[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

Derivatives of α,α-Dimethylphenethylamine[1]

BY G. BRYANT BACHMAN, HENRY B. HASS AND GERARD O. PLATAU[2]

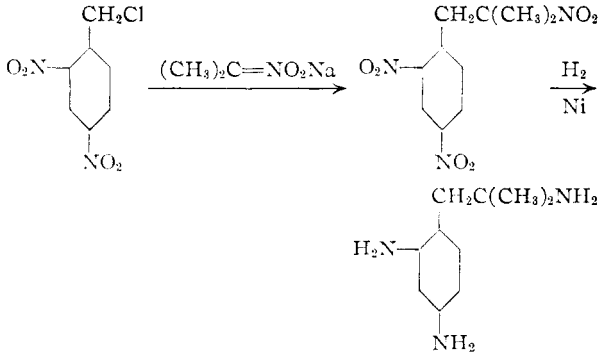
RECEIVED MARCH 19, 1954

The synthesis of a series of derivatives of α,α-dimethylphenethylamine hydrochloride with various substituents in the phenyl ring is described. These compounds were prepared for testing as pressor amines but only one—the *p*-aminophenyl derivative—showed slight activity.

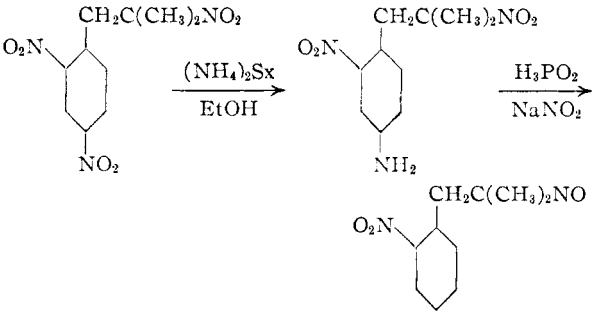
Derivatives of phenethylamine with the amino group on a tertiary alkyl carbon have received little attention. They are especially interesting since they should strongly resist the enzymatic deamination reaction shown to limit the duration of sympathomimetic activity. They cannot be deaminated by living organisms in the usual manner, that is, by oxidation to the corresponding imine followed by hydrolysis, since there is no hydrogen on the carbon atom to which the amino group is attached.

This investigation deals with the synthesis of a series of derivatives of α,α-dimethylphenethylamine with various substituents on the phenyl ring. A convenient approach to their preparation was found to proceed through the corresponding nitrophenylnitropropanes. These were prepared by the method of Hass, Berry and Bender[3,4] which involves alkylation of the sodium salt of 2-nitropropane with nitrobenzyl chlorides. Since *o*-nitrobenzyl chloride is difficult to separate pure from the direct nitration of benzyl chloride, and since other methods employed for the synthesis of this chloride give poor yields, an attempt was made to substitute the more readily obtainable *o*-nitrobenzyl bromide for the chloride. Unfortunately the bromide caused only O-alkylation instead of C-alkylation of the nitronic acid and the desired compound could not be obtained this way.

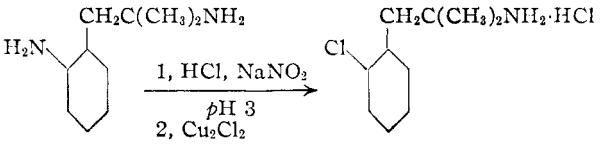
It was found that reduction of nitrophenyl nitroalkanes, obtained from nitrobenzyl chlorides and 2-nitropropane, produced aminophenylalkylamines having the desired structure.



In this manner 1-(*o*-aminophenyl)-2-methyl-2-propylamine, 1-(*p*-aminophenyl)-2-methyl-2-propylamine and 1-(2′,4′-diaminophenyl)-2-methyl-2-propylamine were prepared by low pressure (5 atm.) hydrogenation at 100° with Raney nickel. These amines were converted to the water-soluble hydrochloride salts for physiological testing purposes. The *p*-nitro group in 1-(2′,4′-dinitrophenyl)-2-methyl-2-nitropropane was reduced selectively by ammonium polysulfide. The structure of the product was proven by deamination to 1-(*o*-nitrophenyl)-2-methyl-2-nitropropane.



