to solid (piperidine)$_2 \cdot SO_2$, no reaction ensued. However, on addition of methylene chloride, gas evolution commenced and decomposition was complete after about 30 min. The products, though as yet not wholly identified, contained neither 1-butanesulfonyl piperidide nor *n*-butyl piperidosulfite.

The reddish brown piperidine salt gave a yellow solution in methylene chloride. When *ca.* 0.5 g. of the salt was added to *ca.* 0.01 *M* diphenyldiazomethane in methylene chloride, decomposition of the diazo compound ensued. Although decolorization was complete in about 30 min., no gas evolution was noted.

Acknowledgment.—The support of this research by a Research Grant (CA-4298) from the National Institutes of Health, U. S. Public Health Service, is gratefully acknowledged.

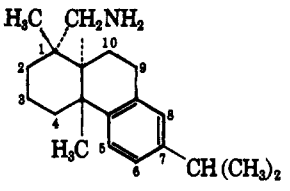
Dehydroabietylamine. A New Resolving Agent[1]

WILLIAM J. GOTTSTEIN AND LEE C. CHENEY

Research Division, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, New York 13201

Received February 17, 1965

Dehydroabietylamine[2] (I) has been isolated in high yield from commercial Amine D.[3] It is an optically active base, inexpensive, relatively nontoxic, and forms



I

highly crystalline salts with many organic acids. These desirable characteristics led us to try dehydroabietylamine as a resolving agent for carboxylic acids. Results were notably favorable. For example, dehydroabietylamine was used advantageously to separate the (+)-enantiomorph[4] of racemic α-phenoxypropionic acid and the D-(−)-enantiomorph of racemic α-benzyloxycarbonylaminophenylacetic acid, when both were required in quantity for the synthesis of the corresponding penicillins.[5-7]

Although racemic α-phenoxypropionic acid has been resolved previously for Fourneau and Sandulesco[8] using yohimbine, we found that dehydroabietylamine afforded higher yields of resolved acid, required smaller volumes of solvents, and obviated the cumbersome task of recovering the resolving agent. The resolution of racemic α-benzyloxycarbonylaminophenylacetic acid gave the desired D-(−)-enantiomorph[6,7] previously prepared by N-acylation of D-(−)-phenylglycine with benzyl chloroformate. The ease in the separation of these enantiomorphs suggests the high potential of dehydroabietylamine for effecting the resolution of other racemic acids and for obtaining the optical isomers of amino acids through their N-benzyloxycarbonyl or N-formyl derivatives.

Experimental[9]

Dehydroabietylamine Acetate.—To a solution of 2.85 kg. of Amine D dissolved in 4.74 l. of toluene was added a solution of 654 g. (10.8 moles) of glacial acetic acid in 1.56 l. of toluene. The solution was stored at 10° for 2 hr. The crystalline salt was collected, washed with cold toluene, and recrystallized from 4.23 l. of boiling toluene. The colorless crystals were collected, washed several times with *n*-pentane, and air dried to obtain 1.365 kg. (78.5%) with m.p. 141–143.5°, $[\alpha]^{25}D$ +30.2° (*c* 5, methanol).

Anal. Calcd. for $C_{22}H_{35}NO_2$: C, 76.48; H, 10.21. Found: C, 76.70; H, 10.25.

Dehydroabietylamine (I).—A mixture of 540 g. (1.57 moles) of dehydroabietylamine acetate was stirred with 2 l. of water on the steam bath until the salt had dissolved. A total of 700 ml. of 10% sodium hydroxide was added, the mixture was chilled, and the amine was extracted with 2.5 l. of ether. The ether solution was washed with water and dried over anhydrous potassium carbonate. After evaporation of the ether, 440 g. (98%) of a pale yellow viscous oil remained which had a refractive index of $n^{33}D$ 1.5480 and crystallized after storage at room temperature for several days: m.p. 44–45°; lit.[10] $n^{30}D$ 1.5498, m.p. 41°.

