Thiolesters. Reaction of Thiols with Acrylyl and Crotonyl Chlorides

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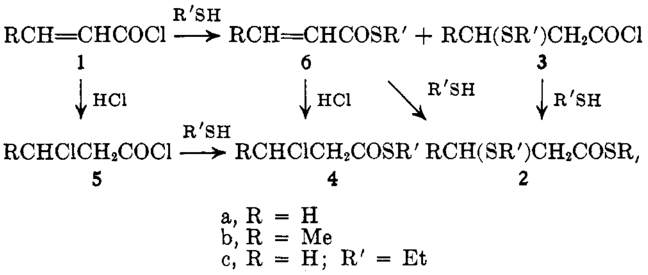
An improved method is described for preparation of thiolcrotonates by reaction of crotonyl chloride with thiols. General convenient and high-yield methods of making the new *dl*-3-chlorothiolbutyrates and the new *dl*-3-alkyl (aryl) thiothiolbutyrates involve addition of hydrogen chloride and of thiols, respectively, to thiolcrotonates. General procedures for making thiolesters by esterification of thiols with anhydrides involve use of 1 mole of amine base in the case of aliphatic thiols and only a catalytic amount of base in the case of aromatic thiols. A convenient, high-yield method for direct addition of thiols to acrylic and crotonic acids involves reaction of a molar quantity of a thiol with the trialkylammonium salt of the acid to produce 3-alkyl (aryl) thiopropionic and butyric acids.

In an investigation of the base-catalyzed reaction of open-chain α,β-unsaturated carboxylic acid anhydrides with thiols, a mixture of products was obtained. It was necessary, therefore, to study the preparation of thiolesters of unsaturated acids, the interaction of thiols with thiolcrotonates, the esterification of thiols with anhydrides in the presence of base, and the base-catalyzed addition of thiols to α,β-unsaturated acids.

Thiolacrylates.—Although thiolesters of saturated carboxylic acids can be prepared conveniently from alkanethiols by several standard acylation techniques,[1] the synthesis of thiolesters of α,β-unsaturated carboxylic acids is tedious. The yields usually are lower because losses are caused by side reactions and by polymerization of the highly reactive unsaturated thiolesters.

The first synthesis of thiolacrylates is that of Reppe and co-workers,[2,3] involving reaction of acetylene with nickel carbonyl and a thiol. Since the crude products from this process have a wide boiling range (up to 30°) it is likely they consist of mixtures of the desired thiolacrylates with their thiol addition products, S-substituted 3-mercaptothiolpropionates. To prevent thiol addition to the activated double bond, α,β-dibromo acid chlorides have been used as starting materials[4-7] and the resulting dibromo thiolesters debrominated to the α,β-unsaturated thiolesters. Somewhat better results are obtained by use of α,β-unsaturated acid chlorides with lead mercaptides in an inert solvent.[8] Acylation with methacrylyl chloride under Schotten–Baumann conditions gives reasonable yields of thiolmethacrylates only with benzenethiols[9] and *sec*- and *t*-alkanethiols,[10] whereas primary alkanethiols yield only the thiol addition products.[10] In acylation with the more reactive acrylyl chloride even benzenethiol and 2-methyl-2-propanethiol produce more addition product than thiolacrylate.[10]

In our work, reaction of acrylyl chloride with ethanethiol in the presence of zinc chloride as the catalyst and cuprous chloride as the polymerization inhibitor produces a rather complex mixture containing none of the desired ethyl thiolacrylate, which apparently reacts further[11] by addition of thiol and of by-product hydrogen chloride or polymerizes as fast as it is formed,[8-10] since polymer always is obtained. The volatile components of the mixture contain recovered acrylyl chloride (**1a**) and as the main product ethyl 3-ethylthiothiolpropionate (**2c**). A middle fraction consists of an inseparable mixture of the isomeric 3-ethylthiopropionyl chloride[13] (**3c**) and ethyl 3-chlorothiolpropionate (**4c**).



$$\begin{tikzcd}
\underset{1}{\mathrm{RCH{=}CHCOCl}} \arrow[r, "\mathrm{R'SH}"] \arrow[d, "\mathrm{HCl}"] & \underset{6}{\mathrm{RCH{=}CHCOSR'}} \arrow[d, "\mathrm{HCl}"] \arrow[dr, "\mathrm{R'SH}"] & +\ \underset{3}{\mathrm{RCH(SR')CH_2COCl}} \arrow[d, "\mathrm{R'SH}"] \\
\underset{5}{\mathrm{RCHClCH_2COCl}} \arrow[r, "\mathrm{R'SH}"] & \underset{4}{\mathrm{RCHClCH_2COSR'}} & \underset{2}{\mathrm{RCH(SR')CH_2COSR'}}
\end{tikzcd}$$

a, R = H
b, R = Me
c, R = H; R' = Et

An authentic sample of 3-ethylthiopropionyl chloride[14] was made from 3-ethylthiopropionic acid[14] and thionyl chloride. Pure ethyl 3-chlorothiolpropionate[15] was made from 3-chloropropionyl chloride[15] (**5a**) and ethanethiol; in this reaction no ethyl 3-ethylthiothiolpropionate was formed, indicating that ethyl 3-chlorothiolpropionate is relatively unreactive with thiols.[16] Products **3c** and **4c** have the same boiling points and refractive indices and their combined infrared spectrum is the same as the infrared spectrum of the aforementioned middle fraction.

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(1) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. IV, Chemical Publishing Co., Inc., New York, N. Y., 1962, p. 24.

(2) W. Reppe and K. Merkel, *Ann. Chem.*, **582**, 31 (1953).

(3) W. Reppe, O. Hecht, and K. H. Merkel, German Patent 856,293 (Nov. 20, 1952); *Chem. Abstr.*, **50**, 1895*h* (1956).

(4) S. L. Jacobs, *Univ. Microfilms* (Ann Arbor, Mich.), Publ. No. 11512; *Dissertation Abstr.*, **15**, 700 (1955); *Chem. Abstr.*, **49**, 10,894*d* (1955).

(5) C. S. Marvel, S. L. Jacobs, W. K. Taft, and B. G. Labbe, *J. Polymer Sci.* **19**, 59 (1956).

(6) C. S. Marvel and J. F. Porter, *J. Org. Chem.*, **24**, 137 (1959).

