hasten to add that the foregoing statement applies only for systems containing relatively small amounts of the second component which would be likely to behave as an ideal solute because of its small concentration and chemical similarity, for example, hydrocarbons containing a small amount of a second component as impurity.

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The Resolution of Atabrine Dihydrochloride

BY F. A. BACHER, R. P. BUHS, J. C. HETRICK,[1] W. REISS[2] AND N. R. TRENNER

In a forthcoming publication Seeler and Malanga[3] describe their findings concerning the comparative activity of the optical isomers of atabrine against avian malaria. In our attempt to prepare the necessary optical isomers used in the above work, the methods of Chelintsev and Osetrova[4] were tried without marked success. As a result we investigated the use of other bromocamphorsulfonic acids and, as will be described below, found that the 3-bromo-[*d*-camphor]-sulfonic acid-7 formed diastereoisomeric salts which were easily separable.

Experimental

3-Bromo-(*d*-camphor)-sulfonic Acid-7.—This substance was prepared using the method of Kipping and Pope,[5] who described the formation of its ammonium salt. The actual free acid was prepared from the ammonium salt by the use of excess barium hydroxide to eliminate the ammonia followed by quantitative addition of 2 *N* sulfuric acid to remove the barium as sulfate. The aqueous solution of the free acid so obtained was concentrated under reduced pressure to a light yellow sirup which crystallized as a hydrate. This was subsequently dried *in vacuo* at 100° to yield the solid anhydrous acid which was not further treated before use.

The Resolution of *d,l*-Atabrine.—Eleven and four-tenths grams of atabrine base and 17.6 g. of 3-bromo-(*d*-camphor)-sulfonic acid-7 were heated on the steam-bath in 10 cc. of ethylene glycol monoethyl ether (cellosolve) until a clear thick sirup was obtained. The sirup was then dissolved in 500 cc. of hot acetone, immediately filtered and the filtrate allowed to stand at room temperature at least overnight, during which time crystallization occurred. Nine grams (fraction 1) of a partially resolved *d*-atabrine 3-bromo-(*d*-camphor)-sulfonate-7 was obtained on filtering.

In following the degree of resolution achieved in any fraction, the following procedure was developed for evaluating the specific rotation. A weighed sample of the atabrine sulfonate salt (about 20 mg.) was dissolved in about 10 cc. of water and after treatment with 2 drops of about 30% sodium hydroxide, to liberate the atabrine base, the whole was extracted with an equal volume of diethyl ether. After equilibration and washing with water, an aliquot of the ether phase (8 cc.) was removed and extracted with 3 cc. of water containing 2 drops of *N* hydrochloric acid. The ether phase was then removed and the aqueous phase freed of dissolved ether by heating on the steam-bath for a few minutes. The optical rotation of this solution was then observed in the usual manner. The atabrine dihydrochloride concentrate was determined by spectrophotometry at the 4250 Å. band head after appropriate dilution with *p*H 2 glycine–hydrochloric acid buffer. Under these conditions the specific absorption of pure atabrine dihydrochloride was $E^{1\,cm.}{}_{1\%}$ 198, and satisfactory agreement with Beer's law was found. The specimen of *dl*-atabrine dihydrochloride used for establishing the above extinction coefficient was found by solubility analysis to be better than 99% pure. Fraction 1 was thus found to correspond to atabrine dihydrochloride of $[\alpha]^{23}D$ +163° (dilute hydrochloric acid).

The 9 g. of fraction 1 was dissolved in 20 cc. of absolute ethanol, 60 cc. of acetone was added, and after seeding and standing overnight 6 g. (fraction 2) of acetone-washed material was obtained by filtration. Fraction 2 was found to correspond to a dihydrochloride of $[\alpha]^{23}D$ +262° (dilute hydrochloric acid).

Fraction 2 was treated like fraction 1, using the ethanol–acetone procedure, whence 3 g. was obtained of fraction 3, corresponding to dihydrochloride $[\alpha]^{23}D$ +310°. Investigation showed that it was no longer profitable to recrystallize the enriched bromocamphorsulfonate salts further, and so they were converted to the free bases by extraction of the ammoniacal solutions with ether. The ammonium 3-bromo-(*d*-camphor)-sulfonate-7 may be easily recovered from these ammoniacal mother liquors. The ether extracts of atabrine bases were treated with aqueous hydrochloric acid and on concentration of these aqueous solutions the dihydrochlorides crystallized out. In this manner fraction 3 yielded a crystalline dihydrochloride which, after drying (two hours *in vacuo* at 76°) and loss of 5.5% moisture, was found to have the following properties.