Dehydroabietylammonium (+)-α-Phenoxypropionate.—To a solution of 914 g. (3.2 moles) of dehydroabietylamine dissolved in 7 l. of methanol was added 537 g. (3.2 moles) of racemic α-phenoxypropionic acid. The stirred solution was slowly diluted with 5.5 l. of water and stored at 10° for 5 hr. The crystals were collected and air dried to obtain 850 g., m.p. 168–170°. Recrystallization from a mixture of 8 l. of methanol and 3.5 l. of water during storage at 10° for 7 hr. gave 650 g. of salt, m.p. 173–177°. A final recrystallization was made from a mixture of 6 l. of methanol and 1.5 l. of water to yield 287 g. of colorless crystals, m.p. 188–189.5°, $[\alpha]^{23}D$ +27.7° (*c* 1, alcohol). Further recrystallization did not raise the melting point or change the rotation.

Anal. Calcd. for $C_{29}H_{41}NO_3$: C, 77.12; H, 9.15. Found: C, 77.03; H, 9.36.

(+)-α-Phenoxypropionic Acid.—To 1 l. of a saturated solution of sodium carbonate were added 287 g. (0.635 mole) of finely ground dehydroabietylammonium (+)-α-phenoxypropionate and 1 l. of ether. The mixture was shaken vigorously until all of the solid had dissolved. The ether layer was separated and the aqueous solution was washed twice with ether and acidified to pH 2 with concentrated hydrochloric acid. The mixture was cooled to 10° for 2 hr., and the white crystals were collected to obtain 76 g. of acid with m.p. 88–89°, $[\alpha]^{23}D$ +40.0° (*c* 1, absolute alcohol), lit.[8] $[\alpha]^{20}D$ +39.3°. A second crop of 22 g. was obtained from the mother liquor on further storage at 10° which had m.p. 88–89°, $[\alpha]^{23}D$ +39.1° (*c* 1, absolute alcohol).

Dehydroabietylammonium D-(−)-α-Benzyloxycarbonylaminophenylacetate.—To a solution of 163 g. (0.57 mole) of racemic α-benzyloxycarbonylaminophenylacetic acid dissolved in 3.7 l. of methanol was added 163 g. (0.57 mole) of dehydroabietylamine. The solution was diluted with 550 ml. of water and stored at 10° for 3 hr. The salt was collected and dried to obtain 203 g., m.p. 170–190°. Recrystallization from a mixture of 6 l. of methanol and 1.5 l. of water gave 103 g. of dry salt. A final recrystallization from a mixture of 4 l. of methanol and 700 ml. of water

(1) After the completion of this manuscript our attention was drawn to the recent report of B. Sjöberg and S. Sjöberg [*Arkiv Kemi*, **22**, 447 (1964)], wherein the use of this resolving base is described.

(2) L. C. Cheney, U. S. Patent 2,787,637 (1957); *Chem. Abstr.*, **51**, 13926*a* (1957).

(3) Amine D, formerly Rosin Amine D, is a trade-name of the Hercules Powder Co. It is composed of an average of 50% dehydroabietylamine (1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethyl-1-phenanthrenemethylamine), 20% dihydroabietylamine (the docecahydro analog of dehydroabietylamine with a double bond in either the 8a–9 or 7–8 position), 20% tetrahydroabietylamine (tetradecahydro analog of dehydroabietylamine), and 10% inert rosin [J. N. Borglin, *Soap Sanit. Chemicals*, **23**, 147 (1947); *Chem. Abstr.*, **43**, 9397*a* (1949)].

(4) A. Fredga and M. Matell [*Arkiv Kemi*, **4**, 325 (1952)] have presented inconclusive evidence that (+)-α-phenoxypropionic acid is related to D-(−)-lactic acid.

(5) Y. G. Perron, *et al.*, *J. Am. Chem. Soc.*, **82**, 3934 (1960).

(6) F. P. Doyle, *et al.*, *J. Chem. Soc.*, 1440 (1962).

(7) F. P. Doyle, J. H. C. Nayler, and H. Smith, U. S. Patent 2,985,641 (1961); *Chem. Abstr.*, **55**, 21472*e* (1961).

(8) E. Fourneau and G. Sandulesco, *Bull. soc. chim. France*, [4] **31**, 988 (1922).