(7) Y. Nakayama, T. Tsuruta, J. Furukawa, A. Kawasaki, and G. Wasai, *Makromol. Chem.*, **43**, 76 (1961); *Chem. Abstr.*, **55**, 17,069*f* (1961).

(8) G. Braude, *J. Org. Chem.*, **22**, 1675 (1957).

(9) M. M. Koton, T. M. Kiselyeva, and K. S. Podgorskaya, *Zh. Obshch. Khim.*, **26**, 475 (1956); *Chem. Abstr.*, **50**, 13,815*a* (1956).

(10) G. Sumrell, G. E. Ham, and E. D. Hornbaker, *J. Am. Chem. Soc.*, **80**, 2509 (1958).

(11) Since sulfur is less electronegative than chlorine,[12] the double bond in thiolacrylates **6a** and in thiolcrotonates **6b** would be expected to be more electron deficient than the double bond in acrylyl chloride or crotonyl chloride. Consequently, thiolacrylates and thiolcrotonates would be expected to be the more vulnerable to nucleophilic attack by thiols and hydrogen chloride.

(12) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, p. 89.

(13) Ref. 10 reports formation of small amounts of 3-*t*-butylthiopropionyl chloride and 3-*t*-butylthioisobutyryl chloride in the reaction of acrylyl chloride and methacrylyl chloride with 2-methyl-2-propanethiol in aqueous sodium hydroxide solution.

(14) I. N. Nazarov, S. M. Makin, and A. F. Grapov, *Zh. Obshch. Khim.*, **27**, 101 (1957); *Chem. Abstr.*, **51**, 12,903*g* (1957).

(15) S. Kushner, H. Dalalian, F. L. Bach, D. Centola, J. L. Sanjurjo, and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 1154 (1955).

(16) According to H. Böhme, H. Pfeifer, and E. Schneider [*Chem. Ber.*, **75**, 902, 908 (1942)] halogen α to a carbonyl group can be replaced by a thio group in acidic medium. However, replacement of halogen β to a carbonyl group under these conditions appears to be unreported.

TABLE I

THIOLCROTONATES, $CH_3CH{=}CHCOSR$

R	Yield, %	B.p., °C. (mm.)[a]	$n^{25}D$	Formula	Sulfur, %		Infrared, cm.$^{-1}$ (C=O)
					Calcd.	Found	
C_2H_5	33.8	84–85 (30)[b]	1.5003[c]	$C_6H_{10}OS$	24.6	24.3	1667
n-C_4H_9	69.0	62–63 (0.8)	1.4940	$C_8H_{14}OS$	20.3	20.6	1670
t-C_4H_9	55.4	99–101 (25)	1.4880	$C_8H_{14}OS$	20.3	19.9	1669
C_6H_5	69.0	91–92 (0.3)[d]	1.5876	$C_{10}H_{10}OS$	18.0	17.9	1680
4-ClC_6H_4	47.6	112–113 (0.3)	1.5983	$C_{10}H_9ClOS$	15.1	14.9[e]	1685

[a] Boiling points are uncorrected. [b] Ref. 8 gives b.p. 74–75° (20 mm.) and 66–67° (13 mm.). [c] J. F. Arens, *et al.* [*Rec. trav. chim.*, **75**, 1471 (1956)], give $n^{20}D$ 1.5042. [d] Ref. 17 gives b.p. 140–153° (5 mm.). [e] Calcd.: Cl, 16.7. Found: Cl, 16.4.

Thiolcrotonates 6b.—Only two thiolcrotonates have been described previously. Ethyl thiolcrotonate[8] has been made by reaction of crotonyl chloride with lead ethyl mercaptide. Phenyl thiolcrotonate[17] has been made by reaction of crotonyl chloride with benzenethiol; an apparently impure product with a wide boiling range is obtained.

In our work crotonyl chloride (**1b**) reacted with thiols in the absence of a catalyst.[18] Since hydrogen chloride is formed in this reaction, the thiolcrotonates **6b** always contain considerable amounts of *dl*-3-chlorothiolbutyrates (**4b**) resulting from addition of hydrogen chloride, as well as appreciable amounts of *dl*-3-alkyl (aryl) thiothiolbutyrates (**2b**) resulting from addition of RSH to the thiolcrotonates. The absence of 3-chlorobutyryl chloride (**5b**) and 3-alkyl(aryl)thiobutyryl chlorides (**3b**) among the products suggests that the *dl*-3-chlorothiolbutyrates and *dl*-3-alkyl (aryl) thiothiolbutyrates are derived primarily from the thiolcrotonates. This view is supported further by the fact that thiolcrotonates add hydrogen chloride very rapidly, whereas crotonyl chloride adds hydrogen chloride only slowly; early in the reaction of crotonyl chloride with thiols hydrogen chloride is evolved from the reaction mixture although unreacted crotonyl chloride is present.

To obtain pure thiolcrotonates, the crude reaction product of crotonyl chloride and thiol, consisting of a mixture of thiolcrotonate and 3-chlorothiolbutyrate usually containing a small amount of an unidentified impurity, found by gas phase chromatography (g.p.c.) analysis, is dehydrochlorinated in benzene solution with triethylamine. The products obtained in this way are then at least 99% pure (g.p.c.). No polymerization of thiolcrotonates was encountered, as contrasted to easy polymerization of thiolacrylates.

Alkyl thiolcrotonates show a carbonyl absorption in the range of 1667–1670 cm.$^{-1}$ in the infrared suggesting a similarity to the carbonyl absorption of a ketone[22] as contrasted to ethyl crotonate which absorbs at 1698 cm.$^{-1}$. Since sulfur is less electronegative than oxygen, the double bond in thiolcrotonates should be more electron deficient than the double bond in crotonates and, therefore, more reactive with nucleophilic reagents. This difference indeed is found, for when ethanethiol is added to ethyl crotonate in the presence of 1 mole of triethylamine,[23] only a small yield (14%) of ethyl *dl*-3-ethylthiobutyrate is obtained after refluxing for 18 hr.; by contrast, essentially quantitative yields of adduct are obtained from ethanethiol and ethyl thiolcrotonate using only a catalytic quantity of triethylamine. This also demonstrates the diminished reactivity of the double bond in the crotonic system compared with the acrylic, because, under the same conditions, ethanethiol adds to ethyl acrylate in 93% yield.[24]

The thiolcrotonates made are shown in Table I.

