The Preparation of Standards for Aldicarb (Temik) Metabolism Study

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The synthesis of 18 compounds of the general structure $CH_3XC(CH_3)_2R$ (where X is S, SO, or SO_2 and R is —CH=NOH, —CN, —COOH, $CONH_2$, $—CH_2OH$, —CONHOH, or —CH=NOCONH$_2$) is described. These materials were prepared to provide standards for a study of the metabolism of aldicarb pesticide (Temik) in cotton plants. Their nmr and infrared spectral properties are presented.

The elucidation of the metabolic fate of a given chemical in a biological system frequently involves the synthesis of possible metabolites either on the basis of experience with similar compounds or as the result of the observation of various chemical and physical properties of the unknowns actually encountered. The compounds thus prepared are then compared with the unknown material. This report is concerned with the synthetic effort required in the study of the metabolism of aldicarb pesticide [2-methyl-2-(methylthio)-propionaldehyde O-methylcarbamoyloxime] in cotton plants (Bartley *et al.*, 1969).

In the study of aldicarb metabolism in plants it is necessary to consider the various sulfur oxidation states (sulfide, sulfoxide, and sulfone) since it is known that aldicarb is rapidly converted to its sulfoxide and sulfone *in vivo* (Coppedge *et al.*, 1967; Metcalf *et al.*, 1966). Each possible class of metabolites considered, therefore, required the synthesis of three sulfur oxidation states.

EXPERIMENTAL

Infrared spectra were determined as 1% KBr pellets or, in the case of liquids, as capillary films on a Baird-Atomic 4-55 spectrometer. The nmr spectra were obtained on a Varian 60 megacycle instrument. Mass spectra were obtained on an A.E.I. MS902b high resolution mass spectrometer.

2-Methyl-2-(methylsulfinyl)propionaldehyde Oxime (T_1O). A solution containing 15 g (0.11 mole) of 2-methyl-2 (methylthio)propionaldehyde oxime (Payne *et al.*, 1966) in 75 ml of ethyl acetate was treated at 5° C with 45.7 g (0.11 mole) of 18.9% peracetic acid in ethyl acetate over a period of 25 min. The reaction mixture, which contained a white precipitate, was stirred overnight, and was then treated with 500 ml of hexane. Filtration yielded a white powder which was recrystallized from a hot toluene-hexane solution to give 10 g (61%) of white needles, m.p. 107–08° C.

Anal. calcd. for $C_5H_{11}NO_2S$: C, 40.28; H, 7.44. Found: C, 39.75; H, 7.34.

Infrared (microns): 3.15 and 3.22 (HO); 6.12 (C=N); 9.75 (SO); 10.3, 10.45 and 10.6 (N–O).

2-Methyl-2-(methylsulfonyl)propionaldehyde Oxime (T_2O). An oxime solution similar to that described above was treated at 5° C with 91.5 g (0.23 mole) of 18.9% peracetic acid over a period of 40 min. The mixture was stirred at room temperature for 24 hr after which the product was precipitated with 1 l. of hexane. The liberated solid was filtered, washed with hexane and recrystallized twice from hot toluene-hexane solution to give 12 g (66%) of fluffy white needles, m.p. 131–31.5° C.

Anal. calcd. for $C_5H_{11}NO_3S$: C, 36.36; H, 6.67. Found: C, 36.40; H, 6.66.

Infrared (microns): 2.98 (HO—); 6.12 (—C=N—) 7.73, 7.84 and 9.0 (SO_2); 10.35 and 10.55 (N—O—).

2-Methyl-2-(methylsulfinyl)propionitrile (T_1N). A solution of 10 g (0.087 mole) of 2-methyl-2-(methylthio)propionitrile (Payne *et al.*, 1966) in 50 ml of ethyl acetate was treated dropwise with 35 g (0.087 mole) of 18.9% peracetic acid in ethyl acetate. The addition was carried out with stirring over a 1-hr period at 5° C. The mixture was stirred overnight at room temperature, after which excess peroxide was destroyed with potassium iodide solution. The organic phase was washed with aqueous potassium carbonate to remove acetic acid and the mixture concentrated *in vacuo*. Distillation (b.p. 69–71° C/0.3 mm) gave 8 g (71%) of product.

