[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE RICE INSTITUTE]

Sulfonation of 2-Pentene by Chlorosulfonic Acid[1]

BY SIMON MIRON[2] AND GEORGE HOLMES RICHTER

The reaction of chlorosulfonic acid with 2-pentene in chloroform solution at 0–5° gave a mixture of isomeric pentenesulfonic acids. It was shown, by reducing the double bond of the isomers and comparing the reduced mixture with pentane-2-sulfonic acid and pentane-3-sulfonic acid, that sulfonation had occurred on the carbon atoms comprising the original position of the double bond, approximately 80% having taken place on carbon atom 2 and 20% on carbon atom 3. The exact position of the double bond in the resulting products was not demonstrated; it would be in the 2 position if no isomerization occurred during the reaction or isolation of the products.

Experimental

Raw Materials.—The 2-pentene was prepared by dehydration of 2-pentanol[3] and was purified by distillation through a laboratory bubble column consisting of eight bubbler units.[4] The fraction collected for use had a boiling range 35.8–36.3° at 763 mm. It probably consisted of approximately 75% *trans*-2-pentene and 25% *cis*-2-pentene[5] and may also have contained a small amount of 1-pentene.[6]

The chlorosulfonic acid (Eastman Kodak Co. "practical" grade) was dark brown in color, and was used without further purification.[7]

Sulfonation of 2-Pentene.—The sulfonation was carried out in a 500-ml. flask surrounded by cracked ice and equipped with agitator (mercury sealed), dropping funnel, thermometer and ice-water condenser. A solution of 35.0 g. (0.50 mole) of 2-pentene in 50 ml. of dry chloroform was introduced in the flask and treated over three hours time, under good agitation, with a solution of 53.6 g. (0.46 mole) of chlorosulfonic acid in 70 ml. of dry chloroform, after which the chloroform solution was extracted with water until neutral. Sulfuric acid was removed from the extract by treatment with barium carbonate and filtration, and most of the chloride ion was removed from the evaporated filtrate by mixing the salt with 85% phosphoric acid[8] and keeping the paste at low pressure over solid potassium hydroxide for several days, with occasional warming. Neutralization of the mixture with barium carbonate resulted in a crude barium salt whose chloride ion content was appreciably diminished; yield, 37 g. (0.085 mole) of crude barium salt (37%).

Anal.[9] Calcd. for $C_{10}H_{18}O_6S_2Ba$: Ba, 31.54. Found: Ba, 31.66.

Properties of the Barium Pentenesulfonate Mixture.—A solution of the barium salt reduced both potassium permanganate solution and bromine water. The salt was slightly soluble in absolute ethanol and quite soluble in warm *i*-amyl alcohol and in 1,4-dioxane, but warm solutions in the latter two solvents tended to gel upon cooling.

Sodium Pentenesulfonates.—A portion of the barium pentenesulfonate mixture was converted to the corresponding sodium salt by treatment of an aqueous solution with sodium sulfate solution until no more barium sulfate precipitated. The suspension was filtered and the filtrate evaporated to dryness. The sodium salt was soluble in hot ethanol and could be freed of most of the contaminating sodium chloride by recrystallization from this medium.

Anal. Calcd. for $C_5H_9O_3SNa$: Na, 13.37. Found: Na, 13.02.

Free Pentenesulfonic Acid Mixture.—The purified barium salt was dissolved in water and treated with excess sulfuric acid followed by excess basic lead carbonate. The supension was filtered and the hot filtrate saturated with hydrogen sulfide. After removal of the excess hydrogen sulfide and treatment with "Norite" carbon, the resulting solution was evaporated to complete dryness over phosphoric anhydride at reduced pressure. The acid was highly viscous, having almost a glassy consistency at room temperature; d^{20}_4 1.277,[10] $n^{20}D$ 1.4735, MR_D (molecular refraction) 33.03. It was soluble in absolute ethanol, chloroform, *i*-amyl alcohol and acetic acid and insoluble in carbon tetrachloride and carbon disulfide. In water it dissolved with considerable evolution of heat. It decolorized bromine water and a carbon tetrachloride solution of bromine, forming an insoluble liquid product without evolution of hydrogen bromide.

