Anal. Calcd. for $C_{19}H_{12}FNO$: C, 78.9; H, 4.2. Found: C, 78.6; H, 4.1.

β-(4-Fluoro-3-methylbenzoyl)propionic acid. A mixture of 55 g. of *o*-fluorotoluene, 50 g. of succinic anhydride, and 75 g. of finely powdered aluminum chloride in 150 ml. of carbon disulfide was refluxed for 4 hr. on the water bath, and then left overnight at room temperature. After decomposition with ice and hydrochloric acid and evaporation of the solvent, the reaction product was taken up in ether, the ethereal solution washed with water and dried over sodium sulfate, and the solvent distilled off. Crystallization of the solid residue from benzene gave 30 g. of colorless prisms, m.p. 119°. The position of the fluorine atom in this compound is assumed from analogy with the acylations.[11]

Anal. Calcd. for $C_{11}H_{11}FO_3$: C, 62.9; H, 5.3. Found: C, 63.2; H, 5.2.

γ-(4-Fluoro-3-methylphenyl)butyric acid (XV). Prepared as for acid II, this compound crystallized from water in shiny colorless tablets, m.p. 64–65°.

Anal. Calcd. for $C_{11}H_{13}FO_2$: C, 67.3; H, 6.6. Found: C 67.0; H, 6.6.

4-Fluoro-1-acetonaphthone. Obtained in 70% yield from 48 g. of 1-fluoronaphthalene, 28 g. acetyl chloride, and 70 g. of aluminum chloride in carbon disulfide as in the case of β-(4-fluoro-3-methylbenzoyl)propionic acid; the ketone was a pale yellow oil, b.p. 288°, n_D^{20} 1.6071.

Anal. Calcd. for $C_{12}H_9FO$: C, 76.6; H, 4.8. Found: C, 76.5; H, 4.6.

4-Fluoro-1-naphthoic acid (XV). Fifteen grams of the foregoing ketone was shaken with an aqueous solution of sodium hypobromite (prepared from 13 ml. of bromine and 26 g. of sodium hydroxide) for 2 hr. at room temperature, the neutral impurities were removed by water-extraction, and the aqueous solution was treated with sodium bisulfite, then acidified with hydrochloric acid. The precipitate, obtained in 70% yield, crystallized from benzene in fine, colorless, sublimable needles, m.p. 226°.

Anal. Calcd. for $C_{11}H_7FO_2$: C, 69.5; H, 3.7. Found: C, 69.2; H, 3.4.

PARIS (V^e), FRANCE.

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(11) Buu-Hoï and Jacquignon, *J. Chem. Soc.*, 4173 (1952).

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

Addition of Mercaptoacetic Acid to Terpenes and Related Compounds

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The reaction of mercaptoacetic acid with *d*- and *l*-limonenes, dipentene, α-pinene, β-pinene, camphene, myrcene, anethole, oleic acid, and allyl chloride was studied. Ultraviolet light and peroxides generally accelerate the reactions and evidence is presented that atmospheric oxygen is sufficient to induce a rapid reaction with *d*-limonene. A different adduct to *d*-limonene was obtained in the presence of sulfuric acid. The products were characterized as *S*-benzylthiuronium salts.

In view of the sparsity of solid derivatives of terpenes, the action of mercaptoacetic acid on several representatives of this class of compounds was studied. Although the adducts were expected to be liquids, the carboxyl groups of the adducts should furnish a point for preparing solid derivatives, such as *S*-benzylthiuronium salts.

As ordinarily carried out, the addition of mercaptans, including mercaptoacetic acid, to unsaturated compounds is generally presumed to be a radical-type reaction. Kharasch, Read, and Mayo[2] have observed that the addition of mercaptoacetic acid to styrene and isobutylene is definitely peroxide-catalyzed and that no reaction occurs in the presence of 5 mole percent of hydroquinone. However, Hoog and Eichwald[3] found that mercaptoacetic acid adds to many "peroxide-free" olefins without ultraviolet light.

Vincent and Etzel[4] have reported the use of the mercaptoacetic acid adducts to limonene, pinene, and camphene as milling aids for butadiene-styrene copolymers. Isobornyl carboxymethyl sulfide was prepared at 95° in the presence of *p*-toluenesulfonic acid from camphene and mercaptoacetic acid. The products were not characterized.

