Synthetic Analgesics. IV. Synthesis of Enantiomers of Basic Anilides Containing the Phenalkyl Moiety[1,2]

W. B. WRIGHT, JR., AND R. A. HARDY, JR.

Organic Chemical Research Section, Lederle Laboratories, a Division of American Cyanamid Company, Pearl River, New York

Received October 18, 1962

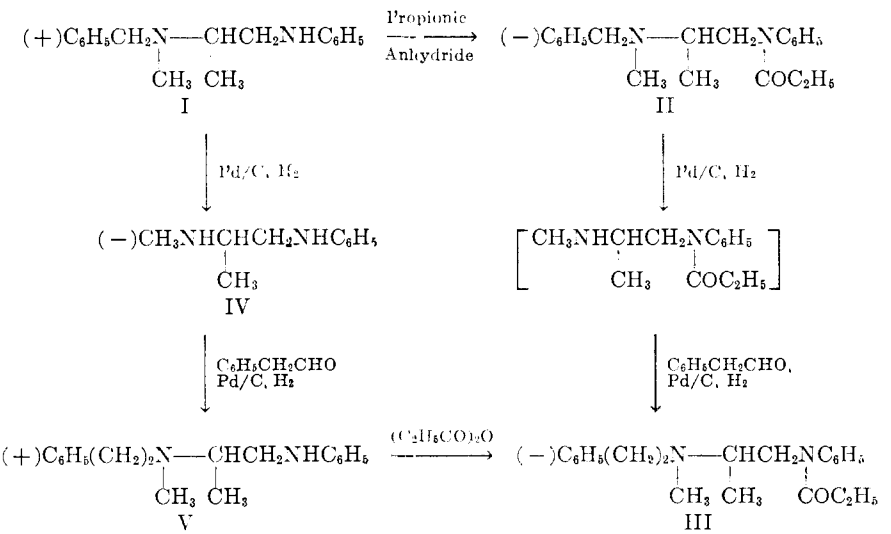
The enantiomers of N-[2-(methylphenethylamino)propyl]propionanilide sulfate, diampromide, and N-[2-(benzylmethylamino)propyl]propionanilide hydrochloride have been prepared. As predicted, one enantiomer of each pair greatly exceeds the other in analgesic activity and the more active enantiomers have the same configuration.

When analgesics which contain an asymmetric carbon atom are resolved, one enantiomer usually retains most of the analgesic activity.[3] Our interest in N-[2-(methylphenethylamino)propyl]propionanilide sulfate, diampromide (III),[4] a potent narcotic-type analgesic in animals and man,[1,5] therefore prompted us to prepare the enantiomers of diampromide (III) and N-[2-(benzylmethylamino)propyl]propionanilide (II).

Attempts to resolve diampromide base (III) and two potential intermediates, N^2-methyl-N^2-phenethyl-N^1-phenyl-1,2-propanediamine (V) and N-[2-(benzylmethylamino)propyl]propionanilide (II) by mixing with available optically active acids failed to give crystalline diastereomeric salts. We were able, however, to prepare crystalline (+)-N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine-(+)-tartrate (I) by warming the racemic base with an aqueous solution of (+)-tartaric acid. When the organic base was recovered from the mother liquor and treated with (−)-tartaric acid, crystalline (−)-N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine-(−)-tartrate (I) was isolated easily. These salts were further purified by recrystallization from water. The bases were liberated and had identical melting points of 60–61° and opposite rotations, $[\alpha]^{25}D$ ±35°.

Two routes were followed for the conversion of (+)-N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine (I) to (−)-N-[2-(methylphenethylamino)propyl]-propionanilide (III). The infrared absorption spectra, boiling points, indices of refraction, and rotation of the products were essentially identical by either route. (+)-N-[2-(Methylphenethylamino)-propyl]propionanilide (III) also was prepared and found to be identical in physical properties, except for the opposite sign of rotation, with the (−)-enantiomer. These data may be considered as evidence that the products were optically pure.

