

## A Rapid, Simplified Synthesis of $\alpha$ -Bromo-d-camphor- $\pi$ -sulfonic Acid and Its Salts

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### Abstract

A rapid, simplified preparation of ammonium  $\alpha$ -bromo-d-camphor- $\pi$ -sulfonate, based upon the method of REGLER and HEIN, has been developed. The product is obtained in 34.5% yield by neutralization of the reaction mixture with aqueous ammonia, followed by evaporation of the solution and extraction of the residue with boiling ethanol. The free acid as well as its other salts may be prepared by cation exchange.

### Inhaltsübersicht

Eine rasche, einfache Darstellung des Ammonium- $\alpha$ -brom-d-campher- $\pi$ -sulfonats, auf das Verfahren von REGLER und HEIN begründet, ist entwickelt worden. Das Produkt wird in 34,5% Ausbente durch Neutralisierung des Reaktionsgemisches mit wasserhaltigem Ammoniak erhalten. Anschließend wird die Lösung eingedampft und der Rückstand mit siedendem Äthanol ausgezogen. Die freie Säure sowohl als ihre anderen Salze mögen durch Kationenaustausch dargestellt werden.

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PASTEUR's method of diastereoisomer formation<sup>1</sup>), the most widely used procedure for resolving racemic mixtures, was severely limited for many years inasmuch as naturally occurring optically active acids and bases are weak and their salts often hydrolyze in aqueous solution. After MARSH and COUSINS' synthesis<sup>2</sup>) of the strong optically active acid,  $\alpha$ -bromo-d-camphor- $\pi$ -sulfonic acid, in 1891, KIPPING and POPE<sup>3</sup>) in 1893 introduced the use of this substance and its salts as much needed and versatile resolving agents applicable to cations containing not only asymmetric carbon atoms<sup>4</sup>) but

<sup>1</sup>) L. PASTEUR, *Compt. rend.* **35**, 176 (1852); **38**, 110 (1853).

<sup>2</sup>) J. E. MARSH and H. H. COUSINS, *ibid.* **59**, 966 (1891).

<sup>3</sup>) F. S. KIPPING and W. J. POPE, *J. chem. Soc. London* **63**, 577 (1893).

<sup>4</sup>) W. J. POPE and J. S. PEACHEY, *Proc. Chem. Soc.* **194**, 122 (1898); *J. chem. Soc. London* **75**, 1067 (1899); W. J. POPE and E. M. RICH, *ibid.* 1093; W. J. POPE and A. W. HARVEY, *ibid.* **79**, 74 (1901); F. S. KIPPING, *ibid.* **81**, 675 (1902); **83**, 873, 889 (1903); G. TATERSALL and F. S. KIPPING, *ibid.* 918; A. E. HUNTER and F. S. KIPPING, *ibid.* 1147; W. J. POPE and C. S. GIBSON, *ibid.* **97**, 2207 (1910); W. J. POPE and J. READ, *ibid.* 2199; W. H. PERKIN and R. ROBINSON, *ibid.* **99**, 775 (1911).

also to other asymmetric atoms as well<sup>5</sup>). By means of the silver salt, WERNER<sup>6</sup>) accomplished the first resolution of a coordination compound, and he subsequently used the acid and its salts for the majority of his historic resolutions<sup>7</sup>).

A number of different syntheses for the acid and its salts have been devised<sup>8</sup>). All of these were critically compared and experimentally evaluated by REGLER and HEIN<sup>9</sup>), who proposed a very practical synthesis based upon the sulfonation of d-bromocamphor. Although their method yields a pure product in good yield, the required filtration of the calcium sulfate and calcium carbonate precipitates and evaporation of extremely large volumes of solution under reduced pressure are very tedious and time-consuming. In the synthesis described below, which avoids these disadvantages, the ammonium salt is separated from the reaction mixture by virtue of its solubility in boiling ethanol. The procedure requires little attention or manipulation and only one day as compared to the several days required for REGLER and HEIN's procedure.

### Experimental

To 20.0 ml of fuming sulfuric acid (spec. grav. 1.865; 7% SO<sub>3</sub>) contained in a 250-ml round-bottom flask is added, with mechanical stirring, 19.0 g (0.0822 mole) of d-3-bromocamphor, in ca. 1-g portions. During the addition (a period of ca. 1/2 hour), the temperature is kept at 15–18 °C by means of an ice bath. The amber-colored solution is then heated to 50–55 °C, a temperature which is maintained for 20 minutes with continuous mechanical stirring.