The aromatic amino group in the various reduction products was also replaced by other functional groups after diazotization under controlled conditions. This approach follows the method of Kornblum and Iffland[5] who found that in a sufficiently acidic medium (*p*H 3 or less) an aryl amino group can be diazotized selectively and then replaced by hydrogen on treatment with hypophosphorous acid even in the presence of an aliphatic amino group. We have now found that in the same fashion an aromatic amino group can be replaced by chlorine, hydroxy and methoxy groups without affecting the aliphatic amino group, *e.g.*



In this manner water-soluble hydrochloride salts of 1-(*o*-chlorophenyl)-2-methyl-2-propylamine, 1-(*p*-chlorophenyl)-2-methyl-2-propylamine, 1-(*p*-hydroxyphenyl)-2-methyl-2-propylamine and 1-(*p*-methoxyphenyl)-2-methyl-2-propylamine were prepared (Table I).

1-(2′-Nitro-4′-aminophenyl)-2-methyl-2-nitropane was converted to 1-(2′-nitro-4′-hydroxyphenyl)-2-methyl-2-nitropropane by diazotization and hydrolysis. The nitro group in the phenyl ring stabilizes the diazonium salt and consequently slows its decomposition to a considerable degree, thus facilitating its coupling with the phenolic

(1) An abstract of a thesis by Gerard O. Platau, submitted to the Faculty of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1950. Presented before the Medicinal Division of the American Chemical Society, Kansas City, Mo., March, 1954.

(2) Abbott Laboratories Research Fellow, 1948–1949.

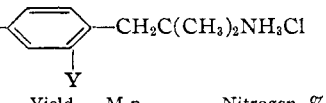
(3) H. B. Hass, E. J. Berry and M. L. Bender, THIS JOURNAL, **71**, 2290 (1949).

(4) H. B. Hass and M. L. Bender, *ibid.*, **71**, 3482 (1949).

(5) N. Kornblum and D. C. Iffland, *ibid.*, **71**, 2137 (1949).

TABLE I

DERIVATIVES OF α,α-DIMETHYLPHENETHYLAMINE HYDROCHLORIDE



Substituents X	Y	Yield, %	M.p., °C.	Nitrogen, % Calcd.	Found
H	NH_3Cl	82	233	11.8	11.5
NH_3Cl	H	80	315	11.8	12.0
H	Cl	44	181	6.36	6.16
Cl	H	50	231	6.36	6.45
OH	H	33	208	6.93	6.90
OCH_3	H	56	162	6.51	6.65
NH_3Cl	NH_3Cl	72	211	14.5	14.5
OH	NH_3Cl	65	184	9.69[a]	9.73

[a] Calculated for the dihydrate.

product as soon as any of the latter is formed and producing an azo dye. This dye formation was suppressed to some extent by carrying out the hydrolysis in a dilute sulfuric acid solution beneath a layer of xylene. The xylene soluble product was isolated and then successfully reduced to 1-(2'-amino-4'-hydroxyphenyl)-2-methyl-2-propylamine.

Pharmacological Testing.—According to tests conducted by the Abbott Research Laboratories, 1-(*p*-aminophenyl)-2-methyl-2-propylamine dihydrochloride showed some pressor activity. The other compounds were inactive. The testing method used involved intravenous injection of the compound into a cat anesthetized with a mixture of phenobarbital and pentobarbital noting any change in blood pressure which resulted.

Experimental[6]

***o*-Nitrobenzyl Halides.**—The *p*-nitrobenzyl chloride (33% yield) and the 2,4-dinitrobenzyl chloride (70% yield) used were readily prepared by the nitration of benzyl chloride with mixed acid or fuming nitric and fuming sulfuric acids, respectively; the *o*-nitrobenzyl chloride, formed at the same time as the *para* isomer when mixed acid was employed, could not be isolated from the reaction mixture by practical procedures. We have investigated its preparation and that of its bromo analog by other methods employing *o*-nitrotoluene as the starting material with the following results: (a) Direct chlorination[7] at 120–130° for 96 hours with S_2Cl_2 as catalyst gave low yields (4.0%). (b) Chlorination with hypohalite ion in strongly basic aqueous solution at zero degrees gave no product. (c) The best procedure found for the preparation of *o*-nitrobenzyl chloride was: oxidation of *o*-nitrotoluene to *o*-nitrobenzal diacetate with chromium trioxide[8] (23% yield), hydrolysis to the aldehyde with 15 *N* sulfuric acid (70% yield), reduction to *o*-nitrobenzyl alcohol with $Al(i\text{-}OC_3H_7)_3$ (90% yield), and conversion to the desired halide with PCl_5 in $CHCl_3$ at zero degrees (80% yield); over-all yield 11.6%. (d) Bromination with N-bromosuccinimide[5,9] in the presence of dibenzoyl peroxide at 78° for 12 hours gave a 46% yield of *o*-nitrobenzyl bromide.

