

from ethanol, and the colorless prisms melted at 103–104°.

*Anal.* Calcd. for  $C_{15}H_{14}O_3S$ : C, 65.67; H, 5.14; S, 11.69. Found: C, 65.77; H, 5.34; S, 11.83.

Hydrolysis with 2.5% ethanolic potassium hydroxide solution furnished a 95% yield of the diol XVII.

**1-Oxo-4,4-dimethylthiadioxane-2,6 (XXI).**—This sulfide was prepared from 2,2-dimethylpropanediol-1,3° in an analogous manner as the diphenyl derivative. The mobile colorless liquid boiled at 89° (33 mm.),  $n_D^{25}$  1.4465. The yield was 70%.

*Anal.* Calcd. for  $C_8H_{10}O_3S$ : C, 39.98; H, 6.71; S, 21.35. Found: C, 40.10; H, 6.63; S, 21.53.

### Summary

1. The nitration of 1-phenyl-1-cyanocyclopropane has been studied.

2. The synthesis of 1-(4-aminophenyl)-1-(2-amino-4-thiazolyl)-cyclopropane from 1-(4-nitrophenyl)-cyanocyclopropane in six steps has been described.

3. 1,1-bis-(4-Aminophenyl)-cyclopropane has been prepared from 1,1-diphenylcyclopropane and its structure has been established.

4. 2,2-Diphenylpropanediol-1,3, prepared from diphenylacetaldehyde, could not be converted to the corresponding 1,3-dihalide. Under the influence of phosphorus tribromide it yields 2-phenylindene, while thionyl chloride converts it to a cyclic sulfite.

CHARLOTTESVILLE, VA. RECEIVED DECEMBER 7, 1948

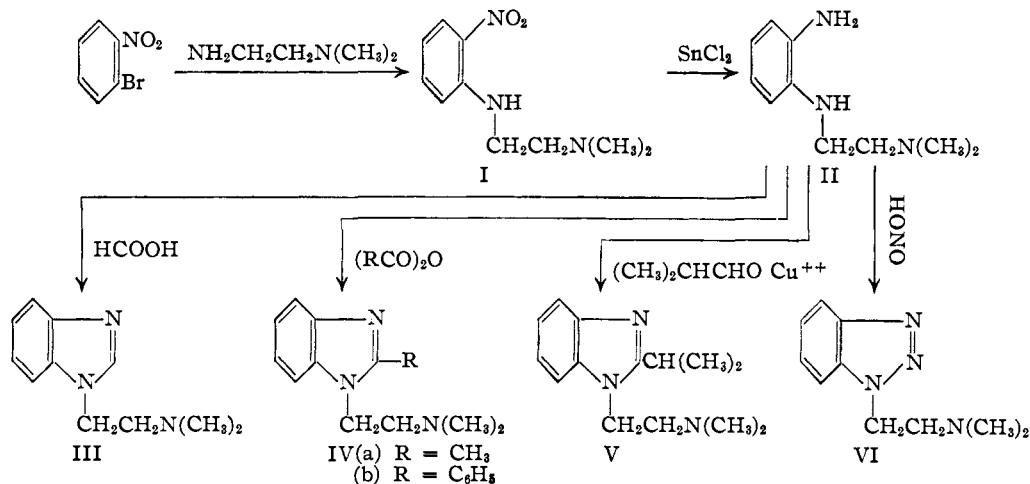
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

## Histamine Antagonists. V. Some 1-( $\beta$ -Dimethylaminoethyl)-benzimidazole Derivatives

By JOHN B. WRIGHT

In continuation of a study of histamine antagonists in progress in this Laboratory<sup>1-4</sup> several 1-( $\beta$ -dimethylaminoethyl)-benzimidazole derivatives and 1-( $\beta$ -dimethylaminoethyl)-benzotriazole

the benzimidazole derivatives mentioned above this compound was synthesized and investigated also. These compounds were prepared according to the scheme



have been synthesized and screened for antihistaminic activity.

