(AgNO₃), and evaporated. Crystallization from 17 vol. of 33% MeOH gave the ester, mp 99-100°.

**N-Acetyl-3-iodo-dl-tyrosine Ethyl Ester.**—Esterification of N-acetyl-3-iodo-dl-tyrosine by the above method gave a 75% yield of the ester, mp 189.5-190.5°, from aqueous ethanol.

*Anal. Caled for C₉H₇IO₂N: C, 41.4; H, 4.3. Found: C, 41.2; H, 4.15.*

**N-Acetyl-3-iodo-dl-tyrosine ethyl ester** was prepared as above but has not yet been crystallized. It was used for the preparation of 3-iodothyronine in the form of a gum.

**Chloro-dl-thyronine.**—Unrecrystallized dip-anisylidodium bromide¹⁰ (21 g, 0.05 mole) and 7.2 g (0.046 mole) of Ag₂SO₄, were stirred 2 hr in 120 ml of water. Some decolorizing charcoal was added, the solids were removed by filtration, and the solution was treated with an aqueous solution of 3 g of NaCl. There resulted 14.5 g (83%) of the iodonium chloride, mp 202-203°, not raised by recrystallization. This salt (3.77 g, 0.01 mole), N-acetyl-3-chloro-dl-tyrosine ethyl ester (3.43 g, 20% excess), and 0.65 g of NaOMe were added to 30 ml of redistilled DMF. The reaction was stirred while being kept at 50-55° for 14 hr. The solvent was removed under vacuum and the residue, treated as before in the analogous method, was treated with di(panisy1)iodoniuni chloride and the salt was precipitated as above. After neutralization with hot (NHaOH), the yield of crude 3-chloro-dl-thyronine was 1.23 g, 0.004 mole, mp 224-225°.

**For analytical purposes.**—The usual method of preparation of racemic ephedrine is by catalytic hydrogenation of acetylbenzoyl in the presence of methylamine. In all previous reports, regardless of reaction conditions or hydrogenation catalyst used, the only basic products isolated were ephedrine and small amounts of pseudoephedrine, *erythro* and *threo* diastereoisomers. In the conversion to the ephedrines the aminomethyl group was found to enter exclusively β to the phenyl group. This was attributed by Manske and Johnson² to deactivation of α-carbonyl group by the phenyl ring. Skita and Keil³ considered the selectivity to be a function of steric control, whereby methylamine reacts with the carbonyl adjacent to the smaller group. Couturier⁴ explicitly stated that no monoamine α to the phenyl or α,β-diamine is formed in this synthesis. The catalysts that have been employed in prior syntheses are PtO₂,⁵ colloidal Pt,⁶ activated Al,⁷ Pt–Pd,⁸ and Raney nickel.⁹

We now wish to report the isolation, characterization, and pharmacology of N,N'-dimethyl-1-phenyl-1,2-propanediamine (I), obtained in the ephedrine synthesis from acetylbenzoyl.

\[
\text{C}_6\text{H}_5\text{COCH}_3 + \text{CH}_3\text{NH}_2\rightarrow \text{H}_1
\]

\[
\text{C}_6\text{H}_5\text{CHOHCH}(\text{CH}_3)\text{NHCH}_3 + \text{C}_6\text{H}_5\text{(CH}_3\text{NCHCH}_3)\text{CH}_1
\]

dl-ephedrine I

The initial catalyst employed was 1:1 5% Pt/C-5% Pd/C since that catalyst system has been found to be very effective for the conversion of isonitrosopropionone to phenylpropanolamine. In almost all of the previous reported ephedrine syntheses 1-2 moles of methylamine/mole of acetylbenzoyl were employed and in the present program the first experiments utilized a ratio of 2.5:1. Catalytic hydrogenation was carried out at ambient temperature except for the initial stage which was approximately 10° higher due to the reaction exotherm. The reaction mixture was treated in the typical manner used to isolate ephedrine hydrochloride, but the melting range of the product was broad and exceeded the reported melting point of ephedrine hydrochloride. The dihydrochloride of I was isolated by virtue of its insolubility in hot 2-

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propanol. Compound I was recovered by neutralization with aqueous NaOH and the identity was confirmed by elemental analysis and infrared and nmr spectra. With the aforementioned quantities of reactants, ephe- drine and I were obtained in almost equal yield, 27 and 28\%, respectively. Even with an equimolar ratio of reactants, the diaminophylline was isolated in 3\% yield which increased to 8\% when the reactants were preheated to 60° and maintained at that temperature during the hydrography.