Anal. calcd. for C_5H_9NOS: C, 45.77; H, 6.93. Found: C, 45.50; H, 7.17.

Infrared (microns): 4.50 (—C≡N); 7.19 and 7.30 ($C(CH_3)_2$); 9.35 (SO).

2-Methyl-2-(methylsulfonyl)propionitrile (T_2N). A solution of 10 g (0.087 mole) of 2-methyl-2-(methylthio)propionitrile (Payne *et al.*, 1966) in 50 ml of ethyl acetate was oxidized with 71 g (0.18 mole) of 18.9% peracetic acid as described above. The product was precipitated by the addition of pentane and chilling to −5° C. The solid was washed with pentane and recrystallized from carbon tetrachloride yielding 10 g (78%) of white needles, m.p. 62–63° C.

Anal. calcd. for $C_5H_9NO_2S$: C, 40.79; H, 6.16; N, 9.52. Found: C, 41.16; H, 5.85; N, 9.26.

Infrared (microns): 4.46 (C≡N); 7.17 and 7.29 [$C(CH_3)_2$]; 7.63 and 8.90 (SO_2).

2-Methyl-2-(methylthio)propionic Acid (TAc). A solution of 140 g (3.5 moles) of sodium hydroxide in 1 l. of water was treated with stirring at 25° C with 188 g (3.9 moles) of gaseous methyl mercaptan over a period of 1 hr. The mixture was allowed to reflux from a dry-ice condenser for a period of 40 min, during which time the temperature fell to approximately 10° C without external cooling. α-Bromoisobutyric acid

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(Smissman, 1954) (150 g, 0.89 mole) was added portionwise over 25 min. The mixture was stirred at 10–15° C for 3 hr and then left at room temperature overnight. The mixture was neutralized by adding 200 ml of conc. hydrochloric acid with stirring. The mixture was extracted with three 200-ml portions of ether, followed by two 200-ml portions of chloroform. The organic extracts were dried over magnesium sulfate and then concentrated *in vacuo* to afford a colorless oil. Distillation on a 36-in. platinum spinning-band column gave 60 g (50%) of the desired acid (b.p. 106–11° C/12 mm). Crystallization from pentane gave white cubic crystals, m.p. 43–47° C.

Anal. calcd. for $C_5H_{10}O_2S$: C, 44.75; H, 7.51. Found: C, 44.55; H, 7.60.

Infrared (microns): 3.27 (HO—); 5.90 (C=O).

2-Methyl-2-(methylsulfinyl)propionic Acid (T_1Ac). A solution of 2-methyl-2-(methylthio)propionic acid in ethyl acetate was oxidized with one equivalent of peracetic acid as described above. The product was collected by flooding the reaction mixture with hexane, and chilling the resultant mixture in an ice bath. Recrystallization of the product from ethyl acetate-hexane solution gave 42% of the acid, m.p. 110–11° C.

Anal. calcd. $C_5H_{10}O_3S$: C, 39.98; H, 6.71. Found: C, 39.87; H, 6.69.

Infrared (microns): 5.85 (C=O), 10.17 (SO).

2-Methyl-2-(methylsulfonyl)propionic Acid (T_2Ac). A solution of 2-methyl-2-(methylthio)propionic acid was oxidized with 2.6 equivalents of peracetic acid as above. After 3½ hr at 25° C, the mixture was warmed to 40–50° C for 30 min. The fluffy, white precipitate was filtered, washed, and recrystallized from ethyl acetate-hexane to give 55% of the desired acid, m.p. 156–59° C (lit. m.p. 164° C, Larsson and Monies, 1945).

