($MgSO_4$), 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 138.5–140.5°, from aqueous ethanol.

Anal. Calcd for $C_{13}H_{16}INO_4$: C, 41.4; H, 4.3. Found: C, 41.2; H, 4.15.

N-Acetyl-3-iodo-*l*-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.

3-Chloro-*dl*-thyronine.—Unrecrystallized di(*p*-anisyl)iodonium bromide[20] (21 g, 0.05 mole) and 7.2 g (0.046 mole) of Ag_2SO_4 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-*l*-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 has been described, was shaken with 40 ml of benzene together with 25 ml of 3% HCl. The separated benzene layer was washed (two 15-ml portions of H_2O, two 10-ml portions of 1 *N* NaOH, three 10-ml portions of H_2O) and dried, the benzene was removed by evaporation, and the residue was treated with 25 ml of petroleum ether (bp 30–60°). The solvent was removed by decantation and the residual oil refluxed in 30 ml of AcOH and 5 ml of HBr (48%) for 3.5 hr. After evaporation under reduced pressure, the residue was taken up in 35 ml of water and extracted twice with ether. The solution was heated to remove ether and neutralized hot (NH_4OH). The yield of crude 3-chloro-*dl*-thyronine was 2.3 g (75%). For purification it was suspended in hot water, dissolved with the help of HCl, treated with charcoal, and reprecipitated (NH_4OH) after the addition of a few drops of AcOH, mp 221–223°. To remove all traces of thyronine for analysis, the hydrochloride was precipitated by adding concentrated HCl to the solution of the amino acid in 2 *N* HCl and reconverted to the free amino acid.

Anal. Calcd for $C_{15}H_{14}ClNO_4$: C, 58.5; H, 4.6; Cl, 11.5. Found: C, 58.3; H, 4.8; Cl, 11.4.

In similar fashion, by substituting 4.5 g of either iodo isomer, 3-iodothyronine results. It is purified by crystallization from 2 *N* HCl without adding concentrated acid.[2e]

3,3′-Dichloro-*dl*-thyronine.—3-Chloro-*dl*-thyronine (1.23 g, 0.004 mole) was dissolved by warming in 20 ml of AcOH. To the cooled solution was added 0.4 ml (0.67 g, 0.005 mole) of SO_2Cl_2. After 1 hr the solution was warmed to 60° then evaporated under vacuum. The residue was taken up in water and precipitated from the hot solution (NH_4OH); yield 1.1 g (80%). A product containing only a trace of trichlorothyronine was obtained by repeating the precipitation from acid solution, but for analysis the hydrochloride was precipitated as above. After neutralization of the hydrochloride in the usual manner, the dichlorothyronine melted at 226–228°.

Anal. Calcd for $C_{15}H_{13}Cl_2NO_4$: Cl, 20.7. Found: Cl, 20.4.

3,3′,5′-Trichloro-*dl*-thyronine.—3-Chloro-*dl*-thyronine (1.23 g, 0.004 mole) was dissolved in 6 ml of AcOH by warming. To the cool solution 0.9 ml (1.5 g, 0.011 mole) of SO_2Cl_2 was added slowly with stirring. The temperature of the reaction was allowed to rise while gas was evolved and a precipitate appeared. After 1 hr the reaction was warmed to 60–70° for 0.5 hr, 6 ml of 3.3 *N* HCl was added, and the hydrochloride, after refrigeration, was filtered and dissolved in 35 ml of 20% ethanol containing a few drops of AcOH. The hot solution was filtered and reheated, and the amino acid precipitated (NH_4OH); yield 1 g (65%), mp 224–225°.

Anal. Calcd for $C_{15}H_{12}Cl_3NO_4$: Cl, 28.2. Found: Cl, 28.0.

Acknowledgment.—This investigation was supported in part by Research Grant AM 09988 from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(20) J. T. Plati, U. S. Patent 2,839,583 (1958).

