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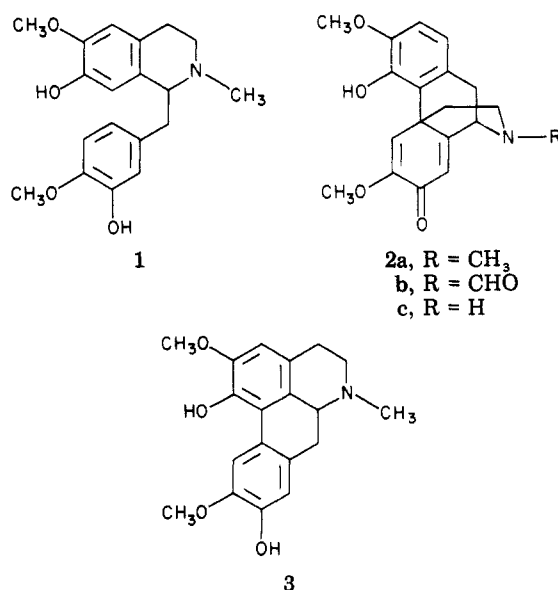
Studies Aimed at the Synthesis of Morphine. 3.¹ Synthesis of (±)-Salutaridine via Phenolic Oxidative Coupling of (±)-Reticuline

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Robinson's seminal suggestions on the biogenesis of morphine² have been further refined by Barton³ and have been supported by in vivo experiments involving the oxidation of reticuline (1) to salutaridine (2a) and the further transformation of this intermediate into morphine.^{4,5}



(1) For part 2 in this series, see C. Szántay, G. Blaskó, M. Bárczai-Beke, P. Péchy, and G. Dörnyei, *Tetrahedron Lett.*, 3509 (1980).

(2) J. M. Gulland and R. Robinson, *Mem. Proc.—Manchester Lit. Philos. Soc.*, 69, 79 (1925).

(3) D. H. R. Barton and T. Cohen, "Festschrift Prof. Dr. Arthur Stoll zum Siebzigsten Geburtstag", Birkhäuser Verlag, Basel, Switzerland, 1957, p 117.

(4) (a) A. R. Battersby, R. Binks, D. M. Foulkes, R. J. Francis, D. J. McCaldin, and H. Ramuz, *Proc. Chem. Soc., London*, 203 (1963); (b) A. R. Battersby, R. Binks, R. J. Francis, D. J. McCaldin, and H. Ramuz, *J. Chem. Soc.*, 3600 (1964); (c) D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, A. R. Battersby, T. A. Dobson, and H. Ramuz, *ibid.*, 2423 (1965); (d) A. R. Battersby, D. M. Foulkes, and R. Binks, *ibid.*, 3323 (1965); (e) A. R. Battersby, D. M. Foulkes, M. Hirst, G. V. Parry, and J. Staunton, *J. Chem. Soc. C*, 210 (1968); (f) R. O. Martin, M. E. Warren, and H. Rapoport, *Biochemistry*, 6, 2355 (1967).

The literature is replete with attempts to convert reticuline, into salutaridine in the laboratory, a transformation which involves para-ortho' phenolic oxidative coupling (*p-o'*). Depending upon experimental conditions, however, only isoboldine (*o-p'* coupling),⁶ isosalutaridine (*p-p'* coupling),⁶ and corytuberine (*o-o'* coupling),⁷ were obtained. The first and so far sole successful transformation of this type was carried out by Barton and co-workers,⁸ who oxidized tritium-labeled (±)-reticuline to (±)-salutaridine using potassium ferricyanide. The product was detected by an isotope-dilution technique and was present in 0.03% yield.

Schwartz and Mami⁹ have found that appreciably improved yields (16–35%, corrected for recovered starting material¹⁰) of the desired *p-o'* products could be accomplished starting with *N*-acetylnorreticulines and using thallium tris(trifluoroacetate) as the oxidizing agent to produce *N*-acetylnorsalutaridine derivatives.