***dl*-3-Chlorothiolbutyrates 4b.**—Hydrogen chloride adds rapidly to the thiolcrotonates producing essentially quantitative yields of *dl*-3-chlorothiolbutyrates. Gas phase chromatography shows that a single product is formed in each instance. The carbonyl absorption of these esters varies from 1672 to 1685 cm.$^{-1}$, depending on the ester group.

The 60-Mc. n.m.r. proton spectrum of phenyl *dl*-3-chlorothiolbutyrate in carbon tetrachloride with tetramethylsilane as a reference consists of a singlet at 7.00 p.p.m. due to the aromatic protons, a sextet at 4.15 p.p.m. due to $>$CHSR, a multiplet centered at 2.76 p.p.m. due to $-CH_2-$, and a doublet at 1.32 p.p.m. (J = 6.9 c.p.s.) due to $-CH_3$. The areas of these peaks are in the ratio of 5:1:2:3. On the basis of this spectrum, the thiolester clearly is the 3-chloro isomer.

No *dl*-3-chlorothiolbutyrates have been described previously. The esters made in this study are listed in Table II.

***dl*-3-Alkyl (Aryl) Thiothiolbutyrates 2b.**—Since hydrogen chloride adds very easily to thiolcrotonates it might have been anticipated that the more strongly nucleophilic thiols would add with even greater facility. We find that alkanethiols do not react with thiolcrotonates in the absence of a catalyst or under free-radical conditions, but react smoothly in the presence of catalytic amounts of base (triethylamine). Essentially quantitative yields of *dl*-3-alkyl (aryl) thiothiolbutyrates usually are obtained. The carbonyl absorption of these esters varies from 1672 to 1697 cm.$^{-1}$ depending upon the substituent present.

The same sequence of relative reactivities of different types of thiols is encountered as in the base-cata-

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(17) K. Miyaki and S. Yamagishi, *J. Pharm. Soc. Japan*, **76**, 436 (1956); *Chem. Abstr.*, **50**, 13,808*b* (1956).

(18) Since acylation of thiols with acid chlorides sometimes is a very slow reaction, zinc chloride has been used as a catalyst[19,20] to increase the rate at lower temperatures. However, zinc chloride may catalyze further attack of the thiol on the thiolester formed to give the orthothioester,[20,21] which, in the presence of a catalytic amount of acid, may split off thiol to give thioacetals of ketenes.[21]

(19) C. M. Himel, U. S. Patent 2,445,142 (July 13, 1948); *Chem. Abstr.*, **24**, 7321*b* (1948).

(20) J. D. Kendall, British Patent 556,815 (Oct. 22, 1943); *Chem. Abstr.*, **39**, 1880[2] (1945); U. S. Patent 2,389,153 (Nov. 20, 1945); *Chem. Abstr.*, **40**, 1540[3] (1946).

(21) L. C. Rinzema, J. Stoffelsma, and J. F. Arens, *Rec. trav. chim.*, **78**, 354 (1959).

(22) It has been reported in ref. 5 that the carbonyl absorption for alkyl thiolacrylates occurs in the range of 1671–1685 cm.$^{-1}$ as compared with 1735 cm.$^{-1}$ for ordinary acrylates. It is concluded "that the carbonyl group in a thiolacrylate has more the character of a ketone carbonyl than does that in an alkyl acrylate."

(23) H. Weber [German Patent 891,391 (Sept. 28, 1953); *Chem. Abstr.*, **48**, 12,791*a* (1954)] reports that addition of alkanethiols to crotonates proceeds in good yields using the corresponding sodium thiolate as the catalyst.

(24) J. L. Szabo and E. T. Stiller, *J. Am. Chem. Soc.*, **70**, 3667 (1948).

TABLE II

3-CHLORO THIOLESTERS, $RCHClCH_2COSR'$

R	R′	Yield, %	B.p., °C. (mm.)[a]	$n^{25}D$	Formula	Chlorine, %		Sulfur, %		Infrared, cm.$^{-1}$ (C=O)
						Calcd.	Found	Calcd.	Found	
H	C_2H_5	79.0	103–105 (23)[b]	1.4890	C_5H_9ClOS	23.2	23.6	21.0	21.2	1675
CH_3	C_2H_5	100.0	100 (20)	1.4810	$C_6H_{11}ClOS$	21.3	21.4	19.2	19.6	1685
CH_3	n-C_4H_9	100.0	60–62 (0.2)	1.4730	$C_8H_{15}ClOS$	18.2	18.1	16.5	16.8	1681
CH_3	t-C_4H_9	94.5	43 (0.1)	1.4714	$C_8H_{15}ClOS$	...	...	16.5	17.1	1672
CH_3	C_6H_5	89.0	119 (1.2)	1.5600	$C_{10}H_{11}ClOS$	16.5	16.6	14.9	15.1	1681

[a] Boiling points are uncorrected. [b] Ref. 15 gives b.p. 75–78° (15 mm.).

TABLE III

3-ALKYL (ARYL) THIOTHIOLESTERS, $RCH(SR')CH_2COSR''$

R	R′	R″	Yield, %	B.p., °C. (mm.)[a]	$n^{25}D$	Formula	Sulfur, %		Infrared, cm.$^{-1}$ (C=O)
							Calcd.	Found	
H	C_2H_5	C_2H_5[b]	37.6	148–150 (55)	1.5093	$C_7H_{14}OS_2$	...	...	1685
CH_3	C_2H_5	C_2H_5	98.0	136–137 (20)	1.5009	$C_8H_{16}OS_2$	33.3	33.0	1685
CH_3	n-C_4H_9	n-C_4H_9	92.0	120–121 (1)	1.4915	$C_{12}H_{24}OS_2$	25.8	25.6	1680
CH_3	C_6H_5	C_6H_5	83.0	172–173 (0.2)	1.6106	$C_{16}H_{16}OS_2$	22.2	22.0	1697
CH_3	4-ClC_6H_4	4-ClC_6H_4	97.0	120–130 (0.001)[c]	1.6166	$C_{16}H_{14}Cl_2OS_2$	17.9	17.5	1695
CH_3	C_6H_5	C_2H_5	92.0	95–100 (0.001)[c]	1.5684	$C_{12}H_{16}OS_2$	26.7	26.5	1672
CH_3	4-ClC_6H_4	t-C_4H_9	85.0	105–110 (0.001)[c]	1.5542	$C_{14}H_{19}ClOS_2$	21.2	21.3[d]	1685

