | 0.191  |
| 14    | 0.24                                      | >1.0   | 0.290  | >1.0   |
| 15    | 0.0457                                    | 0.275  | 0.162  | >1.0   |
| 16    | 0.0447                                    | 0.316  | 0.022  | 0.302  |
| 17    | 0.219                                     | >1.0   | 0.235  | 0.479  |



**Pharmacology.**—All compounds of this series antagonized responses to histamine in the guinea pig ileum, and to serotonin in the rat uterine segment. However, when 2-tetrahydropyridylindoles were tested in an *in vivo* preparation (Konzett-Rössler<sup>6</sup>), only a few antagonized significantly the bronchoconstrictor action of histamine (**7**, **13**, **15**, and **16** and of serotonin (**10**, **13**, **16**, and **17**). Only **13** and **16** produced nearly equipotent antihistaminic and antiserotonon actions, **13** being the most potent (Table II). Therefore, **13** was selected for further pharmacological studies in

(3) R. E. Lyle and P. S. Anderson, *Advan. Heterocycl. Chem.* **6**, 55 (1966).

(4) While the pharmacology of our compounds was being evaluated, an article by D. Beck and K. Schenker, [*Helv. Chim. Acta*, **51**, 260 (1968)], disclosed the synthesis of **10** by the same method.

(5) This is the argument used by P. S. Anderson and R. E. Lyle [*Tetrahedron Lett.*, 153 (1964)] for the assignment of structure to the product obtained from the BH<sub>4</sub><sup>-</sup> reduction of 1,4-dimethyl-2-phenylpyridinium iodide.

(6) H. Konzett and R. Rössler, *Arch. Exp. Pathol. Pharmacol.*, **195**, 71 (1940).

TABLE III  
COMPARATIVE ACTIONS OF **13**, DIPHENHYDRAMINE, AND CYPROHEPTADINE.  
VALUES CORRESPOND TO EITHER LD<sub>50</sub>, EC<sub>50</sub>, OR ED<sub>50</sub>

| Parameter  | <b>13</b> | Diphenhydramine | Cyproheptadine |
|--|-----------|-----------------|----------------|
| LD <sub>50</sub> (mice, mg/kg, i.p.)                         | 524.0     | 60.7            | 56.2           |
| Histamine antagonism   |           |                 |                |
| Ileum segment (guinea pig, $\mu$ g/ml)                       | 0.0085    | 0.057           | 0.00135        |
| Tracheal chain (guinea pig, $\mu$ g/ml)                      | 0.052     | 0.098           | 0.01           |
| Konzett-Rössler preparation (guinea pig, mg/kg, i.v.)        | 0.1       | 0.052           | 0.0126         |
| Histamine aerosol (guinea pig, mg/kg, p.o.)                  | 20.7      | 26.5            | 0.67           |
| Serotonin antagonism   |           |                 |                |
| Konzett-Rössler preparation (guinea pig, mg/kg, i.v.)        | 0.191     |                 | 0.005          |
| Serotonin aerosol (guinea pig, mg/kg, p.o.)                  | 1.85      |                 | 0.18           |
| CNS actions  |           |                 |                |
| Rotarod test (coordinated motor activity) (rat, mg/kg, i.p.) | 130.0     | 29.0            | 41.4           |
| Spontaneous motor activity (rat, mg/kg, i.p.)                | 60.9      | 53.9            | 40.2           |
| CMA/SMA  | 2.14      | 0.54            | 1.03           |
| Antiemetic activity (dog, mg/kg, p.o.)                       | 37.2      | 56.2            |                |
| Anticholinergic action                                       |           |                 |                |
| Ileum segment (guinea pig, $\mu$ g/ml)                       | 2.82      | 0.645           | 0.025          |
| Vagal stimulation blockade (cat, mg/kg, i.v.)                | 13.8      | 3.64            | 0.113          |

which diphenhydramine and cyproheptadine were included as reference compounds (Table III).