In previously reported experiments we have obtained *N*-acyl- or 6'-halogeno-*N*-acetylnorsalutaridines from the corresponding norreticuline derivatives in 14–58% yield, again correcting for recovered starting materials.¹

We now describe the first in vitro replication of the in vivo process, namely, the conversion of (±)-reticuline (1) into (±)-salutaridine (2a) in preparative quantities. Additionally, this is the first report of the preparation of crystalline (±)-salutaridine.¹¹

(±)-Reticuline (1),¹² in absolute dichloromethane (10⁻³ M) was treated with 0.5 equiv of lead tetraacetate in the presence of 3 molar equiv of trichloroacetic acid at -78 °C (4 h). Extraction of the crude product mixture in chloroform with 0.5–5% aqueous sodium hydroxide resulted in a facile separation of the crude monophenolic salutaridine and the diphenolic byproducts and starting material. TLC purification of the organic layer supplied (±)-salutaridine (2a) which was crystallized from EtOAc in 2.7% corrected yield. From the aqueous layer were obtained (±)-isoboldine (3, 14% corrected) and unreacted (±)-reticuline (1, 48%). Up to now neither (±)-isosalutaridine nor any well-defined other products could be isolated.¹³

The spectral data for the isolated (±)-salutaridine compare well with those cited in the literature.^{4c,11,14} In ad-

(5) R. Borkowski, J. S. Horn, and H. Rapoport, *J. Am. Chem. Soc.*, 100, 276 (1978).

(6) A complete literature survey on this topic has been furnished in ref 9.

(7) T. Kametani, M. Ihara, M. Takemura, Y. Satoh, H. Terasawa, Y. Ohta, K. Fukumoto, and K. Takahashi, *J. Am. Chem. Soc.*, 99, 3805 (1977).

(8) (a) D. H. R. Barton, G. W. Kirby, W. Steglich, and G. M. Thomas, *Proc. Chem. Soc., London*, 203 (1963); (b) D. H. R. Barton, D. S. Bhakuni, R. James, and G. W. Kirby, *J. Chem. Soc. C*, 128 (1967).

(9) M. A. Schwartz and I. S. Mami, *J. Am. Chem. Soc.*, 97, 1239 (1975).

(10) M. A. Schwartz, "Proceedings of the 11th IUPAC International Symposium on the Chemistry of Natural Products", Vol. 4, N. Narekov, I. Ognyanov, and A. Orlovich, Eds., Izd. BAN, Sofia, Bulgaria, 1978, Part 2, pp 274–9; *Chem. Abstr.*, 92, 59050 (1980).

(11) (±)-Salutaridine has been synthesized by Kametani and co-workers from 1-benzyltetrahydroisquinolines by a modified Pasch reaction,^{11a} and by a photochemical route^{11bc} in 1.1% and 1% yields, respectively. The product was characterized as an oil. (a) T. Kametani, M. Ihara, K. Fukumoto, and H. Yagi, *J. Chem. Soc. C*, 2030 (1969); (b) T. Kametani, H. Nemoto, T. Nakano, S. Shibuya, and K. Fukumoto, *Chem. Ind. (London)*, 788 (1971); (c) T. Kametani, K. Fukumoto, S. Shibuya, H. Nemoto, T. Nakano, T. Sugahara, T. Takahashi, Y. Aizawa, and M. Toriyama, *J. Chem. Soc., Perkin Trans. 1*, 1435 (1972).

(12) (±)-Reticuline was obtained in 96% yield from the lithium aluminum hydride reduction of *N*-(ethoxycarbonyl)norreticuline in dioxane.