[a] Boiling points are uncorrected. [b] From acrylyl chloride and ethyl mercaptan. [c] Air-bath temperature. [d] Calcd.: Cl, 11.7. Found: Cl, 11.6.

lyzed addition of thiols to maleic anhydride.[25] Benzenethiols react the most rapidly; even at room temperature the highly exothermic reaction is complete after a few minutes. Primary alkanethiols react very slowly at room temperature and rapidly at elevated temperatures (>60°), but the t-alkanethiol, 2-methyl-2-propanethiol, does not add to thiolcrotonates under the conditions investigated. The inability of 2-methyl-2-propanethiol to add may be caused by steric hindrance.[26]

The 60-Mc. n.m.r. proton spectrum of phenyl dl-3-phenylthiothiolbutyrate in carbon tetrachloride with tetramethylsilane as a reference consists of a singlet at 6.87 p.p.m. due to the aromatic protons, a multiplet centered at 3.47 p.p.m. due to >CHSR, a multiplet centered at 2.60 p.p.m. due to $-CH_2-$, and a doublet at 1.19 p.p.m. ($J = 7.0$ c.p.s.) due to $-CH_3$. The areas of these peaks are in the ratio of 10:1:2:3. The spectrum clearly indicates the thiolester is the 3-phenylthio isomer.

No dl-3-alkyl (aryl) thiothiolbutyrates have been described previously. The esters made in this study are listed in Table III.

Base-Catalyzed Esterification of Thiols with Anhydrides.—Acylation of thiols with anhydrides in the presence of base is a known, but not extensively investigated, procedure.[1] Higher-boiling alkanethiols have been acetylated by refluxing for several hours with acetic anhydride containing sodium acetate[27,28] or a catalytic amount of pyridine.[29] Dodecyl monothiolsuccinate has been made from 1-dodecanethiol and succinic anhydride in excess pyridine,[27] and methylbenzenethiols and dimethylbenzenethiols have been acetylated with acetic anhydride in excess triethylamine.[30] The low-boiling alkanethiols have been acetylated by treating aqueous solutions of their sodium salts with acetic anhydride.[28] With 2-methyl-2-propanethiol, however, an acidic catalyst, zinc chloride, has been used for acetylation with acetic anhydride.[31]

A general, convenient, and high-yield method for making thiolesters involves acylation of thiols with anhydrides in the presence of 1 mole of amine base for the alkanethiols and a catalytic amount of base for the aromatic thiols. No solvent is used. Primary and secondary alkanethiols and the aromatic thiols react rapidly, whereas acylation of t-alkanethiols requires several hours at elevated temperatures. Solid thiols are dissolved in the anhydride and base is added to this solution. The low-boiling thiols are added to an equimolar mixture of anhydride and base. The method has been tested with acetic, propionic, 3-ethylthiopropionic,[32] and 3-ethylthiobutyric[32] anhydrides. These thiolesters show carbonyl absorption in the range of 1680 to 1704 cm.$^{-1}$, depending on the substituents present, compared with 1727 cm.$^{-1}$ for ethyl 3-ethylthiopropionate, an analogous normal ester. The results are shown in Table IV.

Base-Catalyzed Addition of Thiols to α,β-Unsaturated Acids.—Benzenethiol has been added to acrylic acid without a catalyst,[33] and thiols have been added to acrylic and cinnamic acids with hydrogen chloride or hydrogen bromide catalysis.[34,35] Light-catalyzed addition of thiols to acrylic and maleic acids[36] and peroxide-catalyzed addition of α-toluenethiol to crotonic

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[25] F. B. Zienty, B. D. Vineyard, and A. A. Schleppnik, *J. Org. Chem.*, **27**, 3141 (1962).

[26] This view is supported by the findings of R. M. Ross [*J. Am. Chem. Soc.*, **71**, 3458 (1949)] on the quaternary base-catalyzed addition of benzenethiol to crotononitrile, 3-isopropylacrylonitrile, and 3-t-butylacrylonitrile which gives yields of 54, 32, and 21%, respectively, of addition product.

[27] R. L. Frank, S. S. Drake, P. V. Smith, Jr., and C. Stevens, *J. Polymer Sci.*, **3**, 51 (1948).

[28] F. W. Wenzel and E. E. Reid, *J. Am. Chem. Soc.*, **59**, 1089 (1937).

[29] P. C. Ray and S. K. Mitra, *J. Indian Chem. Soc.*, **6**, 865 (1929); *Chem. Abstr.*, **24**, 2108 (1930).

[30] P. P. Croitoru and R. W. Freedman, *Anal. Chem.*, **34**, 1536 (1962).

[31] C. M. Himel, U. S. Patent 2,445,142 (July 13, 1948), *Chem. Abstr.*, **42**, 7321*b* (1948).

[32] These anhydrides were made from the corresponding acids by dehydration with acetic anhydride.

[33] B. Holmberg and E. Schjänberg, *Arkiv Kemi Mineral. Geol.*, **15A**, No. 20 (1942); *Chem. Abstr.*, **38**, 2943^4 (1944). These workers also added acetothiolic acid to a variety of acids [*Chem. Abstr.*, **35**, 2113^7 (1941)].

[34] T. Posner, *Chem. Ber.*, **40**, 4788 (1907).

[35] F. Arndt, W. Flemming, E. Scholz, and V. Loewensohn, *ibid.*, **56**, 1269 (1923).

[36] T. Kaneko and S. Mii, *J. Chem. Soc. Japan*, **59**, 1382 (1938); *Chem. Abstr.*, **33**, 2106^2 (1939).

