4-Hydroxy-1-(2′,4′,6′-tribromophenyl)-5-methylpyrazole separates from a mixture of boiling chloroform and light petroleum (b. p. 60–80°) in short colorless prisms, m. p. 177.5–178°.

Anal. Calcd. for $C_{10}H_7ON_2Br_3$: Br, 58.4. Found: Br, 58.5.

1-(2′,4′,6′-Tribromophenyl)-5-methylpyrazolyl-4-benzoate separates from boiling alcohol in clusters of colorless rhombic prisms, m. p. 128–130°.

Anal. Calcd. for $C_{17}H_{11}O_2N_2Br_3$: Br, 46.6. Found: Br, 46.5.

Summary

1. The influence of halogens in the nucleus upon the character of the reaction and the nature of the products obtained when arylhydrazines condense with butyl chloral hydrate in various solvents, is described.

2. 2,5-Dichloro-, 3,5-dichloro- and 4,5-dibromophenylhydrazines condensed in alcohol yield the corresponding β-chloro-α-ketobutaldehyde-arylhydrazones.

3. 2,4,6-Trichloro (or bromo-)-phenylhydrazine condensed in water yields α,β-dichlorocrotonaldehyde-2,4,6-trichloro(or bromo-)-phenylhydrazone, but, when condensed in alcohol, a mixture of this unsaturated hydrazone with β-chloro-α-ketobutaldehyde-2,4,6-trichloro (or bromo)-phenylhydrazone.

4. All the β-chloro-α-ketobutaldehyde-arylhydrazones yield the corresponding members of the new series of 4-hydroxy-1-aryl-5-methylpyrazoles when treated with an alcoholic solution of sodium ethoxide.

THE QUEEN'S COLLEGE
OXFORD, ENGLAND

[CONTRIBUTION FROM THE LABORATORIES OF GEORGE PINESS, M.D., LOS ANGELES]

dl-BETA-PHENYLISOPROPYLAMINES

BY GORDON A. ALLES

RECEIVED AUGUST 10, 1931 PUBLISHED JANUARY 7, 1932

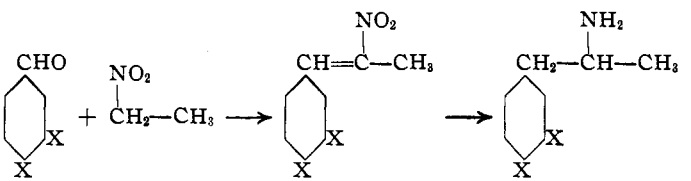
In a previous paper[1] it was demonstrated with *dl*-β-phenylisopropylamine that the introduction of a methyl group into the side chain of β-phenylethylamine furnishes a compound differing from the latter with regard to certain of its effects when administered as a drug compound. The *dl*-β-phenylisopropylamine exerts a pressor effect for a longer period of time and is quite effective after oral administration. Because of the very considerable importance of developing drug compounds of this general type that are active after oral administration, it seemed important to study some derivatives of *dl*-β-phenylisopropylamine having one or more hydroxyl groups introduced into the benzene ring.

The compounds of particular interest for this study, *dl*-β-4-hydroxyphenylisopropylamine and *dl*-β-3,4-dihydroxyphenylisopropylamine, have

[1] Piness, Miller and Alles, *J. Am. Med. Assn.*, **94**, 790 (1930).

been synthesized previously[2] but no satisfactory description of their physiological activities is available. Further, the methods used for synthesis were rather involved and it seemed desirable to develop a simpler synthesis of this type of compound for use in the present study. The syntheses of the parent *dl*-β-phenylisopropylamine and the desired hydroxy derivatives are reported in this paper; the physiological studies of the compounds prepared will be reported in another place.

The synthesis of β-phenylethylamines is often accomplished, especially for proof of structure, by condensing an aromatic aldehyde with nitromethane under suitable conditions and complete reduction of the ω-nitrostyrene so formed, to the hydrogenated amine derivative. It was found that a similar preparative process can be carried out with nitroethane in place of nitromethane, the resultant product being a *dl*-β-phenylisopropylamine.



