SYNTHESIS OF TRITIUM AND CARBON-14 LABELED 1,3-DIOXOLANES

1. *d-* and *l*-2,2-Diphenyl-4-(2-piperidyl)-1,3-dioxolane Hydrochloride.

Richard S. P. Hsi and Richard C. Thomas,Jr.
Research Laboratories
The Upjohn Company
Kalamazoo
Michigan 49001
U.S.A.
Received on February 5, 1973

SUMMARY

Condensation of dimethoxydiphenylmethane-^{14}C (III) with the levoratatory (IIa) and dextrorotatory (IIb) isomers of 2-(2-piperidyl)-1,2-ethanediol hydrochloride, obtained respectively by hydrolysis from the d and l isomers (Ia and Ib) of the lower melting racemate of 2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane hydrochloride, produces the carbon-14 labeled dioxolanes Ic and Id with retention of configuration at the asymmetric carbon atoms. Stepwise reduction of 2,2-diphenyl-4-(1-benzyl-2-pyridyl)-1,3-dioxolane bromide (VI), first with sodium borohydride, followed by catalytic reduction with tritium gas, affords a mixture (Ie) of two tritium-labeled racemates of 2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane. The lower melting racemate was isolated as its dl-tartaric acid salt (If) and resolved to give optically active tritium-labeled dioxolanes Ig and Ih.

INTRODUCTION

Dexoxadrol* (Ia) and levoxadrol* (Ib) are the hydrochloride salts of the

---

*Generic names. Dexoxadrol is also referred to as U-22,559A or CL-911-C in the literature, and levoxadrol as U-22,304A or CL-912-C. These compounds were discovered by Cutter Laboratories.

d and *l* enantiomers obtained by resolution of the lower melting racemate, hereinafter referred to as the α-racemate, of 2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane. They are members of a group of substituted 1,3-dioxolanes which affect the central nervous system.[1] The pharmacology[2,3,4] and physical-chemical properties[5] of Ia and Ib have been reported. The analgesic and anesthetic activities of Ia have been studied clinically.[6-9] In this report we shall describe the synthesis of radioactive forms of Ia and Ib for use in metabolism studies in animals and man. Because of their ketal structure, Ia and Ib are susceptible to acid-catalyzed hydrolysis.[5,10] In order to provide the means for tracing the fragments, should hydrolysis of Ia and Ib occur *in vivo*, we incorporated the carbon-14 label into the dioxolane ring at C-2 and the tritium label into the piperidine ring.

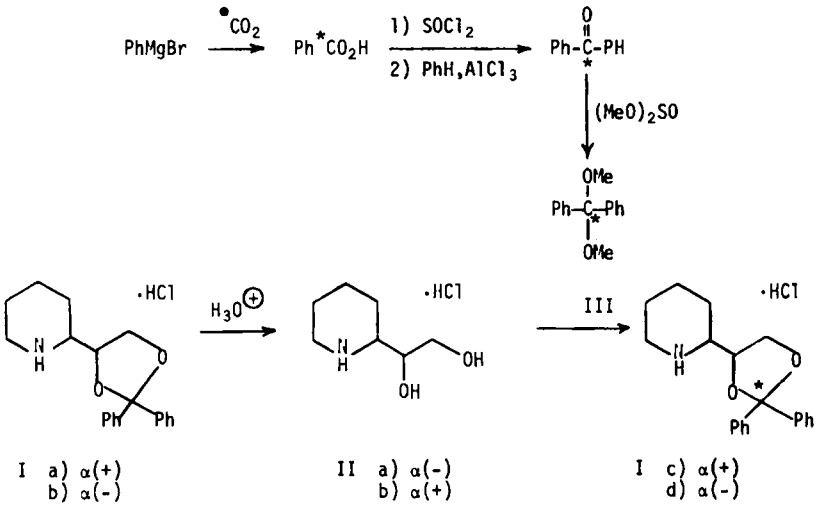
DISCUSSION AND RESULTS

Carbon-14 Labeled Ic and Id

In preparing carbon-14 labeled Ia and Ib, advantage was taken of the fact that hydrolysis of Ia and Ib to the corresponding diols IIa and IIb, and the reverse condensation of IIa and IIb with dimethoxydiphenylmethane (III), occur with retention of configuration at the two asymmetric carbon atoms. It is of interest to note that the α*d* isomer ($[\alpha]_D$ + 35°) of the dioxolane is associated with the α*l* isomer ($[\alpha]_D$ - 8°) of the diol, and α*l*-dioxolane with α*d*-diol. The optically pure diols IIa and IIb obtained from non-radioactive Ia and Ib were condensed with III, as shown in Scheme I, to prepare carbon-14 labeled Ic and Id. This route eliminated the need for separation of racemates and resolution of enantiomers, and maximized radiochemical yields. The ketalization agent III was prepared by treating benzophenone-^{14}C with dimethylsulfite according to known procedures.[11]