Benzimidazole derivatives appeared to be of interest because they have the  $-\text{N}-\text{C}=\text{N}-$  grouping present in *N,N*-dimethyl-*N'*-benzyl-*N'*-( $\alpha$ -pyridyl)-ethylenediamine and certain other well-known antihistaminic agents as well as structures analogous to the imidazole ring of histamine. Since 1-( $\beta$ -dimethylaminoethyl)-benzotriazole could be prepared readily from the same intermediary compounds necessary for the synthesis of

*o*-( $\beta$ -Dimethylaminoethylamino)-nitrobenzene (I) was prepared by the reaction between *o*-bromonitrobenzene and  $\beta$ -dimethylaminoethylamine in the presence of anhydrous sodium acetate. Reduction of the nitro compound with stannous chloride gave the diamine (II) which, upon treatment with anhydrous formic acid,<sup>5</sup> acetic anhydride,<sup>5</sup> benzoic anhydride, isobutyraldehyde and cupric acetate<sup>6</sup> and nitrous acid,<sup>7</sup> gave the benzimidazole and benzotriazole derivatives shown above (III–VI).

(1) Wright, Kolloff and Hunter, *This Journal*, **70**, 3098 (1948).

(2) Reid, Wright, Kolloff and Hunter, *ibid.*, **70**, 3100 (1948).

(3) Reitsema and Hunter, *ibid.*, **70**, 4009 (1948).

(4) Wright, *ibid.*, **71**, 1028 (1949).

(5) Clemo and Swan, *J. Chem. Soc.*, 274 (1944).

(6) Weidenhagen, *Ber.*, **69**, 2263 (1936); Weidenhagen and Train, *ibid.*, **75**, 1936 (1942).

(7) Ladenburg, *Ber.*, **9**, 219 (1876).

Preliminary pharmacological tests<sup>8,9</sup> indicate that these compounds possess only slight antihistaminic activity.

### Experimental<sup>10,11</sup>

*o*-( $\beta$ -Dimethylaminoethylamino)-nitrobenzene (I).—A mixture consisting of 82.9 g. (0.942 mole) of  $\beta$ -dimethylaminoethylamine,<sup>12</sup> 201.9 g. (0.998 mole) of *o*-bromonitrobenzene and 200 g. of anhydrous sodium acetate was stirred and heated in an oil-bath at 120–130° for eight hours. The mixture turned red after several minutes and near the end of the reaction became very viscous, making stirring impossible. The reaction mixture was cooled, diluted with about 1 l. of water, acidified with hydrochloric acid and steam distilled. Ninety-two and four-tenths grams of *o*-bromonitrobenzene was recovered. The residue (about 2–2.5 l.<sup>13</sup> of a red solution) was allowed to cool and was basified by the addition of a cold 20% potassium hydroxide solution. The solution was saturated with potassium carbonate, extracted with ether, the extract dried over anhydrous magnesium sulfate, the ether evaporated and the residue distilled *in vacuo* through a Vigreux column; yield, 100.1 g. (51%) of a red oil, b.p. 125–126° (0.2 mm.),  $n_{25}^D$  1.6148.

*Anal.* Calcd. for  $C_{10}H_{13}N_3O_2$ : N, 20.08. Found: N, 19.61.

*o*-( $\beta$ -Dimethylaminoethylamino)-aniline (II).—To a solution of 13.0 g. (0.062 mole) of *o*-( $\beta$ -dimethylaminoethylamino)-nitrobenzene in 50 ml. of concentrated hydrochloric acid cooled to 5° in an ice-bath was added, in portions with stirring, a solution of 50.0 g. of stannous chloride dihydrate in 72 ml. of concentrated hydrochloric acid. The temperature of the reaction mixture rose to 50° and was allowed to remain at this temperature by removing the ice-bath occasionally. When the heat of the reaction had subsided the reaction mixture was allowed to cool to room temperature. After standing overnight the reaction mixture was cooled in an ice-bath and made strongly basic with a cold 20% sodium hydroxide solution. The resulting mixture was extracted with ether, the ether extracts dried over anhydrous potassium carbonate and the solvent evaporated. Upon cooling the amber residue solidified. Yield of crude product, 10.9 g. (98%), m.p. 50–53°. Recrystallization from low-boiling petroleum ether (Skellysolve A) gave almost colorless glistening plates melting at 54–55°. Sublimation *in vacuo* gave a colorless material of the same melting point. The free base is soluble in water.

