Product Ratio Analysis of the Reaction of Methyl *cis*- and *trans*-β-(Acetylthio)acrylates with Diazomethane[1]

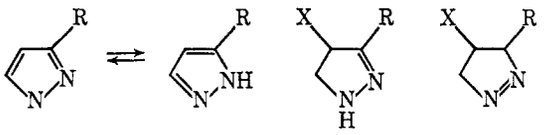
DONALD T. WITIAK AND MATTHIAS C. LU

Division of Medicinal Chemistry, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210

Received May 9, 1968

The relative yield of methyl *cis*-β-(methylmercapto)acrylate (**5**), 1-methyl-5-carbomethoxypyrazole (**6**), 3-carbomethoxypyrazole (**7**), and 1-methyl-3-carbomethoxypyrazole (**8**), when methyl *cis*- or *trans*-β-(acetylthio)-acrylate undergo reaction with excess diazomethane in ether, was determined by means of gas–liquid partition chromatography. The analysis shows product formation to be dependent upon the stereochemistry of the starting methyl β-(acetylthio)acrylate. Competing reaction pathways are proposed to account for the different yields of products.

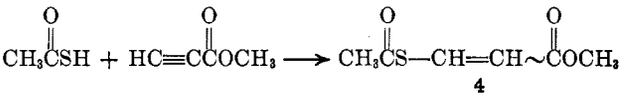
A number of syntheses have been developed for pyrazoles (**1**)[2] and pyrazolines (**2** and **3**).[3] One method involves condensation of aliphatic diazo compounds with olefins containing an activated double bond. Substituted 1- and 2-pyrazolines (R = electron-withdrawing group in **2** and **3**), for example, are



1 **2** **3**

formed from α,β-unsaturated aldehydes, ketones, and esters by concerted reaction with diazomethane.[2-4] Alternatively, pyrazoles are synthesized when one of the vinyl carbon atoms is substituted with a suitable leaving group.[2,5]

The stereochemistry of formation of 1-pyrazolines (**2**) has been elucidated.[4c] Reaction of diazomethane with β-substituted α,β-unsaturated esters affords 1-pyrazolines with the same geometry as the starting olefin. When X in **2** or **3** represents a leaving group pyrazolines may be converted into the corresponding pyrazole by elimination of HX.[2] Use of appropriately substituted pyrazolines shows elimination of HX to be most facile by a *trans* mechanism.[6] For reactions previously studied the intermediate pyrazoline was isolated and conversion into the corresponding pyrazole required either acid or base catalysis or warming depending upon the nature of X. Under reaction conditions similar to those described in this communication pyrazolines could be isolated from reaction of ethyl β-bromoacrylate with diazomethane. On standing the isolated pyrazoline lost HBr, affording the pyrazole, but the reaction was not studied stereochemically.[7] Availability of both methyl *cis*- and *trans*-β-(acetylthio)acrylates (**4**) prompted study of their reaction with diazomethane in ether to determine the mechanism of formation of pyrazoles and the dependence of their formation upon the configuration of the starting olefin.



4

Results and Discussion

A mixture of *cis*- and *trans*-β-(acetylthio)acrylates is obtained by free-radical addition of thiolacetic acid to methyl propiolate.[8] Whereas geometrical isomers of **4** are reportedly separable by spinning-band distillation, in our laboratories pure samples could only be obtained by column chromatography (chloroform on silicic acid). Pure *cis* **4** elutes first, followed by a mixture of *cis* and *trans*, and pure *trans* last. Analysis of the nmr spectra in the vinyl proton region agreed with the reported values of chemical shifts and coupling constants for *cis* and *trans* **4**.[9]