Since various catalysts have been reported to be effective in ephephrine synthesis, the effect of the nature of the metal catalyst on the product distribution was briefly investigated. With 5\% Pt/C, 5\% Pd/C, or PtO\(_2\) as catalyst and 2.5 moles of methylvamine/mole of acetylbenzoyl, the ratio of the yield of yield epinephrine: yield diaminophylline was ca. 4:1 compared with 1:1 for the mixed 5\% Pt/C-5\% Pd/C catalyst. When Raney nickel was used, no evidence for the formation of diaminophylline was observed, even when the methylvamine:acetyl- benzoyl mole ratio was increased to 4:1. The choice, by Couturier, of Raney nickel as the hydrogenation catalyst was likely responsible for the impression that the synthesis of ephedrine is highly selective and only 1 mole of methylvamine may be introduced. It is surprising, however, that diaminophylline formation was not previously observed when other catalysts were employed.

The likely reaction path for the reductive alkylation is hydrogenation of the respective ketamines formed from acetylbenzoyl and methylvamine. The initial rapid reaction and absorption of approximately 1 mole of hydrogen occurs most likely at the 3-ketimine position. Ketimine formation is reversible and the position of equilibrium between the \(\alpha\)-carbonyl and the \(\alpha\)-ketimine is apparently influenced by the nature of the metal catalyst to account for the observed product distribution between ephedrine and the diaminophylline.

\[ \text{Scheme I} \]

\[ \text{CH}_3\text{COOCCH}_3 \xrightarrow{\text{CH}_3\text{NH}_2} \text{CH}_3\text{HOCOC}(=\text{NHCH}_2)\text{CH}_2 + \text{H}_2 \xrightarrow{\text{H}_2\text{O}} \]

\[ \text{C}_3\text{H}_7\text{COCH}(=\text{NHCH}_2)\text{CH}_2 + \text{H}_2 \xrightarrow{\text{H}_2\text{O}} \]

\[ \text{C}_3\text{H}_7\text{COCH}(=\text{NHCH}_2)(\text{NHCH}_2)\text{CH}_2 + \text{H}_2 \xrightarrow{\text{H}_2\text{O}} \]

**Pharmacological Activity.**—The dihydrochloride of I was tested by a typical behavior screening procedure and found to exhibit weak sympathomimetic properties. Significant stimulatory effects were observed only at concentrations that approached lethal dosage.

**Experimental Section**

**N,N'-Dimethyl-1-phenyl-1,2-propane diamine (I).**—A mixture of acetylbenzoyl (29.6 g, 0.20 mole), methylvamine (69 ml, 27\%) (15 g, 0.48 mole, of amine), and methylvamine (120 ml) was hydrogenated in a Parr apparatus in the presence of a mixture of 5.0 g of 5\% Pt/C and 5.0 g of 5\% Pd/C. The initial absorption of hydrogen was rapid and the temperature rose from 25 to 35°. The reaction then moderated and proceeded slowly.

When no further uptake of hydrogen was observed, the shaking was discontinued and the catalyst was separated by filtration. The filtrate was concentrated to one-half the original volume to remove methylvamine, crude acid with methylvamine HCl and concentrated to a wax solid. Trituration with acetone afforded a solid product that was collected by suction filtration, washed with acetone, and dried. Any pseudophenylhydrochloride formed was removed by heating under reflux with two 200-ml portions of CHCl\(_3\). The crude product (mp 177-200°) was heated under reflux with two 200-ml portions of 2-propanol. The insoluble fraction was separated by filtration, and washed with 2-propanol to afford the dihydrochloride of I (14 g, 28\%, of theoretical), mp 250-252° dec. Recrystallization from water-2-propanol did not raise the melting point.

**Dihydrochloride of I.**—For C\(_7\)H\(_7\)NO\(_2\)Cl\(_2\): C, 32.60; H, 8.03; Cl, 28.25; N, 11.13. Found: C, 32.35; H, 8.10; Cl, 28.04; N, 11.13. Found: C, 32.80; H, 11.16; N, 15.48.

**Catalyst Studies.**—When 5\% Pt/C, 5\% Pd/C, or the mixed 5\% Pt/C-5\% Pd/C catalyst was employed for the hydrogenation catalyst, 10 g of catalyzed was employed for 0.2 mole of autamethylenes. With PtO\(_2\), 0.3 g of catalyst was used. Raney No. 28 active nickel catalyst contains approximately 50\% water, and 20 g of wet catalyst was washed with methanol to remove water and used to dehydrate 0.2 mole of acetylbenzoyl.

All other conditions and procedures were identical.

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**1-Anilinopyrimidine-5-carboxylic Acids and Esters with Antiinflammatory and Analgesic Properties**

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Several N-phenylanthranilic acids and esters have been described which show antiinflammatory, analgesic, and antipyretic activities in both pharmacological and clinical tests. These compounds include N-(3-trifluoromethyl)phenyl)anthranilic acid\(^1\) and esters.\(^2\) N-