In route A, (+)-N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine (I) reacted with propionic anhydride and (+)-N-[-2-(benzylmethylamino)propyl]-propionanilide (II) hydrochloride, $[\alpha]^{25}D$ +13.8°, was isolated in 74% yield. This compound was converted to the base, $[\alpha]^{25}D$ −37.6°. The hydrochloride was debenzylated, the crude product was reductively alkylated with phenylacetaldehyde, and (−)-N-[2-(methylphenethylamino)propyl]propionanilide (III), $[\alpha]^{25}D$ −25.2°, was isolated in 30% yield. Similarly, (−)-N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine (I) was converted to (−)-N-[2-(benzylmethylamino)-propyl]propionanilide (II) hydrochloride, $[\alpha]^{25}D$ −14.5°.



In route B, (+)-N^2-benzyl-N^2-methyl-N^1-phenyl-1,2-propanediamine (I) was debenzylated to (−)-N^2-methyl-N^1-phenyl-1,2-propanediamine (IV), $[\alpha]^{25}D$ −29.8°. Reductive alkylation with phenylacetalde-

(1) Previous paper: W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Org. Chem.*, **26**, 485 (1961).

(2) Presented in part by R. A. Hardy, Jr., at the New York Regional Meeting of the American Chemical Society, New York, N. Y., January 22, 1962.

(3) A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, **6**, 986 (1954).

(4) For the sake of simplicity, Roman numerals have been used to designate chemical structure without reference to optical rotation or form of salt.

(5) A. C. Osterberg and C. E. Rauh, *The Pharmacologist*, **1** (No. 2), 78 (1959); we are indebted to Dr. A. C. Osterberg for the AD_{50}'s of the enantiomers described in this work.

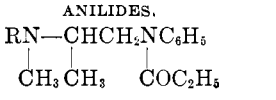
hyde afforded (+)-N²-methyl-N²-phenethyl-N¹-phenyl-1,2-propanediamine (V), $[\alpha]^{25}D$ +13.8°. This was then acylated with propionic anhydride to (−)-N-[2-(methylphenethylamino)propyl]propionanilide (III), $[\alpha]^{25}D$ −25.9°. Similarly (−)-N²-benzyl-N²-methyl-N¹-phenyl-1,2-propanediamine (I) was converted to (+)-N-[2-(methylphenethylamino)propyl]propionanilide (III), $[\alpha]^{25}D$ +25.2°, through (+)-IV and (−)-V.

Attempts were made to prepare salts of (−)-III base by dissolving samples in ethanolic solutions of one molar equivalent of (+)-tartaric, (−)-tartaric, (−)-malic, (+)-10-camphorsulfonic, fumaric, succinic, mandelic, sulfuric, hydrochloric, hydrobromic, salicylic, and malonic acids. Concentration and trituration with various solvents failed to yield crystalline products.

Pharmacology.—These compounds were tested for analgesic activity by the rat-tail radiant-heat procedure described by Osterberg and Rauh,[5] who reported the AD_{50} for *dl*-III sulfate, diampromide. This result and the AD_{50} for the *dl*-benzyl compound (II) hydrochloride were quoted in our previous paper.[1] The activities of the racemates and enantiomers are summarized in Table I.

TABLE I

THE ANALGESIC ACTIVITY OF OPTICALLY ACTIVE PROPIONANILIDES.



Enantiomer	R	Salt	AD_{50},[a] mg./kg.
dl	Benzyl	HCl	8
(+)		HCl	Inactive (50 mg./kg.)
(−)		HCl	4.3
dl	Phenethyl	H_2SO_4	3.7
(+)		(Base)	3.6
(−)		(Base)	11.7
Meperidine		HCl	11

[a] AD_{50} is the subcutaneous dose which elevates the rat-tail radiant-heat response time by 100% in 50% of the animals.