*Anal.* Calcd. for  $C_{10}H_{13}N_3$ : C, 67.00; H, 9.56; N, 23.44. Found: C, 67.28; H, 9.36; N, 23.61.

1-( $\beta$ -Dimethylaminoethyl)-benzimidazole Dihydrochloride (III).—The procedure described is a modification of the method of Clemo and Swan<sup>5</sup> for the preparation of 1-( $\epsilon$ -diethylamino- $\beta$ -pentyl)-6-methoxybenzimidazole. A mixture of 6.2 g. (0.0346 mole) of *o*-( $\beta$ -dimethylaminoethylamino)-aniline and 3.0 ml. of anhydrous formic acid was heated on a steam-bath for two hours and, when cool, was poured into water. The solution was basified with cold 20% sodium hydroxide solution and the resulting mixture worked up as described above for *o*-( $\beta$ -dimethylaminoethylamino)-nitrobenzene; yield 5.5 g. (84%) of a colorless, water-soluble liquid, b.p. 115–20° (0.2 mm.).

The dihydrochloride was prepared by adding an ethereal

(8) For these tests grateful acknowledgment is made to Dr. Milton J. Vander Brook of our Department of Pharmacology.

(9) These tests were carried out on isolated guinea pig small intestine. In all cases the tests were carried out on aqueous solutions of the hydrochloride salts.

(10) All melting points are corrected, unless otherwise stated.

(11) Appreciation is expressed to Mr. Harold Emerson and his staff for analyses reported.

(12) Turner, *THIS JOURNAL*, **66**, 1607 (1946).

(13) If a smaller volume of residue is obtained from the steam distillation an orange precipitate of the hydrochloride salt is obtained upon cooling.

hydrogen chloride solution to a solution of the free base in ether. Recrystallization from ethanol, after treatment with decolorizing charcoal, gave colorless needles, m.p. 234–236° (uncor.).

*Anal.* Calcd. for  $C_{11}H_{15}N_3 \cdot 2HCl$ : C, 50.39; H, 6.54; N, 16.03; Cl, 27.05. Found: C, 50.44; H, 6.50; N, 16.19; Cl, 27.00.

1-( $\beta$ -Dimethylaminoethyl)-2-methylbenzimidazole Dihydrochloride (IVa).—The method of Clemo and Swan<sup>5</sup> for the preparation of 1-( $\epsilon$ -diethylamino- $\beta$ -pentyl)-6-methoxy-2-methylbenzimidazole was employed using 7.16 g. (0.040 mole) of *o*-( $\beta$ -dimethylaminoethylamino)-aniline and 17.5 ml. of acetic anhydride and the product worked up as described above; yield, 6.6 g. (81%), b.p. 117° (0.3 mm.).

The dihydrochloride, prepared as described above, after recrystallization from ethanol consisted of colorless prisms, m.p. 238–239.5° (uncor.).

*Anal.* Calcd. for  $C_{12}H_{17}N_3 \cdot 2HCl$ : N, 15.21; Cl 25.67. Found: N, 15.01; Cl, 25.78.

1-( $\beta$ -Dimethylaminoethyl)-2-phenylbenzimidazole Dihydrochloride (IVb).—A mixture of 1.30 g. (0.0073 mole) of *o*-( $\beta$ -dimethylaminoethylamino)-aniline and 7.35 g. (0.0325 mole) of benzoic anhydride was heated in an oil-bath at 145–150° for sixteen hours. During this time the small amount of material which sublimed to the upper portions of the flask was returned to the reaction mixture by swirling the flask occasionally. When cool the red liquid was poured into a 3% hydrochloric acid solution, the resulting mixture basified with a potassium hydroxide solution and extracted with ether. The ethereal extracts were extracted with 3% hydrochloric acid solution, the acid extracts basified with potassium carbonate and the resulting mixture extracted with ether. The ether extracts were dried over anhydrous potassium carbonate and the ether removed. The amber residue solidified upon scratching; yield, 1.70 g. (88%), m.p. 68–72°. Recrystallization from petroleum ether (Skellysolve C) gave colorless needles, m.p. 72.5–74°.

The dihydrochloride, prepared as described previously, crystallized from absolute isopropyl alcohol as colorless prisms, m.p. 234° (dec.).