Reaction of *cis* **4** with excess distilled diazomethane in ether at −5 to 0° for 8 hr, followed by standing at room temperature for 3.5 days, affords, by gas–liquid partition chromatography, methyl *cis*-β-(methylmercapto)acrylate (**5**), 1-methyl-5-carbomethoxypyrazole (**6**), 3-carbomethoxypyrazole (**7**), and 1-methyl-3-carbomethoxypyrazole (**8**) in a ratio of 3.3:1.8:1.7:1.2, respectively (Figure 1).[10] No detectable quantity of methyl *cis*-β-(methylmercapto)acrylate (**5**) or the corresponding *trans* isomer was obtained during the reaction of *trans* **4** under identical conditions. The major product, 1-methyl-5-carbomethoxypyrazole (**6**), formed in nearly 50% yield, is found along with **7** and **8** in a ratio of 4.8:0.8:1.9, respectively (Figure 2).[10] Methyl thiolacetate was found gas chromatographically. A number of uncharacterized minor products (peaks labeled B in chromatograms, Figures 1 and 2) are obtained during the reaction of both *cis* and *trans* **4** with distilled diazomethane. The unidentified components

(1) Presented at the 1st Central Regional Meetings of the American Chemical Society, Akron, Ohio, May 1968.

(2) A. N. Kost and I. I. Grandberg, *Advan. Heterocycl. Chem.*, **6**, 347 (1966).

(3) (a) R. Huisgen, *Angew. Chem.*, **67**, 439 (1955); (b) R. Locquin and R. Heilmann, *C. R. Acad. Sci., Paris*, **181**, 120 (1925); (c) I. A. D'yakonov, "Aliphatic Diazocompounds," Goshimisday, Leningrad, 1958.

(4) (a) T. L. Jacobs in "Heterocyclic Compounds," Vol. 5, R. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957, p 45 ff; (b) K. D. Gundermann and R. Thomas, *Ber.*, **93**, 883 (1960); (c) T. V. vanAuken and K. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **84**, 3736 (1962); (d) W. R. Brown and J. P. Mason, *J. Chem. Eng. Data*, **11**, 265 (1966).

(5) (a) W. E. Parham and J. L. Bleasdale, *J. Amer. Chem. Soc.*, **72**, 3843 (1950); **73**, 4664 (1951); (b) K. von Auwers and O. Ungemach, *Ber.*, **66**, 1198 (1933); (c) A. N. Nesmeyanov and N. K. Kochetkov, *Dokl. Akad. Nauk SSSR*, **77**, 65 (1951); (d) N. K. Kochetkov, I. Ambrush, and A. I. Usov, *Zh. Obshch. Khim.*, **29**, 2578 (1959).

(6) (a) I. L. Finar and K. E. Godfrey, *J. Chem. Soc.*, 2293 (1954); (b) H. Jörlander, *Ber.*, **49**, 2782 (1916); (c) N. H. Cromwell and G. Mercer, *J. Amer. Chem. Soc.*, **79**, 3815, 3819 (1957); (d) N. H. Cromwell and R. Mohrbacher, *ibid.*, **75**, 6252 (1953); (e) N. H. Cromwell, N. Barker, R. Wankel, P. Vanderhorst, E. Olson, and J. Hill, *ibid.*, **73**, 1044 (1951).

(7) (a) E. Buchner, *Ann.*, **273**, 214 (1893); (b) E. Buchner and M. Fritsche, *Ber.*, **26**, 256 (1893); (c) G. P. Rice, *J. Amer. Chem. Soc.*, **52**, 2094 (1930); (d) A. N. Nesmeyanov and N. K. Kochetkov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 686 (1951).

(8) L. N. Owen and M. U. S. Sultanbawa, *J. Chem. Soc.*, 3109 (1949).

(9) W. H. Mueller, *J. Org. Chem.*, **31**, 3075 (1966).

(10) The reactions studied were run for 3.5 days to ensure completion. However, gas–liquid partition chromatographic analysis showed the same ratio of products to be formed after 6 hr at −5 to 0° and all reactant to be consumed.

