Iodine as a Carrier in the Bromination of Fluorene in the Dark.—A saturated solution of iodine in carbon tetrachloride was found to contain 0.29 g. in 10 cc. Dilutions of this, 1 to 10, and 1 to 100 were made. Fluorene, 0.01 mole, was added to 10 cc. of the carbon tetrachloride solution and then 10 cc. of a 1 molar solution of bromine in the same solvent was added quickly. The reaction was stopped by the addition of potassium iodide solution as usual. The results are in Table I.

TABLE I

BROMINATION OF FLUORENE IN THE DARK WITH IODINE AS CARRIER

Time, min.	0.29 g.	0.029 g.	0.0029 g.
0.5	79%	..	8
0.5	80	..	..
3.0	89	20	..
3.0	89	19	..

For comparison the same concentration of toluene and bromine in the same solvent were tried with 0.29 g. of iodine. There was no bromination in three minutes.

The bromine used was freed from traces of iodine by prolonged shaking with concentrated sulfuric acid, washing with water, drying over phosphorus pentoxide and fractionally distilling.

The authors acknowledge the interest of Dr. E. Emmet Reid in this research.

DEPARTMENT OF CHEMISTRY
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The Optical Rotatory Power of *epi*-Ergostanol

BY KARL J. SAX, LOUIS DORFMAN[1] AND SEYMOUR BERNSTEIN

In their development of a theory on the relationship between optical rotatory power and constitution of the steroids, Bernstein, Kauzmann and Wallis[2] noted a number of compounds for which large discrepancies existed between observed and calculated values of the optical rotation. For *epi*-ergostanol it was stated that the observed value for this compound was in error by at least 10°.[3] Also it has been pointed out[4] that the C_8-diastereomers, ergostanol and *epi*-ergostanol, do not conform to the rule that the C_8 α-form of any steroid will have a higher positive rotatory power than the corresponding β-form.

Accordingly it was of interest to redetermine the optical rotations of ergostanol and *epi*-ergostanol for evaluating the above discrepancies. The rotation of ergostanol was found to be +15.3° which is in excellent agreement with the recorded values of +15.3°[5] and +15.9°.[6] However, for *epi*-ergostanol we have found the rotation to be +16.9° which is higher than the recorded values of +13.5°[7] and +14.6°.[8]

These results show that the diastereomers, ergostanol and *epi*-ergostanol, do not constitute an exception to the above stated rule. Also it may be assumed that the value (+2300) for the constant, E_l^2, derived from *epi*-cholestanol, and used in the calculation of the rotation of *epi*-ergostanol, is incorrect. Use of *epi*-stigmastanol, $[\alpha]_D$ + 25,[9] as the standard substance, gave a E_l value of 0. Recalculation of the rotation of *epi*-ergostanol with this revised value gave +19.1°, which is in good agreement with the observed rotation of +16.9°.

(1) Present address, William R. Warner and Company, Inc., New York.

(2) Bernstein, Kauzmann and Wallis, *J. Org. Chem.*, **6**, 319 (1941).

(3) All rotations are for sodium D light and chloroform solution.

(4) Bernstein, Hicks, Clark and Wallis, *J. Org. Chem.*, **11**, 646 (1946).

(5) Windaus and Brunken, *Ann.*, **460**, 225 (1928).

(6) Reindel, Walter and Rauch, *Ann.*, **452**, 34 (1927).

(7) Reindel and Detzel, *Ann.*, **475**, 78 (1929).

(8) Windaus, *et al.*, *Ann.*, **477**, 268 (1930).

(9) Dalmer, *et al.*, *Ber.*, **68**, 1814 (1935).

LEDERLE LABORATORIES DIVISION
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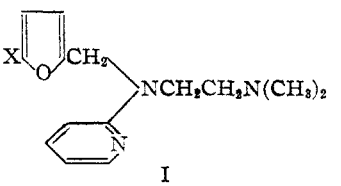
Antihistamine Agents. II. Furan Derivatives

BY J. R. VAUGHAN, JR., AND G. W. ANDERSON

In a continuation of our investigation on the effect of substituting various heterocyclic systems into compounds of known antihistamine activity,[1] we have prepared and tested N,N-dimethyl-N′-(2-pyridyl)-N′-furfurylethylenediamine (I, X = H) and N,N-dimethyl-N′-(2-pyridyl)-N′-(5-bromofurfuryl)-ethylenediamine (I, X = Br). The first of these (I, X = H) has been reported by Viaud to be an active antihistaminic.[2] The compounds may be considered as oxygen analogs of the thiophene substituted ethylenediamines previously reported in which the furan nucleus replaces the thiophene group.



