of the molecular weight gave a value of 234; calcd. for $C_{16}H_{34}$, 226.

Anal. Calcd. for $C_{16}H_{34}$: C, 84.86; H, 15.14. Found: C, 85.36; H, 14.85.

Action of 10% Sodium Amalgam on Active 2-Bromooctane.—Five grams of (+)2-bromoöctane, $[\alpha]^{20}D$ +32.4°, in 25 cc. of pentane was stirred overnight with 3 g. of a 10% sodium amalgam. The pentane was removed and the bromide (5 g.) distilled at 83° (21 mm.), $[\alpha]^{20}D$ +32.4°. There was no high-boiling residue.

Action of Sodium Ethyl on (−)3-Methylnonane.—Sodium ethyl was prepared in the usual manner from 1.1 g. of sodium and 6.1 g. of mercury diethyl in about 40 cc. of pentane. Four cc. of (−)3-methylnonane, $[\alpha]^{20}D$ −0.25° was added, and the mixture stirred overnight at room temperature. The sodium alkyl was destroyed by addition of water, and the amalgam hydrolyzed with dilute sulfuric acid to recover 3.7 g. of mercury, corresponding to a 77% yield of sodium ethyl. The organic layer was dried and the mercury diethyl decomposed as before. The solvent was removed and the residual liquid was heated for one-half hour at 70° under a pressure of 100 mm. It then had a specific rotation $[\alpha]^{25}D$ −0.23° ($\alpha^{25}D$ −0.34°; $l = 2$; homogeneous).

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Summary

The action of sodium ethyl on (−)2-bromooctane, $[\alpha]^{20}D$ −30.7°, in pentane solution leads to the production of octylene, octane, 3-methylnonane, and 7,8-dimethyltetradecane in the approximate molar ratio 9:12:16:1, respectively. The 3-methylnonane (obtained in 25% yield) was optically active, $[M]^{25}D$ −0.34°; although racemization to the extent of 97% occurred during its formation. The 7,8-dimethyltetradecane was optically inactive.

These results are discussed in conjunction with the previous observation[2] that the action of sodium on (+)2-bromobutane leads to optically inactive 3,4-dimethylhexane. It is concluded that the production of an optically inactive di-*s*-alkyl hydrocarbon might in each instance have resulted from the action of a sodium *s*-alkyl on the optically active halide provided the *d* and *l* forms of the carbanion arising from the sodium alkyl were easily interconvertible and reacted at markedly different rates with the *s*-halide, such that only the production of *meso* hydrocarbon occurred.

An alternative mechanism involving free *s*-alkyl radicals as critical reaction intermediates is presented.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Sulfanilamide Compounds. VIII. Homologs of 2-Sulfanilamidothiazoline

BY ALAN H. NATHAN, JAMES H. HUNTER AND H. G. KOLLOFF

Preliminary studies on the chemotherapeutic activity and toxicity of 2-sulfanilamidothiazoline ("sulfathiazoline"), a recently prepared[1] analog of sulfathiazole, have indicated it to be equal to sulfathiazole in activity and at least as free from toxicity.[2] Considering the efficacy and relatively low toxicity reported for the 4-methyl derivative of sulfathiazole,[3] it was of interest to undertake a study of the corresponding sulfathiazoline derivative as well as its isomeric 5-methyl compound. On the basis of preliminary tests in experimental streptococcal and pneumococcal infections in white mice, these two derivatives possess a high order of activity and low toxicity; however, sufficient data have not yet been accumulated to evaluate accurately the place of these new derivatives in relation to sulfathiazole, sulfamethylthiazole and sulfathiazoline.

The requisite aminothiazolines, 2-amino-4-methylthiazoline and 2-amino-5-methylthiazoline, were prepared from 1-bromo-2-aminopropane hydrobromide and 1-amino-2-bromopropane hydrobromide, respectively, by treatment with potassium thiocyanate according to the methods given in the literature.[4,5]

Condensation of acetylsulfanilyl chloride with the aminomethylthiazolines in pyridine–acetone solution resulted in derivatives containing two acetylsulfanilyl groups per molecule of amino-

(1) (a) Jensen and Thorsteinsson, *Dansk. Tids. Farm.*, **15**, 41 (1941); *Chem. Abs.*, **35**, 5109 (1941); (b) Sprague and Kissinger, THIS JOURNAL, **63**, 578 (1941); (c) Raiziss, Clemence and Freifelder, *ibid.*, **63**, 2739 (1941); (d) Raiziss and Clemence, *ibid.*, **63**, 3124 (1941); (e) Kolloff and Hunter, unpublished results.

(2) Kolmer, *J. Lab. Clin. Med.*, **27**, 1043 (1942).

(3) Herrel and Brown, *Proc. Staff Meet. Mayo Clin.*, **14**, 753 (1939); Long, *J. Am. Med. Assoc.*, **114**, 870 (1940); Ruegsegger and Hamburger, *Ohio State Med. J.*, **37**, 25 (1941); Ivanovics, *J. Path. Bact.*, **51**, 91 (1940).

(4) Gabriel and Ohle, *Ber.*, **50**, 813 (1917).