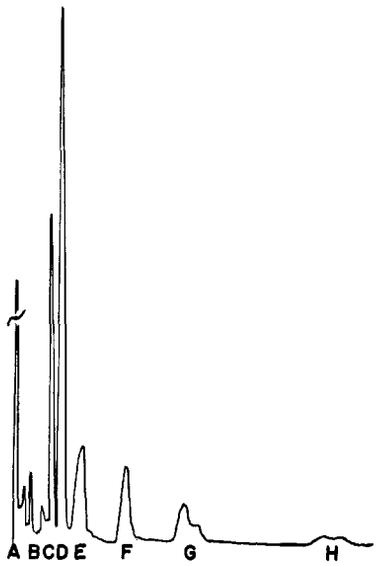
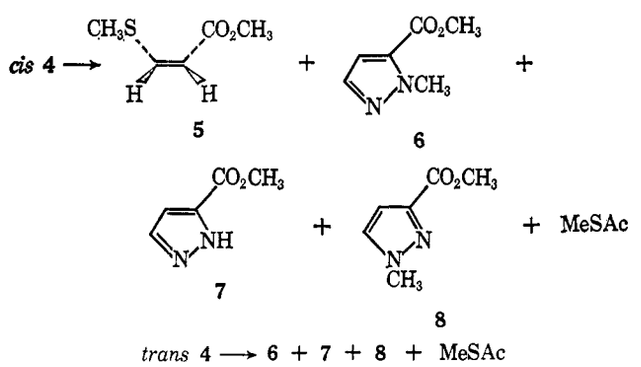


Figure 1.—Gas chromatograph of the reaction products of methyl *cis*-β-(acetylthio)acrylate in distilled diazomethane in ether: A, solvent ether plus methyl thiolacetate; B, uncharacterized minor products; C, 1-methyl-5-carbomethoxypyrazole (6); D, methyl *cis*-β-(methylmercapto)acrylate (5); E, 3-carbomethoxypyrazole (7); F, 1-methyl-3-carbomethoxypyrazole (8); G, uncharacterized; H, uncharacterized.

(G in Figures 1 and 2) are by-products of the reaction of 3-carbomethoxypyrazole (7) and diazomethane under the same conditions (Figure 3).[10]



trans 4 ⟶ 6 + 7 + 8 + MeSAc

If the diazomethane in ether was not distilled, both *cis* and *trans* 4 afforded methyl *cis*-β-(methylmercapto)-acrylate (5) in 20% isolated yield. Gas–liquid partition chromatography of the reaction mixture showed that neither the *cis* nor *trans* isomer of 4 affords any detectable quantity of methyl *trans*-β-(methylmercapto)acrylate. Pure 5 was obtained by column chromatography of the reaction products using chloroform on silicic acid. Its *cis* configuration was confirmed by partial isomerization to the thermodynamically more stable *trans* isomer during distillation. Coupling constants were in agreement with the configurational assignment; J_{AX} for the vinyl protons of the *cis* isomer is 10.3 ± 0.5 cps and J_{AX} for the vinyl protons of the *trans* isomer is 15.0 ± 0.5 cps.[9]

When undistilled diazomethane in ether is used 9 is a most likely intermediate since *cis* 5, free of *trans* isomer, is formed from both *cis* and *trans* 4. The undistilled diazomethane in ether is decanted from KOH pellets. Base-catalyzed hydrolysis of the thiolacetate group of either *cis* or *trans* 4 would yield the thioenolate ions which rapidly isomerize and abstract a proton from

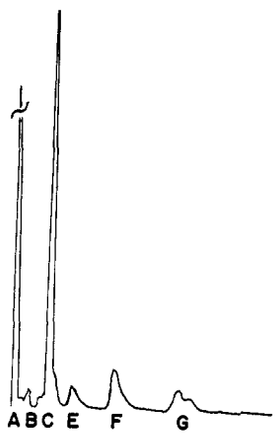
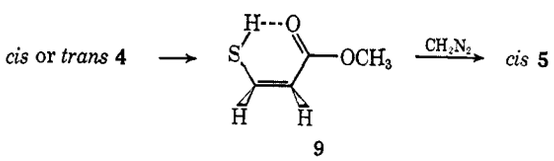