Antihistaminic activity was assessed in the guinea pig ileum, the guinea pig tracheal chain,<sup>7</sup> the Konzett-Rössler preparation, and in the guinea pig bronchospasm induced by histamine aerosol. Antiserotonin activity was evaluated in the Konzett-Rössler preparation and in the guinea pig bronchospasm induced by serotonin aerosol.<sup>8</sup> CNS depression was studied in rats by the rotarod test<sup>9</sup> and by means of an activity cage. Antiemetic activity was evaluated by the protection to emesis induced by apomorphine in dogs.<sup>10</sup> Anticholinergic activity was studied by guinea pig ileum responses to acetylcholine and blockade of heart rate responses of cats to vagal stimulation. The LD<sub>50</sub> was calculated by the method of Litchfield and Wilcoxon,<sup>11</sup> and the EC<sub>50</sub> and ED<sub>50</sub> were determined both by the same method and graphically.

Compound **13** had an antihistaminic potency of the order of diphenhydramine; however, it was clearly less potent than cyproheptadine in antagonizing the actions of both histamine and serotonin. On the other hand, **13** was less toxic and produced less depression of coordinated motor activity and less anticholinergic effects than the two reference compounds. These results suggest that **13** might produce less side effects than diphenhydramine and cyproheptadine.

### Experimental Section<sup>12</sup>

**2-(1-Methyl-1,2,5,6-tetrahydro-3-pyridyl)indole (11).**—A 33.6-g sample of 3-(2-indolyl)-1-methylpyridinium iodide<sup>13</sup> was sus-

pended in 500 ml of 50% aqueous EtOH and then 8 g of NaBH<sub>4</sub> was slowly added. The solid gradually dissolved during the addition. When the vigorous reaction had subsided, the soln was heated under reflux for 1 hr. EtOH was distilled *in vacuo* and the residue stirred with NaOH soln. Extraction with CHCl<sub>3</sub>, drying the extract, and concentration *in vacuo* gave 17.3 g (82%) of material, mp 145–147°. Crystallization from C<sub>6</sub>H<sub>6</sub>-Et<sub>2</sub>O followed by recrystallization (Et<sub>2</sub>O) gave the analytical sample: uv max (MeOH) 218 m $\mu$  ( $\epsilon$  20,100), 301 (20,700); nmr (CDCl<sub>3</sub>, 10%)  $\tau$  6.63 (d, 2, NCH<sub>2</sub>C=CH), 3.93 (m, 1, olefinic), 3.58 (d, 1, J<sub>1,3</sub> = 4.0 cps, indole-C<sub>3</sub>H).

**Maleate.**—A soln of 5.00 g of the base in 200 ml of EtOAc containing a little MeOH was treated with 2.5 g of maleic acid in 30 ml of MeOH-EtOAc; the salt was collected and recrystallized from MeOH-EtOAc; yield 4.83 g.

**1-Benzyl-2-(3-pyridyl)indole.**—A soln of 7.0 g (0.06 mol) of 3-acetylpyridine, 11.5 g (0.06 mol) of 1-benzyl-1-phenylhydrazine, and 0.2 g of *p*-TsOH in 100 ml of dry toluene was heated under reflux for 16 hr while the H<sub>2</sub>O liberated was collected in a Dean-Stark trap. PhMe was distilled *in vacuo* and the residue (17 g) was dissolved in 100 ml of HOCH<sub>2</sub>CH<sub>2</sub>OH. The soln was heated under reflux for 20 hr, then poured into 500 ml of H<sub>2</sub>O. The organic material was extracted into CHCl<sub>3</sub> and the extract was dried and concentrated *in vacuo*. The resulting oil was dissolved in boiling Et<sub>2</sub>O and the solution clarified and cooled; yield 5.0 g, mp 120–121°. Anal. (C<sub>20</sub>H<sub>12</sub>N<sub>2</sub>) N (basic).