N,N′-Dimethyl-1-phenyl-1,2-propanediamine. A Hitherto Unreported Product in Ephedrine Synthesis[1]

SEYMOUR HYDEN, SANTO EMMANUELE, HENRY WETSTEIN, AND GODFREY WILBERT

Nepera Chemical Company, Harriman, New York, a Subsidiary of Warner-Lambert Pharmaceutical Company

Received April 21, 1967

The usual method of preparation of racemic ephedrine is by catalytic hydrogenation of acetylbenzoyl in the presence of methylamine. In all previous reported syntheses, regardless of reaction conditions or hydrogenation catalyst used, the only basic products isolated were ephedrine and small amounts of pseudoephedrine, the *erythro* and *threo* diasteroisomers. 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 Johnson[2] to deactivation of α-carbonyl group by the phenyl ring. Skita and Keil[3] considered the selectivity to be a function of steric control, whereby methylamine reacts with the carbonyl adjacent to the smaller group. Couturier[4] 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 PtO_2,[2,5] colloidal Pt,[3] activated Al,[6] Pt–Pd,[7] and Raney nickel.[4,8]

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.

$$C_6H_5COCOCH_3 \xrightarrow[H_2]{CH_3NH_2-CH_3OH} C_6H_5CHOHCH(CH_3)NHCH_3 + C_6H_5(CHNHCH_3)_2CH_3$$

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 isonitrosopropiophenone to phenylpropanolamine.[9] 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-

(1) Presented at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 9–14, 1967.

(2) R. H. F. Manske and T. B. Johnson, *J. Am. Chem. Soc.*, **51**, 580 (1929).

(3) A. Skita and F. Keil, *Ber.*, **62B**, 1142 (1929).

(4) P. Couturier, *Compt. Rend.*, **207**, 345 (1938).

(5) G. Sunagawa and K. Okuda, *J. Pharm. Soc. Japan*, **72**, 117 (1952).

(6) W. Klavehn, British Patent 336,412 (1930).

(7) K. Kawahara, K. Kato, and I. Sasabe, Japanese Patent 177,598 (1949).

(8) J. Homma and Y. Kato, Japanese Patent 290 (1951).

(9) G. Wilbert and P. Sosis, U. S. Patent 3,028,429 (1962).

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, ephedrine and I were obtained in almost equal yield, 27 and 28%, respectively. Even with an equimolar ratio of reactants, the diamine was isolated in 3% yield which increased to 8% when the reactants were preheated to 60° and maintained at that temperature during the hydrogenation.

Since various catalysts have been reported to be effective in ephedrine 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 methylamine/mole of acetylbenzoyl, the ratio of the yield of ephedrine:yield diamine 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 diamine was observed, even when the methylamine:acetylbenzoyl 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 methylamine may be introduced.[4] It is surprising, however, that diamine formation was not previously observed when other catalysts were employed.

The likely reaction path for the reductive alkylation is hydrogenation of the respective ketimines formed from acetylbenzoyl and methylamine. The initial rapid reaction and absorption of approximately 1 mole of hydrogen occurs most likely at the β-ketimine position. Ketimine formation is reversible and the position of equilibrium between the α-carbonyl and the α-ketimine is apparently influenced by the nature of the metal catalyst to account for the observed product distribution between ephedrine and the diamine.

SCHEME I

$$C_6H_5COCOCH_3 \overset{CH_3NH_2}{\rightleftharpoons} C_6H_5COC(=NCH_3)CH_3 + H_2O \xrightarrow{H_2}$$

$$C_6H_5COCH(NHCH_3)CH_3 \xrightarrow{H_2} \text{ephedrine}$$

$$\uparrow\downarrow CH_3NH_2$$

$$C_6H_5C(=NCH_3)CH(NHCH_3)CH_3 + H_2O \xrightarrow{H_2} \text{I}$$

Pharmacological Activity.—The dihydrochloride of I was tested by a typical behavior screen procedure[10] and found to exhibit weak sympathomimetic properties. Significant stimulatory effects were observed only at concentrations that approached lethal dosage.