Reduction of the Double Bond.—The unsaturated barium sulfonate (8.4 g.) was dissolved in 100 ml. of water and reduced in the conventional manner over 0.25 g. of finely powdered platinum oxide catalyst at 30 p.s.i. gage pressure of hydrogen, reduction being complete in one-half hour. The resulting solution, filtered free of platinum, was completely inert to potassium permanganate, and was evaporated to crystallization. Unlike the unsaturated barium salt, the saturated compound crystallized readily from hot water. The dry salt was white; it burned upon ignition and gave a slight test for chlorides. This saturated barium salt was reserved for proof of structure as described below.

Pentane-2-thiol.—This was prepared from 2-bromopentane[11] by the method of Noller and Gordon.[12] The crude product was oxidized directly to the sulfonic acid.[13]

Barium Pentane-2-sulfonate.—The mixture of pentane-2-thiol and water obtained by reduction of the disulfide

(1) Presented at the Southwest Regional Meeting of the American Chemical Society in Houston, Texas, Dec. 12–13, 1947.

(2) Present address: Pan American Refining Corporation, Texas City, Texas.

(3) James F. Norris, "Organic Syntheses," Coll. Vol. I, ed. Henry Gilman, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 430.

(4) H. T. Clarke and E. J. Rahrs, *Ind. Eng. Chem.*, **18**, 1092 (1926).

(5) H. J. Lucas, M. J. Schlatter and R. C. Jones, THIS JOURNAL, **63**, 23 (1941).

(6) H. J. Lucas and A. N. Prater, *ibid.*, **59**, 1683 (1937).

(7) A run made with freshly distilled, colorless chlorosulfonic acid gave no substantial improvement in yield.

(8) Phosphoric acid appeared to have less tendency to cause charring of the product than did concentrated sulfuric acid.

(9) The analysis was carried out on a sample of the barium salt which had been treated exhaustively to remove chloride ion.

(10) By capillary pycnometer; measurements made only to the third decimal place because of the viscous and hygroscopic nature of the liquid.

(11) Produced by reaction of 2-pentanol and phosphorus bromide at room temperature. Since the tendency of secondary alkyl bromides to isomerize is quite common, the structure of the bromide was confirmed by converting a small portion to the Grignard reagent and reacting with phenyl isocyanate, according to the method of Schwartz and Johnson (A. M. Schwartz and John R. Johnson, THIS JOURNAL, **53**, 1063–1068 (1931)), resulting in N-phenyl-2-methylvaleramide, m. p. 84.5–88.5°.

(12) C. R. Noller and J. J. Gordon, *ibid.*, **55**, 1090–1094 (1933).

(13) A small portion of the crude mercaptan was purified by distillation in order to record its properties, the main fraction boiling in the range 112.9–114.0° at 772 mm.; d^{20}_4 0.828; $n^{23}D$ 1.4395. The lead mercaptide, prepared from an ethanolic solution of the thiol and aqueous lead acetate, came down as a canary-yellow oil which failed to crystallize.

Anal. Calcd. for $C_{10}H_{22}S_2Pb$: Pb, 50.12. Found: Pb, 49.86.

was added slowly to excess 10 *M* nitric acid on the steam-bath, and the mixture was heated until a test sample showed the absence of nitric acid by failing to color a droplet of diphenylamine–sulfuric acid reagent. After dilution with water and treatment with excess barium carbonate, the mixture was filtered and the filtrate purified by extraction with ether and treatment with activated carbon. On evaporation of the ensuing filtrate the barium salt separated in characteristic, lustrous white crystals.

Anal. When dried at 110–120° for 80 min. the salt apparently retained a molecule of water. Calcd. for $C_{10}H_{22}O_6S_2Ba\cdot H_2O$: Ba, 30.01. Found: Ba, 30.07.

Pentane-2-sulfonic Acid.—This acid has been only incompletely described in the literature.[14,15] A solution of barium pentane-2-sulfonate was converted to the lead salt and treated with hydrogen sulfide as described previously. The aqueous solution was concentrated *in vacuo* over phosphoric anhydride. White crystals separated when the water was almost entirely removed, but further drying resulted in complete liquefaction, suggesting that the acid may form a crystalline hydrate. The resulting acid had the following properties: d^{20}_4 1.173, $n^{20}D$ 1.4502, MR_D 34.89.

