Sweat in Schizophrenic Patients: Identification of the Odorous Substance

Abstract. *The substance causing the peculiar odor in sweat of schizophrenic patients has been isolated and identified as* trans*-3-methyl-2-hexenoic acid by gas chromatography, mass spectrometry, and nuclear magnetic resonance spectroscopy. The natural and the synthetic compounds were cleaved across the double bond to give 2-pentanone and oxalic acid, thereby confirming the structure.*

In 1960 Smith and Sines (*1*) demonstrated the existence of a peculiar odor in sweat of schizophrenic patients. They trained rats to discriminate between sweat specimens of schizophrenics and controls ($P = .0001$); a human panel testing the odor was also able to discriminate between the sweat of the patients and controls ($P = .005$). In 1962 Posner, Culpan, and Stewart (*2*) suggested that the "schizophrenic odor" may be due in part to the presence of the organism *Pseudomonas aeruginosa*; but Skinner, Smith, and Rich (*3*) subsequently reported that this organism could not be found in 14 schizophrenic patients with the odor or in 14 other patients without schizophrenia living on the same ward.

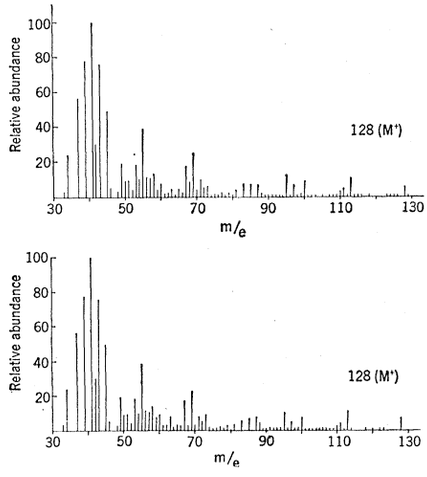
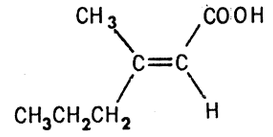


Fig. 1. Mass spectra of isolated (top) and authentic (bottom) *trans*-3-methyl-2-hexenoic acid.

We have identified the odorous substance reported by Smith and Sines (*1*) as *trans*-3-methyl-2-hexenoic acid.



Solubility studies of sweat specimens from patients with schizophrenia (*4*) indicated that the odorous substance was a carboxylic acid (*5*). Programmed dual-column gas-chromatographic analysis (*6*) of the acidic components of sweat from seven schizophrenics and ten controls revealed an acid peculiar only to the schizophrenic specimens. The retention time of the acid was between that of *n*-heptenoic and *n*-octanoic acids, and about 0.1 μg of the acid per milliliter of sweat was estimated to be present in an average sweat specimen (about 100 ml) from a schizophrenic.

In order to obtain enough acid to elucidate its structure, the sweat specimens were acidified to *p*H 1, extracted with ether, dried over magnesium sulfate, and concentrated to 0.3 ml. Preparative gas chromatography of 13 such samples afforded about 230 μg of the unknown acid.

The mass spectrum (*7*) (Fig. 1), infrared spectrum (CCl_4 : 2940, 2908, 2878, 1700, and 1645 cm^{-1}), and gas chromatographic retention time of the isolated acid were virtually identical with those of *trans*-3-methyl-2-hexenoic acid prepared by the dehydration and hydrolysis of ethyl-3-hydroxy-3-methylhexanoate (*8*). That *cis-trans* isomerization does not occur during chromatography was demonstrated by showing that *cis*-4-heptenoic acid does not isomerize to *trans*-4-heptenoic acid (retention times relative to *n*-octanoic acid, 0.85 and 0.77, respectively).

Except for two signals attributed to impurities (a doublet at 4.18 δ and a singlet at 1.25 δ), the time-averaged 100-Mhz nuclear magnetic resonance (NMR) spectrum (*9*) (CCl_4–$DCCl_3$) of the isolated acid (Fig. 2) was identical with the 60-Mhz spectrum (CCl_4) of the authentic acid: 0.92 δ (triplet, 3H), 1.55 δ (sextuplet, 2H), 2.14 δ (triplet, 2H; doublet, 3H; $J = 2.30$ hz), 5.65 δ (quartet, 1H; $J = 2.30$ hz), 12.35 δ (singlet, 1H).

