cating that the changes in the character of the solvent at temperatures close to its freezing point are not sufficiently serious to influence its function in this reaction. The slope of this line gives 11.1 ± 0.5 kcal./mole for the activation energy, $E_a$, from which the calculated values of $\Delta F^{\ddagger}$ and $\Delta S^{\ddagger}$ are 20.3 kcal./mole and −32.7 ± 1 cal./deg., respectively.

TABLE V

DATA FOR THE REACTION OF 2,4-DINITROBENZENESULFENYL CHLORIDE AND CYCLOHEXENE, IN CHLOROFORM, AT 35.2° (RUN 13)

| Min. | Ml. of 0.0305 $N$ thiosulfate equivalent concn. (moles/l.)[a] Cyclohexene | ArSCl | $\log \frac{b(a-x)}{a(b-x)}$ | $k,b \times 10^3$, (moles/l.)$^{-1}$ sec.$^{-1}$ |
|---|---|---|---|---|
| 0 | 24.47 | 9.95 | | |
| 8.5 | 22.52 | 8.00 | 0.05867 | 6.398 |
| 19 | 20.58 | 6.06 | .14014 | 6.609 |
| 31 | 18.93 | 4.41 | .24190 | 6.919 |
| 41.5 | 18.14 | 3.62 | .30911 | 6.577 |
| 53.5 | 17.37 | 2.85 | .39414 | 6.488 |
| 62 | 16.86 | 2.34 | .46690 | 6.623 |
| 74 | 16.20 | 1.68 | .59339 | 7.043 |
| 92.5[c] | 15.77 | 1.25 | .71011 | 6.734 |

[a] The initial concentrations were $a$ = 0.0301 mole/l. for the sulfenyl chloride (I) and $b$ = 0.074 mole/l. for cyclohexene. [b] The values of $k$ are calculated from 0.5 min. as the origin (*Cf.* text). The mean value of $k$ for this run is (6.67 ± 5%) × $10^{-3}$ (mole/l.)$^{-1}$ sec.$^{-1}$; the graphical value from Fig. 2 is 6.68 × $10^{-3}$ (mole/l.)$^{-1}$ sec.$^{-1}$. [c] This point represents 87.4% complete reaction.

The data for the runs in other solvents are summarized in Table IV. The accuracy of these runs is lower than in the acetic acid studies, for the titration end-points were generally not as distinct and the rate in nitrobenzene was quite rapid, causing increased timing errors. The runs in carbon tetrachloride, which lasted up to 15 days, were made with aliquots, in sealed ampoules, to minimize evaporation and reactions with moisture and air. This precaution was not necessary for the runs in the other solvents, all of which gave quantitative reactions in a matter of hours. Run 15, in *sym*-dichloroethane, gave equally good second-order plots,

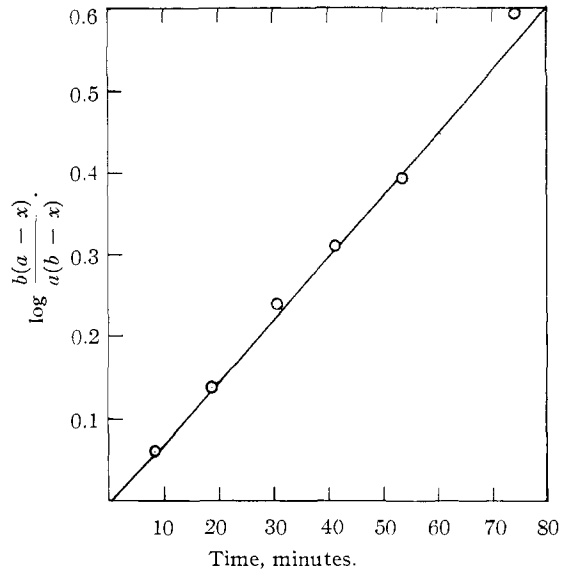


Fig. 2.—Plot of a typical run (no. 13, Table IV) for the reaction of 2,4-dinitrobenzenesulfenyl chloride with cyclohexene, in chloroform, at 35.2°, showing adherence to the second-order rate expression.

whether or not the blank correction was used in calculating the concentration of I throughout the run. To conform with the other runs, however, the value of $k$ in Table IV includes the blank correction, the value of $k$ without using the blank correction being (1.27 ± 7%) × $10^{-2}$ (mole/l.)$^{-1}$ sec.$^{-1}$. The data for one of the runs in chloroform are given in Table V and plotted in Fig. 2. Because of the doubtful validity of the blank in solvents other than acetic acid, the values of $k$, in Table IV, are only of relative, rather than absolute, value but they clearly show the marked effect which increasing polarity of the solvents has on the rates (*cf.* Discussion).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