Infrared (microns): 3.25 and 3.28 (HO); 5.89 (C=O); 7.55 (S—CH_3); 7.72 and 8.93 (SO_2).

2-Methyl-2-(methylthio)propionyl Chloride. A solution of 2-methyl-2-(methylthio)propionic acid (100 g, 0.84 mole) in 300 g of thionyl chloride was heated under reflux for 2½ hr in a flask equipped with an efficient reflux condenser and a drying tube. Excess thionyl chloride was removed under reduced pressure and the residue fractionated through a 6-in. glass-packed column to give 95 g (74%) of product as a pale yellow liquid, b.p. 54.5–58°/13 mm.

Infrared (microns): 3.35 and 3.41 (CH_3); 5.68 (C=O); 7.21 and 7.31 [$C(CH_3)_2$]; 7.58 (CH_3S).

2-Methyl-2-(methylthio)propionamide (TAm). 2-Methyl-2-(methylthio)propionyl chloride (35 g, 0.23 mole) was added dropwise with stirring, during 10 min, to 350 ml of ammonium hydroxide at 20° C. During the addition the temperature rose to 35° C. After the addition was completed the mixture was stirred at room temperature for ½ hr. The solution was evaporated to dryness *in vacuo* and the resulting residue extracted thoroughly with boiling benzene and filtered from insoluble material. The benzene extract was concentrated under reduced pressure and the solid residue recrystallized twice from cyclohexane to give 20 g (65.5%) of the title compound, m.p. 110–13° C.

Anal. calcd. for $C_5H_{11}NOS$: C, 45.08; H, 8.33; N, 10.52. Found: C, 45.00; H, 8.48; N, 10.37.

Infrared (microns): 2.96 and 3.13 (NH); 3.35 and 3.42 (CH_3); 6.06 (C=O); 6.18 (NH_2); 7.28 and 7.35 [$C(CH_3)_2$]: 7.60 (CH_3S).

2-(Methyl-2-(methylsulfinyl)propionamide (T_1Am). A stirred suspension of 2-methyl-2-(methylthio)propionamide (10 g, 0.075 mole) in 100 ml of ethyl acetate at 25° C was treated dropwise during 40 min with 24.5 g of a 23% solution of peracetic acid in ethyl acetate. During the addition the temperature was maintained at 25° C by use of an ice bath. After the addition was completed, the mixture was stirred for 1 hr and then allowed to stand overnight at room temperature. The precipitated solid was collected by filtration and recrystallized from toluene to give 5 g (35.5%) of product, m.p. 128–32° C.

Anal. calcd. for $C_5H_{11}NO_2S$: C, 40.35; H, 7.43; N, 9.39. Found: C, 40.52; H, 7.47; N, 9.19.

Infrared (microns): 2.95, 3.05, 3.10, and 3.15 (NH_2); 6.0 (C=O); 6.19 (NH_2); 7.20 and 7.35 ($C(CH_3)_2$); 7.60 (CH_3S); 9.80 (SO).

Mass spectrum: molecular ion at m/e = 149.

2-Methyl-2-(methylsulfonyl)propionamide (T_2Am). Using the same procedure as that described above, but using 62.1 g of peracetic acid solution there was obtained, after 48 hr, a solid which was recrystallized twice from ethanol to give 7 g (56%) of product, m.p. 190–94° C.

Anal. calcd. for $C_5H_{11}NO_3S$: C, 36.35; H, 6.71; N, 8.48. Found: C, 36.27; H, 6.92; N, 8.29.

Infrared (microns): 2.95, 3.05 and 3.15 (NH_2); 3.32 and 3.41 (CH_3); 5.98 (C=O); 6.22 (NH_2); 7.2 and 7.24 [$C(CH_3)_2$]; 7.77 and 9.03 (SO_2); 7.6 (CH_3S).

Mass spectrum: molecular ion at m/e = 165.