Figure 2.—Gas chromatograph of the reaction products of methyl *trans*-β-(acetylthio)acrylate in distilled diazomethane in ether: A, solvent ether plus methyl thiolacetate; B, uncharacterized minor products; C, 1-methyl-5-carbomethoxypyrazole (6); E, 3-carbomethoxypyrazole (7); F, 1-methyl-3-carbomethoxypyrazole (8); G, uncharacterized.

the medium. The result would be intermediate 9 whose stability is enhanced by intramolecular hydrogen bonding. Similar structures for β diketones have been shown to exist 95% in the intramolecularly hydrogen bonded *cis*-enol form in ether.[11] Reaction of 9 with



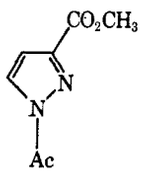
diazomethane by insertion between the S and H atoms of the thiol group would afford *cis* 5. Support for the interpretation of these data was provided by gas–liquid partition chromatographic analysis of the reaction mixture containing *trans* 4 and distilled diazomethane in ether to which 10 mg of KOH powder was added.[10] Methyl *cis*-(β-methylmercapto)acrylate (5) was produced. Further work is needed, however, before the differences in reaction of *cis* and *trans* 4 in distilled diazomethane in ether can be interpreted and the nature of the intermediates (*cis* 4 → *cis* 5) proposed.

In the reaction of *trans* 4 with distilled diazomethane in ether approximately 75% of the total reaction product are pyrazoles 6, 7, and 8. With *cis* 4 they account for only 47% of the reaction products. Competing formation of methyl *cis*-β-(methylmercapto)-acrylate (5) satisfactorily explains the lower yield of pyrazoles when *cis* 4 is the reactant. Gas chromatographic analysis of the reaction of *trans* 4 in distilled diazomethane in ether to which 10 mg of KOH powder was added showed the same product ratio of pyrazoles formed as in the reactions containing distilled diazomethane in ether free of KOH. Therefore, concurrent formation of methyl *cis*-(β-methylmercapto)acrylate (5) has little or no influence on the ratio of pyrazoles formed.

On one occasion, when the reaction was run at room temperature, without previous cooling, a small yield (<1.0%) of 1-acetyl-3-carbomethoxypyrazole (10) was obtained. When diazomethane entrained in a stream

(11) B. Eistert, F. Arndt, L. Loewe, and E. Ayca, *Ber.*, **84**, 156 (1951).

of nitrogen was added to a stirred mixture of *cis* and *trans* **4** at 85°, 1-acetyl-3-carbomethoxypyrazole (**10**) was isolated in 21% yield. This compound results from acetylation of 3-carbomethoxypyrazole (**7**) by either *cis* or *trans* **4**. Heating 3-carbomethoxypyrazole (**7**) with **4** affords **10** in quantitative yields.



10

Pyrazoles **6**, **7**, **8**, and **10** were synthesized by an alternate method and characterized by means of their nmr spectra. Reaction of methyl propiolate with diazomethane in ether by a modified method of Reimlinger[12] yields 3-carbomethoxypyrazole (**7**). Acetylation of **7** in refluxing acetic anhydride yields **10**.[13] Reaction of **7** with excess diazomethane in ether[14] at −5 to 0° affords **6**, **7**, and **8** in a ratio of 5.9:1.2:1.2 (Figure 3).[10]