2-Nitrobenzyl-2-nitropropanes.—The condensations of nitrobenzyl chlorides with 2-nitropropane followed the procedures of Hass, *et al.*[3,4] The yields obtained were in the range reported. Unfortunately the readily prepared *o*-nitrobenzyl bromide gave oxygen-alkylation only and no carbon-alkylation product could be isolated.

1-(2',4'-Diaminophenyl)-2-methyl-2-propylamine Trihydrochloride.—1-(2',4'-Dinitrophenyl)-2-methyl-2-nitropropane[4] (3.00 g., 0.011 mole), Raney nickel (0.5 g.) and 60 ml. of ethanol were placed in a glass pressure bottle enclosed in a steam jacket. The reaction mixture was subjected to hydrogenation at 4.8 atm. for six hours at 100°. The catalyst was filtered from the mixture, ethanol was removed under reduced pressure, and the residual oil was taken up in ether, treated with Norit and dried. Addition of anhydrous hydrogen chloride to the ether extract followed by further purification (dissolution in water, addition of base, extraction with ether, and addition of dry hydrogen chloride gas) gave 1-(2',4'-diaminophenyl)-2-propylamine-trihydrochloride.

1-(2'-Nitro-4'-aminophenyl)-2-methyl-2-nitropropane. (a) **Reduction.**—1-(2',4'-Dinitrophenyl)-2-methyl-2-nitropropane[4] (14.0 g., 0.052 mole), ethanol (80 ml.), ammonium chloride (19.6 g., 0.372 mole) and 4 ml. of 28% ammonium hydroxide were heated to 75°. While stirring, $Na_2S\cdot 9H_2O$ (41.2 g., 0.172 mole) and 2 g. of sulfur were added, and the reaction mixture was refluxed for one hour. The mixture was cooled, filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in anhydrous ether and filtered; the ether solution was decolorized by passage through a 9-inch Norit column. The ether was removed under reduced pressure and the residue was recrystallized from ethanol; m.p. 97°, yield 4.2 g. (34%).

Anal. Calcd. for $C_{10}H_{13}N_3O_4$: N, 17.57. Found: N, 17.62.

(b) **Proof of Structure by Deamination.**—1-(2'-Nitro-4'-aminophenyl)-2-methyl-2-nitropropane (2.0 g., 0.008 mole) was dissolved in 50% hypophosphorous acid (20 g., 0.15 mole) and 15 ml. of water. Sodium nitrite (0.70 g., 0.010 mole) dissolved in 3 ml. of water was added dropwise with stirring at 5°. The solution was placed in a refrigerator for three hours and then kept at room temperature for 24 hours. The suspension was extracted with ether; the ether extract was washed with 20% sodium hydroxide, dried over potassium carbonate and the ether removed under reduced pressure. The residue was recrystallized from petroleum ether (35–37°). 1-(*o*-Nitrophenyl)-2-methyl-2-nitropropane was obtained; yield 0.9 g. (50%), m.p. 54°, lit. m.p. 54–55°.[4]

1-(*p*-Chlorophenyl)-2-methyl-2-propylamine Hydrochloride.—1-(*p*-Aminophenyl)-2-methyl-2-propylamine[3] (4.0 g., 0.024 mole) was dissolved in 9 ml. of 37% hydrochloric acid (0.10 mole) and 40 ml. of water. Sodium nitrite (2.0 g., 0.030 mole) dissolved in 20 ml. of water was added dropwise with stirring at 5°. The cold diazonium solution was rapidly added at 0° to a well-stirred acidic solution of freshly prepared cuprous chloride (3.0 g., 0.030 mole). The cold solution was slowly allowed to reach room temperature and finally was heated to 60°. The suspension was made somewhat basic and extracted with ether. The ether extract was treated with Norit and dried. Addition of anhydrous hydrogen chloride to the ether extract gave 1-(*p*-chlorophenyl)-2-methyl-2-propylamine hydrochloride.