Scheme 1

Synthesis of Carbon-14 Labeled
d- and *l*-2,2-Diphenyl-4-(2-piperidyl)-1,3-dioxolane Hydrochloride



I a) α(+)
b) α(-)

II a) α(-)
b) α(+)

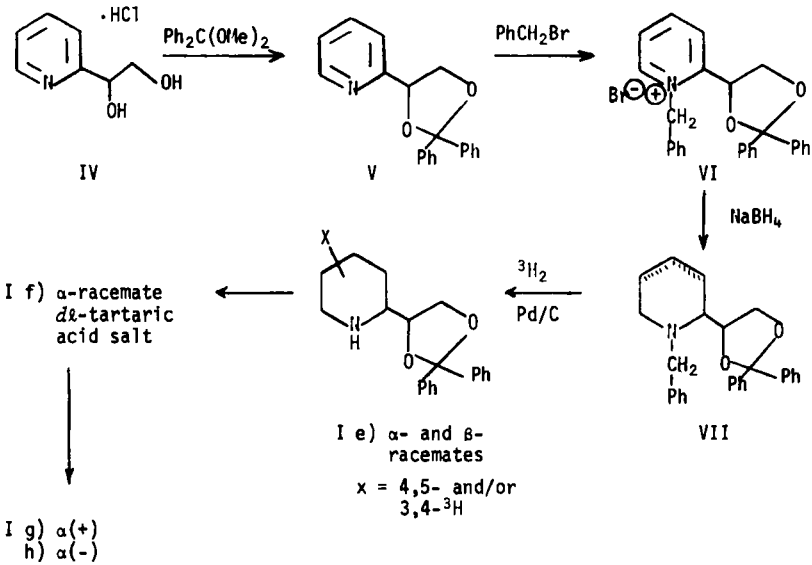
I c) α(+)
d) α(-)

Tritium Labeled Ig and Ih

The preparation of tritium labeled Ig and Ih is outlined in Scheme 2. 2,2-Diphenyl-4-(2-pyridyl)-1,3-dioxolane (V), obtained by reaction of 2-(2-pyridyl)-1,2-ethanediol hydrochloride (IV) with dimethoxydiphenylmethane, was quarternized with benzyl bromide to give VI. Reduction of VI with sodium borohydride afforded a mixture of isomeric 2,2-diphenyl-4-(1-benzyl-tetrahydropyridyl)-1,3-dioxolanes VII. Although by analogy to literature examples,[12,13] the double bond is believed to be at the 4,5-position in the tetrahydropyridine ring, the 3,4-position cannot be ruled out. Further reduction of VII with tritium gas in the presence of palladium on charcoal catalyst produced a mixture (Ie) of the two racemates of 2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane labeled with tritium in the 4- and 5-positions, or 3- and 4-positions, or both, of the piperidine ring. Quantitative infrared spectroscopic analysis of Ie showed that it consisted of 79% of the desired α-racemate and 21% of the β-racemate.[14] The α-racemate was isolated as its *dl*-tartaric acid salt If which was resolved into the enantiomeric Ig and Ih *via* their respective *d*- and *l*-tartaric acid salts.

Scheme 2

Synthesis of Tritium Labeled
d- and *l*-2,2-Diphenyl-4-(2-piperidyl)-1,3-dioxolane Hydrochloride



EXPERIMENTAL

Radioactivity determinations were carried out with a Packard Tri-Carb Model EX-2A liquid scintillation spectrometer, using the internal standard method with Diotol as counting solvent. Optical rotation measurements were made in MeOH solutions. Infrared (IR) spectra were obtained from Nujol mulls with a Perkin-Elmer Model 421 spectrometer. Ultraviolet (UV) spectra were obtained from 95% EtOH solutions with a Cary Model 14 spectrophotometer. Melting points were uncorrected. Microanalyses were obtained for the indicated elements, and the results, except as noted, were within ± 0.4% of theory.