Experimental Section[11]

N,N′-Dimethyl-1-phenyl-1,2-propanediamine (I).—A mixture of acetylbenzoyl[12] (29.6 g, 0.20 mole), methanolic methylamine (69 ml, 22%) (15 g, 0.48 mole, of amine), and methanol (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 methylamine, made acid with methanolic HCl and concentrated to a waxy solid. Trituration with acetone afforded a solid product that was collected by suction filtration, washed with acetone, and dried. Any pseudoephedrine hydrochloride formed was removed by heating under reflux with two 200-ml portions of $CHCl_3$. The crude product (mp 177–230°) 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.

Anal. Calcd for $C_{11}H_{18}Cl_2N_2$: C, 52.60; H, 8.03; Cl, 28.23; N, 11.15. Found: C, 52.35; H, 8.10; Cl, 28.04, 28.13; N, 10.85.

Ephedrine hydrochloride was isolated by concentration of the 2-propanol-soluble fraction (11 g, 27% of theoretical), mp 188–189° (lit.[2,3] mp 189°, 185–186°). The hydrochloride was converted to the free base, mp 75° (lit.[2,3] mp 75°).

An aqueous solution of the dihydrochloride of I was made alkaline (NaOH) and extracted twice ($CHCl_3$). The combined extracts were dried (Na_2SO_4), the solvent was removed, and I was obtained by distillation at 143–145° (20 mm) as a clear liquid: $\nu_{max}^{CHCl_3}$ 3300 cm^{-1} (N–H); nmr ($CDCl_3$) (reference TMS), τ 9.17 (CH_3 doublet), 8.60 (NH), 7.85, 7.72 (N–CH_3), 7.40 (CH multiplet), 6.58 (CH doublet), 2.82 (aromatic CH).

Anal. Calcd for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 73.86; H, 10.16; N, 15.48.

Catalyst Studies.[13]—When 5% Pt/C, 5% Pd/C, or the mixed 5% Pt/C–5% Pd/C was used as the hydrogenation catalyst, 10 g of catalyst was employed for 0.2 mole of acetylbenzoyl. With PtO_2, 0.50 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 hydrogenate 0.2 mole of acetylbenzoyl.

All other conditions and procedures were identical.

Acknowledgments.—We wish to thank Mr. Robert Puchalski and Mr. Arnold Lewis of the Warner-Lambert Research Institute for obtaining the elemental analyses and infrared and nmr spectra. We also wish to thank Mr. Puchalski for his assistance in interpretation of the spectra.

(10) Tested at the Warner-Lambert Research Institute by the procedure of S. Irwin, *Science*, **136**, 123 (1962).

(11) All melting points are uncorrected. Analyses and spectra were obtained by the Warner-Lambert Research Institute.

(12) W. W. Hartman and L. J. Roll in "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 20.

(13) The catalysts employed were all commercial samples; 5% Pt/C, 5% Pd/C, and PtO_2 were obtained from Engelhard Industries, Inc., Newark, N. J. Raney No. 28 Active Nickel Catalyst in Water was obtained from W. R. Grace and Co., Raney Catalyst Division, Chattanooga, Tenn.

4-Anilinopyrimidine-5-carboxylic Acids and Esters with Antiinflammatory and Analgetic Properties[1]

P. F. JUBY AND T. W. HUDYMA

Research Division, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, New York 13201

Received May 26, 1967

Several N-phenylanthranilic acids and esters have been described which show antiinflammatory, analgetic, and antipyretic activities in both pharmacological and clinical tests. These compounds include N-(3-trifluoromethylphenyl)anthranilic acid[2] and esters,[3] N-

(1) Some of the compounds have been reported by P. F. Juby, U. S. Patents 3,254,086 (1966), 3,254,087 (1966), and 3,300,496 (1967).

(2) (a) C. V. Winder, J. Wax, B. Serrano, E. M. Jones, and M. L. McPhee, *Arthritis Rheumat.*, **6**, 36 (1963); (b) E. L. Coodley, *Western Med.*, **4**, 228 (1963); (c) P. Young, *Arthritis Rheumat.*, **6**, 307 (1963).

(3) (a) R. A. Scherrer and F. W. Short, U. S. Patent 3,278,581 (1966); (b) French Patent M2948 (1964).