Anal. Calcd. for $C_{23}H_{30}ON_3Cl\cdot 2HCl$: C, 58.41; H, 6.82; N, 8.90. Found: C, 58.13; H, 6.73; N, 9.08. Specific rotation $[\alpha]^{23}D$ +311° (5.2 g. per 100 cc. water).

Subsequent investigation revealed that the recrystallization of either *d*-enriched or *l*-enriched atabrine dihydrochloride from water always resulted in deposition of the optically inactive racemate thus concentrating the *d* or *l* isomer in the mother liquor. The use of hot absolute ethanol as the crystallization medium circumvented this. Recrystallization of the +311° fraction from absolute ethanol yielded a product having a specific rotation of $[\alpha]^{23}D$ +355° (2.0 g. per 100 cc. water) and a specific absorption coefficient $E^{1\,cm.}{}_{1\%}$ of 198 at 4250 Å. in *p*H 2.05 buffer. Chelintsev and Osetrova reported a value of +357° for the specific rotation of their pure dextro isomer. The material of $[\alpha]^{23}D$ +355° was used by Seeler and Malanga in their avian malaria experiments.

The mother liquors from fraction 1 deposited, on longer standing in the ice-box (2°) and after seeding with a small sample of enriched *l*-atabrine 3-bromo-(*d*-camphor)-sulfonate-7 (these seeds were obtained during a preliminary small scale pilot experiment), 6 g. (fraction 4) of a salt corresponding to dihydrochloride of specific rotation −158°. The levo enriched fraction 4 was converted to the dihydrochloride as described above, and 1.2 g. of the pure levo isomer isolated directly by recrystallization from absolute ethanol. This product was found to have a specific rotation $[\alpha]^{23}D$ of −334° (2 g. per 100 cc. water) and a specific absorption coefficient $E^{1\,cm.}{}_{1\%}$ of 192. These values were determined on undried material. Drying for two hours at 76° *in vcauo* resulted in a weight loss of 9%.

Anal. Calcd. for $C_{23}H_{30}ON_3Cl\cdot 2HCl$: C, 58.41; H, 6.82. Found: C, 58.46; H, 7.09.

This material was also used by Seeler and Malanga in their avian malaria experiments.

Neither of the optical isomers was found by Seeler and Malanga to be more effective than the *d,l* mixture for

(1) Present address: Philadelphia College of Pharmacy and Science.

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(3) A. O. Seeler and C. Malanga, *Proc. Soc. Exptl. Biol.*, forthcoming publication.

(4) Chelintsev and Osetrova, *J. Gen. Chem., U. S. S. R.*, **10**, 1978 (1940); *C. A.*, **35**, 4029 (1941).

(5) F. S. Kipping and W. J. Pope, *J. Chem. Soc.*, **67**, 356 (1895).

avian malaria, nor was any detectable difference in toxicity for mice observed.

RESEARCH LABORATORIES
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Preparation of 3-Cyano-4-piperidone

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Although N-substituted 4-piperidones have been prepared in satisfactory yields by cyclization procedures from N-alkyl-di-(β-carbethoxyethyl)-amines[1] and from N-alkyl-di-(β-cyanoethyl)-amines,[2] results with the N-unsubstituted analogs have been less gratifying.[3] We have found that di-(β-cyanoethyl)-amine may be converted to 3-cyano-4-piperidone in 70% yield by cyclizing in the presence of sodium, sodium amide or sodium alcoholates, followed by hydrolysis of the intermediate 3-cyano-4-iminopiperidine. When sodium is used as the catalyst it is desirable to use a solvent of the ether class (*e. g.*, dioxane) and to employ a metal carrier (*e. g.*, naphthalene).

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Experimental

3-Cyano-4-iminopiperidine.—Dioxane, 400 ml., distilled from sodium, was charged into a 3-neck flask equipped with a nitrogen inlet, a reflux condenser and drying tube, and an efficient stirrer. Naphthalene, 25 g., sodium, 2 g., and bis-(β-cyanoethyl)-amine,[4] 50 g., were added and the air was displaced by nitrogen. The mixture was stirred several hours on a steam-bath. The pale yellow solution gradually became cloudy and precipitated an amorphous brown solid. The product was worked up in two different ways.

Method A.—The hot reaction mixture was poured into one liter of benzene, cooled and filtered. The uncyclized amine is soluble in benzene, whereas the imine is not. The product was crystallized from ethanol, m. p. 187–188° (dec.). It can also be crystallized readily from acetone or from a mixture of dioxane and alcohol (9:1).