During the course of the present work, it was observed that mercaptoacetic acid does add vigorously to *d*-limonene which had been freed of peroxides by distillation, treatment with ferrous salts or absorption of the peroxides on alumina. The products are the same as those obtained in the presence of peroxides and reaction is inhibited by hydroquinone. It appears, therefore, that atmospheric oxygen is sufficient to induce radical-type reactions in this example.

Under appropriate conditions, either a 2:1 or 1:1 adduct to *d*-limonene may be obtained. The 2:1 adduct, as well as the *S*-benzylthiuronium salt isolated from it, retained optical activity. Thus, the addition to at least one of the double bonds occurs contrary to Markownikoff's rule, as ionic addition to both double bonds would afford a symmetrical molecule.

Cunneen[5] has previously reported the "normal" addition of mercaptoacetic acid to 1-methylcyclohexene in the presence of sulfuric acid. Under similar conditions a reaction of mercaptoacetic

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(1) Present address: Department of Chemistry, University of Kentucky, Lexington, Ky.

(2) M. S. Kharasch, A. T. Read, and F. R. Mayo, *Chemistry & Industry*, 752 (1938).

(3) H. Hoog and E. Eichwald, *Rec. trav. chim.*, 58, 481 (1939).

(4) J. R. Vincent and G. Etzel, U.S. Patent 2,429,858 (1947); *cf. Chem. Abstr.*, 42, 1449 (1948).

(5) J. I. Cunneen, *J. Chem. Soc.*, 36 (1947).

acid with *d*-limonene occurs. The product is different from that obtained in the presence of peroxides. The *S*-benzylthiuronium salt isolated from the 1:1 adduct is optically inactive and appears to be identical with that obtained from dipentene under similar conditions. The adduct itself retained only a small amount of activity. The loss of optical activity may be explained by ionic addition to the ring double bond which results in a symmetrical adduct or it may be due to racemization induced by sulfuric acid. Sulfuric acid is known to polymerize *d*-limonene to optically inactive substances.[6] Apparently addition occurred much more rapidly than polymerization, as excellent yields of the 1:1 adduct were obtained. The possibility that racemization occurs without polymerization cannot, however, be excluded. The 2:1 adduct to *d*-limonene prepared in the presence of sulfuric acid was, of course, also devoid of optical activity.

Reaction of mercaptoacetic acid with α-pinene, β-pinene, camphene, and myrcene was also observed to proceed readily in the presence of peroxides or ultraviolet light. Neither pinene sample employed was optically pure and the *S*-benzylthiuronium salts isolated by crystallization were inactive, although the crude adducts retained some activity. The camphene employed was the racemate. It was not determined whether the pinene skeleton remains intact during the course of the reactions. The crystal structures of the three salts from the pinenes and camphene all appear to be different, but nonidentity could not be established by the mixed melting point criterion.

Several optical isomers would be predicted in the peroxidic addition to the limonenes, pinenes, and camphene. In the present work, only that isomer or racemate of the salt which was most easily crystallized was isolated and these were obtained in relatively low yields. Survey experiments indicated that lower-melting, isomeric salts might be separated by fractional crystallization if desired. Such crystallizations must be carried out rapidly, as the salts decompose slowly in boiling solvents.

Adducts to anethole and oleic acid prepared in the presence of peroxides were characterized by means of the *S*-benzylthiuronium salts.

Thiomalic acid was observed to add to anethole in the presence of ultraviolet light and a solid adduct was isolated.

EXPERIMENTAL

All melting points reported herein are uncorrected. The peroxide number (P.N.) refers to the milliequivalents of iodine liberated from potassium iodide–acetic acid per liter of unsaturated compound. Optical rotations were taken with a Rudolph precision Model 80 polarimeter. Ultraviolet light was supplied by a 0.25-ampere, 115-volt, 60-cycle lamp.

The materials employed were good commercial grades unless specified in the Acknowledgments. Mercaptoacetic acid was vacuum distilled at 13 to 20 mm. unless otherwise specified.