The enantiomer (+)-III base was found to be approximately equal to the *dl*-compound (III) sulfate in analgesic activity, while the (−)-III base was only about one-third as active. The *dl*-compound (III) sulfate showed very low physical dependence capacity in monkeys.[6]

In the benzyl analog series, the (−)-enantiomer, (−)-II hydrochloride, was about twice as active as the racemate, *dl*-II hydrochloride, while (+)-II hydrochloride lacked analgesic activity. In this series the racemate exhibited intermediate physical dependence capacity in monkeys, the (−)-enantiomer showed low physical dependence capacity, and the analgesically inactive (+)-enantiomer showed no physical dependence capacity in monkeys.[7] It is interesting to note that the analgesically more active enantiomers, (−)-II hydrochloride and (+)-III base, are both derived from (−)-N²-benzyl-N²-methyl-N¹-phenyl-1,2-propanediamine (I) and must therefore have the same configuration.[8]

(6) G. A. Deneau and M. H. Seevers, Addendum 1 to Minutes of 21st Meeting of Committee on Drug Addiction and Narcotics, Philadelphia, Pa., January, 1960.

(7) G. A. Deneau and M. H. Seevers, Addendum 1 to Minutes of 23rd Meeting of Committee on Drug Addiction and Narcotics, New York, N. Y., January, 1961.

(8) P. S. Portoghese has indicated by private communication that the absolute configuration of these compounds is derived from L-(+)-alanine; this work has been described by P. S. Portoghese and D. L. Larson, *J. Pharm. Sci.*, **51**, 1115 (1962); P. S. Portoghese, *ibid.*, **51**, 1197 (1962).

Experimental[9]

(+)-N²-Benzyl-N²-methyl-N¹-phenyl-1,2-propanediamine (I).—A mixture of 50 g. (0.2 mole) of *dl*-N²-benzyl-N²-methyl-N¹-phenyl-1,2-propanediamine,[1] 29.5 g. (0.2 mole) of (+)-tartaric acid and 1500 ml. of water was heated until solution occurred and then allowed to stand at 25° for 20 hr. The precipitate was filtered off, washed with a little cold water and then dissolved in 400 ml. of water. The solution was allowed to stand at 25° for 3 hr. and was filtered. The crystalline product was washed with cold water and dried in a vacuum desiccator. The combined filtrates were used in the preparation of the (−)-enantiomer. The yield of (+)-I-(+)-tartrate, m.p. 100–103°, was 13.9 g. (32%). To assure optical purity, the product was recrystallized from water, m.p. 101–103°, $[\alpha]^{25}_D$ −4.4°.

Anal. Calcd. for $C_{21}H_{28}N_2O_6 \cdot 2H_2O$: C, 57.2; H, 7.3; N, 6.4; H_2O, 8.2. Found: C, 56.8; H, 7.5; N, 6.4; H_2O, 7.8.

A mixture of 12 g. of (+)-I-(+)-tartrate, 15 ml. of 5 *N* sodium hydroxide and 100 ml. of water was shaken, and the organic base was extracted into ether. The ether layer was washed with water, dried over magnesium sulfate and concentrated. The crystalline residue, 6.5 g., m.p. 58–60°, was recrystallized from ethanol. The yield of (−)I was 5.7 g. (82%), m.p. 60–61°, $[\alpha]^{25}_D$ +34.9°.

Anal. Calcd. for $C_{17}H_{22}N_2$: C, 80.3; H, 8.7; N, 11.0. Found: C, 79.5; H, 8.7; N, 10.9; H_2O, 0.6.[10]

(−)-N²-Benzyl-N²-methyl-N¹-phenyl-1,2-propanediamine (I).—The filtrates saved (above) were treated with 80 ml. of 5 *N* sodium hydroxide, and the organic base was extracted into ether. The ether layer was concentrated to remove the solvent, and the residue, 39.7 g., was dissolved by heating with a solution of 23.5 g. of (−)-tartaric acid in 1000 ml. of water. The solution was allowed to stand at 25° for 20 hr., and the precipitate which separated was filtered, washed with a little cold water, and recrystallized from 300 ml. of water (25°). The yield of (−)-I-(−)-tartrate, m.p. 101–103°, was 20.9 g. (48.5%). The product was recrystallized from water, m.p. 101–103°, $[\alpha]^{25}D$ +5.4°.