**3-(1-Benzyl-2-indolyl)-1-methylpyridinium Iodide.**—To 6 g of 1-benzyl-2-(3-pyridyl)indole in 100 ml of Me<sub>2</sub>CO was added 8 ml of MeI. The mixture was heated under reflux for 30 min. The salt was filtered and washed with Me<sub>2</sub>CO to give 9.4 g of product, mp 146–147°. Anal. (C<sub>23</sub>H<sub>17</sub>IN<sub>2</sub>) N.

**3-[2-(1-Benzyl)indolyl]-1-methyl-1,2,5,6-tetrahydropyridine.**—To 9.4 g of 3-(1-benzyl-2-indolyl)-1-methylpyridinium iodide in 200 ml of MeOH was slowly added 6 g of NaBH<sub>4</sub>. The mixture was heated under reflux for 2 hr. After removal of solvent the residue was made basic with 20% NaOH and extracted with CHCl<sub>3</sub>. Concentration of solvent gave 6.5 g of syrupy material which was chromatographed over 150 g of Florisil. Elution with C<sub>6</sub>H<sub>6</sub>-Et<sub>2</sub>O (1:1) gave 3 g of solid, mp 100–101°. The base was dissolved in 2-PrOH, excess maleic acid was added and the salt which formed was recrystallized twice from *i*-PrOH; yield 2.6 g.

Elmer Model 202 or Beckmann DB-G spectrophotometer. Nmr spectra were obtained with a Varian Model A-60 spectrometer (resonance peaks in  $\tau$  units, relative to MeSi at  $\tau$  10). Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within  $\pm 0.4\%$  of the theoretical values.

(13) A. P. Gray and W. L. Archer, *J. Amer. Chem. Soc.*, **79**, 3554 (1957).

(7) R. W. Foster, *J. Pharm. Pharmacol.*, **12**, 189 (1960).

(8) H. Herxheimer, *Arch. Int. Pharmacodyn.*, **106**, 371 (1956).

(9) N. W. Dunham and T. S. Miya, *J. Amer. Pharm. Assoc. Sci. Ed.*, **46**, 208 (1957).

(10) C. D. Schmidt, E. Sata, K. R. Brizzee, and H. L. Borison, *Proc. Soc. Exp. Biol. Med.*, **82**, 441 (1953).

(11) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99–113 (1949).

(12) Melting points were taken on a Büchi melting point determination apparatus and are uncorrected. Uv spectra were recorded on a Perkin-

The base was regenerated from the maleate with  $\text{Na}_2\text{CO}_3$  and recrystallized from pentane to give analytical material: ir max ( $\text{CHCl}_3$ ) no indole NH; uv max (MeOH) 295  $\text{m}\mu$  ( $\epsilon$  13,500).

**1-Benzyl-2-(1-methyl-1,2,5,6-tetrahydro-3-pyridyl)indole (14).**—A soln of  $\text{C}_6\text{H}_5\text{MgBr}$  in 50 ml of THF was prepared using 4.45 g (0.0283 mol) of  $\text{C}_6\text{H}_5\text{Br}$  and 0.680 g (0.0283 g-atoms) of Mg turnings under  $\text{N}_2$ . A soln of 6.00 g (0.0283 mol) of **11** in THF was added to the Grignard reagent with stirring. After 0.5 hr, the reaction mixture was cooled to  $0^\circ$  and 3.98 g (0.0283 mol) of  $\text{C}_6\text{H}_5\text{COCl}$  was added over a 15-min period at this temperature. After stirring for 12 hr at room temperature, the mixture was hydrolyzed with cold saturated  $\text{NH}_4\text{Cl}$  soln. The THF layer was separated, dried, and evaporated, and the residue chromatographed on Florisil using  $\text{C}_6\text{H}_6$  as eluent. An oily base (3.0 g) was obtained; ir max ( $\text{CHCl}_3$ ) no indole NH in the 3400–3500  $\text{cm}^{-1}$  region.