General method. Mercaptoacetic acid is sparingly soluble in all the unsaturated compounds studied herein except anethole. Most of the reactions proceed with evolution of heat. Therefore, it is advantageous to observe whether a homogeneous layer is formed and to follow temperature changes in determining when reaction occurs.

The mixture of mercaptoacetic acid and the unsaturated compound was stirred vigorously. When reaction was complete, the mixture was washed with water and the crude adduct was extracted with ether or benzene. The solvent was evaporated, the residue dissolved in dilute alkali, any insoluble material separated, and the aqueous solution acidified with dilute hydrochloric acid. The adduct was dried *in vacuo* over sulfuric acid.

A further purification of the adducts may be accomplished by preparing a benzene solution (1 g. in 30 ml.), passing the solution through a column of silica gel or alumina, eluting the adduct with ethanol and evaporating the solvent. This treatment was not generally required for our purposes.

S-Benzylthiuronium salts were prepared by a conventional method[7] in approximately 5 millimole quantities.

Data obtained on the adducts are recorded in Table I, and that on the *S*-benzylthiuronium salts in Table II.

d-Limonene. The *2:1 adduct prepared in the presence of peroxides* was obtained using 5.00 g. of *d*-limonene (n^{20}_{D}, 1.4720; $[\alpha^{20}_{D}]$, +118; P.N., 47) and 10.00 g. of mercaptoacetic acid. With stirring, the temperature rose rapidly to 60° and a homogeneous solution was formed. The adduct was isolated and the *S*-benzylthiuronium salt was prepared by the general procedure. Upon standing in a vacuum desiccator for several weeks, the adduct partially crystallized. The mixture was pressed between circles of filter paper and the crystals melted at 65–66°. Analyses indicated that the solid was one of the optical isomers of the adduct.

Anal. Calcd. for $C_{14}H_{24}O_4S_2$: C, 52.47; H, 7.55. Found: C, 52.80; H, 7.83.

The S-benzylthiuronium salt melted at the same temperature as the salt isolated from the crude mixture of adducts and the melting point of mixtures was the same as those of individual samples.

A potassium acid salt of the crude adduct was obtained in 40% yield by dissolving 1.00-g. quantities of the adduct in equimolar amounts of 20% potassium hydroxide, placing the solution in a refrigerator overnight and separating the crystals.

Anal. Calcd. for $C_{14}H_{23}KO_4S_2$: K, 10.89. Found: K, 10.64.

A dipotassium salt was precipitated in 85% yield by dissolving 1.00 g. of the adduct in a solution of potassium hydroxide in 95% ethanol containing excess alkali.

Anal. Calcd. for $C_{14}H_{22}K_2O_4S_2$: K, 19.60. Found: K, 19.55.

The *2:1 adduct prepared in the presence of sulfuric acid* was obtained using 10.0 g. of freshly distilled *d*-limonene, 20.0 g. of mercaptoacetic acid, and 10 drops of sulfuric acid.

The *1:1 adduct prepared in the presence of sulfuric acid* was obtained using 10.0 g. of peroxide-free *d*-limonene, 6.80 g. of mercaptoacetic acid, and 4 drops of 80% sulfuric acid.

l-Limonene. The 2:1 adduct was prepared using 5.00 g. of *l*-limonene (n^{20}_{D}, 1.4740; $[\alpha]^{20}_{D}$, −97; P.N., 15) and 10.00 g. of mercaptoacetic acid.

Dipentene. The sample of dipentene (n^{20}_{D}, 1.4752; P.N., 14) reacted more slowly than did the limonenes alone and ultraviolet light was employed. The quantities used were the same as those used in preparing the corresponding adducts to *d*-limonene.

α-Pinene. The adduct was prepared using 5.0 g. of α-

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(6) A. M. Clover, *Philippine J. Sci.*, 2, 1; *Chem. Zentr.*, I, 1793 (1907).

(7) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, Inc., New York, 1956, p. 202.