(13) The reaction is supposed to proceed via a Wessely-type *p*-quinol acetate; this intermediate, however, could not be isolated or identified from the reaction mixture. (a) F. Wessely, J. Swoboda, and V. Guth, *Monatsh. Chem.*, 95, 649 (1964); (b) B. Umezawa, O. Hoshino, *Heterocycles*, 3, 1005 (1975).

dition to spectroscopic adequacy, the hydrolysis of the previously reported^{1,10} (\pm)-*N*-formylnorsalutaridine (**2b**) was carried out to provide (\pm)-norsalutaridine (**2c**) which was immediately *N*-methylated by the Eschweiler-Clarke method to supply (\pm)-salutaridine (**2a**) identical with the material obtained by direct oxidation of (\pm)-reticuline (**1**).

The present effort represents the first preparation of salutaridine from reticuline in preparative amounts and adds further weight to the previously formulated hypotheses concerning the biogenesis of morphine-type alkaloids.

Experimental Section

General Procedures. The melting points are uncorrected. UV spectra were determined in methanol on a Unicam SP-700 spectrophotometer. IR spectra were recorded on Nicolet-7199 and Spectromom 2000 infrared spectrophotometers. ¹H NMR spectra were determined on a disk-augmented Varian XL-100-15 instrument, and ¹³C NMR spectra were determined on the same spectrometer in the FT mode operating at 25.16 MHz. Deuteriochloroform was used as solvent and Me₄Si as an internal standard. Chemical shifts are reported as δ values in parts per million relative to Me₄Si. Mass spectra were obtained with an AEI MS-902 instrument (70 eV, direct insertion). Silica gel PF-254 coated plates (E. Merck) were used for the purposes of qualitative TLC and preparative layer chromatography (PLC).

All the reactions and solvent evaporations were carried out under an argon atmosphere. MgSO₄ was used as the drying agent. The dichloromethane used in oxidation reactions was treated with concentrated H₂SO₄, water, and concentrated NaOH, dried over CaCl₂, distilled, and stored over 4-Å molecular sieves.

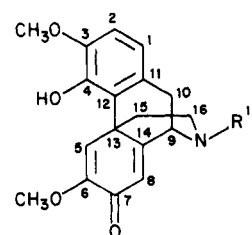
Oxidation of (\pm)-Reticuline (1**) with Lead Tetraacetate.** Preparation of (\pm)-Salutaridine (**2a**). In a carefully dried flask and under an argon atmosphere was dissolved (\pm)-reticuline (**1**; 150 mg, 0.45 mmol) in a mixture of dry dichloromethane (390 mL) and trichloroacetic acid (223 mg, 1.35 mmol) at -78 °C. Acetic acid free lead tetraacetate (100 mg, 0.225 mmol) was added to the mixture in two portions (with a 1-h delay). The solution was stirred for additional 4 h at -78 °C, and then it was treated with water (40 mL). The organic layer was separated and washed with aqueous sodium chloride solution (4 × 20 mL), and finally the solvent was removed under reduced pressure.

The residue was taken up in chloroform (30 mL), extracted with sodium hydroxide solutions (3 × 10 mL (0.5%), 10 mL (2%), and 10 mL (5%) solutions consecutively; the last two extracts were reextracted with small portions of chloroform). The combined organic phase was washed with aqueous sodium chloride solution (2 × 5 mL) and evaporated under reduced pressure. The remaining material was purified by PLC with a chloroform-methanol (10:1 v/v) system (*R_f* 0.40) to give pure amorphous (\pm)-salutaridine (**2a**) that was crystallized from ethyl acetate. The colorless crystals of **2a** (2.1 mg, 2.7% yield, corrected for recovered starting material) melted at 202–204.5 °C.