# Studies on Thioesters Related to Coenzyme A. A Kinetic Study of Aminolysis and Hydrolysis of β-(N-Methylacetamino)-ethyl Thioacetate, N,S-Diacetylaletheine and γ-Acetaminopropyl Thioacetate[1]

BY D. STANLEY TARBELL AND DONALD P. CAMERON[2]

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The synthesis of β-(N-methylacetamino)-ethyl thioacetate and of γ-acetaminopropyl thioacetate is described. Rates of alkaline hydrolysis and of aminolysis by *n*-butylamine of these thioesters and of N,S-diacetylaldetheine in aqueous solution at 0° have been measured; the kinetics of the reactions have been discussed. The above thioesters, containing some of the structural features of coenzyme A, do not differ greatly among themselves or with ethyl thioacetate and β-acetaminoethyl thioacetate, with respect to the reactivity of the thioester grouping under the conditions specified.

The increasing recognition of the central role of coenzyme A in enzymatic processes has made detailed study of the thioester grouping desirable.[3] It was shown recently[4] that the rates of aminolysis and of hydrolysis in aqueous solution for ethyl thioacetate (I) and β-acetaminoethyl thioacetate (II) were not markedly different; hence the acet-

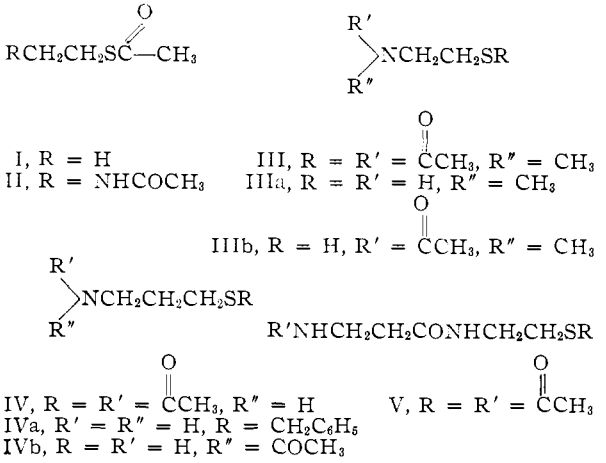
(1) This research was supported in part by the United States Air Force, through the Office of Scientific Research of the Air Research and Development Command.

(2) Predoctoral Fellow of the United States Public Health Service.

(3) For some recent studies on the rates of hydrolysis of simple thioesters, *cf.* P. N. Rylander and D. S. Tarbell, THIS JOURNAL, **72**, 3021 (1950); B. K. Morse and D. S. Tarbell, *ibid.*, **74**, 416 (1952); L. H. Noda, S. A. Kuby and H. A. Lardy, *ibid.*, **75**, 913 (1953); F. J. McQuillin and J. Stewart, *J. Chem. Soc.*, 2966 (1955); J. T. G. Overbeek and V. V. Koningsberger, *Koninkl. Nederl. Akademie van Wetenschapen-Amsterdam*, **57B**, 311, 465 (1954); **58B**, 49 (1955). Among other recent studies on thioesters, see M. J. Cronyn, M. P. Chang and R. A. Wall, THIS JOURNAL, **77**, 3031 (1955); R. Schwyzer, *Helv. Chim. Acta*, **36**, 414 (1953); T. Wieland and E. Bokelmann, *Ann.*, **576**, 20 (1952); J. C. Sheehan and C. W. Beck, THIS JOURNAL, **77**, 4875 (1955).

(4) P. J. Hawkins and D. S. Tarbell, *ibid.*, **75**, 2982 (1953).

amino group did not markedly affect the reactivity of the thioester function. In the present paper, a similar study is reported of the thioester function in three other compounds containing some of the structural features of coenzyme A: β-(N-methylacetamino)-ethyl thioacetate (III), γ-acetaminopropyl thioacetate (IV) and N,S-diacetylaletheine (β-[(N-acetyl-β-alanyl)-amino]-ethyl thioacetate) (V). Compounds III and IV and some of the intermediates employed are new compounds; the methods of synthesis employed are described adequately in the Experimental part below. N,S-Diacetylaletheine was prepared by a modification of several published procedures.