Assignment of the substituent position for pyrazoles **6**, **8**, and **10** was determined by nmr.[13,15] The chemical shift for the H_4 proton in 1,3,5-trisubstituted or 3,5-disubstituted pyrazoles may be calculated[15a] according to eq 1, where δ_4 (S) is the chemical shift for the H_4

$$\delta_4 = \delta_4\,(\mathrm{S}) + \alpha_1 + \alpha_3 + \alpha_5 \qquad (1)$$

proton of 1,3,5-trimethylpyrazole in solvent S, and α_1, α_3, and α_5 are empirical constants representing the effect of replacing a methyl group by another substituent at position 1, 3, and 5, respectively. The calculated and experimental results (Table I) are in excellent agreement. Coupling constants are also in accord with those reported in the literature for N-methyl-substituted pyrazoles.[15a,c]

TABLE I[a]

Compd	δ_4, calcd	δ_4, found	δ_3	δ_5	δ_{N-CH_3}	$J_{4,5}$, cps	$J_{3,4}$, cps
10	6.94	6.92		8.32		3.0	
6	6.66	6.68	7.42		3.72		1.9
8	6.62	6.64		7.42	3.82	2.2	

[a] Coupling constants and chemical shifts were taken in deuteriochloroform at 10% concentrations utilizing trimethylsilane as an internal standard.

More data are necessary before all of the possibilities concerning intermediates in pyrazole formation from *cis* and *trans* **4** may be sorted out and the differences in pyrazole product ratio explained. However, by considering these results in conjunction with similar reactions, some tentative proposals can be made. Concerted addition of diazomethane to *cis* and *trans* **4** is expected to yield intermediate 1-pyrazolines **11** and **12**, respectively.[4c] Since *cis* and *trans* **4** yield different product ratios of N-methylpyrazoles, the results cannot be accounted for on the basis of a single reaction

(12) H. K. Reimlinger, *Ber.*, **93**, 1857 (1960).
(13) J. K. Williams, *J. Org. Chem.*, **29**, 1377 (1964).
(14) (a) K. von Auwers and H. Hollmann, *Ber.*, **59**, 1282 (1926); (b) K. von Auwers and T. Breyhan, *J. Prakt. Chem.*, [2] **143**, 259 (1935).
(15) (a) L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966); (b) J. D. Albright and L. Goldman, *ibid.*, **31**, 273 (1966); (c) C. L. Habraken and J. A. Moore, *ibid.*, **30**, 1892 (1965).

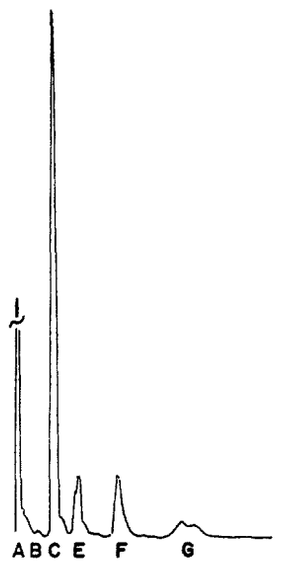
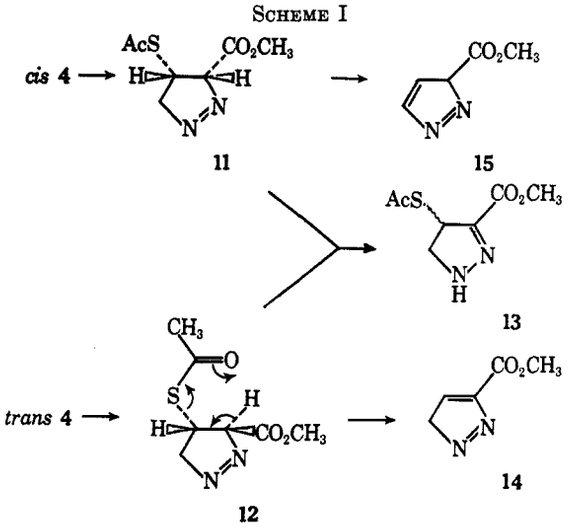