**Hydrochloride.**—An  $\text{Et}_2\text{O}$  solution of 3.0 g of the above base was treated with a slight excess of HCl in *i*-PrOH; yield 2.0 g; ir max (KCl) 1690 (indole-NC=O)  $\text{cm}^{-1}$ .

**1-Benzyl-2-(1-methyl-3-piperidyl)indole (7).**—A soln of 5.1 g of 1-benzyl-2-(1-methyl-1,2,5,6-tetrahydro-3-pyridyl)indole in HOAc containing 0.2 g of  $\text{PtO}_2$  was hydrogenated at 3.5  $\text{kg}/\text{cm}^2$  (room temperature). After 1 hr, 1 mol equiv of  $\text{H}_2$  had been absorbed and no further uptake was observed. The catalyst was removed and the filtrate concentrated *in vacuo*. The residual oil was stirred with  $\text{NaHCO}_3$  soln and the organic material was extracted into  $\text{CHCl}_3$ . Drying and concentration *in vacuo* gave 5.1 g of thick oil; ir max ( $\text{CHCl}_3$ ) no indole NH absorption; uv max (MeOH) 281–282  $\text{m}\mu$  ( $\epsilon$  5950).

The base was converted into the maleate in  $\text{Me}_2\text{CO}-\text{Et}_2\text{O}$ ; mp 150–151°. *Anal.* [ $\text{C}_{21}\text{H}_{24}\text{N}_2 \cdot (\text{CHCO}_2\text{H})_2$ ] C, H, N.

Compound **11** was converted into the known 2-(1-methyl-3-piperidyl)indole<sup>13</sup> in the same way.

**1-Benzyl-2-(1-methyl-1,2,3,6-tetrahydro-2-pyridyl)indole (17).**— $\text{NaBH}_4$  (7.6 g, 0.20 mol) was added in small portions to a MeOH soln of 19.2 g (0.045 mol) of 1-benzyl-2-(2-pyridyl)indole methiodide (mp 169–171°, prepared by thermal indolization and subsequent quaternization). The mixture was stirred under reflux for 3 hr, then worked up in the usual way. A  $\text{C}_6\text{H}_6$  soln of the crude base was chromatographed on a silicic acid column. The material obtained by elution with  $\text{EtOAc}$  was recrystallized twice from pentane to give 4.0 g of product: mp 92–94°; nmr ( $\text{CDCl}_3$ , 10%)  $\tau$  7.52 (m, 2, tetrahydropyridine- $\text{C}_3\text{H}$ ), 6.20 (q, 1, tetrahydropyridine- $\text{C}_2\text{H}$ ); 4.20 (m, 2, olefinic), 3.34 (s, 1, indole- $\text{C}_3\text{H}$ ), 2.30 (1, indole- $\text{C}_7\text{H}$ ); uv max (MeOH) no absorption in the 300– $\text{m}\mu$  region.

**Maleate.**—The base described above was dissolved in  $\text{Et}_2\text{O}$  and maleic acid (2.3 g) in  $\text{Me}_2\text{CO}$  was added. The salt was recrystallized from  $\text{Me}_2\text{CO}-\text{Et}_2\text{O}$ , yield 4.0 g.

**1-Benzyl-2-(1-cyano-1,2,5,6-tetrahydro-3-pyridyl)indole.**—A  $\text{C}_6\text{H}_6$  soln of 1.50 g (0.005 mol) of **13** was added dropwise to a  $\text{C}_6\text{H}_6$  soln of 0.64 g (0.006 mol) of  $\text{CNBr}$  over a 1-hr period.

The mixture was stirred overnight, a small amount of insoluble material was filtered and the filtrate concentrated *in vacuo*. Crystallization from  $\text{MeOH}-\text{H}_2\text{O}$  yielded 1.0 g of product: mp 97–99°; ir 2225 ( $\text{C}\equiv\text{N}$ )  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ , 20%)  $\tau$  4.59 (s, 2, benzylic), 4.02 (m, 1, olefinic); absence of NMe signal at 7.87. *Anal.* ( $\text{C}_{21}\text{H}_{19}\text{N}_3$ ) N.