TABLE I

ADDUCTS OF MERCAPTOACETIC ACID AND UNSATURATED COMPOUNDS

Compound	Yield, %	n_D^{20}	Optical rotation[a] $[\alpha]_D^{20}$	Formula	Analyses Calcd. C	Found C	Calcd. H	Found H
d-Limonene[b,c]	85	1.536	+48	$C_{14}H_{24}O_3S_2$	52.47	52.44	7.55	7.98
d-Limonene[b,d]	64	1.531	+58	$C_{12}H_{20}O_2S$	63.13	62.92	8.83	8.54
d-Limonene[c,e]	86	1.532	0	$C_{14}H_{24}O_4S_2$	52.47	52.77	7.55	7.93
d-Limonene[d,e]	79	1.536	+1	$C_{12}H_{20}O_2S$	63.13	62.84	8.83	8.61
l-Limonene[b,c]	80	1.538	−43	$C_{14}H_{24}O_4S_2$	52.47	52.45	7.55	7.63
Dipentene[b,c,f]	80	1.534		$C_{14}H_{24}OS_2$	52.47	52.62	7.55	7.84
Dipentene[d,e]	78	1.530		$C_{12}H_{20}O_2S$	63.13	63.01	8.83	8.72
α-Pinene[b,f]	63	1.518	−13	$C_{12}H_{20}O_2S$	63.13	62.83	8.83	8.48
β-Pinene[b]	82	1.542	−30	$C_{12}H_{20}O_2S$	63.13	62.85	8.83	8.72
dl-Camphene[f,g]	83	1.520		$C_{12}H_{20}O_2S$	63.13	63.29	8.83	8.91
Anethole[b,f,h]	90	1.559		$C_{12}H_{16}O_3S$	59.97	60.14	6.71	7.00
Oleic acid[f,g]	84	1.483		$C_{20}H_{38}O_4S$	64.13	63.77	10.22	10.14
Allyl chloride[b]	74	1.530		$C_5H_9ClO_2S$	35.61	35.49	5.38	5.50

[a] In ethanol (c = 1.00). [b] Peroxidic. [c] 2:1 adduct. [d] 1:1 adduct. [e] In presence of sulfuric acid. [f] In presence of ultraviolet light. [g] Heated to 50°. [h] Reaction time: 3.5 hr.

TABLE II

S-BENZYLTHIURONIUM SALTS OF THE ADDUCTS

Compound	Yield, %	M.P. (°C)	Optical Rotation[a] $[\alpha]_D^{20}$	Formula	Analyses Calcd. C	Found C	Calcd. H	Found H
d-Limonene[b,c]	26	171–172	+47	$C_{30}H_{44}N_4O_4S_4$	55.18	55.00	6.79	7.08
d-Limonene[b,d]	28	177–178	+58	$C_{20}H_{30}N_2O_2S_2$	60.87	60.43	7.66	7.48[e]
d-Limonene[c,f]	33	151–152	0	$C_{30}H_{44}N_4O_4S_4$	55.18	55.55	6.79	6.96
d-Limonene[d,f]	34	135–136	0	$C_{20}H_{30}N_2O_2S_2$	60.87	60.56	7.66	7.95
l-Limonene[b,c]	28	171–172	−42	$C_{30}H_{44}N_4O_4S_4$	55.18	55.23	6.79	6.88
Dipentene[b,c,g]	26	160–161		$C_{30}H_{44}N_4O_4S_4$	55.18	55.20	6.79	7.14
Dipentene[d,f]	32	135–136		$C_{20}H_{30}N_2O_2S_2$	60.87	60.62	7.66	7.84
α-Pinene[b,g]	26	156.5–157.5[h]	0	$C_{20}H_{30}N_2O_2S_2$	60.87	60.90	7.66	7.90
β-Pinene[b]	18	161–162[h]	0	$C_{20}H_{30}N_2O_2S_2$	60.87	60.52	7.66	7.95
Camphene[g]	66	167–168[h]		$C_{20}H_{30}N_2O_2S_2$	60.87	60.63	7.66	7.75
Anethole[b]	35	154–155		$C_{20}H_{26}N_2O_3S_2$	59.08	59.09	6.44	6.82
Oleic acid[g,i]	58	128–129		$C_{36}H_{58}N_4O_4S_3$	61.15	61.52	8.27	8.57[j]
Allyl chloride[b]	51	156–157		$C_{13}H_{19}ClN_2O_2S_2$	46.62	46.99	5.72	5.79