Figure 3.—Gas chromatograph of the reaction products of 3-carbomethoxypyrazole in distilled diazomethane in ether: A, solvent ether; B, uncharacterized minor products; C, 1-methyl-5-carbomethoxypyrazole (**6**); E, 3-carbomethoxypyrazole (**7**); F, 1-methyl-3-carbomethoxypyrazole (**8**); G, uncharacterized.

pathway and/or a common intermediate such as the 2-pyrazoline **13** which could result from isomerization of either **11** or **12** (Scheme I).[16]

SCHEME I



When either *trans* **4** or 3-carbomethoxypyrazole (**7**) serves as the reactant, the same ratio of pyrazoles is obtained. This is evidence that **6** is an intermediate in the reaction of *trans* **4** with diazomethane. Subsequent methylation of **7** by excess diazomethane would afford **6** and **8**. Apparently, *cis* **4** undergoes a competing reaction pathway since N-methylpyrazoles **6** and **8** are formed in nearly equal amounts and in a different ratio than when *trans* **4** serves as starting material.

One explanation for the exclusive formation of intermediate **7** from *trans* **4** and not *cis* **4** is that the 1-pyrazoline **12** undergoes a relatively faster *cis* elimina-

(16) 1-Pyrazolines were isolated even when the 2-pyrazolines contained conjugated systems. Rearrangement to 2-pyrazolines occurs on recrystallization or brief heating with halogen acid. See (a) L. I. Smith and W. Pings, *J. Org. Chem.*, **2**, 23 (1937); (b) L. I. Smith and K. L. Howard, *J. Amer. Chem. Soc.*, **65**, 159, 165 (1943).

tion (12 → 14) of thiolacetic acid (detected gas chromatographically as methyl thioacetate) than does the 1-pyrazoline 11 (*i.e.*, 11 → 15) since the proton α to the carbomethoxy group in the former case is more acidic. Apparently, *cis* elimination (12 → 14) also is faster than isomerization (11 or 12 → 13) under these reaction conditions.[16] Intermediate 14 could gain aromatic stabilization by rapidly tautomerizing to 7.[17] Although small quantities of impure compounds having physical properties expected for 13 were obtained by chromatography of the *cis* 4 reaction mixture, failure to identify these substances and study their reaction with diazomethane precludes further speculation on the product ratio differences.

Experimental Section[18]

Methyl β-(acetylthio)acrylate (4) was prepared by a modification of the method of Owen and Sultanbawa.[8] A mixture of 64 g (0.81 mol) of methyl propiolate and 138 g (1.81 mol) of thiolacetic acid was allowed to stand for 1 week at room temperature and then heated on a steam bath for 2 hr. Removal of excess thiolacetic acid along with unreacted methyl propiolate under reduced pressure followed by fractional distillation of the residue gave 35.7 g (28%) of methyl β-(acetylthio)acrylate. Repetition of this procedure utilizing recovered methyl propiolate and thiolacetic acid in two consecutive runs increased the over-all yield to 75%. Column chromatography on silicic acid 40% chloroform in Skellysolve C afforded the respective *cis* and *trans* isomers. Recrystallization from methanol yielded the *cis* compound, mp 58–59° (lit.[8] mp 58–58.5°), and the *trans* compound, mp 82–83.5° (lit.[8] mp 84.5°). The nmr spectra indicated each isomer to be free of the other and the parameters were in agreement with those reported in the literature.[9] Infrared absorption spectra showed characteristic bands at 1362, 997, 810, and 785 cm^{-1} for the *cis* isomer and at 1312, 1010, 978, 850, and 825 cm^{-1} for the *trans* compound.