The kinetic studies were carried out in the manner previously described,[4] in aqueous solution at 0°, and the rate of disappearance of the thioester group was determined spectrophotometrically. The rate constants for the base-catalyzed hydrolysis of the thioesters are given in Table I, where most of the rate constants were determined under pseudo first-order conditions. In Table I, E = thioester, $k_1$ = pseudo first-order hydrolysis constant, defined by the equation

$$d[E]/dt = k_1[E]$$

TABLE I

ALKALINE HYDROLYSIS OF THIOESTERS, $CH_3COSR$, IN WATER AT 0°

| [E], mole/l. × $10^4$ | $[OH^-]$, mole/l. × $10^2$ | $k_1$ × $10^2$, min.$^{-1}$ | $k_2 = k_1/[OH^-]$, mole/l./min. |
|---|---|---|---|
| A. $CH_3COSCH_2CH_2N(CH_3)COCH_3$ (III) | | | |
| 5.863 | 1.315 | 1.47 | 1.12 |
| 10.22[a] | 0.395 | | 0.97 |
| 6.91 | 1.315 | 1.35 | 1.03 |
| 2.43 | 0.658 | 0.697 | 1.07 |
| 3.43 | 1.315 | 1.40 | 1.08[b] |
| B. $CH_3COSCH_2CH_2CH_2NHCOCH_3$ (IV) | | | |
| 6.28 | 2.128 | 1.59 | 0.747 |
| 5.99 | 1.064 | 0.779 | 0.732[c] |
| 12.57 | 2.174 | 2.58 | 1.19 |
| 4.735 | 1.087 | 1.34 | 1.23[d] |

[a] Second-order constant, $k_2$, was obtained directly. [b] Average value of $k_2$ from 16 runs was 1.04, with average deviation of 0.05. [c] Average value of $k_2$ from 5 runs was 0.733, with average deviation of 0.017. [d] Average value of $k_2$ from 4 runs was 1.21, with average deviation of 0.01.

and $k_2$ is the second-order hydrolysis constant, defined by

$$d[E]/dt = k_2[E][OH^-] \quad (1)$$

and

$$k_2 = k_1/[OH^-] \quad (2)$$

The results of the aminolysis runs, using *n*-butylamine in excess to obtain a pseudo first-order reaction in thioester, are given in Table II. The quantity $[RNH_2]$ is the actual free amine concentration, calculated from the two simultaneous equations

$$[RNH_2] + [RNH_3^+] = \text{total amine concn.} \quad (3)$$

$$[RNH_3^+]^2 = [RNH_2]K_b \quad (4)$$

Equation 4 follows from the equation for the basic ionization constant of the amine

$$K_b = [RNH_3^+][OH^-]/[RNH_2] \quad (5)$$

by substituting $[RNH_3^+]$ for $[OH^-]$ in eq. 5, which is proper, because in these solutions, there is no hydroxyl ion except that produced by hydrolysis of the free amine.

The value of $K_b$ used was $1.74 \times 10^{-4}$, calculated[5] from the data of Hall and Sprinkle,[6] and is more accurate than the value used previously.[4] The $k_{obs}$ values given in Table II are the observed pseudo first-order constants for the rate of disappearance of the thioester by aminolysis and concurrent hydrolysis.

TABLE II

AMINOLYSIS OF THIOESTERS, $CH_3COSR$, BY *n*-BUTYLAMINE IN WATER AT 0°

| [E] × $10^4$, mole/l. | $[RNH_3] + [RNH_3^+]$ × $10^4$, mole/l. | $[RNH_2]$ × $10^4$, mole/l. | $k_{obs.}$ × $10^2$, min.$^{-1}$ |
|---|---|---|---|
| A. $CH_3COSCH_2CH_2N(CH_3)COCH_3$ (III) | | | |
| 4.62 | 116.6 | 103.2 | 2.59 |
| 5.71 | 163.2 | 147.2 | 4.18 |
| 5.36 | 139.9 | 125.1 | 3.50 |
| 1.997 | 56.9 | 47.80 | 0.956 |
| B. $CH_3COSCH_2CH_2CH_2NHCOCH_3$ (IV) | | | |
| 6.96 | 188.6 | 171.3 | 3.90 |
| 8.22 | 188.6 | 171.3 | 3.85 |
| 6.22 | 113.8 | 100.6 | 1.85 |
| 5.82 | 113.8 | 100.6 | 1.79 |
| 1.932 | 56.9 | 47.80 | 0.700 |
| C. $CH_3COSCH_2CH_2NHCOCH_2CH_2NHCOCH_3$ (V) | | | |
| 8.27 | 185.8 | 168.7 | 6.24 |
| 7.11 | 163.2 | 147.2 | 5.23 |
| 4.52 | 116.6 | 103.2 | 3.11 |
| 4.86 | 116.6 | 103.2 | 3.05 |
| 1.842 | 56.9 | 47.8 | 1.20 |