I

They were synthesized by an initial reaction of furfuryl alcohol, or 5-bromofurfuryl alcohol, with thionyl chloride in toluene solution at −30 to −40°. The intermediate furfuryl chlorides obtained are extremely unstable[3] and were not isolated but were treated directly with the sodium salt of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine, also in toluene solution, at low tempera-

(1) Clapp, Clark, Vaughan, English and Anderson, THIS JOURNAL, **69**, 1549 (1947).

(2) Viaud, *Technologie Produits Pharmaceutiques*, **2**, 53 (1947); *Drug Trade News*, **22** [9], 63 (1947). We have been unable to obtain the original article but have been advised that the name "methylfurfuryl" used by the *Drug Trade News* is intended to mean "furylmethyl" or furfuryl.

(3) Gilman and Vernon, THIS JOURNAL, **46**, 2576 (1924).

ture. Two molar equivalents excess of the sodium salt were used to neutralize the acidic by-products present from the chlorination reaction. After hydrolysis of the reaction mixture, the desired products were obtained by distillation of the toluene layer *in vacuo* as light yellow, unstable oils which decompose rapidly at room temperature and slowly even at −80°. In the presence of mineral acids, the compounds are destroyed within a few seconds to yield blue–violet solutions or tars. They are stable, however, to alkali and to organic acids and were isolated crystalline as their colorless, non-hygroscopic dihydrogen citrate salts.

When tested in guinea pigs by the histamine aerosol technique or by intravenous injection of histamine,[4] the furfuryl derivative (I, X = H) was found to be equally as effective as N,N-dimethyl - N′ - (2 - pyridyl) - N′ - benzylethylenediamine (Pyribenzamine)[5] in protecting against death while the bromofurfuryl derivative (I, X = Br) was only slightly less effective. The results on the furfuryl derivative are in agreement with those reported by Viaud.[2] When tested for acute, twenty-four-hour toxicity by intraperitoneal injection in white mice, the furfuryl derivative had the same toxicity as Pyribenzamine, whereas the bromofurfuryl derivative was approximately 50% less toxic.

We are indebted to Dr. J. T. Litchfield, Jr., and to the Misses Maxine R. Adams and Marion S. Jaeger of these Laboratories for the pharmacological data reported here.

Experimental[6]

N,N-Dimethyl-N′-(2-pyridyl)-N′-furfurylethylenediamine.—To a suspension of 36 g. (1.5 moles) of sodium hydride in 1500 cc. of dry toluene was added 248 g. (1.5 moles) of N,N - dimethyl - N′ - (2 - pyridyl) - ethylenediamine[5,7] and the mixture heated at reflux for one and one-half hours, or until the evolution of hydrogen ceased, and then cooled to 15° in an ice-bath. In a separate flask, 49 g. (0.5 mole) of redistilled furfuryl alcohol was placed in 300 cc. of dry toluene and the solution cooled with stirring to −30° in a Dry Ice–acetone-bath. A solution of 59.5 g. (0.5 mole) of thionyl chloride in 50 cc. of toluene was then added dropwise at this temperature over a twenty to thirty minute period while passing a steady stream of nitrogen through the apparatus. A large amount of tar and resin was formed toward the end of the addition. The clear, dark green toluene solution was decanted from the resin and added over a five- to ten-minute period to the previously prepared suspension of the sodium salt of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine also in toluene. The resulting exothermic reaction was maintained at 15° for forty-five minutes. The reaction mixture was then allowed to warm to room temperature and hydrolyzed cautiously with 750 cc. of water. The toluene layer was separated, concentrated, and the residue distilled *in vacuo* to yield 30.2 g. (25%) of impure product as a light yellow oil, b. p. 100–140° (0.4 mm.). Also obtained was 137.5 g. (83% of theoretical recovery) of the excess starting ethylenediamine, b. p. 70–85° (0.5 mm.). The crude material was refractionated to yield 18.6 g. (15%) of pure product, b. p. 136–137° (0.7 mm.); $n^{30}D$ 1.5486. This is obtained in 95% yield as a stable, non-hygroscopic dihydrogen citrate by precipitation of the salt from alcohol solution with ether and recrystallization from methyl ethyl ketone, m. p. 95–97°.