TABLE IV

THIOLESTERS, RCOSR′

R	R′	Method	Yield, %	B.p. °C. (mm.) Found[a]	B.p. °C. (mm.) Lit.	$n^{25}D$ Found	$n^{25}D$ Lit.	Infrared, cm.$^{-1}$ (C=O)
CH_3	CH_3[b]	A	91.5	98–99 (760)	98 (760)[b]	1.4598	1.4600[b]	1698
CH_3	C_2H_5[b]	A	81.5	116 (760)	116.4 (760)[b]	1.4547	1.4540[b]	1695
CH_3	i-C_3H_7[c]	A	88.0	127 (760)	126–127 (760)[c]	1.4489	1.4502[c,d]	1695
CH_3	n-C_4H_9[b]	A	77.5	161–162 (760)	163.4 (760)[b,e]	1.4558	1.4570[b]	1695
CH_3	t-C_4H_9[f]	A	79.0	135 (760)	130–133[f]	1.4483	1.4435[f,g]	1695
CH_3	t-C_8H_{17}[h]	A	92.4	102–103 (14)	149–167[h]	1.4670		1693
CH_3	t-$C_{12}H_{25}$[i]	A	80.6	74–84 (1)	95–105 (2)[i]	1.4676–1.4695	1.4780[i,j]	1697
CH_3	C_6H_5[k]	B	90.0	60 (0.5)	82 (3)[k]	1.5671	1.5700[k,j]	1702
CH_3	4-ClC_6H_4[l]	B	91.0	142 (15)[m]	153–154 (35)[l]	1.5797	1.5830[l]	1704
C_2H_5	C_2H_5[n]	A	92.5	136 (760)	136[n]	1.4548	1.4584[n,j]	1680
C_2H_5	t-C_4H_9[o]	A	76.6	96–97 (100)		1.4495		1680
$C_2H_5SCH_2CH_2$	C_2H_5[p]	A	85.9	144–145 (26)		1.5077		1685
$C_2H_5SCH(CH_3)CH_2$	C_2H_5[q]	A	93.0	136–137 (20)		1.5009		1685

[a] All boiling points are uncorrected. [b] Ref. 28. [c] P. N. Rylander and D. S. Tarbell, *J. Am. Chem. Soc.*, **72,** 3021 (1950). [d] At 23.5°. [e] L. H. Noda, S. A. Kuby, and H. A. Lardy [*J. Am. Chem. Soc.*, **75,** 914 (1953)] report 159–160° (738 mm.). [f] R. E. Dunbar and A. N. Bolstad, *ibid.*, **77,** 4672 (1955). [g] At 30°. [h] Ref. 31. [i] Ref. 31. [j] At 20°. [k] D. S. Tarbell and A. H. Herz, *J. Am. Chem. Soc.*, **75,** 1670 (1953). [l] F. Taboury, *Ann. chim. phys.*, [8]**15,** 23 (1908). [m] M.p. 31–32°; lit.[k] m.p. 39–40°. [n] M. L. Wolfrom and J. V. Karabinos, *J. Am. Chem. Soc.*, **68,** 1455 (1946). [o] Calcd. for $C_7H_{14}OS$: S, 21.9. Found: S, 21.1. [p] Calcd. for $C_7H_{14}OS_2$: S, 35.9. Found: S, 35.3. [q] Calcd. for $C_8H_{16}OS_2$: S, 33.3. Found: S, 33.0.

TABLE V

3-ALKYLTHIO- AND ARYLTHIOPROPIONIC AND *dl*-BUTYRIC ACIDS, $RCH(SR')CH_2COOH$

R	R′	Yield, %	B.p., °C. (mm.)	$n^{25}D$	Formula	Sulfur, % Calcd.	Sulfur, % Found	Infrared, cm.$^{-1}$ (C=O)
H	C_2H_5	80.6	90–91 (2)[a]	1.4800[b]	$C_5H_{10}O_2S$	23.85	23.8	1695
H	n-C_4H_9	87.0	121–122 (0.4)[c]	1.4754	$C_7H_{14}O_2S$	19.76	19.8	1698
H	t-C_4H_9	53.8	94–95 (0.2)[d]	1.4728	$C_7H_{14}O_2S$	19.76	19.8	1700
H	t-C_8H_{17}[e]	97.5	134–138 (0.3)	1.4814	$C_{11}H_{22}O_2S$	14.48	15.3	1700
H	t-$C_{12}H_{25}$[e]	76.5	170–171 (0.5)	1.4794	$C_{15}H_{30}O_2S$	11.68	12.1	1700
H	t-$C_{16}H_{33}$	97.0	[f]	1.4800	$C_{19}H_{38}O_2S$	9.70	9.7	1695
CH_3	C_2H_5	84.5	91 (0.1)	1.4738	$C_6H_{12}O_2S$	21.63	21.0	1700
CH_3	n-C_4H_9	97.5	116–117 (0.7)	1.4716	$C_8H_{16}O_2S$	18.19	18.2	1698
CH_3	t-C_8H_{17}	24.6	139–140 (0.5)	1.4774	$C_{12}H_{24}O_2S$	13.80	13.5	1695
CH_3	C_6H_5	98.1	151 (0.8)[g]	1.5541	$C_{10}H_{12}O_2S$	16.34	16.3	1708
CH_3	4-ClC_6H_4	93.0	163–164 (0.3)	1.5661	$C_{10}H_{11}ClO_2S$	13.90	14.3[h]	1705

[a] Ref. 49 reports b.p. 131.5° (5 mm.). [b] Ref. 50 reports $n^{25}D$ 1.4756. [c] Ref. 50 gives b.p. 168–169° (20 mm.), $n^{25}D$ 1.4706. [d] T. L. Gresham and F. W. Shaver [U. S. Patent 2,449,992 (Sept. 28, 1948), *Chem. Abstr.*, **43,** 1054*f* (1949)] report b.p. 98–99° (1 mm.). [e] A technical grade mixture of isomers was used. [f] Decomposed upon attempted distillation at about 180°. An analytical sample was prepared by removing all volatile material at 140° (0.1 mm.). [g] F. Krollpfeiffer, H. Schultze, E. Schlumbohm, and E. Sommermeyer [*Chem. Ber.*, **58,** 1663 (1925)] report b.p. 185° (10 mm.) and 60% yield. [h] Calcd.: Cl, 15.4. Found: Cl, 14.9.

acid[37] are reported. Benzenethiol adds to crotonic acid at 180° using a catalytic amount of piperidine.[38] Isopropylidenemalonic acid adds thiols when an excess of triethylamine is used, but 3,3-dimethylacrylic acid does not.[39] Thioglycolic acid adds to acrylic, methacrylic, and maleic acids[40,41] in aqueous solution without a catalyst, and other thiols react with aqueous solutions of salts of α,β-unsaturated carboxylic acids.[42–44]

Since the ionic mechanism for thiol additions is favored by a highly polar reaction medium no solvent was used and the liquid triethylammonium salts of the unsaturated carboxylic acids were treated directly with the thiols. A small excess of base usually was favorable. Under these conditions with a few exceptions both acrylic and crotonic acids added thiols directly in satisfactory to excellent yields.