The initial condensation step in the process was found to be most simply carried out by the method of Knoevenagel and Walther[3] when the X groups were H, OCH_3 or similarly substituted hydroxyl, but condensation does not occur by this method when one or both of the groups is an hydroxyl. The second step, the complete reduction, involves considerable difficulty but the described electrolytic reduction method gives fair yields of the desired amines while several attempts at catalytic hydrogenation or reduction with various metals or their amalgams were not at all successful. Since the initial condensation step of the above process does not occur when the X groups are hydroxyl, it was necessary to demethylate the corresponding methoxyl derivatives of phenylisopropylamine to obtain the desired hydroxyphenylisopropylamines. This was attempted following the procedure of Mannich and Jacobsohn,[2] using concentrated hydriodic acid, but no satisfactory product could be isolated from the demethylation of *dl*-β-4-methoxyphenylisopropylamine by this method. However, demethylation with concentrated hydrochloric acid under pressure did yield a good preparation of the desired *dl*-β-4-hydroxyphenylisopropylamine hydrochloride.

Experimental Part

The details of preparation of the *dl*-β-phenylisopropylamine and its 4-methoxy and 3,4-dimethoxy derivatives differ only in the aldehyde used and the intermediate and final products isolated.

[2] Mannich and Jacobsohn, *Ber.*, **43**, 189 (1910).

[3] Knoevenagel and Walther, *ibid.*, **37**, 4502 (1904).

Condensation of Aldehyde and Nitroethane.—0.2 Mole of aldehyde, 0.2 mole of nitroethane and 0.02 mole of *n*-amylamine were mixed and set aside at room temperature in the dark. After a day water began to separate from the mixture; after several days the mixture became quite solid. After two weeks, the mixture was dissolved to a homogeneous solution by warming with 50 cc. of ethanol and then on cooling a fine crystal product was obtained. From benzaldehyde, 0.15 mole of phenylnitropropylene melting at 65–66° was obtained. The melting point of this compound has been reported as 64°.[3] From anisaldehyde, 0.15 mole of 4-methoxyphenylnitropropylene melting at 43–44° was obtained. The melting point of this compound has been reported as 48°.[3] From veratraldehyde, 0.31 mole of 3,4-dimethoxyphenylnitropropylene melting at 70–71° was obtained.

Reduction of Phenylnitropropylenes.—0.1 Mole of phenylnitropropylene dissolved in a catholyte of 100 cc. of ethanol, 50 cc. of acetic acid and 50 cc. of 12 *N* sulfuric acid was placed above a 40-sq. cm. mercury cathode in a porous cell surrounded by a 3 *N* sulfuric acid anolyte with a water-cooled lead anode. Four amperes was passed for twenty hours and the temperature in the catholyte was kept between 30 and 40°.

The resultant catholyte was partially evaporated, then made strongly alkaline and the separated basic layer taken up with benzene. The desired amine was then extracted from the benzene by just neutralizing with dilute hydrochloric acid and separating the aqueous layer. This was then evaporated and the product crystallized. From phenylnitropropylene, 0.02 mole of *dl*-β-phenylisopropylamine hydrochloride melting at 144–145° was obtained. The melting point of this compound has been reported as 145–147°.[4]

Anal. Subs., 0.1737: 20.22 cc. of 0.05 *N* $AgNO_3$. Calcd. for $C_9H_{14}NCl$: Cl, 20.67. Found: Cl, 20.64.

From 4-methoxyphenylnitropropylene, 0.02 mole of *dl*-β-4-methoxyphenylisopropylamine hydrochloride melting at 208–209° was obtained. The melting point of this compound has been reported as 210°.[2]

Anal., Subs., 0.1000: 9.90 cc. of 0.05 *N* $AgNO_3$. Calcd. for $C_{10}H_{16}ONCl$: Cl, 17.59. Found: Cl, 17.56.

From 3,4-dimethoxyphenylnitropropylamine, 0.02 mole of *dl*-β-3,4-dimethoxyphenylisopropylamine hydrochloride melting at 151–152° was obtained. The melting point of this compound has been previously reported as 144°.[2]

Anal. Subs., 0.1400: 12.10 cc. of 0.05 *N* $AgNO_3$. Calcd. for $C_{11}H_{18}O_2NCl$: Cl, 15.31. Found: Cl, 15.32.