*Anal.* Calcd. for  $C_{17}H_{19}N_3 \cdot 2HCl$ : N, 12.42; Cl, 20.96. Found: N, 12.41; Cl, 21.29.

1-( $\beta$ -Dimethylaminoethyl)-2-isopropylbenzimidazole (V).—The method of McKee, McKee and Bost<sup>14</sup> for the preparation of 5-chloro-1-(1-diethylamino-4-pentyl)-2-*p*-methoxyphenylbenzimidazole was modified by using 7.16 g. (0.040 mole) of *o*-( $\beta$ -dimethylaminoethylamino)-aniline, 3.10 g. (0.043 mole) of freshly distilled isobutyraldehyde and corresponding quantities of the other reagents. The aqueous solution was saturated with potassium carbonate prior to extraction of the final product with ether; yield, 3.08 g. (33%) of a yellow oil, b.p. 136–40° (1.1 mm.).

The dipicrate was recrystallized from ethanol (about 1 l. per g.) to give yellow rectangular prisms, m.p. 235–236° (dec., uncor.).

*Anal.* Calcd. for  $C_{14}H_{21}N_3 \cdot 2C_6H_5N_3O_7$ : C, 45.28; H, 3.95; N, 18.28. Found: C, 45.34; H, 3.80; N, 18.07.

1-( $\beta$ -Dimethylaminoethyl)-benzotriazole Hydrochloride (VI).—The procedure of McKee, McKee and Bost<sup>14</sup> for 5-chloro-1-(1-diethylamino-4-pentyl)-benzotriazole was modified by using 7.52 g. (0.042 mole) of *o*-( $\beta$ -dimethylaminoethylamino)-aniline. The solution was saturated with potassium carbonate prior to extraction of the final product with ether; yield, 5.76 g. (72%) of a yellow-orange oil, b.p. 115–117° (0.3 mm.).

The hydrochloride, prepared in the manner described previously, recrystallized from absolute ethanol as colorless needles, m.p. 170.5–171.5°.

*Anal.* Calcd. for  $C_{10}H_{14}N_4 \cdot HCl$ : C, 52.98; H, 6.67; N, 24.71; Cl, 15.64. Found: C, 53.11; H, 6.66; N, 24.64; Cl, 15.68.

(14) McKee, McKee and Bost, *THIS JOURNAL*, **68**, 1904 (1946).

### Summary

1. Four new 1-( $\beta$ -dimethylaminoethyl)-benzimidazole derivatives containing various groups in the 2-position and 1-( $\beta$ -dimethylaminoethyl)-benzotriazole hydrochloride have been prepared.
2. The results of preliminary pharmacological

tests on these compounds for anti-histaminic activity is reported.

3. *o*-( $\beta$ -Dimethylaminoethylamino)-nitrobenzene and *o*-( $\beta$ -dimethylaminoethylamino)-aniline have been prepared.

KALAMAZOO, MICHIGAN

RECEIVED JANUARY 7, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

## The Preparation of Synthetic Estrogens. IV.<sup>1</sup> Condensation of Biacetyl with Phenols

BY KEIITI SISIDO, HITOSI NOZAKI AND TATUO IWAKO

While aromatic  $\alpha$ -diketones, *e. g.*, benzil<sup>2</sup> and acenaphthenequinone,<sup>3</sup> are known to condense with phenol yielding tertiary aromatic monoacetones of a pinacolone type, we have observed that the same is true also in the reaction of an aliphatic  $\alpha$ -diketone, biacetyl. When biacetyl was condensed with phenol in the presence of sulfuric acid 2,2-bis-(*p*-hydroxyphenyl)-3-butanone (Ia)<sup>4</sup> was obtained. This butanone derivative was characterized by methylation which afforded 2,2-di-*p*-anisyl-3-butanone.<sup>5,6</sup>

The condensation of *o*-cresol and biacetyl gave an analogous product, 2,2-bis-(*p*-hydroxy-*m*-tolyl)-3-butanone (Ib). The structure of this new compound was assigned on the basis of analytical data as well as of its behavior as mentioned below.

Reduction of this condensation product (Ib) led to the corresponding alcohol (IIb), which was dehydrated under retro-pinacolone rearrangement to  $\alpha, \alpha', 3, 3'$ -tetramethyl-4,4'-stilbenediol (IIIb). For confirmation of the structure the same stilbenediol was prepared by our previous method<sup>6</sup> starting from *p*-methoxy-*m*-methylacetophenone. The products of both procedures showed no depression in a mixed melting point determination.