Anal. Calcd. for $C_{21}H_{28}N_2O_6 \cdot 2H_2O$: C, 57.2; H, 7.3; N, 6.4; H_2O, 8.2. Found: C, 57.3; H, 7.5; N, 6.3; H_2O, 7.3.

This product was converted to (−)I, m.p. 60–61°, $[\alpha]^{25}_D$ −34.9°, as described for the (+)-enantiomer.

Anal. Calcd. for $C_{17}H_{22}N_2$: C, 80.3; H, 8.7; N, 11.0. Found: C, 79.4; H, 8.7; N, 10.9; H_2O, 0.5.

(+)-N-[2-(Benzylmethylamino)propyl]propionanilide (II) Hydrochloride.—A mixture of 76 g. (0.3 mole) of (+)-N²-benzyl-N²-methyl-N¹-phenyl-1,2-propanediamine and 150 ml. of propionic anhydride was heated on the steam bath for 3 hr. and then concentrated to remove most of the propionic acid and propionic anhydride. The residue was warmed with 50 ml. of ethanol and again concentrated. The viscous oil was triturated with 115 ml. of 2.9 *N* ethanolic hydrogen chloride, concentrated, and triturated 3 times with ether (decanted) and finally with 50 ml. of acetone. Crystallization occurred. The cooled reaction mixture was filtered and the product was washed with cold acetone and then ether. The yield of (+)II hydrochloride, m.p. 140–141°, was 70 g. (68%). The product was recrystallized from acetone, m.p. 141–142°, $[\alpha]^{25}D$ +13.8°. A sample was converted to the base, $[\alpha]^{25}D$ −37.6°.

Anal. Calcd. for $C_{20}H_{26}N_2O \cdot HCl \cdot 0.5\ H_2O$: C, 67.5; H, 7.9; Cl, 10.0; N, 7.9; H_2O, 2.5. Found: C, 67.3; H, 7.6; Cl, 10.1; N, 8.1; H_2O, 2.8.

(−)-N-[2-(Benzylmethylamino)propyl]propionanilide (II) Hydrochloride.—This compound was prepared as described for the (+)-enantiomer, m.p. 141–142,° $[\alpha]^{25}D$ −14.5°.

Anal. Calcd. for $C_{20}H_{26}N_2O \cdot HCl \cdot 0.5\ H_2O$: C, 67.5; H, 7.9; Cl, 10.0; N, 7.9. Found: C, 67.8; H, 7.8; Cl, 10.2; N, 8.1.

(−)-N²-Methyl-N²-phenethyl-N¹-phenyl-1,2-propanediamine (V).—A mixture of 7.6 g. (0.03 mole) of (−)I, 120 ml. of 90% ethanol and 1 g. of 10% palladium-on-carbon catalyst was shaken in a Parr hydrogenator under about 3.099 kg. hydrogen/cm.² until 1 *M* equivalent of hydrogen was absorbed. The pressure bottle was opened and 3.6 g. (0.03 mole) of phenylacetaldehyde and 1 g. of fresh 10% palladium-on-carbon catalyst were added. The reduction was continued for 24 hr. The catalyst was filtered off and the reaction mixture was concentrated to remove the sol-

(9) Melting points and boiling points are uncorrected. Melting points were obtained with a Hershberg apparatus or a Fisher-Johns block. Optical rotations were determined on 3–4% solutions in ethanol.

(10) The bases are hygroscopic and also absorb carbon dioxide from the air; this accounts for the low carbon analyses reported in this paper.

vent. The residue was treated with 50 ml. of *N* hydrochloric acid and the aqueous solution was extracted with ether. The ether layer was discarded. The aqueous layer was made alkaline by the addition of 15 ml. of 5 *N* sodium hydroxide and the organic base was extracted into ether. The ether layer was washed with water, dried over magnesium sulfate and distilled. A low-boiling forerun was discarded and (−)V was collected at 144–148° (0.08 mm.). The yield was 4.6 g. (57%), $n^{25}D$ 1.562, $[\alpha]^{25}D$ −13.3°.

