analogs of known antihistaminic agents have been prepared and evaluated.

Whereas N,N-dimethyl-N′-phenyl-N′-(2-thenyl)-ethylenediamine (2740 R. P.) (II), the thiophene analog of Antergan,[5] recently was reported to be devoid of antihistaminic activity,[6] our compound proved to be approximately two-thirds as active as Antergan. The diethyl analog (III) of (II) is only one-fifth as active as Antergan; (I) is more active than (II) and has given encouraging results in man.

2-[N-(2′-Thenyl)-anilinomethyl]-2-imidazoline (IV), the thiophene analog of Antistine,[7] 2-(N-benzylanilinomethyl)-2-imidazoline, was found to be only 5% as active as Antergan, and the thiophene analog (V) of N-(2-pyridyl)-benzamide[8] proved to be inactive.

The products were tested for pharmacologic and therapeutic activity in the Lilly Research Laboratories.

Experimental[9]

N,N-Dimethyl-N′-phenyl-N′-(2-thenyl)-ethylenediamine (II).—N,N-Dimethyl-N′-phenylethylenediamine (VI)[10] (26.6 g.) in 100 cc. of benzene was converted to the monohydrochloride, 10.7 g. of 2-thenyl chloride in 35 cc. of benzene was added, and the mixture was stirred at 65–70° for six hours. The mixture was agitated with 80 g. of 25% sodium hydroxide solution at 60° for one hour, and the benzene layer was separated. A dark-colored liquid, weight 15 g., was present between the aqueous and benzene layers; this probably was a quaternary compound resulting from reaction of 2-thenyl chloride with the dimethylamino group. The benzene layer yielded upon distillation 15.8 g. of recovered (VI) and 7.0 g. (42.5%) of (II), a yellow oil, b. p. 185–186° (8 mm.).

The base (II), dissolved in a 3:1 solution of carbon tetrachloride and acetone, upon treatment with hydrogen chloride yielded the monohydrochloride, which was recrystallized from acetone containing a small amount of water; m. p. 183–184°.

Anal. Calcd. for $C_{15}H_{20}N_2S\cdot HCl$: Cl, 11.9. Found: Cl, 11.9.

When it was endeavored to prepare (II) by the procedure used for (III), the quaternary salt was the chief product. Attempts to prepare (II) by the reaction of N-(2-thenyl)-aniline (VII) and N,N-dimethyl-β-chloroethylamine hydrochloride proved unsuccessful, since none of the high boiling amines obtained corresponded in properties with those of (II).

N,N-Diethyl-N′-phenyl-N′-(2-thenyl)-ethylenediamine (III).—A solution of 6.6 g. (0.05 mole) of 2-thenyl chloride in 65 cc. of benzene was dropped into a solution of 19.2 g. (0.10 mole) of N,N-diethyl-N′-phenylethylenediamine (VIII)[11] in 100 cc. of butanol at 25° during two hours. The mixture was stirred at 25° for twenty hours, treated with excess aqueous alkali, and the organic layer was separated and distilled. Nine grams of (VIII) was recovered and 9 g. (59%) of (III)[12] was obtained; b. p. 157–160° (2 mm.).

When (III) was treated with hydrogen chloride as under (II), the dihydrochloride was precipitated as an oil which soon solidified. After recrystallization from aqueous acetone, the salt melted at 144–145°.

Anal. Calcd. for $C_{17}H_{24}N_2S\cdot 2HCl$: Cl, 19.6. Found: Cl, 19.7.

N-(2-Thenyl)-aniline (VII).—One mole (93 g.) of aniline was heated with agitation at 95–100° as 39.8 g. (0.3 mole) of 2-thenyl chloride was added in one and one-half hours. The mixture was maintained at 95–100° for four hours, cooled and treated with aqueous sodium hydroxide (0.3 mole). The oil layer was separated, washed with water, and dried over sodium sulfate. The crude product was fractionated under reduced pressure. After a forerun of recovered aniline, there was obtained 43 g. (76%) of (VII); b. p. 150–155° (4 mm.), $n^{20}D$ 1.6295.

Anal. Calcd. for $C_{11}H_{11}NS$: N, 7.4. Found: N, 7.8.

Ethyl N-Phenyl-N-(2-thenyl)-aminoacetate (IX).—A mixture of 30 g. (0.16 mole) of (VII) and 9.8 g. (0.08 mole) of ethyl chloroacetate was heated at 120° for six hours. The mixture was cooled, treated with aqueous sodium hydroxide (0.1 mole), benzene was added, and the organic layer was separated, washed with water and dried. After removal of the solvent, the crude product was fractionated; yield, 10 g. (45%) of (IX), b. p. 155–165° (0.3 mm.).

Anal. Calcd. for $C_{15}H_{17}NO_2S$: N, 5.1. Found: N, 5.1.