**1-Benzyl-2-(1,2,5,6-tetrahydro-3-pyridyl)indole (8).**—The above intermediate (1.0 g) in 50 ml of  $\text{MeOH}-20\%$  aq NaOH (1:1) was heated under reflux overnight. MeOH was distilled and the oil extracted into  $\text{CHCl}_3$ . The extract was dried and concentrated *in vacuo* to give 0.82 g of material, ir ( $\text{CHCl}_3$ ) absence of  $\text{C}\equiv\text{N}$  absorption band at 2225  $\text{cm}^{-1}$ .

**Maleate.**—The base was converted into the maleate in  $\text{Me}_2\text{CO}-\text{MeOH}$  to give 0.80 g of product, mp 185–186°. *Anal.* [ $\text{C}_{20}\text{H}_{20}\text{N}_2 \cdot (\text{CHCO}_2\text{H})_2$ ] C, H, N.

**1-Benzyl-2-methyl-3-(3-pyridyl)indole.**—A mixture of 14.6 g (0.11 mol) of 3-pyridylacetone<sup>14</sup> and 21.0 g (0.11 mol) of 1-benzyl-1-phenylhydrazine in 200 ml of PhMe was heated under reflux for 2 hr while collecting the water in a Dean-Stark trap. After removal of solvent the residue was dissolved in 300 ml of AcOH and the solution heated at  $90^\circ$  for 3 hr. The AcOH was distilled *in vacuo*, the residue treated with  $\text{NaHCO}_3$  soln, and then extracted into  $\text{CHCl}_3$ . Drying of the extract and concentration *in vacuo* gave 26 g of material whose ir spectrum ( $\text{CHCl}_3$ ) showed complete removal of the  $\text{NN}=\text{C}$  band at 1635  $\text{cm}^{-1}$ .

**Methiodide.**—The crude indole was dissolved in 200 ml of  $\text{Me}_2\text{CO}$  and 40 ml of MeI. The mixture was heated under reflux for 16 hr, then the solvent and excess MeI were removed *in vacuo*. Stirring with a little  $\text{Me}_2\text{CO}$  gave 23 g of product, mp 194–196°. An analytical sample was prepared by recrystallization from a small amount of MeOH, mp 196–198°. *Anal.* ( $\text{C}_{22}\text{H}_{21}\text{IN}_2$ ) N (basic).<sup>15</sup>

**1-Benzyl-2-methyl-3-(1-methyl-1,2,5,6-tetrahydro-3-pyridyl)indole (9).**—A 33-g sample of the above methiodide was reduced with 14 g of  $\text{NaBH}_4$  in the usual way. The free base obtained (12 g) failed to crystallize, but was characterized by its nmr spectrum ( $\text{CDCl}_3$ , 10%)  $\tau$  7.54 (s, 3, NMe), 7.42 (s, 3, indole- $\text{C}_3\text{Me}$ ), 4.1 (m, 1, olefinic); absence of indole- $\text{C}_3\text{H}$  signal in the  $\tau$  3.5 region.

**Oxalate.**—The base was converted into the oxalate in *i*-PrOH. Recrystallization from  $\text{MeOH}-i\text{-PrOH}$  gave the analytical sample, mp 195–197°. *Anal.* [ $\text{C}_{22}\text{H}_{24}\text{N}_2 \cdot (\text{CO}_2\text{H})_2$ ] N.

**Acknowledgment.**—The authors wish to thank Dr. Dale A. Stauffer and associates for the analytical services.

(14) A. Burger and C. R. Walter, Jr., *J. Amer. Chem. Soc.*, **72**, 1988 (1950).

(15) Titration in AcOH containing  $\text{Hg}(\text{OAc})_2$ , using standard  $\text{HClO}_4$  as titrant.