Biological assay of this stilbene derivative (IIIb), which represents an isomer of diethylstilbestrol, has been carried out in the Laboratory of Prof. R. Kinoshita of Osaka University Medical School. The new estrogen proved to be about one-half as active as diethylstilbestrol.

In contrast with these condensations, when *m*- or *p*-cresol was condensed with biacetyl, the reaction took a different course yielding a cyclic ether of a coumarano-coumarane type. Crystalline substances melting at 115° and 196–197°, respectively, were isolated from the products of the latter reactions. They are insoluble in caustic alkali-

lies and accordingly are assumed to have no free phenolic hydroxyl groups.

Baker and McGowan<sup>7</sup> have prepared  $\alpha$ -2,3,5,5'-tetramethylcoumarano-3',2',2,3-coumarane (IVa), m. p. 151°, by dehydrating the  $\alpha$ -pinacol of *o*-acetyl-*p*-cresol (Va) with boiling acetic acid. Although they were unable to dehydrate the corresponding  $\beta$ -pinacol under the same condition, they did obtain a mixture of m. p. 150–183° by treatment with alcohol containing a trace of concentrated hydrochloric acid.

We have found that both the  $\alpha$ - and  $\beta$ -pinacols afford a substance, m. p. 196–197°, upon treatment with a mixture of acetic acid and a trace of sulfuric acid.<sup>8</sup> In view of its alkali-insoluble character together with the analytical figures the product is considered to be the  $\beta$ -isomer of 2,3,5,5'-tetramethylcoumarano-3',2',2,3-coumarane (IVa) which the English authors failed to obtain in a pure state. This  $\beta$ -coumarano-coumarane derivative showed no depression of the melting point on admixture with the condensation product obtained from *p*-cresol and biacetyl.

Similar dehydration of the pinacols from 6-acetyl-*m*-cresol (Vb) led to 2,3,6,6'-tetramethylcoumarano-3',2',2,3-coumarane (IVb) and, indeed, depending on the dehydrating conditions mentioned above, either the  $\alpha$ -compound, m. p. 139–140°, or the  $\beta$ -isomer, m. p. 115°, were obtained. The latter was found to be identical with the condensation product between biacetyl and *m*-cresol.

6,6'-Dihydroxy-2,3-dimethylcoumarano-3',2',2,3-coumarane has been reported by Niederl and Nagel<sup>9</sup> in the condensation of biacetyl with resorcinol. The present condensation of *m*- or *p*-cresol with biacetyl seems to take a similar course. These cresols react ortho to the phenolic hydroxyl with biacetyl,<sup>10</sup> while phenol and *o*-cresol react at

(1) Previous paper: Sisido and Nozaki, *THIS JOURNAL*, **70**, 3326 (1948).

(2) Niederl, Niederl and Nagel, *ibid.*, **63**, 1235 (1941).

(3) Matei, *Ber.*, **62**, 2095 (1929).

(4) Adler, v. Euler and Gie, *Arkiv Kemi, Mineral. Geol.*, **18A**, No. 1, 21 pp. (1944). We thank the authors for the reprint.

(5) Price and Mueller, *THIS JOURNAL*, **66**, 634 (1944).

(6) Sisido and Nozaki, *ibid.*, **70**, 776 (1948).

(7) Baker and McGowan, *J. Chem. Soc.*, 559 (1937).

(8) Cf. Gie, *Arkiv Kemi, Mineral. Geol.*, **19A**, No. 11, 15 pp. (1945); *C. A.*, **41**, 1661 (1947).

(9) Niederl and Nagel, *THIS JOURNAL*, **63**, 580 (1941).

(10) The condensation of *m*-alkylphenols with ketones occurs usually ortho to the hydroxyl group. See for example: (a) Niederl, *ibid.*, **50**, 2230 (1928); (b) Niederl and Nagel, *ibid.*, **62**, 324 (1940); (c) Niederl and Ziering, *ibid.*, **62**, 1157 (1940); (d) Baker and Besly, *J. Chem. Soc.*, 1103 (1940).