[a] In 95% ethanol (c = 0.50). [b] Peroxidic. [c] 2:1 adduct. [d] 1:1 adduct. [e] *Anal.:* Calcd. for $C_{20}H_{30}N_2O_2S_2$: N, 7.10. Found: N, 7.10. [f] Prepared in the presence of sulfuric acid. [g] Prepared in the presence of ultraviolet light. [h] Mixed melting points of salts: α-pinene and β-pinene, 155–161°; α-pinene and camphene, 155–165°; β-pinene and camphene, 159–165°. [i] di-*S*-benzylthiouronium salt. [j] *Anal.* Calcd. for $C_{36}H_{58}N_4O_4S_3$: N, 7.93. Found: N, 7.49.

pinene (n_D^{20}, 1.4663; $[\alpha]_D^{20}$, +20, P.N., 28) and 5.0 g. of mercaptoacetic acid in the presence of ultraviolet light.

β-Pinene. To obtain the adduct, 5.0 g. of β-pinene (n_D^{20} 1.4802; $[\alpha]_D^{20}$, −36; P. N., 21) and 6.4 g. of mercaptoacetic acid were used.

dl-Camphene. A mixture of 10.0 g. of camphene (m.p. 44–46°; P.N., 1) and 9.1 g. of 80% aqueous mercaptoacetic acid was stirred, heated to 50° and irradiated with ultraviolet light.

Anethole. The adduct was prepared using 10.0 g. of anethole (n_D^{20}, 1.5596; P.N., 6) and 7.0 g. of mercaptoacetic acid in the presence of ultraviolet light. Reaction at room temperature without light was slow. At 45° reaction occurred readily and the melting point and mixed melting point of the *S*-benzylthiuronium salt was identical with that obtained using ultraviolet light.

Oleic acid. A mixture of 17.9 g. of freshly vacuum distilled oleic acid (n_D^{20}, 1.4581) and 10.4 g. of 80% mercaptoacetic acid was stirred, heated to 50° and irradiated with ultraviolet light.

Allyl chloride. A mixture of 20.0 g. of allyl chloride (n_D^{20}, 1.4092; P.N., 60) and 31.5 g. of 80% mercaptoacetic acid was allowed to react under a reflux condenser. Reaction with freshly distilled mercaptoacetic acid was slow, but the addition of water to dilute the acid to 80% resulted in a rapid temperature rise and the formation of a homogeneous solution. No reaction was observed between peroxide-free allyl chloride and distilled mercaptoacetic acid in the presence of sulfuric acid.

Myrcene. A sample of peroxidic myrcene (n_D^{20}, 1.4717; P.N., 12) was observed to react rapidly with mercaptoacetic acid but the product was not characterized.

Addition of thiomalic acid to anethole. A solution of 3.00 g. of thiomalic acid (m.p. 149–150°) and 2.60 g. of anethole in 10 ml. of ethanol was irradiated with ultraviolet light for 2 hr. The resulting solution was diluted with 100 ml. of water, basified, and extracted with benzene. The aqueous solution was acidified with dilute hydrochloric acid and the crude adduct (4.82 g. after being dried) was obtained as a semisolid. The adduct was recrystallized from water several times and 2.95 g. of colorless solid was obtained (m.p. 107–108°).

Anal. Calcd. for $C_{14}H_{18}O_5S$: C, 56.36; H, 6.08. Found: C, 56.02; H, 5.86.

Acknowledgments. This work was supported in part (C. N. Y.) by a grant from the Richmond Fellowship Fund. The samples of β-pinene, *l*-limonene, and myrcene were gifts from the Southern Regional Research Laboratories, New Orleans, and the thiomalic acid, from Evans Chemetics, New York. Some of the microanalyses reported herein were carried out by Messrs. John Fissekis and W. T. Lewis and the Geller Laboratories, Hackensack, N. J.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICH.]

1-Aryl-3,3-dialkyltriazenes as Tumor Inhibitors

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A series of 1-aryl-3,3-dialkyltriazenes was prepared by coupling a diazonium salt with a secondary (occasionally primary) amine in basic medium. Preliminary tests against Sarcoma-180 in the mouse indicate that at least one methyl group at N-3 is essential for activity.