(9) Melting points are uncorrected and were obtained on a Fisher-Johns apparatus. Optical rotations were measured on a Rudolph polarimeter. The authors wish to thank R. M. Downing for the microanalyses.

(10) A. Zvejnieks, *Svensk Kem. Tidskr.*, **66**, 316 (1954); *Chem. Abstr.*, **49**, 15809*e* (1955).

afforded 75 g. of colorless crystals, m.p. 199–200°, $[\alpha]^{25}D$ −93.2° (*c* 0.8, alcohol).

D-(−)-α-**Benzyloxycarbonylaminophenylacetic Acid.**—The aforementioned diastereomeric salt (75 g., 0.131 mole) was treated with 1 l. of saturated sodium carbonate solution and 2 l. of ether as described for the isolation of (+)-α-phenoxypropionic acid. The acid was isolated by extraction of the aqueous layer at pH 2 with three 500-ml. portions of ether. The ether extracts were combined, washed with water, and dried over anhydrous sodium sulfate. The ether was evaporated to one-fifth its original volume and 1 l. of Skellysolve B (petroleum ether, b.p. 60–71°) was added. The crystals weighed 30 g. after drying *in vacuo* over P_2O_5: m.p. 128–129°, $[\alpha]^{25}D$ −116.5° (*c* 1, absolute alcohol); lit.[6] m.p. 130–130.5°, $[\alpha]^{21}D$ −119° (*c* 4, alcohol).

2-Hydrazino- and 2-(2,2-Dimethylhydrazino)-2-thiazoline[1]

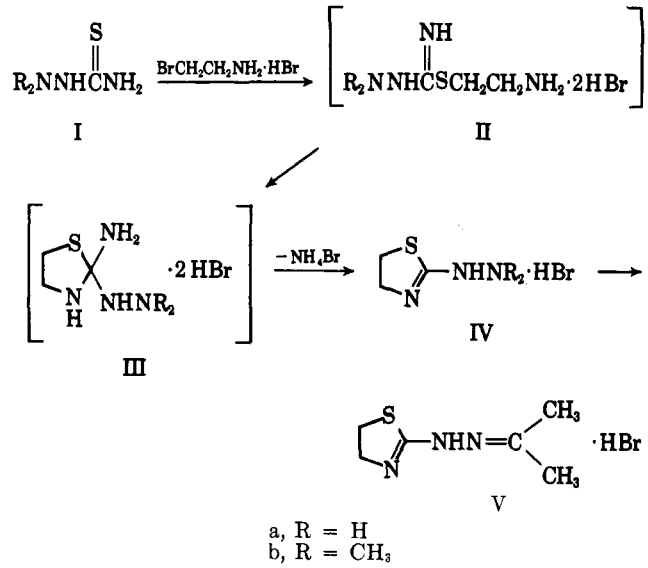
THOMAS P. JOHNSTON, CARL R. STRINGFELLOW, JR., AND ANNE GALLAGHER

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

Received January 19, 1965

The interaction of equivalent amounts of thiosemicarbazide and 2-bromoethylamine hydrobromide under conditions chosen to minimize thiazoline formation (that is, in refluxing 2-propanol[2] for 45 min.) resulted in the isolation of a small amount of 2-hydrazino-2-thiazoline hydrobromide (IVa), which was characterized as a picrate and also, subsequently, as acetone (2-thiazolin-2-yl)hydrazone hydrobromide (V). The structure of IVa was deduced initially from an infrared spectral comparison with 2-amino-2-thiazoline hydrobromide. The only product that could be isolated from the remaining reaction mixture was additional IVa and not 2-aminoethyl thiocarbazimidate dihydrobromide (IIa), which, being a close structural relative of AET [2-(2-aminoethyl)-2-thiopseudourea dihydrobromide],[3] was desired as a potential antiradiation agent. The yield of pure IVa, which precipitated from the cooled reaction mixture, was eventually increased to 35% by prolonging the reflux period to 5 hr.,[4] ammonium bromide (and not hydrazinium bromide) precipitating from the hot reaction mixture as a result of elimination from the assumed intermediate III.