Phenylhydrazine Pentane-2-sulfonate.—The phenylhydrazine salt was selected as a characterizing derivative and was prepared according to Latimer and Bost,[16] using 0.55 g. (0.0013 mole) of recrystallized barium pentane-2-sulfonate and 0.24 ml. (0.0026 mole) of phenylhydrazine. The phenylhydrazine salt separated from the ethanol-ether solution as small white flakes, which were washed with ether and dried in a desiccator, m.p. 121.6–123.6°.

Anal. Calcd. for $C_{11}H_{20}O_3N_2S$: C, 50.74; H, 7.74. Found: C, 50.75; H, 7.55.

Barium Pentane-3-sulfonate.—This was prepared by oxidation of the disulfide of 3-bromopentane.[17] A solution of 46.5 g. (0.194 mole) of sodium sulfide nonahydrate and 8.8 g. (0.271 mole) of powdered sulfur in aqueous methanol was heated to boiling and 41.0 g. (0.271 mole) of 3-bromopentane was added. After seventy minutes of refluxing the mixture was poured into water and the disulfide layer separated and washed with water; yield of wet disulfide, 26 g.

Six grams of the disulfide was oxidized by 40 ml. of hot 10 *M* nitric acid, in the manner described for pentane-2-thiol. The barium salt crystallized in lustrous white platelets; yield, 8.6 g. (62.4% theoretical yield).

Anal. Calcd. for $C_{10}H_{22}O_6S_2Ba\cdot H_2O$: Ba, 30.01. Found: Ba, 30.29.

Pentane-3-sulfonic Acid.—No reference to this acid is found in the literature through 1947.

The free acid was obtained from the barium salt by the procedure described for pentane-2-sulfonic acid, and as in that instance, white crystals were observed when the acid was almost dry but disappeared on further removal of water; d^{20}_4 1.186, $n^{20}D$ 1.4525, MR_D 34.66. The similarity in molecular refractions for pentane-2 and -3 sulfonic acids is as expected for isomers.

Phenylhydrazine Pentane-3-sulfonate.—This product was prepared as described for the isomeric salt. The crystals were deposited as feathery white needles. The m.p. was 97.4–99.2° after ordinary drying, but after fusion to removal all traces of water was 104.7–106.8°.

Anal. Calcd. for $C_{11}H_{20}O_3N_2S$: C, 50.74; H, 7.74. Found: C, 50.91; H, 7.48.

Phenylhydrazine Salt of the Reduced Pentenesulfonic Acid Mixture.—A portion of the semi-pure barium pentanesulfonate mixture from the catalytic reduction of the unsaturated salt was carefully freed of contaminating chloride ion and converted to the phenylhydrazine salt, m.p. 111–117.4°.

In order to determine the relative ratio of the two isomers in the above salt, mixtures of the two pure derivatives in stepwise concentrations varying by 10% were prepared, fused, resolidified and powdered finely. The capillary melting points (cor.) were taken, the bath temperature being allowed to rise very slowly, and the point of complete disappearance of the crystals observed with a lens and recorded as the melting point. A melting point diagram was then prepared, shown in Fig. 1.

According to Fig. 1, the reduced mixture appeared to consist of approximately 80% of the "2" isomer. As a further check, mixed melting points were taken using equal parts of the reduced mixture and the known 80% "2"–20% "3" mixture, as well as with samples of the known 90–10 and 70–30 mixtures. Results are shown in Table I.

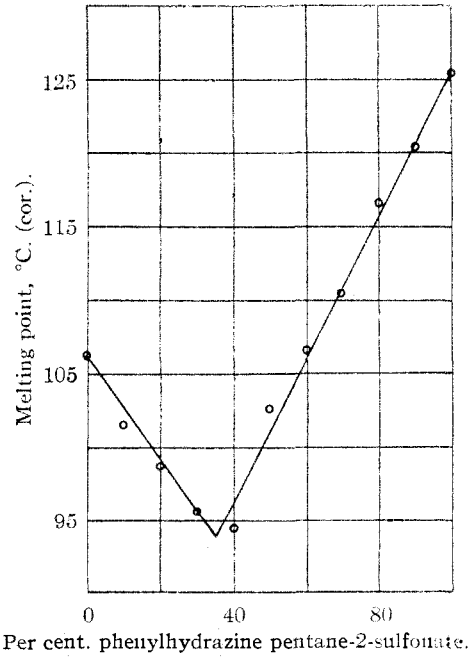

Fig. 1.—Melting points of phenylhydrazine pentane-2-sulfonate and phenylhydrazine pentane-3-sulfonate mixtures.