2-[N-(2′-Thenyl)-anilinomethyl]-2-imidazoline (IV).—A mixture of 13 g. (0.047 mole) of (IX) and 25 g. of ethylenediamine (97.4% assay) was heated at the boiling point as ethanol, water, and some ethylenediamine were removed slowly through a small fractionating column over a period of twenty hours. The vapor temperature at the end was 116° and the batch temperature rose to 130–135°. After removing the excess ethylenediamine, the residue was fractionated to yield 7 g. (55%) of (IV), b. p. 190–200° (0.4 mm.). The base was converted to the monohydrochloride, which was recrystallized from acetone-ethanol; m. p. 219–220°.

Anal. Calcd. for $C_{15}H_{17}N_3S\cdot HCl$: Cl, 11.5. Found: Cl, 11.8.

N-(2-Pyridyl)-2′-thiophenecarboxamide (V).—To a solution of 47 g. (0.5 mole) of 2-aminopyridine in 250 cc. of dry toluene 12 g. (0.5 mole) of sodium hydride was added, and the mixture was warmed slowly to reflux as hydrogen was evolved. After refluxing for one and one-half hours, the resulting slurry of the sodium derivative of 2-aminopyridine was cooled to 80° and 73.3 g. (0.5 mole) of 2-thenoyl chloride[13] was added dropwise in one hour. The mixture then was refluxed for two hours, cooled, filtered and the salt cake was washed with toluene. The filtrate upon distillation yielded 87 g. (85%) of (V), b. p. 165–170° (2 mm.). The product, which solidified on cooling, was converted to the monohydrochloride in methyl ethyl ketone–ethanol mixture and the salt was allowed to crystallize; m. p. 215–217°, with slight previous softening.

Anal. Calcd. for $C_{10}H_8N_2OS\cdot HCl$: Cl, 14.7. Found: Cl, 14.6.

(5) Halpern, *Arch. intern. pharmacodynamie*, **68**, 339 (1942).

(6) Viaud, *Produits Pharmaceutiques*, **2**, 53 (1947).

(7) Meier and Bucher, *Schweiz. med. Wochschr.*, **76**, 294 (1946); Schindler, *ibid.*, **76**, 300 (1946); abstract in *J. Am. Med. Assoc.*, **131**, 1536 (1946).

(8) Mayer, *J. Allergy*, **17**, 153 (1946).

(9) All melting points are corrected.

(10) Huttrer, Djerassi, Beears, Mayer and Scholz, THIS JOURNAL, **68**, 2001 (1946).

(11) Dewar, *J. Chem. Soc.*, 622 (1944).

(12) A sample of this base was prepared by Mr. D. G. Sheets.

(13) Blicke and M. F. Zienty, THIS JOURNAL, **63**, 2945 (1941); Jones and Hurd, *ibid.*, **43**, 2444 (1921).

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The Vibration Spectrum of Nitric Acid

BY OTTO REDLICH

The fairly weak Raman line 1538 cm.$^{-1}$ in the Raman spectrum of pure nitric acid was interpreted[1] as due to the out-of-plane vibration for

(1) O. Redlich and L. E. Nielsen, THIS JOURNAL, **65**, 654 (1943).

the reason that the other eight lines and vibrations were satisfactorily correlated. The large difference between 1538 and the frequency 830 of the out-of-plane vibration of the nitrate ion was pointed out.

M. Freymann and R. Freymann[2] recently reported a moderately strong double band 771 and 792 cm.$^{-1}$ in the infrared spectrum of nitric acid vapor corresponding to a weak line 768 in the Raman spectrum of Simon and Hoeppner.[3] The correlation of this band with the out-of-plane vibration, mentioned but not finally adopted by Freymann and Freymann, is strongly supported by the fact that 1538 cannot be correlated with any other vibration. Obviously the Raman line 1538 represents not the fundamental but the first harmonic of the out-of-plane vibration.

With this change the earlier analysis of the vibration spectrum appears to represent all known data in a satisfactory way. Some of our conclusions coincide with earlier results of Mathieu and Massignon.[4]

The somewhat unusual intensity of 1538 can hardly be explained by accidental degeneracy with vibration 4 (1669 cm.$^{-1}$) since the selection rules for C_{2v} do not permit this resonance. A slight interaction with 1301 cm.$^{-1}$ appears to be possible.

The author is obliged to Professor G. Herzberg for a helpful discussion.

(2) M. Freymann and R. Freymann, *Compt. rend.*, **222**, 1339 (1946).

(3) A. Simon and H. Hoeppner, *Kolloid-Z.*, **85**, 8 (1939).

(4) J. P. Mathieu and D. Massignon, *Ann. phys.*, **16**, 5 (1941).

SHELL DEVELOPMENT COMPANY
EMERYVILLE, CALIFORNIA RECEIVED JUNE 7, 1947

The Allergenic Principles of Poison Ivy. VI. Note on the Synthesis of 3-Substituted Catechols[1,1a]

BY HOWARD S. MASON

In this study, 3-bromocatechol and its diphenylmethylene ether have been synthesized to provide the nuclear fragment for the synthesis of unsaturated allergens related to the catechols of poison ivy. 2,3-Dimethoxydihydrocinnamyl halides have also been prepared; these substances proved refractory toward demethylation.