Similar results were obtained in the attempted conversion of 1,1-dimethyl-3-thiosemicarbazide (Ib) to 2-aminoethyl 3,3-dimethylthiocarbazimidate dihydrobromide (IIb). Unreported until recently,[6] Ib was made available for this work by a convenient displacement of methanethiol from methyl 3,3-dimethyldithiocarbazate[7] by ammonia. Thiazoline formation



occurred in 2-propanol at reflux and in N,N-dimethylformamide at 80–90°; however, unchanged Ib (58%) was recovered after 0.5 hr. in methanol at reflux. 2-(2,2-Dimethylhydrazino)-2-thiazoline hydrobromide (IVb) could not be obtained as a crystalline solid and was first characterized as a picrate.

The attempted basic hydrolysis of IVa under conditions that effected the conversion of 2-amino-2-thiazoline hydrobromide to (2-mercaptoethyl)urea[8] resulted in the isolation of an unstable red oil, which was identified as the free base of IVa by conversion to a stable, characterizable hydrochloride. The same treatment of crude IVb (that is, a 2-hr. reflux period in 2 *N* sodium hydroxide under nitrogen) did not cause appreciable opening of the thiazoline ring as evidenced by an 80% recovery of pure, crystalline 2-(2,2-dimethylhydrazino)-2-thiazoline, the structure of which is supported by the p.m.r. spectrum determined in chloroform: the single signal at τ 7.54 is assigned to the methyl groups, the group of signals centered at about τ 6.65, to the thiazoline methylene groups (an A_2B_2 system), and the single signal at τ 3.54, to the NH of the hydrazino group. When the reaction time was extended to 18 hr., 30% of the starting material precipitated (as the free base) from the reaction mixture saturated at pH 8 with sodium bromide; a nitroprusside-positive reaction mixture attested ring opening, but no characterizable products could be isolated. The stability of these hydrazinothiazolines toward basic hydrolysis relative to 2-aminothiazoline may be attributed to a greater over-all electron density, which makes C-2 more resistant to attack by hydroxyl ion.

Experimental

1,1-Dimethyl-3-thiosemicarbazide (Ib).—A mixture of methyl 3,3-dimethyldithiocarbazate[10] (121 g., 0.803 mole) and concentrated ammonium hydroxide (1.5 l.) was heated gradually to the boiling point and the resulting solution was refluxed for 4 hr. The solution, now yellow, was cooled slightly. More ammonium hydroxide (150 ml.) was added, and refluxing was continued over-

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2028.

(2) (a) D. G. Doherty, R. Shapira, and W. T. Burnett, Jr., *J. Am. Chem. Soc.*, **79**, 5667 (1957); (b) R. Shapira, D. G. Doherty, and W. T. Burnett, Jr., *Radiation Res.*, **7**, 22 (1957).

(3) The radioprotective properties of AET are comprehensively reviewed by D. G. Doherty ("Radiation Protection and Recovery," A. Hollaender, Ed., Pergamon Press, New York, N. Y., 1960, pp. 56–66).

(4) Hydrazinothiazoline formation in buffered or unbuffered aqueous systems[2a,5] was not investigated.

(5) (a) J. X. Khym, R. Shapira, and D. G. Doherty, *J. Am. Chem. Soc.*, **79**, 5663 (1957); (b) J. X. Khym, D. G. Doherty, and R. Shapira, *ibid.*, **80**, 3342 (1958).

(6) J. Sandstrom and S. Sunner, *Acta Chem. Scand.*, **17**, 731 (1963).

(7) T. P. Johnston and A. Gallagher, *J. Org. Chem.*, **26**, 3780 (1961).

(8) A. Schöberl and G. Hansen, *Chem. Ber.*, **91**, 1055 (1958).

(9) Infrared absorption spectra were determined in pressed potassium bromide disks with a Perkin-Elmer Model 221-G spectrophotometer; melting points are uncorrected.

(10) The published procedure[7] was adapted to the preparation of large amounts only after decomposition was circumvented by removing the solvent, N,N-dimethylformamide, *in vacuo* under 40°.