[CONTRIBUTION FROM THE STERLING CHEMICAL LABORATORY OF YALE UNIVERSITY]

American Musk. III. The Scent of the Common Skunk

BY PHILIP G. STEVENS

The scent of the common skunk (*Mephitis mephitis*) is so extraordinarily powerful and persistent that from time to time it has attracted attention from chemists. That some sulfur compound was present was recognized early,[1] but it remained for Aldrich[2] to show that the principal odoriferous material is *n*-butyl mercaptan, accompanied by alkyl sulfides. Almost simultaneously Beckmann[3] noted the occurrence of *n*-butyl mercaptan in the scent of the teledu (*Mydaus marchei Huet*, a member of the Mustelidae family and thus closely related to the skunks) of the Philippine Islands, and believed the higher-boiling oil was a disulfide. Not until 1937 was further work done on this type of secretion when Fester and Bertuzzi[4] undertook a study of the scent of the South American zorrino (*Conepatus suffocans*), isolating by steam distillation a small amount of oil which, from analytical data, appeared to contain *n*-butyl mercaptan, and an unsaturated C_4 mercaptan, and the corresponding disulfide.

In connection with attempts to discover new natural musks[5,6] and in view of reference in the literature to skunk scent and perfumes,[4,7] an investigation of skunk scent was undertaken to learn whether any large ring compounds were present. Fresh scent (from *Mephitis mephitis nigra*) was treated with alcoholic mercuric chloride to remove mercaptans, and supposedly sulfides also, and the unchanged material was separated into two volatile and a non-volatile fraction. The latter material containing any large ring compounds present, was saponified, and the neutral material was fractionated, yielding a small amount of oil which, though having a not unpleasant, somewhat floral odor, and boiling as would a large ring alcohol or ketone, had a composition corresponding approximately to $C_{11}H_{20}S_2$, and gave, on oxidation, products with no musk odor. The scent therefore contains no large ring compounds of the musk or civet type; any fixative value, if any, must depend on other compounds.

The volatile oils were repulsive in odor. The main, more volatile fraction, A, had the composition $C_8H_{14}S$, was insoluble in dilute potassium hydroxide, added bromine avidly, gave a precipitate with aqueous mercuric chloride,[8] and was therefore an unsaturated sulfide. On treatment with methyl iodide at room temperature, A yielded trimethylsulfonium iodide, indicating that both alkyl groups of the unsaturated sulfide had been replaced,[9] that both groups were of the allyl type,[10] and that A was possibly dicrotyl sulfide. Comparison of the sulfide and its mercuric chloride addition product with corresponding authentic specimens established the structure as dicrotyl sulfide (Table I).

Many thanks are due to Francis Peterson of Essex, Connecticut, for the collection of the skunk sacs, and to Ralph C. Morrill, Chief Taxidermist to the Peabody Museum of Yale University, for the extraction of the scent from the sacs..

Experimental Part

Isolation of the Various Fractions.—The scent (about 9 ml. from each sac), withdrawn from the anal sacs[11] (often imbedded in flesh) with a hypodermic needle, was reddish, and, after several months, separated into two layers with yellow, flaky, fatty material suspended at the interface. The mercaptides formed on treatment of 210 g. of scent with ethanolic mercuric chloride for several days were filtered off, and, after considerable time, the solvent was evaporated *in vacuo* through a fractionating column from the reclarified filtrate. The residue and the alcoholic distillate were added to water, the respective insoluble oils were extracted with low-boiling petroleum ether, the extracts were combined, washed with water, dried over anhydrous sodium sulfate, and fractionated *in vacuo* yielding: "A," a yellow oil, 25 ml. b. p. 80–90° (17 mm.) and "B," a yellow-orange oil, 15 ml. b. p. 90–135° (17 mm.) (not further investigated). The red-black distillation residue was saponified with 10% ethanolic potassium hydroxide, and the acidic products were separated in the usual way from the neutral products which, on distillation at 0.8 mm., gave three fractions: 1, b. p. 105–130°; 2, 130–150°; 3, 150–163°, none of which gave a precipitate with 2,4-dinitrophenylhydrazine, nor a musk odor when oxidized with chromic acid. Fraction 2 had C, 61.4; H, 9.3; S, 26.0; fraction 3 had C, 60.3; H, 9.4; S, 29.2, thus indicating an approximate composition of $C_{11}H_{20}S_2$ and showing that the fractions were complex disulfides.