Experimental

2,3-Dimethoxybromobenzene.—2,3-Dimethoxybenzoic acid was prepared from 2,3-dimethoxybenzaldehyde[2] in 84% yield by permanganate oxidation.[3] This substance was converted to 2,3-dimethoxybenzamide in 88% yield.[4] The amide furnished 2,3-dimethoxyaniline in 83% yield by adapting to the synthesis the procedure for the Hofmann rearrangement worked out by Buck and Ide.[5] Bigelow's procedure for the Sandmeyer replacement[6] was then modified for the preparation of 2,3-dimethoxybromobenzene; this resulted in a considerably improved yield. To a cuprous bromide solution prepared in 275 ml. of water was added a solution of 2,3-dimethoxybenzenediazonium sulfate prepared from 52 g. of 2,3-dimethoxyaniline hydrochloride. The addition required two hours; the reaction mixture was kept boiling vigorously and the product steam-distilled out as formed. The principal product distilled at 111–113° at 9 mm. and weighed 53 g. (89%). After cooling overnight, the compound solidified. It then melted at 22.7–23.2°. Simonsen and Rau[7] report a boiling point of 114° at 5 mm. Their product did not crystallize.

Anal. Calcd. for $C_8H_9O_2Br$: C, 44.3; H, 4.18. Found: C, 44.5; H, 4.45.

The compound was further identified by the preparation of 2,3-dimethoxy-5-nitrobromobenzene, which melted at 112.3–112.7°. The reported melting point is 112–113°.[7]

3-Bromocatechol.—2,3-Dimethoxybromobenzene was most efficiently demethylated by treating this ether with aluminum trichloride in chlorobenzene.[8] To 50 ml. of dry chlorobenzene was added 5.0 g. of 2,3-dimethoxybromobenzene and 5.0 g. of anhydrous aluminum trichloride. The mixture was refluxed for three and one-half hours, then poured into water and extracted with ether (400 ml.). The ether solution was dried and the solvent evaporated; the residue was then distilled. The principal fraction was an oil which boiled at 118–120° at 9 mm. After crystallization from isoöctane–pentane, long silky needles melting at 40.5–41.5° were obtained. The product weighed 3.5 g. (80%).

Anal. Calcd. for $C_6H_5O_2Br$: C, 38.1; H, 2.68. Found: C, 38.3; H, 2.71.

2,3-Diacetoxybromobenzene.—This substance crystallized from aqueous methanol in needles melting at 83–84°.

Anal. Calcd. for $C_{10}H_9O_4Br$: C, 44.0; H, 3.32. Found: C, 44.1; H, 3.37.

3-Bromocatechol Diphenylmethylene Ether.—3-Bromocatechol (19 g.) and dichlorodiphenylmethane (24 g.) were mixed with a little dry benzene and warmed on a hot-plate until hydrogen chloride no longer evolved. The product crystallized from methanol in white tablets melting at 75.5–76°; the yield was 97%.

Anal. Calcd. for $C_{19}H_{13}O_2Br$: C, 64.6; H, 3.71. Found: C, 64.6; H, 3.68.

Ethyl 2,3-Dimethoxycinnamate.—The procedure for the Claisen reaction developed by Marvel and King[9] was adapted to this synthesis. The principal product from 83 g. of 2,3-dimethoxybenzaldehyde distilled at 195–197° at 15 mm. and weighed 101 g. (86%). For identification, this ester was hydrolyzed to 2,3-dimethoxycinnamic acid, m. p. 179–180°; this m. p. has previously been reported to be 181°.[10]

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.5; H, 5.77. Found: C, 63.6; H, 5.79.

Ethyl 2,3-Dimethoxydihydrocinnamate and 2,3-Dimethoxydihydrocinnamyl Alcohol.—Ethyl 2,3-dimethoxycinnamate was hydrogenated over copper chromite catalyst according to the general directions of Folkers and Adkins.[11]

(1) Article not copyrighted. For the fifth paper in this series, see Mason, THIS JOURNAL, **67**, 1538 (1945).

(1a) The author regrets that the work of Keil, Wasserman and Dawson, *J. Exp. Med.*, **80**, 275 (1944), was not mentioned in the last article.

(2) The starting material was generously furnished by the Monsanto Chemical Company.

(3) Perkin and Robinson, *J. Chem. Soc.*, **105**, 2383 (1914).

(4) Mauthner, *J. prakt. Chem.*, **149**, 328 (1937).

(5) Buck and Ide, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, editor, John Wiley and Sons, Inc., London, 1943, p. 44.

(6) Bigelow, "Organic Syntheses," 2nd ed., Coll. Vol. I, H. Gilman and A. H. Blatt, editors, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 136.

(7) Simonsen and Rau, *J. Chem. Soc.*, **113**, 785 (1918).

(8) Dawson, Wasserman and Keil, THIS JOURNAL, **68**, 534 (1946).

(9) Marvel and King, "Organic Syntheses," 2nd ed., Coll. Vol. I. H. Gilman and A. H. Blatt, editors, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 252.

(10) Chakravarti, *J. Indian Chem. Soc.*, **6**, 207 (1929).

(11) Folkers and Adkins, THIS JOURNAL, **54**, 1145 (1932).