1-(*o*-Chlorophenyl)-2-methyl-2-propylamine Hydrochloride.—This salt was prepared from 1-(*o*-aminophenyl)-2-methyl-2-propylamine in the same manner as its *para* isomer.

1-(*p*-Hydroxyphenyl)-2-methyl-2-propylamine Hydrochloride.—1-(*p*-Aminophenyl)-2-methyl-2-propylamine[3] (3.0 g., 0.018 mole) was dissolved in 150 ml. of water containing 4.1 ml. of 96% sulfuric acid (0.072 mole). Sodium nitrite (1.4 g., 0.020 mole) dissolved in 20 ml. of water was added dropwise with stirring at 5°. The cold diazonium solution was added slowly below the surface of a well-stirred boiling solution of 3 ml. of 96% sulfuric acid in 200 ml. of water. The reaction mixture was made slightly basic after cooling, and then neutralized with carbon dioxide. The aqueous suspension was extracted repeatedly with ether, the ether extract treated with Norit and dried. Addition of anhydrous hydrogen chloride to the ether extract gave 1-(*p*-hydroxyphenyl)-2-methyl-2-propylamine hydrochloride.

1-(*p*-Methoxyphenyl)-2-methyl-2-propylamine Hydrochloride.—1-(*p*-Aminophenyl)-2-methyl-2-propylamine[3] (4.0 g., 0.024 mole) was dissolved in 100 ml. of methanol and 9 ml. of 37% hydrochloric acid (0.10 mole). Sodium nitrite (2.0 g., 0.030 mole) dissolved in 3 ml. of water was added dropwise with stirring at 5°. After two hours the mixture was allowed to reach room temperature and was then refluxed for three more hours. The material was cooled, filtered and the methanol was removed under reduced pressure. The residue was dissolved in water, made somewhat alkaline and extracted with ether. The ether extract was treated with Norit and dried. Addition of

(6) All melting points are corrected; microanalyses by Dr. H. Galbraith.

(7) Vanino, "Handbuch der Präparativen Chemie," Vol. II, Edwards Bros., Inc., Ann Arbor, Mich., 1943, p. 459.

(8) A. H. Blatt, "Organic Synthesis," Vol. XXIV, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 75.

(9) K. Ziegler, *Ann.*, **551**, 80 (1942).

anhydrous hydrogen chloride to the ether solution gave 1-(*p*-methoxyphenyl)-2-methyl-2-propylamine hydrochloride.

1-(2′-Nitro-4′-hydroxyphenyl)-2-methyl-2-nitropropane.—1-(2′-Nitro-4′-aminophenyl)-2-methyl-2-nitropropane (6.0 g., 0.025 mole) was added to a boiling solution of 12 ml. of 37% hydrochloric acid (0.145 mole) and 38 ml. of water. When complete dissolution was accomplished, the solution was cooled to 5°. Sodium nitrite (2.0 g., 0.030 mole) dissolved in 10 ml. of water was added dropwise with stirring. The cold diazonium solution was added slowly to the bottom of a solution of 3 ml. of 96% sulfuric acid in 200 ml. of water covered with a layer of xylene. The solution was stirred intermittently, the temperature being maintained at 95°. The xylene layer was separated and extracted with 5% sodium hydroxide. The alkaline solution was acidified and extracted with ether. The ether extract was treated with Norit, dried and evaporated under reduced pressure. The residue was recrystallized from benzene–petroleum ether (60–70°) giving 1-(2′-nitro-4′-hydroxyphenyl)-2-methyl-2-nitropropane; yield 2.0 g. (33%), m.p. 75–76°.

Anal. Calcd. for $C_{10}H_{12}N_2O_5$: N, 11.62. Found: N, 11.68.

1-(2′-Amino-4′-hydroxyphenyl)-2-methyl-2-propylamine Dihydrochloride.—1-(2′-Nitro-4′-hydroxyphenyl)-2-methyl-2-nitropropane (2.0 g., 0.008 mole) was reduced with Raney nickel and hydrogen. The diamine was converted to its hydrochloride salt. This salt is extremely hygroscopic and was dried at 80° under vacuum; heating to higher temperatures caused decomposition of the material. Two molecules of water of crystallization were retained.

LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

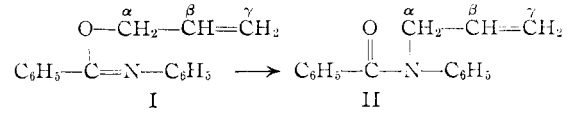
The Rearrangement of N-Phenylbenzimidoyl γ,γ-Dimethylallyl Ether

BY W. M. LAUER AND ROBERT G. LOCKWOOD[1]

RECEIVED MARCH 20, 1954

The N-phenylbenzimidoyl allyl ethers, which have been studied previously, undergo rearrangement to form N-allylbenzanilides. Migration of the allyl group from the oxygen to nitrogen occurs with inversion. The present study describes the rearrangement of N-phenylbenzimidoyl γ,γ-dimethylallyl ether; in this case migration of the γ,γ-dimethylallyl group takes place without inversion and instead of becoming attached to the nitrogen, the group enters an *ortho* position of the aromatic nucleus.

The transformation of N-phenylbenzimidoyl allyl ether (I) to N-allylbenzanilide (II), described in 1937 by Mumm and Möller[2] bears considerable resemblance to the phenyl allyl ether rearrangement.

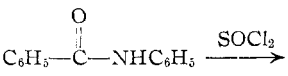


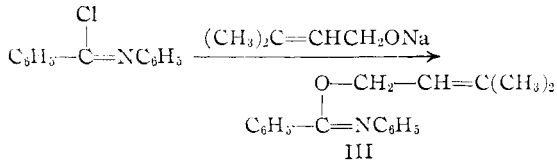
I II

For example, these investigators were able to demonstrate that inversion of the α- and the γ-methylallyl group occurs in this transformation. Thus, N-phenylbenzimidoyl α-*methyl*allyl ether on heating yielded N-γ-*methyl*allylbenzanilide and N-phenylbenzimidoyl γ-*methyl*allyl ether gave N-α-*methyl*allylbenzanilide.

In order to obtain further information concerning the similarity of this transformation and the phenylallyl ether rearrangement it was of interest to learn whether some of the abnormal phenyl allyl ether rearrangements, previously described,[3] are duplicated in the case of the N-phenylbenzimidoyl allyl ethers. N-Phenylbenzimidoyl γ,γ-dimethylallyl ether was chosen for this study since no normal rearrangement product was obtained in the case of the γ,γ-dimethylallyl ether of ethyl *p*-hydroxybenzoate.

N-Phenylbenzimidoyl γ,γ-dimethylallyl ether (III) was obtained as a result of the following series of reactions

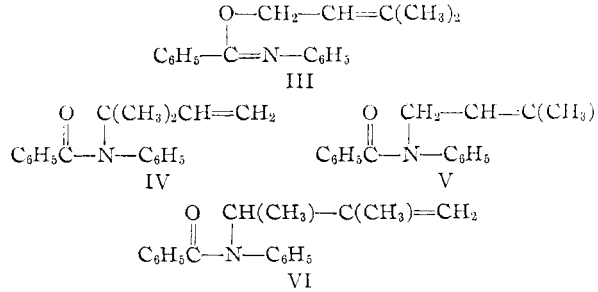




III

γ,γ-Dimethylallyl bromide, prepared by the addition of hydrogen bromide to isoprene, was converted to the corresponding acetate. Hydrolysis of the acetate yielded γ,γ-dimethylallyl alcohol. N-Phenylbenzimidoyl chloride in benzene solution, treated with sodium γ,γ-dimethylallyl oxide gave the desired ether, N-phenylbenzimidoyl γ,γ-dimethylallyl ether (III). This ether on hydrolysis gave the expected products, benzoic acid, aniline and γ,γ-dimethylallyl alcohol.

Pyrolysis of the liquid ether led to the formation of a solid rearrangement product in excellent yield. At the outset three structures (IV, V and VI) were considered as likely possibilities for the product of rearrangement. They were the following substituted N-allylbenzanilides.



III

IV V

VI

However, as the study progressed it became evident that none of these structures was the correct one and that instead of oxygen to nitrogen migration of the substituted allyl group, this group be-

(1) From the Ph.D. Thesis of R. G. Lockwood submitted in June, 1953.

(2) O. Mumm and F. Möller, *Ber.*, **70**, 2214 (1937).

(3) *Inter alia* (a) W. M. Lauer and W. Filbert, THIS JOURNAL, **58**, 1388 (1936); (b) C. D. Hurd and M. A. Pollack, *J. Org. Chem.*, **3**, 550 (1939); (c) W. M. Lauer and O. Moe, THIS JOURNAL, **65**, 289 (1943).