Anal. Calcd. for $C_{18}H_{24}N_2$: C, 80.5; H, 9.0; N, 10.4. Found: C, 80.1; H, 8.9; N, 10.7.

(+)-N²-Methyl-N¹-phenethyl-N¹-phenyl-1,2-propanediamine (V).—A mixture of 25.4 g. (0.1 mole) of (+)I, 200 ml. of 90% ethanol and 1.5 g. of 10% palladium-on-carbon catalyst was reduced and treated with 12 g. of phenylacetaldehyde as described for the (−)-enantiomer (V). The yield of product, b.p. 148–152° (0.05 mm.), $n^{25}D$ 1.564, $[\alpha]^{25}D$ +13.8°, was 60%.

Anal. Calcd. for $C_{18}H_{24}N_2$: C, 80.5; H, 9.0; N, 10.4. Found: C, 80.5; H, 9.3; N, 10.5.

(−)-N²-Methyl-N¹-phenyl-1,2-propanediamine (IV).—The forerun from the distillation of the above reaction product was redistilled and the portion which distilled at 88–92° (0.1 mm.) was collected, $n^{25}D$ 1.543, $[\alpha]^{25}D$ −29.8°.

Anal. Calcd. for $C_{10}H_{16}N_2$: C, 73.1; H, 9.8; N, 17.1. Found: C, 72.8; H, 10.2; N, 17.0.

(+)-N-[2-(Methylphenethylamino)propyl]propionanilide (III).—A mixture of 1.8 g. of (−)-N²-methyl-N²-phenethyl-N¹-phenyl-1,2-propanediamine and 5 ml. of propionic anhydride was heated on the steam bath for 2 hr. and distilled. (+)III was collected at 160–165° (0.1 mm.), $n^{25}D$ 1.544, $[\alpha]^{25}D$ +25.2.°

Anal. Calcd. for $C_{21}H_{28}N_2O$: C, 77.7; H, 8.7; N, 8.6. Found: C, 76.9; H, 8.6; N, 8.7.

(−)-N-[2-(Methylphenethylamino)propyl]propionanilide (III). Method A.—(+)-N²-Methyl-N²-phenethyl-N¹-phenyl-1,2-propanediamine was treated with propionic anhydride as described for (+)III. (−)III was collected at 162–166° (0.05 mm.), $n^{25}D$ 1.545, $[\alpha]^{25}D$ −25.9°.

Anal. Calcd. for $C_{21}H_{28}N_2O$: C, 77.7; H, 8.7; N, 8.6. Found: C, 76.7; H, 8.8; N, 8.5; H_2O, 1.2.

Method B.—A mixture of 3.0 g. of (+)-N-[2-(benzylmethylamino)propyl]-propionanilide hydrochloride and 10 ml. of *N* sodium hydroxide was shaken and the organic base was extracted into ether. The ether layer was dried over magnesium sulfate and concentrated to remove the solvent. The residue was mixed with 80 ml. of 90% ethanol and 0.5 g. of 10% palladium-on-carbon catalyst and reduced in a Parr hydrogenator under about 3.099 kg./cm.² of hydrogen. The reaction flask was opened, 1.08 g. of phenylacetaldehyde and 0.5 g. of catalyst was added and the reduction was continued for 20 hr. The catalyst was filtered off and the mother liquor was concentrated to remove solvents. The residue was dissolved in 20 ml. of *N* hydrochloric acid, extracted with ether and the ether layer was discarded. The aqueous layer was made alkaline by addition of 8 ml. of 5 *N* sodium hydroxide and the organic base was extracted into ether. The ether layer was distilled and 1.4 g. (50% of (−)III, $n^{25}D$ 1.543, $[\alpha]^{25}D$ −25.2°, was collected at 160–165° (0.1 mm.).

