Salicylates of 2-Guanidyl-3-methylbutanethiol and 2-Amino-5-hexylthiazoline

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The conditions influencing the rearrangement of aminoalkylisothiuronium salts to mercaptoalkylguanidines or to thiazolines have been investigated.[1] Compounds in these series have been found to confer protection against ionizing radiation[2] on animals.

The hydrobromide salts of the rearrangement products can be isolated, but crystallization is slow and difficult. The previously reported mercaptoalkylguanidines have been isolated as flavianate salts,[1c] which are not suitable for pharmacological studies. This report concerns the isolation and purification of salicylate derivatives of 2-guanidyl-3-methylbutanethiol and 2-amino-5-hexylthiazoline, each derived from the corresponding aminoalkylisothiuronium bromide hydrobromide. The syntheses are described beginning with amino acids.

EXPERIMENTAL[3]

S,2-Amino-3-methylbutylisothiuronium bromide hydrobromide. DL-Valine (1018 g., 8.69 moles) was reduced with lithium aluminum hydride[4] in tetrahydrofuran to valinol (454 g., 4.41 moles) in 50.9% yield, b.p. 66–73° (1 mm.). Valinol (440 g., 4.27 moles) was treated with hydrobromic acid[5] to give 2-amino-3-methylbromobutane hydrobromide (560 g., 2.28 moles) in 53.3% yield. The hydrobromide (450 g., 1.83 moles) dissolved in 2-propanol was added to an acetonitrile:2-propanol solution of thiourea[1b] (139 g., 1.83 moles). A crystalline precipitate (396 g., 1.23 moles) was obtained in 62.7% yield, m.p. 118–121°. The flavianate was prepared, m.p. 240–245° (dec).

Anal. Calcd. for the hydrobromide, $C_6H_{12}N_3SBr_2$: N, 13.00; S, 9.92. Found: N, 13.64; S, 10.43.

2-Guanidyl-3-methylbutanethiol salicylate. Under a nitrogen atmosphere, the isothiuronium salt (448 g., 1.51 moles) was dissolved in water, treated with 15*N* ammonium hydroxide to *p*H 9, and neutralized with conc. hydrobromic acid while cooling with an ice bath. The solution was evaporated to near dryness under vacuum, the residue extracted with 2-propanol, and the extract evaporated under vacuum to give a sirup (274 g., 1.13 moles) in a 74.8% yield. The product gave positive responses to the 2,6-dichloroindophenol[1a] and sodium nitroprusside tests for the sulfhydryl group, and to the Sakaguchi test[6] for the guanidyl group. The sirup crystallized slowly during a three-month period, but could not be recrystallized. The hydrobromide (203 g., 0.836 mole) was dissolved in water and treated with aqueous sodium salicylate (134 g., 0.837 mole) to give a tan, waxy solid precipitate (202 g., 0.675 mole) in 80.6% yield. Recrystallization of the crude solid from water gave a poor yield (52 g.) of white crystals, m.p. 137–140°. Evaporation under vacuum of the crystallization liquor gave additional waxy solid (66 g.) and an uncrystallizable oil. The waxy solid (50 g.) was dissolved in acetonitrile (50 ml.), diluted with dichloromethane (500 ml.), and passed through a silica gel column. Pentane was added dropwise to the stirred solution, and each successive cloudy precipitate was removed by the addition of Norit, followed by filtration, until 200 ml. of pentane had been added. The addition of more pentane (100 ml.) followed by chilling then gave a white crystalline solid (28.0 g.), m.p. 135–139°. A sample was recrystallized from acetonitrile–2-propanol, m.p. 137–139°. The flavianate, m.p. 99–101°, and the picrate, m.p. 145–147°, were prepared from the hydrobromide.

Anal. Calcd. for the salicylate, $C_{13}H_{21}N_3O_3S$: C, 52.15; H, 7.07; N, 14.04; S, 10.71. Found: C, 52.25; H, 6.92; N, 14.03; S, 10.79. Calcd. for the flavianate, $C_{16}H_{21}N_5O_8S_2$: C, 40.41; H, 4.45; N, 14.73. Found: C, 40.36; H, 4.67; N, 14.64. Calcd. for the picrate, $C_{12}H_{18}N_6O_7S$: C, 36.92; H, 4.65; N, 21.53. Found: C, 37.06; H, 4.68; N, 21.37.

S-2-Aminooctylisothiuronium bromide hydrobromide. DL-Aminooctanoic acid (610 g., 3.84 moles) was reduced with lithium aluminum hydride[7] in tetrahydrofuran to give 2-aminooctanol (254 g., 1.75 moles) in 45.6% yield, b.p. 106–112° (1 mm.). 2-Aminooctanol (250 g., 1.72 moles) was treated with hydrobromic acid to give 2-aminobromooctane hydrobromide (210 g., 0.729 moles) in 42.2% yield, and recrystallized from toluene-pentane, m.p. 115–117°. The hydrobromide (200 g., 0.694 mole) was dissolved in 2-propanol and treated with thiourea[1b] (52.8 g., 0.694 mole) in acetonitrile–2-propanol. A small amount of solid ammonium bromide precipitated. Attempts to obtain a solid product were not successful. The solvent was removed under vacuum giving a clear sirup (231 g.).

2-Amino-5-hexylthiazoline salicylate. The isothiuronium salt reaction product (231 g.), which had been standing 4 months in the cold,[8] was dissolved in water and treated with 15*N* ammonium hydroxide to *p*H 9, neutralized with 6*N* hydrobromic acid, and treated with aqueous sodium salicylate (106 g., 0.662 mole). A solid precipitate was formed (199 g., 0.567 mole) in 81.7% yield based on thiourea. The crude solid (158 g.) was dissolved in chloroform (500 ml.), passed through a silica gel column, and treated with pentane (770 ml.) as described in a previous paragraph. Two crops of crystalline solid were obtained, (56.2 g.) m.p. 93–94°, and (27.4 g.) m.p. 89–92°. A sample was recrystallized from isopropyl ether, m.p. 95–97°.

Anal. Calcd. for $C_{16}H_{24}N_2O_3S$: C, 59.23; H, 7.46; N, 8.64; S, 9.88. Found: C, 59.27; H, 7.36; N, 8.53; S, 10.06.

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(1) (a) J. X. Khym, R. Shapira, and D. G. Doherty, *J. Am. Chem. Soc.*, **79**, 5663 (1957); (b) D. G. Doherty, R. Shapira, and W. T. Burnett, Jr., *J. Am. Chem. Soc.*, **79**, 5667 (1957); (c) J. X. Khym, D. G. Doherty, and R. Shapira, *J. Am. Chem. Soc.*, **80**, 3342 (1958).

(2) R. Shapira, D. G. Doherty, and W. T. Burnett, Jr., *Radiation Research*, **7**, 22 (1957).

(3) Melting points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(4) O. Vogl and M. Pöhm, *Monatsh.*, **83**, 541 (1952).

(5) F. Cortese, *Org. Syntheses*, Coll. Vol. II, 91 (1943).

(6) K. Oto, K. Kono, and K. Sugino, *J. Org. Chem.*, **23**, 1319 (1958).

(7) O. Vogl and M. Pöhm, *Monatsh.*, **84**, 1097 (1953).

(8) The conversion to the thiazoline most probably occurred while the isothiuronium salt was standing under acid conditions during four months. The aminoethylisothiuronium salt was reported to yield 47% thiazoline in twenty minutes at *p*H 4.5, ref. 1a.

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