Reaction of Methyl *cis*-β-(Acetylthio)acrylate (4) in Undistilled Diazomethane in Ether.—To undistilled diazomethane in ether,[19] decanted from KOH pellets, was added 1.0 g (6.3×10^{-3} mol) of methyl *cis*-β-(acetylthio)acrylate. The temperature was maintained at −5 to 0° for approximately 8 hr and then allowed to warm to room temperature. After standing for 3.5 days[10] the solvent ether[20] was removed under reduced pressure. The residue was chromatographed on silicic acid with chloroform yielding the following compounds: **methyl *cis*-β-(methylmercapto)acrylate (5)**, bp 43–45° (0.5 mm) [lit.[9] bp 35–38° (0.25 mm)], 208.4 mg (21%) (*Anal.* Calcd for $C_5H_8O_2S$: C, 45.45; H, 6.06; S, 24.24. Found: C, 45.63; H, 6.17; S, 24.19.); **1-methyl-5-carbomethoxypyrazole (6)**, bp 49–51° (0.5 mm) [lit.[21] bp 103–104° (7 mm)], 185.6 mg (19%) (*Anal.* Calcd for $C_6H_8N_2O_2$: C, 51.35; H, 5.75; N, 19.99. Found: C, 50.87; H, 5.76; N, 19.54.); **1-methyl-3-carbomethoxypyrazole (8)**, bp 126–127° (1.4 mm), 34 mg (3.5%)[22] (*Anal.* Calcd for $C_6H_8N_2O_2$: C, 51.35; H, 5.75; N, 19.99. Found: C, 50.81; H, 5.71; N, 19.81.).

Similar yields were obtained for 5, 6, and 8 when methyl *trans*-β-acetylthioacrylate (4) was employed in the above reaction.

Reaction of Methyl *cis*-β-(Acetylthio)acrylate (4) in Distilled Diazomethane in Ether.—A procedure analogous to the above reaction was utilized.[20] The reaction mixture was analyzed gas chromatographically on silicone gum rubber (UC-W98)[23] on Chromosorb W (80–100 mesh), 4 ft × 0.25 in. glass column with column temperature of 125°, detector temperature of 210°, injection port temperature of 275°, inlet pressure of 35 psi, and carrier gas (He) flow rate of 50 ml/min gave a retention time of 0.9 min for 1-methyl-5-carbomethoxypyrazole (6), 1.12 min for methyl β-(methylmercapto)acrylate (5), 1.5 min for carbomethoxypyrazole (7), 2.3 min for 1-methyl-3-carbomethoxypyrazole (8), and 3.5 and 6.2 min for other uncharacterized compounds (Figure 1).

Reaction of Methyl *trans*-β-(Acetylthio)acrylate (4) in Distilled Diazomethane in Ether.—The same reaction and gas chromatography conditions were used as in the reaction with 4 above.[20] The retention times observed were 0.9 min for 6, 1.5 min for 7, 2.3 min for 8, and 3.5 min for an uncharacterized product (Figure 2).

Reaction of Methyl *cis*-β-(Acetylthio)acrylate (4) with Diazomethane at 85°.—Methyl *cis*-β-(acetylthio)acrylate (1 g, 6.3×10^{-3} mol) was heated to 85°. To this liquid was bubbled diazomethane entrained in N_2[24] for approximately 3 hr. The reaction mixture was further heated for 6 hr at 85°. The residual oil was chromatographed on silicic acid with chloroform yielding **methyl *cis*-β-(methylmercapto)acrylate (5)**, 200 mg (20%), and **1-acetyl-3-carbomethoxypyrazole (10)**, mp 77–78° (ether–chloroform), 203 mg (21%) (*Anal.* Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.65. Found: C, 49.70; H, 4.77; N, 16.92.).

3-Carbomethoxypyrazole (7) was prepared by a modification of the method of Reimlinger.[12] Methyl propiolate (8.4 g, 0.1 mol) was treated with dry ethereal diazomethane solution at −5 to 0°. The reaction product immediately precipitated from the ether solution. Concentration under reduced pressure followed by recrystallization from ether afforded 11.3 g (90%) 3-carbomethoxypyrazole, mp 136–138° [lit.[25] mp 138° (140°)].[12] *Anal.* Calcd for $C_5H_5N_2O_2$: C, 47.63; H, 4.80; N, 22.21. Found: C, 48.06; H, 4.82; N, 21.84.