N-Hydroxy-2-methyl-2-(methylthio)propionamide (THA). A stirred suspension of free hydroxylamine (Hurd, 1939) (19 g, 0.58 mole) in 250 ml of benzene at 20° C was treated dropwise during 45 min with 2-methyl-2-(methylthio)propionyl chloride (35.1 g, 0.23 mole). During the addition the temperature rose to 25° C and was maintained at that point by external cooling. After the addition was completed, the mixture was stirred for 2½ hr. The precipitated solid was filtered and washed with ca. 30 ml of water. The benzene filtrate was evaporated to dryness under reduced pressure and the solid thus obtained combined with the above solid and the combined material recrystallized from benzene-cyclohexane mixture to give 22.5 g (65.6%) of product, m.p. 128–32° C.

Anal. calcd. for $C_5H_{11}NO_2S$: C, 40.35; H, 7.43; N, 9.39. Found: C, 40.52; H, 7.47; N, 9.19.

Infrared (microns): 2.97, 3.05, 3.10, and 3.15 (NH_2); 3.35, 3.38, and 3.43 (CH_3); 6.0 (C=O); 6.19 (NH_2); 7.2 and 7.35 ($C(CH_3)_2$): 7.60 (CH_3S); 9.80 (SO).

Mass spectrum: molecular ion m/e = 149.

N-Hydroxy-2-(methylsulfonyl)propionamide (T_2HA). A stirred suspension of N-hydroxy-2-methyl-2-(methylthio)-propionamide (10 g, 0.067 mole) in 75 ml of ethyl acetate at 25° C was treated dropwise during 45 min with 78.2 g of a 16.3% solution of peracetic acid in ethyl acetate. During the addition the temperature was maintained at ca. 25° C by use of an ice bath. When the addition was completed the mixture was stirred overnight at room temperature. The precipitated solid was collected and recrystallized from ethanol to give product, 7.8 g (64%), m.p. 178.5–81° C dec.

Anal. calcd. for $C_5H_{11}NO_4S$: C, 33.14; H, 6.12; N, 7.73. Found: C, 32.98; H, 5.87; N, 7.61.

Infrared (microns): 3.03 and 3.08 (NH, OH); 3.30 and 3.40 (CH_3); 6.05 (C=O); 6.44 (NH); 7.22 and 7.30 ($C(CH_3)_2$); 7.82 and 8.97 (SO_2).

Mass spectrum: molecular ion at m/e = 181.

N-Hydroxy-2-methyl-2-(methylsulfinyl)propionamide (T_1HA). Using the same procedure as that just described, but employing 31.3 g (an equivalent) of the peracetic acid solution, there was obtained 9 g of product, m.p. 135–36.5° C, whose infrared and nmr spectra showed it to be approximately 50% product and 50% sulfone (T_2HA).

Mass spectrum: two molecular ions at m/e = 181 and 165.

2-Methyl-2-(methylthio)propanol (TAl). To a stirred suspension of 20 g (0.5 mole) of lithium aluminum hydride in 900 ml of anhydrous ethyl ether was added, dropwise over a 30-min period at 30 to 35° C, a solution of 120 g (0.8 mole) of 2-methyl-2-(methylthio)propionyl chloride in 100 ml of ether. The mixture was stirred at 35° C for 45 min after the addition was completed, and was then cooled to 0° C and 200 ml of cold water was added slowly with stirring. Subsequently 400 ml of 10% sulfuric acid was added at 10° C and the ether layer was separated. The aqueous layer was thoroughly extracted with ether, and the combined ether layers were washed with dilute potassium carbonate, and dried over magnesium sulfate. Concentration gave 77 g of crude alcohol, which was distilled through a 36-in. spinning-band column yielding 61 g (63%) of product, b.p. 59–61°/7 mm.

Anal. calcd. for $C_5H_{12}OS$: C, 50.00; H, 10.00. Found: C, 50.12; H, 9.93.

Infrared (microns): 2.97 (HO); 7.20, 7.29, and 7.37 ($C(CH_3)_2$ and CH_3S); 9.50 (primary HO).