The assignment of the *trans* configuration is based on the chemical shift of the allylic methyl protons. In β,β-dimethylacrylic acid, for example, the chemical shift of the methyl protons *cis* to the carboxyl group is 0.25 part per million (ppm) downfield from the methyl protons *trans* to the carboxyl group (*10*). In the 3-methyl-2-hexenoic acid, the allylic methylene and allylic methyl protons have the same chemical shift because of deshielding of the allylic methyl protons by the carboxyl group. In the *cis* isomer the allylic methylene protons would be expected downfield from the allylic methyl protons.

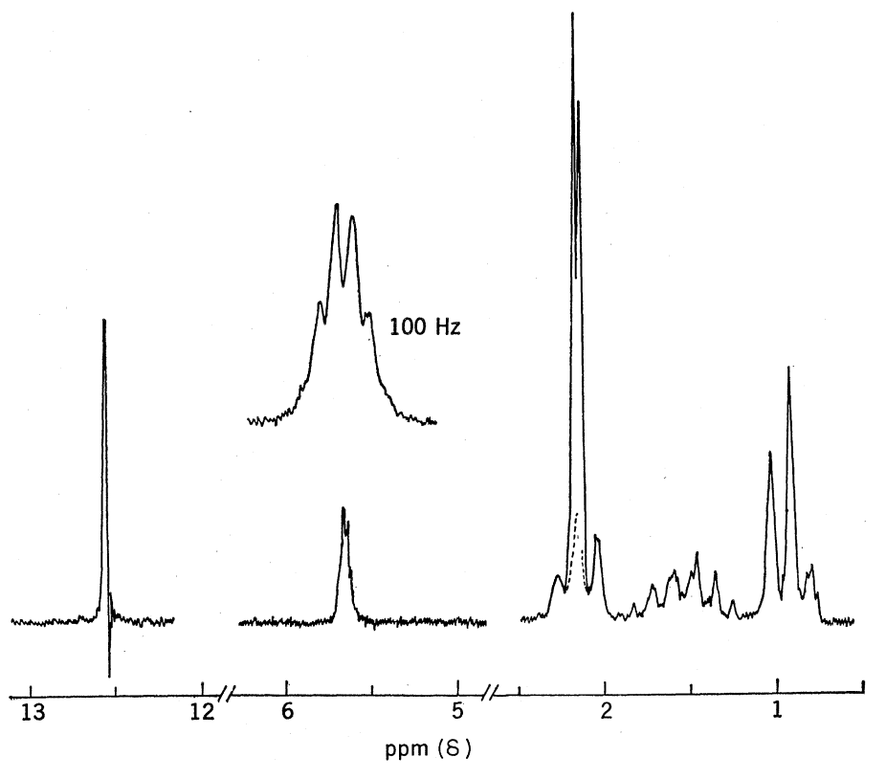


Fig. 2. The NMR spectrum of isolated *trans*-3-methyl-2-hexenoic acid.

Further confirmation of the location of the double bond in both the isolated and synthesized acids was obtained by (i) cleavage of the unsaturated acids with alkaline permanganate to give 2-pentanone and by (ii) cleavage of the corresponding ozonides of the unsaturated acids with toluenesulfonic acid in ethanol to give diethyl oxalate.

Because the odorous substance is acidic, and because the only detectable difference in composition between the samples from schizophrenic patients and controls is the presence of *trans*-3-methyl-2-hexenoic acid, this acid is presumed to be responsible for the peculiar odor in the "sweat" of schizophrenic patients.

Crystals of this synthetic acid were added to "normal sweat" and a panel of four trained observers agreed that the odor produced was identical with the peculiar odor characteristic of the sweat of schizophrenic patients. This work represents a first step in an attempt to identify the metabolic disorder responsible for nuclear schizophrenia.