Aromatic thiols react rapidly in an exothermic reaction. Primary alkanethiols require several hours' refluxing and the reluctant *t*-alkanethiols react even more slowly; however, yields increase with increasing molecular weight and the boiling point of the reaction mixture. This would suggest that, with any of the lower-boiling alkanethiols, reaction at elevated temperatures by operation under pressure would be favorable to both yield and reaction time. Crotonic acid is distinctly much less reactive than acrylic acid.

With the exception of *t*-hexadecylthiopropionic acid all of the substituted propionic and *dl*-butyric acids are colorless, distillable liquids which slowly yellow on storage at room temperature. The results are shown in Table V.

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(37) R. Brown, W. E. Jones, and A. R. Pinder, *J. Chem. Soc.*, 3315 (1951).

(38) J. C. Petropoulos, M. A. McCall, and D. S. Tarbell, *J. Am. Chem. Soc.*, **75,** 1130 (1953).

(39) Z. Földi and J. Kollonitsch, *J. Chem. Soc.*, 1683 (1948).

(40) I. G. Farbenindustrie A.-G., French Patent 845,793 (Sept. 1, 1939); *Chem. Abstr.*, **35,** 1070^9 (1941).

(41) E. Larsson, *Chem. Abstr.*, **40,** 2796^4 (1946).

(42) C. D. Hurd and L. L. Gershbein, *J. Am. Chem. Soc.*, **69,** 2334 (1947).

(43) E. W. Bousquet, U. S. Patent 2,434,100 (Jan. 6, 1948); *Chem. Abstr.*, **42,** 2289*c* (1948).

(44) J. G. Hendrickson and L. F. Hatch, *J. Org. Chem.*, **25,** 1747 (1960).

Experimental[45]

Reaction of Ethanethiol with Acrylyl Chloride.—To a stirred mixture of 18.1 g. (0.2 mole) of acrylyl chloride,[46] 0.5 g. of cuprous chloride, and 0.1 g. of anhydrous zinc chloride, heated to 50°, there was added 12.4 g. (0.2 mole) of ethanethiol. Evolution of hydrogen chloride started at once; the mixture turned greenish and then became dark. Heating was continued, to 100°, until hydrogen chloride evolution ceased, and the mixture was distilled through a column packed with helices. Three fractions were collected: (a) b.p. 70–100° (55 mm.), n^{25}D 1.4701, 4.6 g., consisting mainly of acrylyl chloride containing only a trace of ethyl thiolacrylate, which polymerized on standing; (b) b.p. 100–140° (55 mm.), n^{25}D 1.4865, 2.8 g., a mixture of 3-ethylthiopropionyl chloride and ethyl 3-chlorothiolpropionate; and (c) b.p. 140–150° (55 mm.), n^{25}D 1.5093, 6.7 g., almost pure ethyl 3-ethylthiothiolpropionate. Four grams of a dark resin remained in the still.

Reaction of Ethanethiol with Crotonyl Chloride.—A mixture of 20.9 g. (0.2 mole) of crotonyl chloride[47] and 12.4 g. (0.2 mole) of ethanethiol was warmed gently. Hydrogen chloride evolution started at about 50° and heating and stirring were continued until the temperature had reached 150° and hydrogen chloride evolution had stopped. The dark product was distilled, b.p. 34–133° (14 mm.), yielding 26.3 g. of a colorless liquid. G.p.c. analysis showed the following composition: crotonyl chloride, 31.5%; unknown low-boiling component, 1.5%; ethyl thiolcrotonate, 34.2%; ethyl *dl*-3-chlorothiolbutyrate, 19.8%; and ethyl *dl*-3-ethylthiothiolbutyrate, 12.9%. This amounts to a recovery of 0.147 mole of crotonyl chloride and 0.135 mole of ethanethiol.

In an attempt to prevent addition, the reaction was conducted in pyridine at low temperature. However, thiol addition again occurred, producing only 34% ethyl thiolcrotonate and 47% of ethyl *dl*-3-ethylthiothiolbutyrate.[48]

Reaction of 1-Butanethiol with Crotonyl Chloride.—The reaction mixture from 1-butanethiol and crotonyl chloride was fractionated carefully through a 10-in. column packed with helices. Five fractions were taken: (a) b.p. 43–55° (0.25 mm.), n^{25}D 1.4803, 0.9 g., impure crotonyl chloride; (b) b.p. 55–58° (0.25 mm.), n^{25}D 1.4880, 25.3 g. [on redistillation, after a small forerun of 0.7 g., b.p. 27–52° (0.7 mm.), the product had n^{25}D 1.4928–1.4931 and a center cut of this product contained 3.1% of an unidentified low-boiling material, 93.6% of *n*-butyl thiolcrotonate, and 3.3% of *n*-butyl *dl*-3-chlorothiolbutyrate]; (c) b.p. 58–94° (0.25 mm.), n^{25}D 1.4782, 8.0 g., a mixture of *n*-butyl thiolcrotonate and *n*-butyl *dl*-3-chlorothiolbutyrate; (d) b.p. 94–105° (0.25 mm.), n^{25}D 1.4903, 3.8 g., almost pure *n*-butyl *dl*-3-*n*-butylthiothiolbutyrate, containing only a very small amount of *n*-butyl *dl*-3-chlorothiolbutyrate; and (e) b.p. 105–106° (0.25 mm.), n^{25}D 1.4908, 11.4 g., pure *n*-butyl *dl*-3-*n*-butylthiothiolbutyrate.

When the 1-butanethiol was added dropwise with stirring to the crotonyl chloride, less chlorothiolbutyrate and 3-*n*-butylthiothiolbutyrate were formed than in the previous experiment.

Dehydrochlorination of Crude *n*-Butyl Thiolcrotonate.—The fractions, 46.1 g., containing *n*-butyl thiolcrotonate and *n*-butyl *dl*-3-chlorothiolbutyrate were diluted with an equal volume of benzene and 20 ml. of triethylamine was added with stirring. The solution darkened, deposition of triethylamine hydrochloride started at once, and the dehydrochlorination was finished by warming to 95° for 1 hr. Then the amine salt was removed by filtration, washed with benzene, and dried, yielding 5.3 g., corresponding to 1.4 g. of hydrogen chloride or 7.5 g. of *n*-butyl *dl*-3-chlorothiolbutyrate. The filtrate was flash-distilled (heavy foaming): the dark residue was distilled through a 10-in. column packed with helices. After a forerun of 3.5 g., b.p. 43–62° (0.8 mm.), n^{25}D 1.4929, in which a low-boiling impurity was concentrated, the *n*-butyl thiolcrotonate was obtained, 35.4 g., 99% pure (g.p.c.).