1-Acetyl-3-carbomethoxypyrazole (10) from 3-Carbomethoxypyrazole (7) and Acetic Anhydride.—3-Carbomethoxypyrazole (7, 1 g, 7.2×10^{-3} mol) was refluxed with 2 ml of acetic anhydride for 48 hr. The excess acetic anhydride and acetic acid were removed under reduced pressure. The residue was recrystallized from methanol yielding 1.2 g (90%) of 1-acetyl-3-carbomethoxypyrazole (10).

1-Acetyl-3-carbomethoxypyrazole (10) from 3-Carbomethoxypyrazole (7) and Methyl *cis*- or *trans*-β-(Acetylthio)acrylate.—Methyl *cis*- or *trans*-β-(acetylthio)acrylate (0.48 g, 3×10^{-3} mol) and 3-carbomethoxypyrazole (0.41 g, 3×10^{-3} mol) were heated for 24 hr at 85°. The crude product was recrystallized from methanol affording 0.4 g (90%) of 1-acetyl-3-carbomethoxypyrazole (10).

1-Methyl-3(5)-carbomethoxypyrazole (6 and 8).—3-Carbomethoxypyrazole (1 g, 7.2×10^{-3} mol) was treated with excess distilled diazomethane in ether at −5 to 0° for 8 hr. The mixture was allowed to warm to room temperature and after standing for 3.5 days the solution was filtered and the solvent removed under reduced pressure. The residual oil was chromatographed on silicic acid with chloroform affording 328 mg (32%) of 1-methyl-5-carbomethoxypyrazole (6). A small amount of 1-methyl-3-carbomethoxypyrazole (8) was detected gas chromatographically.

In another reaction the mixture was analyzed by gas–liquid partition chromatography under the same conditions employed for analysis of the reactions involving *cis* and *trans* 4. The retention times observed were 0.9 min for 6, 1.5 min for 7, 2.3 min for 8, and 3.5 min for an uncharacterized product (Figure 3).

Registry No.—Diazomethane, 334-88-3; 4 (*cis*), 17830-98-7; 4 (*trans*), 17830-99-8; 6, 17827-60-0; 8, 17827-61-1; 10, 17827-62-2.

Acknowledgment.—We are grateful to the National Center for Radiological Health, National Institutes of Health, Rockville, Md., for support of this work through Grant No. RH-00529.

(17) The well-established tautomerization of pyrazoles is assumed during this discussion. See ref 2 and 15c.

(18) Nmr spectra were recorded utilizing a Varian A-60A spectrometer. Infrared spectra were recorded utilizing a Beckman IR-5a and IR-10. Gas chromatographs were taken using an F & M Model 402 gas chromatograph equipped with flame ionization detector and glass columns. Melting points are corrected and were taken with a Thomas–Hoover melting point apparatus. Analyses were run by Clark Microanalytical Laboratory, Urbana, Ill.

(19) H. A. Blatt, Ed., "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1955, p 165.

(20) A small amount (<1%) of white polymeric material separated from the ether solution during the reaction.

(21) V. F. Vasil'eva, V. G. Yashunskii, and M. N. Shchukina, *Zh. Obshch. Khim.*, **32**, 2888 (1962).

(22) Gas chromatographic analysis shows 1-methyl-3-carbomethoxypyrazole is formed in 7% yield.

(23) Hewlett-Packard, Moseley Division, Pasadena, Calif.

(24) F. W. Breitbeil, J. J. McDonnell, T. A. Marolewski, and D. T. Dennerlein, *Tetrahedron Lett.*, 4627 (1965).

(25) H. von Pechmann and E. Burkard, *Ber.*, **33**, 3594 (1900).