Dimethoxydiphenylmethane-^{14}C (III)

Benzoic acid-α-^{14}C (sp. act. 2.78 mCi/mM) was prepared by the carbonation

of phenyl magnesium bromide with $^{14}CO_2$ according to the procedure of Eberson.[15] Benzophenone-^{14}C (sp. act. 2.69 mCi/ml) was prepared from benzoic acid-α-^{14}C according to the procedure of Speer and Jeanes.[16] A mixture of 1.85 g (10.2 mmoles) of benzophenone-^{14}C, 1.2 ml (13.6 mmoles) of dimethylsulfite and 3 ml of MeOH was heated to reflux with stirring under nitrogen. Heating was discontinued for the refluxing to subside and anhydrous HCl gas was passed into the stirred, hot mixture for 2 min. The mixture was then refluxed with stirring under nitrogen for 4 hrs and kept at room temperature overnight. The mixture containing crystals was diluted with 2 ml of ice-cold MeOH and filtered. The crystals were washed with 5 ml of cold MeOH and dried. There was obtained 1.73 g (76.4%) of III, mp 107-108°C (lit.[11] mp 106-107°C).

Hydrolysis of Ia and Ib

A mixture of 3.46 g of Ia ($[\alpha]_D$ + 35°) and 40 ml of H_2O was heated on steam bath until a homogeneous solution was obtained. To this hot solution was added 10 ml of 1 *N* HCl and the mixture was heated on steam bath for 15 min. The mixture was cooled and extracted twice with 50 ml of Et_2O. The aqueous layer was stirred with 15-20 g of Dowex 3 and filtered. The neutral filtrate was treated with Darco G-60 and again filtered. The filtrate was concentrated at 50°C and water aspirator pressure. The partially solidified residue was crystallized from 15 ml of *i*-PrOH to give 1.53 g (84.2%) of IIa, mp 137-138°C, $[\alpha]_D$ -8° in MeOH, *anal.* ($C_7H_{16}ClNO_2$) C, H, Cl, N. Similarly, Ib ($[\alpha]_D$ -35°) was hydrolyzed to give IIb, mp 136.5-138°C, $[\alpha]_D$ + 8°.

α(+) and α(-) 2,2-Diphenyl-4-(2-piperidyl)-1,3-dioxolane-2-^{14}C Hydrochloride (Ic and Id)

A mixture of 0.955 g (5.25 mmoles) of IIa, 0.850 g of C^{14}-labeled and 0.425 g of non-labeled dimethoxydiphenylmethane (total 5.58 mmoles) and 3 ml of *i*-PrOH was heated to reflux with stirring under nitrogen. The mixture was cooled enough to stop the refluxing and 0.1 ml of a solution of 5 g of anhy-

drous HCl in 100 ml of *i*-PrOH was added to the stirred mixture. Gentle refluxing was resumed under nitrogen for 2.5 hrs. The mixture was then kept at room temperature under nitrogen overnight, filtered, and the crystals were washed in 15 ml of *i*-PrOH in portions followed by Et_2O and dried. There was obtained 1.618 g (89.1%) of Ic, mp ∠54-255°C; $[\alpha]_D$ + 35°; sp. act. 1.85 mCi/mM; IR and UV spectra conformed with standards; *anal.* ($C_{20}H_{24}ClNO_2$) C, H, Cl, N. In a similar manner from 0.955 g (5.25 mmoles) of IIb, there was obtained 1.594 g (87.8%) of Id, mp 254-255°C; $[\alpha]_D$ - 34°; sp. act. 1.86 mCi/mM; IR and UV spectra conformed with standards; *anal.* ($C_{20}H_{24}ClNO_2$) C, H, Cl, N.

2,2-Diphenyl-4-(2-pyridyl)-1,3-dioxolane (V)

A suspension of 52.7 g (0.30 mole) of 2-pyridyl-1,2-ethanediol hydrochloride (IV) (mp 121-122.5°C) and 75.4 g (0.33 mole) of dimethoxydiphenylmethane in 160 ml of *i*-PrOH was heated to reflux with stirring under nitrogen. To this hot mixture was added 6 ml of a solution of 5 g of anhydrous HCl in 100 ml of *i*-PrOH. The mixture was refluxed with stirring under nitrogen for 4 hrs and kept at room temperature overnight. Ether was added and the solids were filtered, thoroughly washed with Et_2O and dried. The solids (62.8 g) were added in small portions to 400 ml of vigorously stirred ice-cold 1.5 *N* NaOH. The solids were filtered, washed with H_2O, and dried. The solids were triturated with ether and any insoluble material was removed by filtration. The Et_2O solution was concentrated and the residue was recrystallized from EtOH-H_2O to give 34.3 g (37.7%) of V, mp 69.5-70.5°C; UV $\lambda_{sh.}^{EtOH}$ 217 nm (ε, 12,050), 227 (5800), 255 (4050), $\lambda_{max.}^{EtOH}$ 260 nm (ε, 4550), and 266 (3250), IR and NMR spectra compatible with the assigned structure; *anal.* ($C_{20}H_{17}NO_2$) C, H, N.