The aminolysis data were first treated by the method of the earlier paper,[4] by plotting $k_{obs}/[RNH_2]^{1/2}$ against $[RNH_2]$. This treatment is compatible with the following kinetic equation

$$-d[E]/dt = k_2[E][OH^-] + k_3[E][RNH_2][OH^-] \quad (6)$$

The plot of $k_{obs}/[RNH_2]^{1/2}$ against $[RNH_2]$ should yield an intercept $k_4$, which is related to $k_2$, the second order hydrolysis constant, as

$$k_4 = k_2K_b^{1/2} \quad (7)$$

(5) P. J. Hawkins and I. Piscalnikow, THIS JOURNAL, **77**, 2771 (1955).

(6) N. F. Hall and M. R. Sprinkle, *ibid.*, **54**, 3473 (1932).

In the earlier work,[4] reasonable agreement was obtained between $k_2$ determined from the plot (with the use of eq. 7), and $k_2$ as determined in separate hydrolysis experiments. This result was obtained by using the value of $K_b$ for 25° instead of 0°. Application of the above treatment to the data in Table II, using the extrapolated value of $K_b$ at 0°, gave values of $k_2$ as obtained from the plots which were greater, by a fairly constant amount, than the values of $k_2$ determined experimentally.

In a recent careful study of the rate of aminolysis and hydrolysis of α-naphthyl acetate,[5] it was shown that the results were described more accurately by a plot obtained from the equation

$$-d[E]/dt = k_{obs}[E] = k_2[E][OH^-] + k_3[E][RNH_2][OH^-] + k_5[E][RNH_3^+] \quad (8)$$

which transforms to

$$-\frac{k_{obs}}{[RNH_3^+]} - \frac{k_2[OH^-]}{[RNH_3^+]} = \frac{k_3[RNH_2][OH^-]}{[RNH_3^+]} + k_5 \quad (9)$$

A plot of the function on the left *vs.* $[RNH_2][OH^-]/[RNH_3^+]$ was linear and yielded $k_3$ and $k_5$, in runs where there was excess hydroxyl ion present, as well as in runs where $[OH^-] = [RNH_3^+]$.

The treatment of Hawkins and Piscalnikow[5] was applied to the present data and to those obtained previously.[4] Since in our experiments $[OH^-] = [RNH_3^+]$, $K_b^{1/2}[RNH_2]^{1/2}$ can be substituted for $[RNH_3^+]$ in eq. 9, giving

$$\frac{k_{obs}}{K_b^{1/2}[RNH_2]^{1/2}} k_2 = k_3[RNH_2] + k_5 \quad (10)$$

A plot of the left-hand side of the equation against $[RNH_2]$ gives $k_3$ as the slope and $k_5$ as the intercept. The results are given in Table III and include those calculated for the two thioesters studied previously.

TABLE III

CONSTANTS OBTAINED FOR AMINOLYSIS OF THIOESTERS FROM EQ. 8

| Compound | $k_3$, mole/l./min. | $k_5$, mole/l./min. |
|---|---|---|
| $CH_3COSCH_2H_5$[a] | 1135 | 0.891 |
| $CH_3COSCH_2CH_2NHCOCH_3$[a] | 1827 | 2.11 |
| $CH_3COSCH_2CH_2N(CH_3)COCH_3$ | 1611 | 1.82 |
| $CH_3COSCH_2CH_2CH_2HNCOCH_3$ | 1200 | 1.09 |
| $CH_3COSCH_2CH_2NHCOCH_2CH_2NHCOCH_3$ | 1952 | 2.08 |

[a] Obtained from data in ref. 4, by using value of $1.74 \times 10^{-4}$ for $K_b$ at 0° and using eq. 8.

It thus appears that the present results are in agreement with earlier ones[4,5] in indicating that aminolysis, like hydrolysis, is catalyzed by both acids and bases, which is also indicated by the work of Overbeek and Koningsberger.[3] Equation 8 is not unique in fitting the kinetic data; other kinetically equivalent equations, such as the following,[5] are equally satisfactory on kinetic grounds, and may be preferred for other reasons.

$$-d[E]/dt = k_2[E][OH^-] + k_3[E][RNH_2][OH^-] + k_6[E][RNH_2][H^+] \quad (11)$$