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References and Notes

1. K. Smith and J. Sines, *Arch. Gen. Psychiat.* **2**, 184 (1960).
2. H. S. Posner, R. Culpan, A. Stewart, *ibid.* **7**, 108 (1962).
3. K. Skinner, K. Smith, E. Rich, *Amer. J. Psychiat.* **121**, 64 (1964).
4. The method of collecting sweat specimens is described in (*1*). The term "sweat" as used in this article refers to skin secretions. The chemical substance is thought to be of sebaceous gland origin rather than eccrine or apocrine in origin.
5. R. L. Shriner, R. C. Fuson, D. Y. Curtin, in *The Systematic Identification of Organic Compounds* (Wiley, New York, 1956), p. 63.
6. All the gas chromatography was carried out on columns containing 10 percent diethylene glycol adipate and 2 percent phosphoric acid (85 percent) on acid-washed Chromosorb-W.
7. Mass spectra were obtained on a Consolidated Electrodynamics mass spectrometer (model 21-104) equipped with an F and M (model 810) gas chromatograph.
8. Ethyl-3-hydroxy-3-methylhexanoate, prepared by the Reformatsky reaction of ethyl bromoacetate with 2-pentanone, was dehydrated with phosphorus oxychloride according to the method of L. Canonica, E. Fedeli, A. Castelnuovo [*Gazz. Chim. Ital.* **87**, 998 (1957)].
9. The NMR spectrum of the isolated acid was obtained with a Varian HA-100 spectrometer equipped with a C-1024 time-averaged computer (tetramethylsilane, internal standard). The sample was examined with two successive accumulations of spectra, each totaling 137 scans.
10. Spectrum No. 114, NMR Spectra Catalog, Varian Associates, Palo Alto, California.
11. We thank R. Frederickson and P. Kingslan for help with the experimental work, the Monsanto Chemical Company for determining the mass spectra, and Varian Associates for determining the nuclear magnetic resonance spectra. Supported by grants MH 05415, MH 5938, and MH 5804 from the National Institutes of Health.

9 December 1968; revised 10 July 1969

Animals Respond for Food in the Presence of Free Food

Abstract. *Pigeons pecked a response disk to gain access to grain rewards while identical grain was freely available from a cup within the experimental chamber. Similarly, rats pressed a lever for food pellets while free pellets were present. It is not necessary, therefore, to deprive an animal of food before it will engage in instrumental responding for food. Such responding can serve as its own motivation and reward.*

An animal will perform instrumental responses for food after being deprived of food but will not respond after eating a large meal. This common observation suggests that responding to obtain food is primarily motivated by hunger or, more exactly, by food deprivation. But is it true that the animal must be deprived in order to work reliably for food? The answer to this question is usually yes (*1*). However, this study shows that pigeons and rats respond for food when they are not deprived of food and when a cup filled with identical food is continuously available.

Two male White Carneaux pigeons with no previous experimental training were used for the basic study. Each bird lived alone in an operant-conditioning chamber (48 cm long, 28 cm wide, and 31 cm high), the front wall of which contained a continuously lighted response disk (1.9 cm in diameter) and a feeder mechanism (*2*). A peck by the pigeon of at least 0.15 newton force on the disk gave the bird 5 seconds of access to mixed grain in the feeder. A 7-watt bulb illuminated the feeder while grain was presented. Cups (8.9 cm high and 7.6 cm in diameter) were secured in the rear corners of the chamber: one cup always contained water; the other sometimes contained mixed grain identical to that in the feeder and sometimes was empty. The pigeon lived in the chamber throughout the experiment except for approximately ½ hour each day while the chamber was cleaned and resupplied.

Each pigeon was deprived of food and taught to peck the disk for grain reward. The free-food cup was empty (so that the pigeon had to peck the disk to get food) and was kept empty for 7 days while the feeder was operated by pecking. One pigeon responded about 270 times per day during the last 3 days of this base-line condition (Fig. 1), and the second pigeon responded about 1100 times (a difference that is attributable to pigeon 2 eating for a relatively short time after each response).

The free-food cup was then filled with grain for 15 days. Since responses continued to produce access to feeder grain, there were now two sources of identical food, free and response-produced; yet both pigeons continued to peck the disk at relatively high frequencies (Fig. 1). Pigeon 1 responded only 33 times during the first day of this condition, but increased its responding over the next few days; pigeon 2 responded at high frequency throughout. Gross measures indicated that (i) grain was taken from both feeder and cup, (ii) more grain was eaten from feeder than from cup, and (iii) both birds occasionally responded but did not eat from the feeder.

In the first of four control studies, responding depended on access to feeder grain rather than merely on the sound of the feeder operating or the sight of grain (*3*). Pigeon 1 remained in the chamber for 13 days during which the feeder was empty; pigeon 2 was in the chamber for 10 days while a transparent shield covered the feeder, thereby permitting the bird to see the grain but not to reach it. As before, each response operated the feeder, and free grain was available from the cup; but under this condition, frequencies of responding decreased to low levels (Fig. 1). When responses again produced access to grain (for 11 days), frequencies of responding again increased (Fig. 1).

To explore the generality of the above findings, two female albino rats with no previous experimental experience were studied under similar conditions. The rats were individually housed in an operant-conditioning chamber containing two metal levers (*2*). A response of at least 0.32 newton force on the left lever caused one 45-mg Noyes pellet to appear in a recessed food tray (the right lever was not