Spectral data for (\pm)-salutaridine are found dispersed throughout the literature. The values we obtained, which are listed here, compare well with the literature data: UV (MeOH) λ_{\max} 238 nm (log ϵ 4.33), 276 (3.81);^{4c,11b,14} IR (KBr) ν_{\max} 1484, 1620, 1640, 1670 cm⁻¹; ¹H NMR (CDCl₃, 100 MHz) δ 2.44 (s, 3 H, NCH₃), 3.74 (s, 3 H, OCH₃), 3.88 (s, 3 H, OCH₃), 6.31 (s, 1 H, H-8), 6.69 (d, *J* = 7 Hz, 1 H, H-1), 6.76 (d, *J* = 7 Hz, 1 H, H-2), 7.55 (s, 1 H, H-5);^{4c,14} mass spectrum, *m/e* (relative intensity) 328 (i, 23), 327 (M⁺, 100), 326 (11), 312 (39), 310 (5), 299 (18), 298 (6), 284 (37), 268 (10), 242 (12), 227 (8), 226 (8).^{11c,14} For ¹³C NMR data see Table I.

Isolation of (\pm)-Isoboldine (3**) and Recovery of the Unreacted (\pm)-Reticuline (**1**).** The sodium hydroxide extracts from the oxidation were combined. The pH was adjusted to 9 with 1% aqueous hydrogen chloride and the mixture extracted with chloroform (3 × 6 mL). After removal of the solvent the crude mixture was separated by PLC with chloroform-methanol (40:3 v/v) with initial ammonia treatment (8 min): *R_f* (**3**) 0.6, *R_f* (**1**) 0.5. The separation provided (\pm)-isoboldine (**3**; 21 mg, 14%

Table I. ¹³C NMR Spectral Data of **2a** and **2c**



2a, R = CH₃
c, R = H

| carbon assignment | chemical shifts, ppm | |
|---------------------------------|----------------------|-----------|
| | 2a | 2c |
| 1 | 119.4 ^a | 118.8 |
| 2 | 110.2 | 109.9 |
| 3 | 145.8 | 145.8 |
| 4 | 143.4 | 143.7 |
| 5 | 119.5 ^a | 120.5 |
| 6 | ^b | 164.0 |
| 7 | 180.4 | 181.4 |
| 8 | 125.1 | 121.3 |
| 9 | 61.5 | 54.4 |
| 10 | 33.3 | 39.0 |
| 11 | 123.7 | 124.1 |
| 12 | 127.4 | 129.8 |
| 13 | 42.8 | 44.3 |
| 14 | 151.4 | 150.8 |
| 15 | 35.1 | 42.7 |
| 16 | 46.9 | 39.6 |
| 17 | 41.0 | |
| C ₃ OCH ₃ | 56.4 | 56.3 |
| C ₆ OCH ₃ | 55.0 | 54.8 |

^a Assignments may be interchanged. ^b Due to the small amount of **2a** the low-intensity signal could not be identified.

corrected yield) and (\pm)-reticuline (**1**; 73.4 mg, 48%). For **3**, mp 194–195 °C dec (CH₂Cl₂; measured in a sealed tube) (lit. mp 185–190^{15a} and 200–203 °C^{15b}). Its spectral data were identical with previously published data.^{15b,16}

(\pm)-Norsalutaridine (2c**).** *N*-Formylnorsalutaridine (**2b**;^{1,10} 120 mg, 0.35 mmol) was dissolved in methanol (20 mL) and 18% aqueous hydrogen chloride (4 mL) and kept at room temperature for 3 days. The methanol was removed under reduced pressure. The residue was basified with ammonium hydroxide then extracted with dichloromethane (4 × 10 mL). Removal of the solvent gave amorphous (\pm)-norsalutaridine (93.1 mg, 85%) which was purified by PLC (*R_f* 0.3 in methylenechloride-methanol, 10:1 v/v) for spectroscopic measurements. The IR and ¹H NMR spectra were identical with literature data:¹⁷ UV (MeOH) λ_{\max} 239 nm (log ϵ 4.93), 278 (sh, 4.56); mass spectrum, *m/e* (relative intensity) 313 (M⁺, 100), 312 (22), 298 (27), 285 (52), 284 (22), 283 (9), 282 (8), 270 (43), 255 (11), 254 (15), 242 (15), 228 (14), 149 (11). For ¹³C NMR data see Table I.