Fraction A.—This material was extracted successively with 7% hydrochloric acid and 10% alkali, dried with anhydrous sodium sulfate, fractionated twice *in vacuo* and yielded 5 ml. of a colorless oil (b. p. 71–72° (10 mm.). *Anal.* calcd. for $C_8H_{14}S$: C, 67.6; H, 9.9; S, 22.5. Found: C, 67.5; H, 10.2; S, 22.0; N, 0.39.) which had an odor similar to dicrotyl sulfide, absorbed bromine at once both in acetic acid and carbon tetrachloride without appearance of coloration, and gave a precipitate with concentrated (20%) ethanolic mercuric chloride. The partially crystalline mass, after fractional crystallization from warm ethanol, yielded clusters of thin plates, m. p. 61–63° with preliminary sintering at 60.5°. After melting, the material became opaque at about 85–90°, and decomposed at 145–

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(1) Swarts, *Ann.*, **123**, 266 (1862).

(2) Aldrich, *J. Exptl. Med.*, **1**, 323 (1896).

(3) Beckmann, *Pharm. Centralhalle*, **37**, 557 (1896).

(4) Fester and Bertuzzi, *Revista de la Facultad de Quimica Industrially Agricola*, **5**, 85 (1937), Universidad Nacional del Litoral, Rosario, Argentina.

(5) Stevens and Erickson, THIS JOURNAL, **64**, 144 (1942).

(6) Stevens, *ibid.*, **65**, 2471 (1943).

(7) *Ind. Eng. Chem., News Ed.*, **19**, 1134 (1941).

(8) For various reasons, the sulfide escaped removal with the mercaptides.

(9) Unless the distribution were $CH_3—S—C_7$, which was very unlikely.

(10) Because only such groups as benzyl (Schöller, *Ber.*, **7**, 1274 (1874)) and presumably allyl groups (Steinkopf and Bessaritch, *J. prakt. Chem.*, [2] **109**, 230 (1925)) are split off by methyl iodide at room temperature (Klinger and Maason, *Ann.*, **252**, 241 (1898); Brjuchonenko, *Ber.*, **31**, 3176 (1898)).

(11) Which had been stored in methyl alcohol.

TABLE I

	B. p. 765 mm., °C.	$n^{25}D$	d^{25}_4	$\alpha^{22}D$	$HgCl_2$ complex M. p.	$HgCl_2$ complex Mixed m. p.
Compound A	187–189	1.4888	0.8830	0.00°	61–63°[a]	61.5–65°[d]
$(CH_3CH{=}CHCH_2)_2S$	186–187[b]	1.4938	0.8873	0.00°	63–65°[c]	

[a] Preliminary sintering at 60.5°. [b] At 766 mm. [c] Preliminary sintering at 62°. [d] Preliminary sintering at 61°.

150°. The failure to achieve complete purification can be attributed to the presence of complexes from isomeric or related sulfides, difficult to remove, as well as to the somewhat unstable character of the complex.

The action (evident within one, and apparently complete after three days) of methyl iodide upon A at 25° yielded crystals of trimethylsulfonium iodide, which after separation from the adhering red oil, were recrystallized from ethanol. The feather-like crystals dissociated to gaseous products at 202–203°—a characteristic of trimethyl sulfonium iodide.[12]

Dicrotyl Sulfide.—This compound,[13] after careful fractionation (b. p. 81° (17 mm.)) gave, with aqueous chloramine-T, *p*-toluenesulfonamide instead of a sulfilimine.[14] With 20% ethanolic mercuric chloride, it yielded an addition compound, as clusters of thin plates which, after recrystallization from warm ethanol, sintered at 62°, melted at 63–65°, became opaque at about 95°, and decomposed at 145–150°, thus paralleling the behavior of the same compound obtained from A of the skunk scent.

Summary

1. No large ring alcohols or ketones of the musk or civet type are present in the scent of the common skunk.

2. Dicrotyl sulfide has been identified as present in the scent.

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(12) Steinkopf and Müller give 203–207°, *Ber.*, **56**, 1926 (1923).