2-Methyl-2-(methylsulfinyl)propanol (T_1Al). To a solution of 30 g (0.25 mole) of 2-methyl-2-(methylthio)propanol in 300 ml of ethyl acetate cooled to −40° C was added dropwise with stirring 61 g (0.2 mole) of 24.9% peracetic acid in ethyl acetate over a period of 2 hr. When addition was complete, the mixture was stirred for an additional 2 hr at −30° C to −40° C and then concentrated *in vacuo* at room temperature. The residue was distilled through a 1-ft packed column to give 26 g (76%) of product, b.p. 125–27° C/1 mm; m.p. 30–35° C.

Anal. calcd. for $C_5H_{12}O_2S$: C, 44.12; H, 8.82. Found: C, 43.93; H, 8.54.

Infrared (microns): 3.05 (HO); 7.24 and 7.35 [$C(CH_3)_2$]; 9.85 (SO); 9.42 (primary HO).

2-Methyl-2-(methylsulfonyl)propanol (T_2Al). To a solution of 6 g (0.05 mole) of 2-methyl-2-(methylthio)propanol in 60 ml of ethyl acetate, 40 g (excess) of 21% peracetic acid in ethyl acetate was added dropwise with stirring at 20° C to 25° C over a period of 30 min. The mixture was stirred at room temperature for 6 hr and then concentrated *in vacuo* at room temperature to a white crystalline residue. This, upon recrystallization from toluene, gave 5 g (66%) of product, m.p. 124–27° C.

Anal. calcd. for $C_5H_{12}O_3S$: C, 39.47; H, 7.90. Found: C, 39.45; H, 7.89.

Infrared (microns): 2.90 (HO); 7.25 and 7.35 [$C(CH_3)_2$]; 7.83 and 9.00 (SO_2); 9.45 (primary HO).

2-Methyl-2-(methylsulfinyl)propionaldehyde O-Carbamoyloxime (DT_1). A solution of 5 g (0.029 mole) of 2-methyl-2-(methylthio)-propionaldehyde O-carbamoyloxime (Payne *et al.*, 1966) in 50 ml of ethyl acetate was held at 5–10° C while 13 g of 16.3% peracetic acid (0.027 mole) in ethyl acetate was added dropwise over a 30-min period. After stirring overnight the mixture was recrystallized from ethyl acetate, yielding a 1:1 mixture (74%) of sulfoxide to sulfone, m.p. 88–90.5° C. The infrared, nmr, and elemental analyses supported this composition.

Anal. calcd. for $C_6H_{12}N_2O_{3.5}S$: C, 36.00; H, 6.00; N, 14.00. Found: C, 36.01; H, 6.33; N, 13.82.

2-Methyl-2-(methylsulfonyl)propionaldehyde O-Carbamoyloxime (DT_2). A stirred solution of 5 g (0.0295 mole) of 2-methyl-2-(methylthio)propionaldehyde O-carbamoyloxime (Payne *et al.*, 1966) in 125 ml of ethyl acetate was oxidized at 5–10° C with 30 g (0.06 mole) of 16.3% peracetic acid as described above. Concentration of the reaction mixture *in vacuo* followed by recrystallization of the resultant solid residue from ethyl acetate yielded 77% of the desired product, m.p. 103–05° C.