2,2-Diphenyl-4-(1-benzyl-2-pyridyl)-1,3-dioxolane Bromide (VI)

A mixture of 20.0 g (0.066 mole) of V and 20 ml of benzyl bromide was heated with stirring in an oil bath at 120°C for 12 hrs and then kept at room temperature overnight. The resulting solids were dissolved in 200 ml CH_2Cl_2

and 160 ml of Et_2O was added to the solution dropwise with stirring. The crystals were filtered and washed with CH_2Cl_2-Et_2O, followed by Et_2O and dried. There was obtained 27.8 g (88.8%) of VI, mp 167-168°C; UV $\lambda_{max.}^{EtOH}$ 268 nm (ε, 8100), $\lambda_{sh.}^{EtOH}$ 263 nm (ε, 7300), and 277 (6200), IR and NMR spectra compatible with the assigned structure, *anal.* ($C_{27}H_{24}BrNO_2$) C, H, Br, N.

Sodium Borohydride Reduction of VI to VII

A solution of 15.0 g (0.0316 mole) of VI in 300 ml of MeOH was cooled to 5°C in an ice bath. Sodium borohydride (4.5 g, 0.119 mole) was added in portions over a period of 20 min while the bath temperature was held at 5-7°C. The mixture was stirred at room temperature for 2.5 hrs and 120 ml of 1 *N* NaOH was added. The mixture was stirred at room temperature for 1 hr and concentrated at 28°C *in vacuo*. The residue was diluted with 100 ml of H_2O and extracted with 350 ml of Et_2O in two portions. The combined Et_2O extracts were washed with H_2O followed by saturated NaCl solution. After drying for 20 min over magnesium sulfate, the Et_2O solution was filtered and concentrated to about 120 ml and then kept at room temperature overnight. The solution was filtered and concentrated to give 12.80 g (~100% yield) of a light straw-colored syrup which was used without further purification in the next step. This material was unstable and became discolored even when stored under nitrogen. NMR spectrum of this material indicated the assignment of the gross structure VII was correct. The double bond could be at either the 3-4 or 4-5 position.

2,2-Diphenyl-4-(2-piperidyl)-1,3-dioxolane-H^3, α- and β-Racemates (Ie)

A solution of 12.35 g (0.031 mole) of crude VII from above in 150 ml of anhydrous tetrahydrofuran was hydrogenated, using a Paar hydrogenation apparatus, in the presence of 4 Ci of tritium gas and 12.35 g of 10% Pd-C catalyst at an initial pressure of 40 psi. The apparatus was twice refilled with H_2 at 4 and 30 min as the pressure dropped to 3 and 9 psi, respectively. After 2 hrs the uptake had essentially stopped. The mixture was shaken for another 2.5 hrs

before the apparatus was vented and flushed with H_2. Shaking was resumed for 16 hrs at 40 psi to ensure complete removal of the N-benzyl group. The mixture was filtered through a cake of activated charcoal. The filtrate concentrated *in vacuo* and the residue repeatedly redissolved in MeOH and evaporated to remove labile tritium. Quantitative IR analysis of the resulting pale yellow oil (8.71 g, 90.7% yield) showed that it contained 79% of the desired α-racemate and 21% of the ß-racemate. Thin layer chromatographic analysis (silica gel, 25% v/v EtOAc in cyclohexane) indicated that the hydrogenation and hydrogenolysis were complete.

2,2-Diphenyl-4-(2-piperidyl)-1,3-dioxolane-^{3}H, α-Racemate, *dl*-Tartaric Acid Salt (If)

A warm solution of 2.326 g (0.015 mole) of *dl*-tartaric acid in 26 ml of MeOH was added to a solution of 8.622 g (0.0279 mole) of Ie in 35 ml of MeOH. Crystallization, which began immediately, was allowed to proceed for 2.5 hrs. The crystals were filtered, washed with 50 ml of MeOH followed by Et_2O, and dried. There was obtained 7.864 g (73.3% yield) of the α-racemate *dl*-tartrate If, mp 224-225°C.