TABLE I

Mixture	M. p., °C. (cor.)
90% "2"–10% "3"	120.3
80% "2"–20% "3"	116.6
70% "2"–30% "3"	110.4
Reduced derivative (average)	117.4
Equal parts reduced + (90-10 mixture)	121.5
Equal parts reduced + (80-20 mixture)	117.2
Equal parts reduced + (70-30 mixture)	114.8

The fact that the melting point of the reduced mixture was unchanged upon incorporation with the 80–20 mixture, and that incorporation with the 70–30 mixture served to *raise* the melting point of the latter would indicate the relative non-interference of incidental impurities. It was, therefore, concluded that the reduced derivative consisted of approximately 80% of phenylhydrazine-pentane-2-sulfonate and 20% of phenylhydrazine-pentane-3-sulfonate, and that, consequently, the sulfonation of 2-

(14) P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **75**, 587–605 (1927).

(15) F. C. Wagner and E. E. Reid, THIS JOURNAL, **53**, 3407–3413 (1931).

(16) P. H. Latimer and R. W. Bost, *ibid.*, **59**, 2500–2501 (1937).

(17) Prepared from 3-pentanol and phosphorus tribromide at room temperature. Reaction of the corresponding Grignard reagent with phenyl isocyanate gave N-phenyl-2-ethylbutyramide, m. p. 121–124.5°, thus confirming the structure of the bromide.

pentene by chlorosulfonic acid had taken place largely on carbon atom 2, with about 20% on carbon atom 3.[18]

Summary

1. Sulfonation of 2-pentene by chlorosulfonic acid in chloroform solution at 0–5° gave a mixture of isomeric pentenesulfonic acids.

2. By comparison of the catalytically-reduced mixture with pentane-2 and -3-sulfonic acids, the sulfonation was shown to have occurred to the extent of approximately 80% on carbon atom number 2 and 20% on carbon atom number 3.

(18) Inasmuch as Lucas, Schlatter and Jones[5] claim that 2-pentene derived from 2-pentanol consists of approximately 75% *trans*- and 25% *cis*-isomer, it is possible that the *trans*-isomer may have sulfonated in the 2-position and the *cis*- isomer in the 3-position. However, proof of this possibility would rest upon sulfonation experiments with the pure isomers.

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[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

Synthetic Antimalarials. Some Derivatives of 8-Aminoquinoline. II[1]

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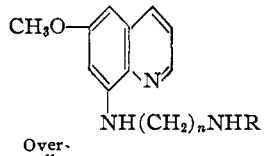
Continuing the research that led to the synthesis of pentaquine (SN 13,276),[2,3] a number of new 8-aminoquinolines have been synthesized. In eleven of these, only the terminal amino group of SN 13,276 has been varied; in seven more, the length of the side chain has been changed. One compound containing an additional nuclear substituent has also been made.

Two general methods were used for the synthesis of all but one of the drugs. Method I consisted of heating 8-amino-6-methoxyquinoline in the presence of water with the appropriate side chain chloride hydrochloride in much the same manner as was reported for the synthesis of SN 13,276.[3] Method II consisted of the reductive alkylation of the appropriate 6-methoxy-8-aminoalkylaminoquinoline with the requisite aldehyde or ketone in ethanol solution in the presence of Adams catalyst at room temperature.[4] The condensation of isopropyla-