Anal. Calcd. for $C_{14}H_{19}N_3O \cdot C_6H_8O_7$: C, 54.91; H, 6.22; N, 9.61. Found: C, 54.96, 55.22; H, 5.98, 6.06; N, 9.34, 9.49.

N,N-Dimethyl-N′-(2-pyridyl)-N′-(5-bromofurfuryl)-ethylenediamine.—The sodium salt of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine was prepared as in the previous example from 13 g. (0.54 mole) of sodium hydride and 89 g. (0.54 mole) of the diamine in 200 cc. of toluene. In a separate flask 32 g. (0.18 mole) of 5-bromofurfuryl alcohol[8] dissolved in 150 cc. of toluene was treated with 21.5 g. (0.18 mole) of thionyl chloride in 50 cc. of toluene at −30°, as described above, and the reaction mixture was added to the previously prepared suspension of the sodium salt of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine. After reaction and hydrolysis were complete, the product was isolated as before and distilled *in vacuo* to yield 26.5 g. (44% of the theoretical recovery) of the excess ethylenediamine used, and 16 g. (28%) of impure product, b. p. 140–175° (1 mm.). This material was refractionated to yield 10 g. (17%) of pure product as a greenish yellow oil, b. p. 156–158° (0.5 mm.); $n^{30}D$ 1.5603. Treatment of this with one equivalent of alcoholic citric acid and precipitation with ether gave the stable dihydrogen citrate salt in 97% yield. After recrystallization from methyl ethyl ketone, the colorless crystals melt at 105–107°.

Anal. Calcd. for $C_{14}H_{18}BrN_3O \cdot C_6H_8O_7$: C, 46.52; H, 5.08; Br, 15.48; N, 8.14. Found:[9] C, 46.88, 46.91; H, 5.12, 5.28; Br, 15.41, 15.31; N, 8.14, 8.24.

(4) Litchfield, Adams, Goddard, Jaeger and Alonso, *Bull. Johns Hopkins Hosp.*, **81**, 55 (1947).

(5) Huttrer, Djerassi, Beears, Mayer and Scholz, THIS JOURNAL, **68**, 1999 (1946).

(6) All melting points are corrected. The microanalyses were carried out in these Laboratories under the direction of Dr. J. A. Kuck, to whom we are indebted for these data.

(7) Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945).

(8) Prepared from 5-bromofurfural [Gilman and Wright, THIS JOURNAL, **52**, 1170 (1930)] by the crossed Cannizzaro reaction method of Davidson and Bogert, *ibid.*, **57**, 905 (1935); *cf.* Chute, Orchard and Wright, *J. Org. Chem.*, **6**, 157 (1941).

(9) Carbon values were obtained using silver pumice mixed with copper oxide as a substitute for the copper oxide–lead chromate layer in the Pregl microcombustion tube. Unsatisfactory high values were consistently obtained when the conventional tube filling was used.

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Concerning the Acylation of Kojic Acid at Elevated Temperatures

BY L. L. WOODS

The acylation of kojic acid at elevated temperatures with acetic anhydride in a modified Nencki[1] reaction is anomalous. The reaction described produces a ketone, I, having an empirical formula $C_{10}H_{18}O_7$. Under hydrolytic conditions the latter compound loses an acetyl group (compound II). Data are lacking for assignment of structures to these two compounds, although some pertinent observations should be noted. The compounds do not have the phenolic character of the parent compound and do contain one aceto group as evidenced by their reactivity toward carbonyl reagents.

(1) Blatt, "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, New York, N. Y., p. 304.