The recent observation that 1-phenyl-3,3-dimethyltriazene (I, Ar = C_6H_5) and its *p*-tolyl and *p*-nitrophenyl analogs exhibited inhibition of mouse Sarcoma-180[1] prompted the synthesis and testing of a variety of their relatives. We wish to report the preparation and properties of some of these compounds, together with preliminary tests

$$\mathrm{Ar}\overset{1}{\mathrm{N}}{=}\overset{2}{\mathrm{N}}{-}\overset{3}{\mathrm{N}}(\mathrm{CH_3})_2 \qquad \mathrm{I}$$

against mouse Sarcoma-180.[2]

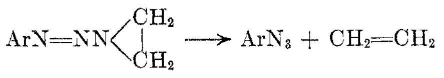
The method of synthesis of these triazenes involved coupling of an aryldiazonium chloride with an amine, usually in a basic aqueous solution. The various modifications of this procedure are given in the experimental section. The physical properties are given in Table I.

Structural variations of I included introduction of one or more substituents in the aryl group at N-1 or use of a heterocyclic aryl group, and replacing one or both methyl groups at N-3 by hydrogen, higher alkyl and substituted alkyl, or a heterocyclic ring containing N-3. The changes were accomplished by use of an appropriately substituted diazonium salt or the desired primary or secondary aliphatic amine.

When a diazonium salt was coupled with methylamine, both mono- and disubstitution occurred, and the product was a mixture of the 1-aryl-3-methyltriazene and the 1,5-diaryl-3-methylpentazdiene (II). These were readily separated by virtue of the insolubility of II in methanol. Some of the triazenes with a hydrogen at N-3 were thermally unstable and decomposed vigorously on attempted vacuum distillation.

$$\mathrm{ArN{=}N{-}N(CH_3){-}N{=}N{-}Ar} \qquad \mathrm{II}$$

The products derived by coupling diazonium salts with ethylenimine were likewise thermally unstable. Those which were solids could in some cases be purified by careful crystallization, but the liquids invariably decomposed on distillation. The isolated product from benzene- or *p*-toluenediazonium chloride and ethylenimine was the aryl azide. The other product (not isolated) was presumably ethylene. This facile pyrolytic cleavage at 60–75° of triazenes has not previously been reported.



$$\mathrm{ArN{=}N}\mathrm{N}\left\langle\begin{matrix}\mathrm{CH_2}\\ |\\ \mathrm{CH_2}\end{matrix}\right. \longrightarrow \mathrm{ArN_3} + \mathrm{CH_2{=}CH_2}$$

It would be of interest to study the pyrolysis of the unstable 1-aryl-3-alkyltriazenes, which might give an aryl azide and an alkane.

The preliminary results of animal tests show that tumor inhibition is exhibited to some extent only by triazenes having at least one methyl group at N-3, including 1-phenyl-, 1-*p*-nitrophenyl-, 1-*p*-methoxyphenyl-, 1-*o*-tolyl-, and 1-*m*-trifluoromethyl-3,3-dimethyltriazene. 1-*p*-Tolyl-3-methyltriazene and 1-*p*-tolyl-3-methyl-3-cyclohexyltriazene also showed some activity. 1-Phenyl-3,3-dialkyltriazenes where both alkyl groups were larger than methyl, as well as those containing a heterocyclic ring incorporating N-3, were inactive.

EXPERIMENTAL

The aromatic amines were commercial samples, purified when deemed necessary. The aliphatic amines were obtained chiefly from the Eastman Kodak Co. and were used as received in most cases.

The aromatic amine was diazotized in the presence of 3 moles of hydrochloric acid, except in the few cases where the amine was so weakly basic as to require more acid. The solution was then filtered. The coupling with the aliphatic amine was carried out in one of the following ways, where the letters refer to the procedures in Table I.

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[1] Clarke, Barclay, Stock, and Rondestvedt, *Proc. Soc. Expt. Biol. Med.*, 90, 484 (1955).

[2] Testing is being carried out at the Sloan-Kettering Institute for Cancer Research, under the direction of Dr. D. A. Clarke and Dr. C. Chester Stock. The details will be reported elsewhere.