α(+) and α(-) 2,2-Diphenyl-4-(2-piperidyl)-1,3-dioxolane-^{3}H Hydrochloride (Ig and Ih)

The α-racemate *dl*-tartrate If (5.97 g, 15.5 mmole) was stirred with 50 ml of 1 *N* NaOH and 150 ml of Et_2O until all solids were in solution. The aqueous layer was extracted with Et_2O. The combined Et_2O layers were washed with H_2O followed by saturated NaCl solution and concentrated *in vacuo* to give 5.06 g of oil which was shown by IR analysis to be 99% pure α-racemate.[14] The oil was dissolved in 20 ml of absolute MeOH and to the solution was added 0.565 g (3.76 mmole) of *d*-tartaric acid in 17 ml of MeOH. The mixture was kept at room temperature for 50 min and the resulting crystals were filtered, washed with MeOH followed by Et_2O and dried, 2.543 g (85.2% yield), mp 243-244.5°C. This material was basified with 1 *N* NaOH and the liberated free base was extracted

into Et_2O. The Et_2O extracts were washed with H_2O followed by saturated NaCl solution, dried over anhydrous sodium sulfate, and treated with anhydrous HCl in *i*-PrOH to give 2.168 g (80.9% yield) of Ig, mp 243-247°C; sp. act. 16.42 mCi/mM; $[\alpha]_D$ + 33°; UV and IR spectra conformed with standards; *anal.* ($C_{20}H_{24}ClNO_2$) C, H, Cl, N.

The methanolic mother liquor above, from which the *d*-tartaric acid salt of the α(+) isomer of 2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane-^{3}H had been removed, was concentrated at 30°C *in vacuo* and the residue was triturated with Et_2O. The mixture was filtered to remove insoluble solids (0.384 g) and the filtrate was concentrated *in vacuo*. The residue was dissolved in 18 ml of absolute MeOH and treated with 0.550 g (3.66 mmole) of *l*-tartaric acid to give 2.520 g (84.4% yield) of the *l*-tartaric acid salt of the α(-) isomer of 2,2-diphenyl-4-(2-piperidyl)-1,3-dioxolane-^{3}H, mp 243-245°C. The latter was converted to the α(-) hydrochloride salt Ih, using the same procedure as described above for Ig. There was obtained 1.956 g (73.0% yield based on If) of Ih, mp 243-247°C; sp. act. 16.45 mCi/mM; $[\alpha]_D$ - 33°; UV and IR spectra conformed with standards; *anal.* ($C_{20}H_{24}ClNO_2$) C, H, Cl, N.

ACKNOWLEDGMENT

We are indebted to Messrs. R. C. Anderson and P. A. Spinelli for microanalyses, Mrs. B. F. Zimmer and Mr. P. A. Meulman for obtaining UR and IR spectra, and Mr. G. T. Louthan for optical rotation measurements. Technical assistance by Messrs. R. W. Judy and H. Harpootlian is greatly appreciated.

BIBLIOGRAPHY

1. Hardie W. R., Hidalgo J., Halverstadt I. F., and Allen R. E., *J. Med. Chem.*, 9, 127 (1966).
2. Hidalgo J. and Thompson C. R., *Proc. Soc. Exptl. Biol. Med.*, 114, 92 (1963).

3. Hidalgo J. and Thompson C. R., *Arch. Intern. Pharmacodyn. Therp.*, 153, 105 (1965).

4. Collins R. J. and Weeks J. R., *Psychopharmacologia*, 11, 287 (1967).

5. Kramer S. F. and Flynn G. L., Abstr., APhA Academy of Pharmaceutical Sciences, p. 59, 1972.

6. Lasagna L. and Pearson J. W., *Proc. Soc. Exptl. Biol. Med.*, 118, 352 (1965).

7. Kast E. C., *Int. J. Neuropsychiat.*, 3, 15 (1967).

8. Williams M. W., Williford E. A. Jr., Williams C. S., and Towne J. C., *Arch. Int. Pharmacodyn. Therp.*, 178, 26 (1969).

9. Simopoulos A. M., Pinto A., Babikow P. W., Kurland A., and Savage C., *Dis. Nerv. Syst.*, 31, 203 (1970).

10. Brown L. W. and Forist A. A., "Kinetics of Dexoxadrol Hydrolysis," manuscript submitted to the Journal of Pharmaceutical Sciences.

11. Voss W., *Ann. Chem.*, 485, 283 (1931).

12. Lyle R. E., Nelson B. A., and Anderson T. S., *Tetrahedron Lett.*, 553 (1962).

13. Anderson T. S. and Lyle R. E., *ibid.*, 153 (1964).

14. Krueger W. C. and Hoffman R. A. Jr., The Upjohn Company, unpublished results.

15. Eberson L., *Acta Chem. Scand.*, 16, 781 (1962).

16. Speer R. J. and Jeanes J. K., *J. Am. Chem. Soc.*, 74, 2443 (1952).