(5) Hirsch, *ibid.*, **23**, 965 (1890).

thiazoline. Since it has been demonstrated[1d,6] that these two groups most probably occupy positions 2 and 3, respectively, when the corresponding condensation takes place with 2-aminothiazoline, a similar structure is postulated here. Hydrolysis in aqueous hydrochloric acid solution produced the desired sulfamethylthiazolines, together with small amounts of partially hydrolyzed derivatives which are presumed to be 2-sulfanilimido-3-sulfanilyl-4 (and 5)-methylthiazoline; the latter derivatives could also be hydrolyzed to the sulfamethylthiazolines. That the sulfanilamido group is attached to the 2-position of the thiazoline nucleus is indicated by the ready solubility of the end-products in dilute sodium hydroxide, which should only be the case if a labile hydrogen atom remained attached to the amide nitrogen. It should be mentioned that, contrary to the findings of Raiziss and Clemence on sulfathiazoline,[1d] the corresponding 4- and 5-methyl derivatives of 3-sulfanilyl-thiazolidone-(2)[7] were not detected during the course of the hydrolysis.

Experimental

Condensation with Acetylsulfanilyl Chloride.—Ten and one-half grams (0.091 mole) of 2-amino-4-methylthiazoline[4] was dissolved in 14.5 cc. of pyridine and 60 cc. of acetone, and 42.2 g. (0.181 mole) of acetylsulfanilyl chloride added in small portions with shaking and sufficient cooling to keep the temperature below 45°. The clear, pale yellow solution was shaken vigorously after addition was complete, and allowed to stand in a stoppered flask overnight. The contents of the flask were then poured into 500 cc. of cold water containing 5 cc. of concentrated hydrochloric acid, the precipitate collected and washed well with cold water. The yield of crude product, melting with decomposition at 133.5–139°,[8] was 60% of the theoretical. Recrystallized from dilute alcohol it formed needles and scales, m. p. 150–153° (dec.).

Anal.[9] Calcd. for $C_{20}H_{22}O_6N_4S_3 \cdot H_2O$: N, 10.60; S, 18.16; H_2O, 3.41. Found: N, 10.12; S, 18.09; H_2O, 3.54.

The water of crystallization was easily driven off by drying *in vacuo* over phosphorus pentoxide at 116°; the m. p. remained unchanged.

The corresponding 5-methylthiazoline derivative was prepared in a similar manner from 2-amino-5-methylthiazoline in 93% yield. It was obtained as minute needles, m. p. 185.5–186.5°, by recrystallization from 95% alcohol.

Anal. Calcd. for $C_{20}H_{22}O_6N_4S_3$: N, 10.97. Found: N, 10.95, 10.84.

Hydrolysis of the Di-acetylsulfanilyl Derivatives.—The 4-methyl compound was hydrolyzed by refluxing with approximately 10 volumes of 10% hydrochloric acid for one and one-half hours, and the product, obtained by neutralizing the reaction mixture with aqueous sodium carbonate, was purified by dissolving it in dilute aqueous sodium hydroxide (in which there was rapid and practically complete solution), filtering, and re-precipitating the 2-sulfanilamido-4-methylthiazoline by careful neutralization of the filtrate with dilute hydrochloric acid. The yield was 66.5% of theoretical; after several recrystallizations from 40% alcohol it melted sharply at 176°.

Anal. Calcd. for $C_{10}H_{13}O_2N_3S_2$: N, 15.49. Found: N, 15.40.

Hydrolysis of the di-acetylsulfanilyl derivative of the 5-methylthiazoline to 2-sulfanilamido-5-methylthiazoline was carried out in a similar manner except that the period of refluxing was prolonged to two hours. The purification was effected in the same way as described above, with prisms melting at 177.5–178.5° being obtained by recrystallization from dilute alcohol.

Anal. Calcd. for $C_{10}H_{13}O_2N_3S_2$: N, 15.49. Found: N, 15.80, 15.76.

Disulfanilyl Derivatives.—These were obtained when the di-acetyl sulfanilyl derivatives were hydrolyzed by refluxing in 10% hydrochloric acid for one-half hour instead of for the longer periods given above. They were isolated as the alkali-insoluble fraction from the purification of the 2-sulfanilamido derivatives, which were produced concomitantly. The presence of free amino groups was indicated by their ready solubility in dilute mineral acids.

2-Sulfanilimido-3-sulfanilyl-4-methylthiazoline.—Recrystallized from either 50% alcohol or 50% pyridine, m. p. 225–226°.

Anal. Calcd. for $C_{16}H_{18}O_4N_4S_3$: N, 13.14. Found: N, 13.36, 12.98.

2-Sulfanilimido-3-sulfanilyl-5-methylthiazoline.—Recrystallized from 95% alcohol, m. p. 176.5–177° (a mixed melting point with 2-sulfanilamido-5-methylthiazoline, which melted at 177.5–178.5°, was depressed to 150–158°).

Anal. Calcd. for $C_{16}H_{18}O_4N_4S_3$: N, 13.14. Found: N, 13.02, 13.36.

Summary

The preparation of 2-sulfanilamido-4-methylthiazoline, 2-sulfanilamido-5-methylthiazoline, and several intermediate derivatives is described.

These two products show promise of high chemotherapeutic activity and low toxicity in experimental streptococcal and pneumococcal infections in mice.

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(6) Jensen, *Helv. Chim. Acta*, **24**, 1249 (1941).

(7) These compounds have been prepared by Hunter and Kolloff, THIS JOURNAL, **65**, 156 (1943).

(8) All melting points are uncorrected.

(9) Analyses by Mr. H. Emerson and Mr. W. A. Struck.