TABLE I



UM No.	R	n	Method of synthesis	Salt[a] prepared	Overall yield[b] of salt, %	M. p.[c] of salt, °C.	Analyses,[d] % Calculated Carbon	Calculated Hydrogen	Found Carbon	Found Hydrogen	Homogeneity %[e]
137 Q	$CH(CH_3)CH_2CH_2CH_3$	5	I	A	15	167.1–168.2	65.75	8.67	65.48, 65.41	8.66, 8.84	
135 Q	$CH(C_2H_5)_2$	5	I	B	41	103–105	45.71	7.10	45.80, 45.75	7.33, 7.18	
136 Q	$CH(CH_3)C_2H_5$	5	I	C	54	164.3–165.1	57.57	7.57	57.67, 57.50	7.62, 7.56	
139 Q	$CH(CH_3)_4CH_3$	5	I	A	12	168–169	66.8	8.48	66.64	8.44	
170 Q	$CH_2C(CH_3)_3$	5	I	A	22	188.9–189.5	65.75	8.76	66.00, 65.85	8.75, 8.65	98 ± 2
177 Q	$CH_2CH(CH_3)_2$	5	II	C	20	175.7–176.9	57.57	7.57	57.79, 57.70	7.61, 7.81	98 ± 2
178 Q	$CH_2CH(CH_3)C_2H_5$	5	II	C	26	149.5–150.5	65.75	8.73	65.52, 65.81	9.02, 9.04	98 ± 2
179 Q	$(CH_3)_3CH_2$	5	I	C	14	135.6–136.8	57.57	7.57	57.90, 57.62	7.17, 7.28	94 ± 3
180 Q	$(CH_2)_4CH_3$	5	I	C	27	123.5–124.9	58.54	7.80	58.73, 58.89	7.90, 7.94	94 ± 3
181 Q	$CH_2CH_2CH(CH_3)_2$	5	I	C	5	143.3–144.6	58.54	7.80	58.74, 58.88	7.92, 7.93	98 ± 2
182 Q	$CH(CH_3)CH(CH_3)_2$	5	I	C	7	164.2–165.1	58.54	7.80	58.54, 58.81	7.68, 7.94	97 ± 2
183 Q	$CH(CH_3)CH(CH_3)_2$	4	II	C	7	173.4–175.0	57.57	7.57	57.55, 57.78	7.65, 7.67	98 ± 2
171 Q	$CH_2C(CH_3)_3$	4	II	A	41	197.2–198.6	64.96	8.55	65.10, 65.02	8.45, 8.55	91 ± 5
165 Q	$CH_2C(CH_3)_3$	3	I	C	10	200.1–201.1	56.54	7.33	56.57, 56.48	7.30, 7.28	98 ± 2
168 Q	$CH(C_2H_5)_2$	3	I	D	41	133–135	46.67	6.31	46.89, 46.75	6.45, 6.39	
172 Q	$CH(C_2H_5)_2$	2	I	D	40	237.0–237.4	45.43	6.01	45.67, 45.64	6.21, 6.19	
176 Q	$CH(CH_3)CH_2CH_2CH_3$	2	I	D	17	233.1–233.9	45.43	6.01	45.83, 45.62	6.37, 6.26	
166 Q	$CH_2C(CH_3)_3$	2	I	D	6	235.6–236.8	45.43	6.01	45.76, 45.85	6.22, 6.17	96 ± 3

[a] A represents the monohydrochloride; B, a diphosphate; C, a monohydrobromide; and D, a dihydrobromide. [b] The yields for those compounds prepared by Method I were calculated from the amino alcohol. Those prepared by method II were calculated from the aminoalkylaminoquinoline. [c] Melting points in this table and in following tables are corrected. [d] Analyses by Miss Eleanor Werble, Mrs. Mary Aldridge and Byron Baer. [e] Homogeneities were determined by the countercurrent extraction technique. See Williamson and Craig, *J. Biol. Chem.*, 168, 687 (1947). For simplified method of calculation see Lieberman, *ibid.*, **173**, 63 (1948).

(1) This work was entirely supported by a grant-in-aid from the United States Public Health Service (RG-191).

(2) N. L. Drake, *et al.*, THIS JOURNAL, **68**, 1536 (1946).

(3) N. L. Drake, *et al.*, *ibid.*, **68**, 1529 (1946).

(4) A. C. Cope, private communication. This general method was used by Cope to make 8-(4-isopropylamino-*n*-butylamino)-6-methoxyquinoline (SN-13,275).