Method B.—The hot dioxane mixture was diluted with about 10% by volume of hot alcohol and the product allowed to crystallize. For the hydrolysis to the piperidone either the benzene or dioxane–alcohol precipitate can be used satisfactorily.

Anal. Calcd. for $C_6H_5N_3$: C, 58.48; H, 7.35; N, 34.10. Found: C, 58.46, 58.55; H, 7.21, 7.30; N, 34.05, 34.12.

Phenyl isothiocyanate derivative had a m. p. 170–171° (dec.).

Anal. Calcd. for $C_{13}H_{14}N_4S$: S, 12.37. Found: S, 12.26, 12.32.

3-Cyano-4-piperidone.—3-Cyano-4-iminopiperidine, 50 g., and 150 ml. of 5 *N* hydrochloric acid were heated to 100° for twenty minutes. The solution was cooled and neutralized to *p*H 4–5 with concentrated sodium hydroxide solution, keeping the temperature below 30°. The fine white crystals were filtered, more sodium hydroxide was added to *p*H 6–7, and the product was again filtered. This process was repeated until the filtrate became alkaline to litmus paper. The crystalline product, after washing with water and alcohol, weighed 41 g. (82% yield). To recrystallize the product it was dissolved in aqueous ammonia and vacuum distilled (water pump) on a steam-bath. The first crop of crystals appeared after half the solution had been distilled. It was filtered off and the filtrate was further concentrated to obtain a second and a third crop. The product was washed with water and alcohol. It gave a red-brown color with ferric chloride but showed no definite m. p. It was amphoteric and the titration curve showed a break at *p*H 3.1.

Anal. Calcd. for $C_6H_4ON_2$: C, 58.05; H, 6.49; total N, 22.57; amino N, 11.29. Found: C, 57.82, 57.93; H, 6.50, 6.53; total N, 22.53, 22.47; amino N (by potentiometric titration), 11.1, 11.2.

(1) McElvain and Stork, THIS JOURNAL, **68**, 1049 (1946).
(2) Cook and Reed, *J. Chem. Soc.*, 399 (1945).
(3) Kuettel and McElvain, THIS JOURNAL, **53**, 2692 (1931).
(4) Wiedeman and Montgomery, *ibid.*, **67**, 1995 (1945).

DEPARTMENT OF CHEMISTRY
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Cyanoacetal—A Correction

BY WALTER H. HARTUNG AND HOMER ADKINS

We reported in 1927 that we had obtained cyanoacetal[1] through the reaction of bromoacetal with potassium cyanide in an alcohol–water solution containing potassium iodide. Jacob van de Kamp and others have called our attention to the fact that they had been unable to obtain cyanoacetal by following the procedure described by us. Uhle and Jacobs[2] obtained cyanoacetal in 14% yield by carrying out the reaction in a manner similar to that described in our paper. They worked on a larger scale and followed a different procedure in isolating the desired product. Uhle and Jacobs graciously ignored our paper although it is clear from a comparison of the data in the two papers, that we had not isolated cyanoacetal. Since we did not have cyanoacetal in hand, the figure for the equilibrium constant reported in our paper for the reaction

$$CNCH_2CH(OC_2H_5)_2 + H_2O \rightleftharpoons CNCH_2CHO + 2C_2H_5OH$$

is not significant. We regret very much our mistake and appreciate the forbearance of our friends.

Robert L. Clarke and S. M. McElvain, of this Laboratory, have obtained the same results as those reported by Uhle and Jacobs. They will publish their results in the near future as well as a description of their preferred procedure whereby cyanoacetal was prepared in excellent yield by a series of reactions through $(C_2H_5O)_2CHCH_2CO_2C_2H_5$.

(1) Hartung and Adkins, THIS JOURNAL, **49**, 2520 (1927).
(2) Uhle and Jacobs, *J. Org. Chem.*, **10**, 81 (1945).

UNIVERSITY OF WISCONSIN
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Equilibrium Studies on the Dehydrogenation of Primary and Secondary Alcohols. II. Cyclohexanols

BY ADRIAN H. CUBBERLEY AND MAX B. MUELLER

Free energies, heats and entropies of dehydrogenation of a number of alcohols were recently reported from this Laboratory.[1]

Further results obtained using the same appara-

(1) Cubberley and Mueller, THIS JOURNAL, **68**, 1149 (1946).