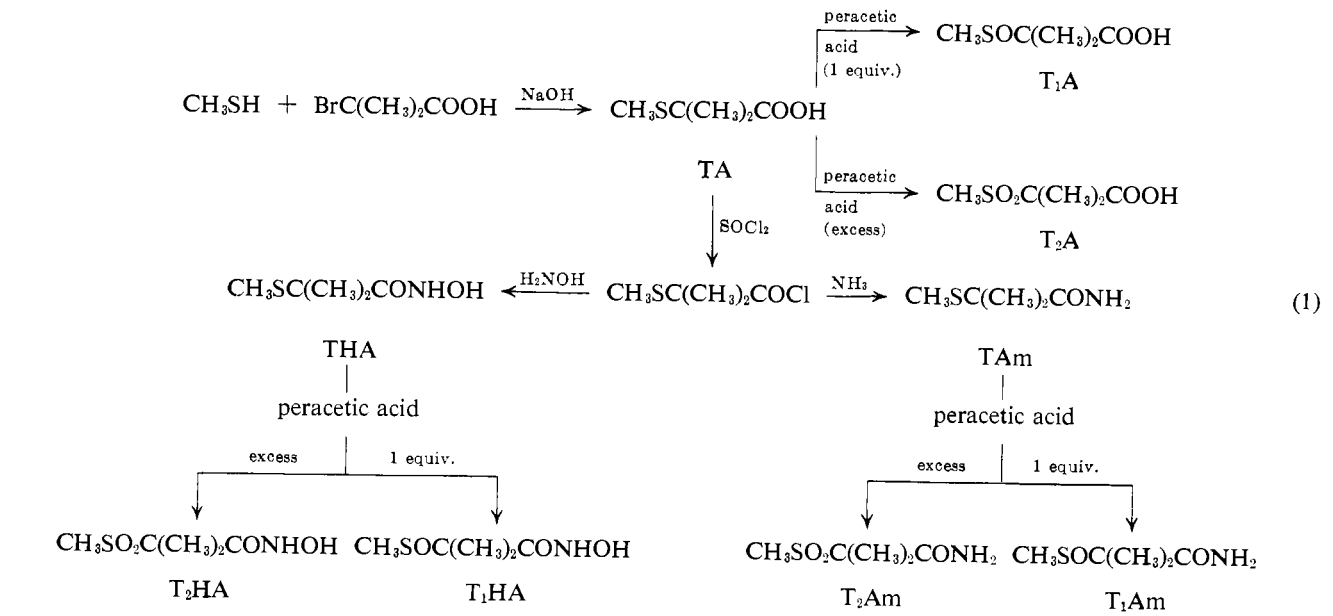
Anal. calcd. for $C_6H_{12}N_2O_4S_2$: C, 34.62; H, 5.77; N, 13.46. Found: C, 34.62; H, 5.79; N, 13.54.

Infrared (microns): 2.93, 3.06, 3.13, and 6.25 (NH_2); 5.63 (C=O); 6.11 (C=N); 7.28 ($C(CH_3)_2$); 7.38 (C—O); 7.67 and 8.98 (SO_2).

DISCUSSION

The syntheses of the various classes of compounds studied were accomplished in a straightforward manner. Aldicarb oxime [TO, 2-methyl-2-(methylthio)propionaldehyde oxime] (Payne *et al.*, 1966) was oxidized with peracetic acid to give the corresponding sulfoxide (T_1O) and sulfone (T_2O). In a similar manner 2-methyl-2-(methylthio)propionitrile (TN, aldicarb nitrile) (Payne *et al.*, 1966) was oxidized to the corresponding sulfoxide (T_1N) and sulfone (T_2N).

The preparation of the various propionic acids, amides, and hydroxamic acids standards are summarized in Equation 1. No difficulty was encountered in the syntheses of the acids (TA, T_1A, and T_2A), the amides (TAm, T_1Am, and T_2Am), or the hydroxamic acids (THA and T_2HA).



(1)