***t*-Butyl Thiolcrotonate.**—To 20.8 g. (0.2 mole) of crotonyl chloride containing 0.2 g. of anhydrous zinc chloride, there was added with stirring 18.0 g. (0.2 mole) of 2-methyl-2-propanethiol. A fast and exothermic reaction started at once and was allowed to proceed freely. When heat evolution ceased all the acid chloride had been consumed. The dark liquid was diluted with 40 ml. of benzene, 10.1 g. of triethylamine was added, and the mixture was refluxed for 30 min.; then it was poured into water. The organic layer was washed with 5% hydrochloric acid and water, dried over calcium chloride, and worked up in the usual way. Distillation of the crude afforded, after a small forerun, 17.2 g. (55.4%) of product.

Ethyl *dl*-3-Chlorothiolbutyrate.—Anhydrous hydrogen chloride was passed into 2.6 g. (0.02 mole) of ethyl thiolcrotonate. An exothermic reaction took place and g.p.c. showed that the thiolcrotonate was consumed rapidly and a single new compound was formed. After completion of the reaction, excess hydrogen chloride was pumped off under reduced pressure and the 3.4 g. (100%) of crude product was distilled as a colorless liquid.

Ethyl *dl*-3-Ethylthiothiolbutyrate.—Ethyl thiolcrotonate, 3.6 g. (0.027 mole), and 1.85 g. (0.03 mole) of ethanethiol were dissolved in 5 ml. of toluene, and 1 drop of triethylamine was added. At room temperature the addition proceeded slowly and was finished in 3 days. Distillation afforded 5.1 g. (98%) of the product, a greenish liquid.

Ethyl *dl*-3-Phenylthiothiolbutyrate.—Ethyl thiolcrotonate, 1.30 g. (0.01 mole), and 1.10 g. (0.01 mole) of benzenethiol were mixed, and 1 drop of a 1 *N* solution of triethylamine in benzene added. A highly exothermic reaction occurred and the addition reaction was complete after 5 min. according to infrared and g.p.c. examination. The solution was diluted with ether, washed with 5% hydrochloric acid and water, dried over calcium chloride, and worked up in the usual way. The crude product was distilled in a short-path apparatus. The yield was 2.2 g. (92%) of a colorless liquid, which turned yellow on standing at room temperature.

Ethyl *dl*-3-Ethylthiobutyrate.—A mixture of 22.8 g. of ethyl crotonate, 20.2 g. of triethylamine, and 12.4 g. of ethanethiol (0.2 mole each) was refluxed for 18 hr. and left at room temperature for 2 days. Then the mixture was washed with water, 5% hydrochloric acid, and again with water, dried over calcium chloride, and distilled. After a forerun of 16.3 g. (0.143 mole) of ethyl crotonate, b.p. 136–141°, distillation was continued under reduced pressure and the adduct was collected at 113–114° (18 mm.), n^{25}D 1.4518, 5.0 g. (14.2%).

Anal. Calcd. for $C_8H_{16}O_2S$ (176.27): S, 18.2. Found: S, 18.0.

Base-Catalyzed Esterification of Thiols with Anhydrides. Method A.—A molar quantity of base was used.

Methyl Thiolacetate.—Methanethiol, 14.4 g. (0.3 mole), was fed into a stirred mixture of 30.6 g. (0.3 mole) of acetic anhydride and 30.3 g. (0.3 mole) of triethylamine. An exothermic reaction took place; the temperature was held at 60–70° with a cold-water bath. The thiol was consumed immediately. After addition was completed the reaction mixture was poured into ice-water, the organic layer was separated, and the aqueous phase was extracted with ether. The combined organic layer and ethereal extract were washed with cold 10% hydrochloric acid, water, sodium bicarbonate solution, and water again, dried over sodium sulfate, and distilled through a 10-in. column packed with helices. The yield was 24.8 g. (91.5%).

***t*-Dodecyl Thiolacetate.**—A mixture of 40.2 g. (0.2 mole) of *t*-dodecanethiol (Phillips Petroleum "Sulfole"), 20.4 g. (0.2 mole) of acetic anhydride, and 20.2 g. (0.2 mole) of triethylamine was heated with stirring at 130° for 3 hr. and then worked up in the usual way. Distillation through a 10-in. packed column afforded 5.7 g. of a forerun, b.p. 55–74° (1 mm.), mainly unreacted thiol, and 30.3 g. (80.6%) of product.

Method B.—A catalytic quantity of base was used.

4-Chlorophenyl Thiolacetate.—4-Chlorobenzenethiol, 14.4 g. (0.1 mole), was dissolved in 10.2 g. (0.1 mole) of acetic anhydride with stirring. Then 3 drops of triethylamine was added and the highly exothermic reaction was allowed to proceed freely. The usual work-up afforded on distillation 16.9 g. (91.0%) of product, which crystallized on standing, m.p. 31–32°.

Direct Addition of Thiols to α,β-Unsaturated Acids. *dl*-3-Ethylthiobutyric Acid.—A mixture of 43.0 g. (0.5 mole) of crotonic acid, 33.0 g. (0.5 mole) of ethanethiol, and 50.5 g. (0.5 mole) of triethylamine was refluxed for 44 hr.; a highly efficient double-jacketed condenser was used. The reaction temperature

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(45) All melting and boiling points are uncorrected. The infrared spectra were taken on a Perkin-Elmer Infracord spectrophotometer.

(46) C. E. Rehberg, M. B. Dixon, and C. H. Fisher, *J. Am. Chem. Soc.*, **67**, 209 (1945).

(47) H. Staudinger, J. Becker, and H. Hirzel, *Chem. Ber.*, **49**, 1991 (1916).