Preparation of (\pm)-Salutaridine (2a**) by Methylation of (\pm)-Norsalutaridine (**2c**).** (\pm)-Norsalutaridine (**2c**; 93 mg, 0.30 mmol) was dissolved in 98% formic acid (6 mL) and 38% aqueous formaldehyde solution (6 mL). The mixture was refluxed for 1 h, cooled, basified with ammonium hydroxide, and then extracted with dichloromethane (5 × 10 mL). The organic layer was washed with saturated ammonium chloride solution, dried, and evaporated. The remaining material was purified by PLC with dichloromethane-methanol (150:12 v/v) to supply (\pm)-salutaridine (**2a**; 57.5 mg, 50.2%; *R_f* 0.35) which was identical in every respect

(14) S. Pfeifer and L. Kuhn, *Pharmazie*, **23**, 267 (1968).

(15) (a) T. Kametani, H. Sugi, S. Shibuya, and K. Fukumoto, *Tetrahedron*, **27**, 5375 (1971). (b) M. A. Schwartz, *Synth. Commun.*, **3**, 33 (1973).

(16) (a) A. H. Jackson, J. A. Martin, *J. Chem. Soc. C*, 2061 (1966); (b) W. Wan-Chiu Chan and P. Maitland, *ibid.*, 753 (1966).

(17) (a) M. A. Schwartz, U.S. Patent 4 003 903; (b) I. S. Mami, Ph.D. Dissertation, The Florida State University, 1978, p 62.

with that obtained from the direct phenolic oxidative coupling of (\pm)-reticuline (1).

Acknowledgment. We thank the CHINOIN Pharmaceutical and Chemical Works (Budapest) for financial support and Dr. E. Baitz-Gács for the NMR and Dr. J. Tamás for the mass spectral measurements.

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Aromatic Substitution. 50.¹ Mercury(II)-Promoted Azeotropic Nitration of Aromatics over Nafion-H Solid Superacidic Catalyst

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In the course of our continued studies of nitration, we have previously reported² a new improved method of the nitration of aromatic compounds with nitric acid over a solid superacidic perfluorinated resin sulfonic acid (Nafion-H) catalyst.³ We have subsequently also examined the nitration of aromatic compounds with a variety of other nitrating agents with Nafion-H catalysis.^{2,4} With a solid superacid catalyst, the need for sulfuric acid (or other acids) can be eliminated, which also results in ease of workup. The catalyst can simply be separated, at the end of the reaction, by filtration. Further, one of the main problems with nitrations using nitric acid-sulfuric acid mixtures is that the nitration produces a molar equivalent of water, which causes dilution of the acid. Consequently, only a small portion of nitric acid is utilized during the reaction as the rate of nitration slows down considerably upon dilution. It is therefore highly desirable to remove water during the course of nitration with nitric acid. We have carried out Nafion-H-catalyzed nitrations both with concentrated and fuming nitric acid under conditions of azeotropic removal of water. It was thus possible to utilize nitric acid to a much larger degree than under conventional conditions of nitration.

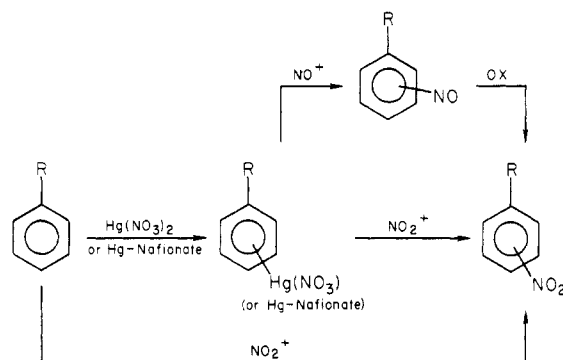
It is highly desirable in aromatic nitration to be able to change the obtainable isomer ratios of products from those obtained in conventional acid-catalyzed nitrations. One of the reported methods, in extension of similarly known effects in sulfonation,⁵ is the nitration of aromatics with nitric acid in the presence of mercury(II) salts. Recently Stock has investigated in detail such nitrations in solution.^{6,7} These nitrations provide isomer ratios significantly