Table I. Nmr Spectral Data of Aldicarb Metabolites and Related Standards

$CH_3—X—C(CH_3)_2—R$

Compound	Chemical Shifts (δ)			
	CH_3—	—X—	—$C(CH_3)_2$—	—R
T_1O[a]	2.41	SO	1.35 and 1.43	—CH=NOH (7.51)
T_2O[a]	2.78	SO_2	1.48	—CH=NOH (7.32)
T_1N[b]	2.70	SO	1.53 and 1.68	—C≡N
T_2N[b]	3.12	SO_2	1.77	—C≡N
TAm[b]	2.09	S	1.51	—$CONH_2$ (6.80)
T_1Am[b]	2.53	SO	1.29 and 1.63	—$CONH_2$
T_2Am[b]	2.93	SO_2	1.66	—$CONH_2$
TAl[b]	1.96	S	1.22	—CH_2—OH (3.36), (3.28)
T_1Al[b]	2.51	SO	1.21 and 1.26	—CH_2—OH (3.66), (4.97)
T_2Al[b]	2.96	SO_2	1.38	—CH_2—OH (3.80), (3.50)
DT_1[a]	2.53	SO	1.44 and 1.53	—CH=NOCNH$_2$ (7.82), (6.55) (O)
DT_2[a]	2.97	SO_2	1.62	—CH=NOCNH$_2$ (7.87), (6.53)
TAc[b]	2.13	S	1.50	—COOH (11.53)
T_1Ac[c]	2.62	SO	1.51	—COOH
T_2Ac[a]	3.08	SO_2	1.61	—COOH (11.09)
THA[a]	2.03	S	1.47	—CONHOH
T_1HA[c]	2.58	SO	1.49 and 1.50	—CONHOH
T_2HA[c]	3.13	SO_2	1.64	—CONHOH

[a] Acetone-d_6. [b] $CDCl_3$. [c] D_2O.

However, the hydroxamic acid sulfoxide (T_1HA) was obtained in a 1:1 mixture with its corresponding sulfone (T_2HA), as indicated by spectral and tlc data. The mixture was satisfactory for use as a tlc standard.

The "desmethyl aldicarb" derivative, 2-methyl-2-(methylthio)propionaldehyde O-carbamoyloxime, DT, and the corresponding sulfoxide DT_1, and sulfone DT_2, were prepared according to Equation 2. No difficulty was encountered in the synthesis of DT and DT_2, but DT_1, like the preceding hydroxamic acid, T_1HA, was obtained as a mixture with the corresponding sulfone.

Again, due to competing sulfone formation, the sulfoxide alcohol (T_1Al) was difficult to prepare in pure form. At room temperature with 1 equivalent of TAl and with 0.9 equivalent of peracetic acid, the product was a 70:30 mixture of sulfoxide and sulfone, respectively. At 0° C the product contained 3 to 5% of sulfone. The use of sodium metaperiodate, a reagent reported to give a high degree of selectivity in the sulfide to sulfoxide oxidation (Leonard and Johnson, 1962) gave results similar to those obtained with peracetic acid at 0° C. T_1Al was obtained in high purity by a reaction

$$CH_3SC(CH_3)_2CH{=}NOH \xrightarrow{COCl_2} CH_3SC(CH_3)_2CH{=}NOCOCl \xrightarrow{NH_3} CH_3SC(CH_3)_2CH{=}NOCONH_2$$

TO

DT

peracetic acid

excess | 1 equiv.

$CH_3SO_2C(CH_3)_2CH{=}NOCONH_2$ (DT_2) $\quad$ $CH_3SOC(CH_3)_2CH{=}NOCONH_2$ (DT_1) (2)

The propanol derivatives (TAl, T_1Al, and T_2Al) were prepared according to Equation 3.

$$CH_3SC(CH_3)_2COCl \xrightarrow[Et_2O]{LAlH_4} CH_3SC(CH_3)_2CH_2OH$$

TAl

peracetic acid

excess | 1 equiv., −30° C

$CH_3SO_2C(CH_3)_2CH_2OH$ (T_2Al) $\quad$ $CH_3SOC(CH_3)_2CH_2OH$ (T_1Al) (3)

involving slightly less than one equivalent of peracetic acid at −40° to −30°C.

The following compounds described in this paper were identified as metabolites of aldicarb in cotton plants (Bartley *et al.*, 1970) (Table I); T_1O, T_2O, T_1N, T_1Am, T_1Al, T_1Ac, and T_2Ac. In each case, sufficient quantities of these materials were synthesized for the required toxicological studies.

The nmr spectra of these compounds are summarized in Table I.

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