Acknowledgment.—We wish to thank Mr. L. Brancone and staff for the microanalyses and Mr. W. Fulmor and associates for the determination of optical rotations.

New Psychotropic Agents.[1a] IV. Derivatives of Dibenzo[a,d][1,4]cycloöctadiene

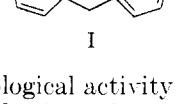
STANLEY O. WINTHROP,[1b] M. A. DAVIS,[1b] F. HERR,[1c] J. STEWART,[1c] AND ROGER GAUDRY

Ayerst Research Laboratories, Montreal, Canada

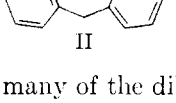
Received September 14, 1962

A series of 5-dialkylaminoalkyl-5-hydroxydibenzo[a,d][1,4]cycloöctadienes was prepared by treating dibenzo[a,d][1,4]cycloöctadien-5-one with basically substituted Grignard reagents. The corresponding 5-dialkylaminoalkyl- and 5-dialkylaminoalkylidenedibenzo[a,d][1,4]cycloöctadienes also were synthesized. Several of the compounds exhibited central and peripheral pharmacological activities similar to amitriptyline and other dibenzo[a,d][1,4]cycloheptadiene compounds. In general they were less potent centrally than amitriptyline and had less pronounced mydriatic effects.

A previous paper[2] in this series described the preparation of a number of compounds derived from dibenzo[a,d][1,4]cycloheptadiene (I). Other laboratories also have reported their investigations[3] on these and closely related compounds. Because of the pronounced pharmacological activity exhibited by many of the dibenzo[a,d][1,4]cycloheptadienes it became of interest to extend our investigations to the synthesis of related compounds derived from the homologous dibenzo[a,d][1,4]cycloöctadiene ring system (II).



I



II

Dibenzo[a,d][1,4]cycloöctadien-5-one (VI) has been reported[4] as an impure solid which was characterized only as its 2,4-dinitrophenylhydrazone. Since the reported synthesis is rather lengthy and the final product was obtained in low yield, an alternative method was developed which gave the desired ketone more readily. *o*-Phthalaldehydic acid (III) was treated with phenethylmagnesium bromide to form 3-(2-phenethyl)-phthalide (IV). Reduction with hydriodic acid and red phosphorus then produced 2-(3-phenylpropyl)benzoic acid (V) which underwent cyclodehydration with polyphosphoric acid to yield the ketone VI as a solid which easily was purified and characterized.

Attempts were made to synthesize 3-chlorodibenzo[a,d][1,4]cycloöctadien-5-one and dibenzo[a,d][1,4]-cyclononadien-5-one by a similar scheme to that described for VI. In both cases the syntheses failed at the cyclization step. Varying the reaction times and

(1) (a) Paper III in this series: S. O. Winthrop, M. A. Davis, F. Herr, J. Stewart, and R. Gaudry, *J. Med. Pharm. Chem.*, **5**, 1207 (1962); (b) Department of Chemistry; (c) Department of Pharmacology.

(2) S. O. Winthrop, M. A. Davis, G. S. Myers, J. G. Gavin, R. A. Thomas, and R. Bacher, *J. Org. Chem.*, **27**, 230 (1962).

(3) (a) M. Protiva, V. Hnevsova-Seidlova, Z. S. Veidelek, J. Jirkovsky, Z. Vejdova, and J. Metysova, *J. Med. Pharm. Chem.*, **4**, 411 (1961); (b) F. J. Villani, C. A. Ellis, C. Teichman, and C. Bigo, *ibid.*, **5**, 373 (1962); (c) E. L. Engelhardt, M. E. Christy, H. C. Zell, C. M. Dylion, M. B. Freedman, and J. M. Sprague, American Chemical Society, 141st Natl. Meeting Abstracts, March 26, 1962.

(4) C. D. Gutsche, E. F. Jason, R. S. Coffey, and H. E. Johnson, *J. Am. Chem. Soc.*, **80**, 5756 (1958).