After the solution, which is now deep red, has been cooled to 20 °C in an ice bath, it is poured through a 3-inch funnel filled with cracked ice into a 250-ml beaker containing 50 ml of iced water. The resulting violet suspension is placed in an ice bath and is cautiously neutralized with concentrated aqueous ammonia (28%) (ca. 55 ml) until just basic to litmus. By means of a heating mantle, it is then gently and cautiously evaporated as nearly to dryness as possible. Any remaining liquid is removed by filtration and similarly evaporated.

<sup>5</sup>) W. J. POPE and J. S. PEACHEY, Proc. Chem. Soc. **16**, 42, 116 (1900); J. chem. Soc. London **77**, 1072 (1900); S. SMILES, *ibid.* 1174; W. J. POPE and A. NEVILLE, *ibid.* **81**, 1552 (1902); E. WEDEKIND and E. FRÖHLICH, Ber. dtsh. chem. Ges. **38**, 3438, 3933 (1905); J. MEISENHEIMER and L. LICHTENSTADT, *ibid.* **44**, 356 (1911); T. M. LOWRY and F. L. GILBERT, J. chem. Soc. London **1929**, 2867; J. C. BAILLAR and R. W. AUTEN, J. Amer. chem. Soc. **56**, 774 (1934).

<sup>6</sup>) A. WERNER, Ber. dtsh. chem. Ges. **44**, 1887 (1911).

<sup>7</sup>) A. WERNER, Ber. dtsh. chem. Ges. **44**, 2445, 3132, 3272 (1911); *idem* and G. TSCHERNOFF, *ibid.* **45**, 3294 (1912); A. WERNER, Ber. dtsh. chem. Ges. **46**, 3674 (1913); **47**, 1961 (1914); Helv. chim. Acta **1**, 5 (1918); *idem*, J. E. SCHWYZER and W. KARRER, *ibid.* **4**, 113 (1921).

<sup>8</sup>) F. S. KIPPING and W. J. POPE, J. chem. Soc. London **67**, 356 (1895); W. J. POPE and J. S. PEACHEY, *ibid.* **73**, 895 (1898); W. J. POPE and J. READ, *ibid.* **97**, 2200 (1910); J. MEISENHEIMER, Ber. dtsh. chem. Ges. **41**, 3973, Anm. (1908).

<sup>9</sup>) H. REGLER and F. HEIN, J. prakt. Chem. **148**, 1 (1937).

The combined residues are refluxed overnight with 150 ml of absolute ethanol in a Soxhlet apparatus<sup>10</sup>), and the resulting brownish extract is evaporated to dryness under reduced pressure<sup>11</sup>) with gentle heating. The light tan residue is washed with four 10-ml portions of acetone in order to remove unreacted bromocamphor<sup>12</sup>). The yield of air-dried ammonium salt is 9.3 g (34.5%). Decomposition point, 268–270°C. For a 2.184% aqueous solution in a 1-dm tube,  $n_D^{22} = +1.79^\circ$ , and  $[\alpha]_D^{22} = +81.9^\circ$ .

The product may be converted quantitatively into the parent acid or into its other salts by allowing a concentrated solution of the ammonium salt to flow through a column of the appropriate form of a strongly acidic cation exchange resin<sup>13</sup>) and by evaporating the effluent to dryness under reduced pressure<sup>11</sup>). For example, for a 1.606% aqueous solution of the silver salt ( $\text{AgC}_{10}\text{H}_{14}\text{O}_4\text{BrS}$ , recrystallized from ethanol) in a 1-dm tube,  $n_D^{22} = -1.004^\circ$ , and  $[\alpha]_D^{22} = +62.5^\circ$ .

The financial assistance of the Petroleum Research Fund of the American Chemical Society (Grant 1152-B), the California State College at Fresno Research Committee (NSF Institutional Research Grant), and of the National Science Foundation (Undergraduate Research Participation Program-GY 372) is gratefully acknowledged. The author also wishes to thank GARY L. ANDERSON and RICHARD HOUGHTEN for experimental assistance.

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<sup>10</sup>) The ethanol-insoluble residue, which consists largely of ammonium sulfate, is optically inactive.

<sup>11</sup>) Rotary vacuum evaporator 1007-4 N, Rinco Instrument Co., Greenville, Illinois, USA.

<sup>12</sup>) Unreacted starting material may be recovered from the acetone washings by addition of about ten times their volume of water. After filtration and air-drying, the resulting precipitate can amount to as much as 7 g of d-3 bromocamphor.

<sup>13</sup>) Dowex 50, X 8, -50 + 100 mesh was used.

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Bei der Redaktion eingegangen am 24. Februar 1966.