(13) Prepared according to Charon, *Ann. chim.*, [7] **17**, 197 (1899).

(14) Davies and Oxford, *J. Chem. Soc.*, 224 (1931).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF RICHMOND]

Phenylacetates, Diphenylacetates and Phenylalkylacetates of β-Methyl-β-monoalkylaminopropanols[1,2]

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In this Laboratory we have synthesized various aromatic acid esters of β-monoalkylaminoalkanols[3,4,5] in a study of local anesthetics. This paper deals with the synthesis of phenylacetates, phenylalkylacetates and diphenylacetates of β-methyl-β-monoalkylaminopropanols. These alkamine esters are being examined for antispasmodic properties. Several β-monoalkylaminoethyl and β-monoalkylaminobutyl diphenylacetates were prepared but as the hydrochlorides of most of these substances were obtained as oils, these products are not included in this paper.

The β-methyl-β-monoalkylaminopropanols used in this work were prepared by methods previously described.[3,4] The phenylalkylacetic acids were made from phenylacetonitrile by alkylation and hydrolysis. The chlorides from these acids were reacted with the dry hydrochlorides of the amino alcohols. The esters thus formed were purified by modifications of methods previously described.[3,4,5]

Pharmacological tests on these compounds are being carried out by Dr. Charles C. Haskell. The results will be reported elsewhere.

Experimental

Phenylethylacetic Acid.[6]—Phenylacetonitrile was alkylated by heating with equimolar quantities of ethyl iodide and sodium hydroxide under reflux at 100, 130 and 165° for approximately two hours at each temperature. The phenylethylacetonitrile formed by this reaction, after the unethylated phenylacetonitrile was removed by treatment with benzaldehyde, was hydrolyzed by heating for forty hours at 155° in a sealed tube with 6 *N* hydrochloric acid, yielding phenylethylacetic acid, boiling at 155–160° at 15 mm.; yield 24%.

Diphenylacetyl Chloride.[7]—In a typical run, 42.5 g. (0.2 mole) of diphenylacetic acid and 95 g. (0.8 mole) of thionyl chloride were heated on an oil-bath at 100° for one and a half hours. The excess thionyl chloride was removed *in vacuo*, several 10-ml. portions of dry benzene being added to remove the last traces. The diphenylacetyl chloride was divided into aliquot portions for reaction with amino alcohol hydrochlorides.

Phenylethylacetyl Chloride.—A mixture of 23.7 g. (0.145 mole) of phenylethylacetic acid and 71 g. (0.6 mole) of thionyl chloride was heated under reflux at 112° for three hours. The excess thionyl chloride was removed *in vacuo* and the phenylethylacetyl chloride, 25 g. (94%), was collected at 112–115° at 15 mm.

Alkamine Ester Hydrochlorides.—β-Methyl-β-monoalkylaminopropyl aryl acetate hydrochlorides were prepared by ester formation between amino alcohol hydrochlorides and acid chlorides by methods described previously.[3,4] In a typical run of 0.05 mole each of β-methyl-β-*n*-amylaminopropanol hydrochloride and diphenylacetyl chloride, the ester was purified as follows: The thick oil remaining in the flask was dissolved in 35 ml. of warm alcohol and the solution poured into 400 ml. of 0.5 *N* sodium hydroxide solution. The oil which separated was dissolved in 100 ml. of isopropyl ether. This solution was washed with 400 ml. of 0.5 *N* sodium hydroxide solution and extracted with 400 ml. of 0.5 *N* hydrochloric acid

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(2) This research was made possible by a grant from Chas. C. Haskell and Co., Inc., Richmond, Va.

(3) J. Stanton Pierce, J. M. Salsbury and J. M. Fredericksen, THIS JOURNAL, **64**, 1691–1694 (1942).

(4) J. Stanton Pierce, J. M. Salsbury, Walter W. Haden and L. H. Willis, *ibid.*, **64**, 2884–2885 (1942).

(5) J. Stanton Pierce, Robert D. Gano and J. M. Lukeman, *ibid.*, not yet published.

(6) K. Neure, *Ann.*, **250**, 151 (1889).

(7) F. Klingemann, *ibid.*, **275**, 84 (1893).