(48) In pyridine 4-chlorobenzenethiol with crotonyl chloride affords about equal amounts of thiolcrotonate and 4-chlorophenyl *dl*-3-(4′-chlorophenylthio)thiolbutyrate.

rose gradually from 46 to 109°. The crude product was poured into water, the clear solution was acidified with concentrated hydrochloric acid, the oily product was separated, and the aqueous layer was extracted with two 100-ml. portions of ether. Distillation afforded 3.5 g. of a forerun, b.p. 62–90° (0.1 mm.), which partially solidified and consisted mainly of recovered crotonic acid, and 62.5 g. (99%) of product.[49,50]

dl-**3-Phenylthiobutyric Acid.**—To a mixture of 17.2 g. (0.2 mole) of crotonic acid and 20.2 g. (0.2 mole) of triethylamine there was added with stirring 22.0 g. (0.2 mole) of thiophenol. An exothermic reaction took place, the temperature rose rapidly to 65°, remained there for about 10 min., and then dropped. The mixture was heated for 10 min. at 115°; a small sample of the reaction mixture was completely soluble in water. The usual work-up afforded on distillation 38.5 g. (98.1%) of colorless viscous liquid product.

3-*t*-Octylthiopropionic Acid.—A mixture of 29.2 g. (0.2 mole) of *t*-octanethiol (technical grade, mixture of isomers), 20.2 g. (0.2 mole) of triethylamine, and 14.4 g. (0.2 mole) of acrylic acid was refluxed for 16 hr., then worked up in the usual way.[51] Distillation afforded 42.5 g. (97.5%) of colorless product.

Acknowledgment.—The n.m.r. spectra were run and interpreted by Dr. Martin W. Dietrich.

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(49) M. H. Palomaa and T. Kaski [*Suomen Kemistilehti*, **19B**, 85 (1946); *Chem. Abstr.*, **41**, 5453 (1947)] made the analogous propionic acid.

(50) L. J. Desha and G. H. Denny, Jr. (thesis, Washington and Lee University, 1950, cited in E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. III, Chemical Publishing Co., Inc., New York, N. Y., 1960, p. 208) reported the corresponding propionic acid.

(51) The triethylamine salts of the higher *t*-alkylthiopropionic acids tend to form gels in water.

Aminocyanopyrazoles

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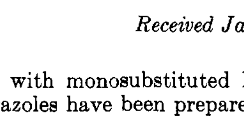
Tetracyanoethylene reacts with monosubstituted hydrazines and hydrazides to give 5-amino-3,4-dicyanopyrazoles. A number of pyrazoles have been prepared from a variety of cyanoethylenes that contain replaceable groups.

The synthesis of aminopyrazoles from cyanoethylenes containing a replaceable group on the 2-position and hydrazine or substituted hydrazines has been reported.[1] In these cases, the group replaced was alkoxy, amino, or alkylthio. We have applied this method to a number of cyanoethylenes in which the leaving group is cyano, sulfonyl, or chloro. In these cases, the reaction conditions are very mild, and hydrazides work as well as or better than hydrazines.

Tetracyanoethylene reacts with hydrazine to give the highly colored acid, 1,1,2,5,6,6-hexacyano-3,4-diazahexadiene.[2] We have now found that the reaction of monosubstituted hydrazines and hydrazides with tetracyanoethylene gives 5-amino-3,4-dicyanopyrazoles in excellent yields. The facile reaction takes place at or below room temperature.

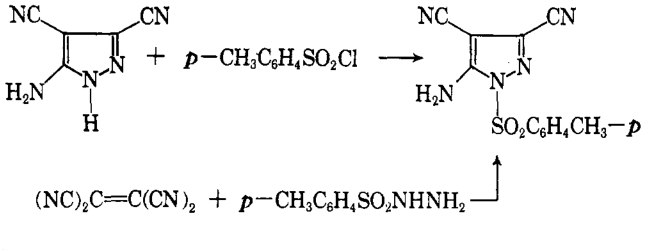
$$(NC)_2C{=}C(CN)_2 + RNHNH_2 \longrightarrow [(NC)_2C{=}C(CN)NHNHR]$$



The initial step involves replacement of a cyano group to give a tricyanovinylhydrazine intermediate, which then cyclizes to the aminodicyanopyrazole. With semicarbazide, the reaction was run in water, and a yellow color characteristic of tricyanovinylamines appeared in an early stage of the reaction. A white crystalline product slowly separated, and the yellow color diminished in intensity as more product formed. Since substituted hydrazines react much faster, the stages of reaction are not so evident.

Since initial attack on tetracyanoethylene by arylhydrazines or hydrazides would be expected to be by the unsubstituted nitrogen, the product from cyclization would be expected to be the 3-amino isomer rather than the 5-amino isomer. The product from methylhydrazine should be the 5-amino isomer, however, since the nitrogen to which the methyl group is attached is the more nucleophilic.

Although 5-amino-3,4-dicyanopyrazole cannot be prepared from hydrazine and tetracyanoethylene directly, it is readily available from 5-amino-3,4-dicyano-1-carbamoylpyrazole by hydrolysis in boiling water. A number of 1-substituted derivatives of 5-amino-3,4-dicyanopyrazole can be prepared by acylation, alkylation, or reaction with isocyanates. By the action of *p*-toluenesulfonyl chloride, dimethylcarbamoyl chloride, or isocyanic acid on 5-amino-3,4-dicyanopyrazole, we were able to prepare compounds identical with those from the reaction of tetracyanoethylene with *p*-toluenesulfonyl hydrazide, 4,4-dimethylsemicarbazide, or semicarbazide. Alkylation with dimethylsulfate gave two isomers. The lower melting isomer, obtained in lower yield, was identical with that from methylhydrazine and tetracyanoethylene. That the major product from methylation would be expected to be the 5-amino isomer by analogy with the acylation experiments is consistent with the assignments of the 3-amino structure to the methylhydrazine–tetracyanoethylene product.



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[1] (a) W. J. Middleton and V. A. Engelhardt, *J. Am. Chem. Soc.*, **80**, 2829 (1958); (b) R. A. Carboni, D. D. Coffman, and E. G. Howard, *ibid.*, **80**, 2838 (1958); (c) R. K. Robins, *ibid.*, **78**, 784 (1956); (d) R. Gomper and W. Töpfl, *Ber.*, **95**, 2881 (1962); (e) E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.*, **81**, 2452 (1963).

[2] W. J. Middleton, E. L. Little, D. D. Coffman, and V. A. Engelhardt, *ibid.*, **80**, 2795 (1958).