Demethylation of *dl*-β-4-Methoxyphenylisopropylamine.—Five grams of *dl*-β-4-methoxyphenylisopropylamine hydrochloride was placed in a pressure bottle with 20 cc. of concentrated hydrochloric acid and heated in an autoclave under 15 pounds per sq. in. steam pressure for six hours. The product was evaporated to dryness and then crystallized from ethanol and ether; 3.8 g. of crystals melting at 171–172° was obtained. These are readily soluble in water and alcohol. The water solution gives no coloration with a ferric chloride solution but gives positive phenol tests with Millon and Folin reagents.

Anal. Subs., 0.1500: 15.97 cc. of 0.05 *N* $AgNO_3$. Calcd. for $C_9H_{14}ONCl$: Cl, 18.90. Found: Cl, 18.88.

Demethylation of *dl*-β-3,4-Dimethoxyphenylisopropylamine.—Three grams of *dl*-β-3,4-dimethoxyphenylisopropylamine hydrochloride was boiled with 15 g. of hydriodic acid (sp. gr. 1.7) through which was passed a stream of carbon dioxide gas. After twenty minutes the major portion of the hydriodic acid was distilled off and the residue

[4] Hey, *J. Chem. Soc.*, 18 (1930).

shaken with an aqueous suspension of freshly precipitated silver chloride. After filtering off the insoluble silver salts, the filtrate was evaporated. With much difficulty a crystalline product was obtained, 1.5 g. of gray-white crystals melting at 192°. The melting point of this compound has been previously reported as 190–192°.[2] The product is readily soluble in water and alcohol. The water solution gives a green coloration with a ferric chloride solution and a blue coloration with Folin phosphotungstic reagent after making alkaline.

Anal. Subs., 0.010: 0.68 mg. of N as NH_3 by micro-Kjeldahl analysis. Calcd. for $C_9H_{14}O_2NCl$: N, 6.87. Found: N, 6.8.

Summary

1. A new synthetic method for preparing *dl*-β-phenylisopropylamine and certain of its derivatives has been developed.

2. 4-Hydroxy- and 3,4-dihydroxyphenylisopropylamines have been prepared by this method for physiological studies.

LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE FURMAN CHEMICAL LABORATORY, VANDERBILT UNIVERSITY]

SOLUBILITY RELATIONSHIPS AMONG OPTICALLY ISOMERIC SALTS.

I. THE MALATES OF ALPHA-PARA-XENYLETHYLAMINE[1]

BY A. W. INGERSOLL AND E. G. WHITE

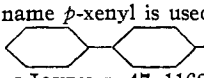
RECEIVED AUGUST 10, 1931 PUBLISHED JANUARY 7, 1932

In previous papers a method has been described by which it is possible,[2] in certain instances, to obtain both active forms of an externally compensated base or acid in an optically pure condition. For example, in the resolution of a base (*dl*B), as much as possible of one active form, for instance, *l*B, is obtained in the usual way by Pasteur's third method. The residual, partially active base (*dl*B + *d*B) is then recovered from the mother liquors, combined with any suitable inactive (externally compensated) acid (*dl*A) and the salts fractionally crystallized. In this step either of two mixtures of salts may be obtained, depending on whether the inactive acid is resolved by the active base present in excess (Equation 1) or forms a stable, partially racemic salt with it (Equation 2).

$$(dl\text{B} + d\text{B}) + dl\text{A} \longrightarrow dl\text{B}dl\text{A} + d\text{B}d\text{A} + d\text{B}l\text{A} \quad (1)$$

$$(dl\text{B} + d\text{B}) + dl\text{A} \longrightarrow dl\text{B}dl\text{A} + d\text{B}dl\text{A} \quad (2)$$

According to the usual results of fractional crystallization it may be expected that when any of the salts containing only the active base (here *d*B) is the least soluble, it can be purified and a complete resolution of the base results. On the other hand, should the totally racemic salt be the least

[1] The radical name *p*-xenyl is used in this paper as a brief designation of the *p*-diphenylyl radical,  .

[2] Ingersoll, THIS JOURNAL, **47**, 1168 (1925); **50**, 2264 (1928).