Table I. Hg²⁺-Promoted Nitrations of Aromatics over Nafion-H Catalyst

| substrate | yield, ^a % | isomer (distribution, %) |
|-------------------|--------------------------|---|
| benzene | 71 | |
| toluene | 67 | 2-nitro (33), 3-nitro (7), 4-nitro (60) |
| ethylbenzene | 66 | 2-nitro (38), 3-nitro (5), 4-nitro (44), acetophenone (13) |
| tert-butylbenzene | 72 | 2-nitro (11), 3-nitro (17), 4-nitro (72) |
| o-xylene | 56 | 3-nitro (33), 4-nitro (67) |
| m-xylene | 48 | 2-nitro (11), 4-nitro (89) |
| chlorobenzene | 59 | 2-nitro (37), 3-nitro (2), 4-nitro (61) |
| bromobenzene | 76 | 2-nitro (44), 4-nitro (56) |
| naphthalene | 77 | 1-nitro (97), 2-nitro (3) |

^a Yields are based on the amount of nitric acid.

Scheme I



different from those obtained in the absence of mercury salts. It seemed, however, of interest to try to extend the scope of such nitrations by developing a catalytic method for mercury-promoted nitration.

Results and Discussion

In continuation of our studies of the development of new nitration methods, we report now on the mercury(II)-impregnated Nafion-H-catalyzed nitration of aromatics with nitric acid under conditions of azeotropic removal of water.

Nitration of various aromatic substrates was carried out with concentrated nitric acid (70%) over Nafion-H catalyst in the presence of mercuric nitrate (20% by weight with respect to Nafion-H). The reactions were carried out under conditions of azeotropic removal of water. Table I summarizes the results of present study.

The yields of nitro aromatics (Table I) vary substantially. This is due to the fact that part of the nitric acid distills over in the form of binary and ternary azeotropes (which can be, however, reused if needed upon concentration). Further nitric acid also undergoes some decomposition under the reaction conditions, liberating nitrous gases. As the water formed is removed azeotropically from the reaction vessel, the catalyst (mercury-impregnated Nafion-H)⁸ can be recovered without loss of activity and reused. The mercury(II) ion partly is bound to the acidic Nafion resin (Nafion-Hg) but is also soluble in the nitric acid layer. Regardless of this, under the azeotropic conditions of water removal the mercury salt is not removed, and the Nafion-H impregnated with Hg²⁺ stays catalytic.

The function of the superacidic Nafion-H catalyst is to promote the formation of NO₂⁺ from nitric acid. The

(1) For part 49, see: Olah, G. A.; Narang, S. C.; Olah, J. A. *Proc. Natl. Acad. Sci. U.S.A.* 1981, 78, 3298.

(2) Olah, G. A.; Malhotra, R.; Narang, S. C. *J. Org. Chem.* 1978, 43, 4628.

(3) Nafion is the trade name of Du Pont Co. for a commercially available perfluorinated resin sulfonic acid. The active H form was generated as described earlier.²

(4) Olah, G. A.; Narang, S. C. *Synthesis* 1978, 690.

(5) The mercury-promoted sulfonation of polycyclic aromatics is a well-recognized industrial process. For a discussion, see: Cerfontain, H. "Mechanistic Aspects in Aromatic Sulfonation and Desulfonation"; Interscience: New York, 1968; p 37.

(6) Stock, L. M.; Wright, T. L. *J. Org. Chem.* 1977, 42, 2875.

(7) Stock, L. M.; Wright, T. L. *J. Org. Chem.* 1979, 44, 3467.

(8) Any aqueous washing of the catalyst removes the mercury salt and regenerates Nafion-H without any loss of activity.