The data in Tables I and III show that the reactivity of the thioester group, as measured by the rate of alkaline hydrolysis and aminolysis, does not vary much in going from ethyl thioacetate to the more complex derivatives containing some of the structural features of S-acetylcoenzyme A. In particular, methylation of the amide nitrogen has little effect, as does lengthening the carbon chain of the β-aminoethyl mercaptan. It is possible that the phosphate groups in 5-acetylcoenzyme A may have a marked effect on the reactivity of the thioester grouping, because by proper coiling of the chain, the phosphate groups may come near enough to the thioester to exert a strong electrostatic effect. The enzymatic processes involving acyl transfer of coenzyme A derivatives occur, of course, under quite different conditions from the present *in vitro* experiments; they occur at *p*H near neutrality, require the presence of a specific protein which doubtless absorbs both coenzyme A and the other reactant, and may be promoted by heavy metal ions.[7]

## Experimental[8]

N-Methylethylenimine (b.p. 26–28°) was prepared from β-methylaminoethanol[9] in 47% yield by a modification of published procedures[10] for synthesis of ethylenimines.

**β-Methylaminoethyl Mercaptan (IIIa).**[11]—Dry hydrogen sulfide was passed into 200 cc. of absoute methanol cooled in a Dry Ice-bath, until 100 g. had been absorbed. To this solution was added with stirring, during a 2-hr. period, a cold solution of 34 g. of N-methylethylenimine in 200 cc. of absolute methanol. During the addition, dry hydrogen sulfide was slowly bubbled through the solution, and the reaction mixture was kept at Dry Ice–acetone temperature. After the addition was complete, the reaction mixture was brought to room temperature overnight, while an atmosphere of dry nitrogen was maintained. The solvent was then removed at room temperature under water-pump vacuum; during the concentration, white prisms were gradually deposited on the side of the flask. This product was washed with 50 cc. of dry cold pentane, and filtered under nitrogen; it weighed 29 g. (53%) and melted at 50–53°. An analytical sample, prepared by sublimation, melted[12] at 52–53°. The product was basic, gave a mercaptan test with iodine–potassium iodide, and was very hygroscopic, the latter property apparently causing the low carbon value on analysis.

*Anal.* Calcd. for $C_3H_9NS$: C, 39.59; H, 9.97. Found: C, 38.31; H, 9.48.

An attempt to prepare the picrate of the aminomercaptan gave only the picrate of the corresponding disulfide, which melted, in agreement with Gabriel and Colman,[12] at 157–160°, and gave a satisfactory carbon and hydrogen analysis.

**β,β'-(Methylamino)-diethyl Disulfide (Disulfide of IIIa).**—From the filtrate obtained above in the initial isolation of β-methylaminoethyl mercaptan was obtained, on concentration and vacuum distillation of the residue, 20 g. (31%) of a colorless liquid, b.p. 89° (0.4 mm.), $n^{20}D$ 1.5337. The picrate and hydrochloride melted at the points recorded by Gabriel and Colman.

**β-(N-Methylacetamino)-ethyl Thioacetate (III).**—Ketene gas[13] was bubbled through a stirred solution of 29 g. of β-methylaminoethyl mercaptan in 1 l. of dry ether at 0° for 6 hr., at a rate of 0.3 mole hr. The solvent was removed *in vacuo*, and the residue was distilled twice, giving 40 g. of product, b.p. 104–109° (0.5–0.75 mm.), $n^{20}D$ 1.5060.

(7) R. Schwyzer and C. Hurlimann, *Helv. Chim. Acta*, **37**, 155 (1954).

(8) Analyses by Micro-Tech Laboratories and Miss Annette Smith; temperatures are uncorrected.

(9) Prepared by the action of methylamine on β-chloroethyl chlorocarbonate, followed by saponification of the resulting urethan (*cf.* W. E. Hanby and H. N. Rydon, *J. Chem. Soc.*, 517 (1947)).

(10) H. Wenker, THIS JOURNAL, **57**, 2328 (1935); R. C. Elderfield and H. C. Hageman, *J. Org. Chem.*, **14**, 623 (1949).

(11) For the analogous reaction of hydrogen sulfide with ethylenimine, see E. J. Mills, Jr., and M. T. Bogert, THIS JOURNAL, **62**, 1175 (1940); J. Barnett, *J. Chem. Soc.*, 5 (1944).

(12) β-Methylaminoethyl mercaptan is described by S. Gabriel and J. Colman, *Ber.*, **45**, 1653 (1912), as an extremely hygroscopic crystalline mass, but no m.p. is given.

(13) Generated in a lamp of the type described by J W. Williams and C. D. Hurd, *J. Org. Chem.*, **5**, 122 (1940).

This material, however, was acidic to litmus and gave a poor analysis. Fractionation through an 18 in. helix-packed column led to the isolation of a small amount of crystalline product as needles from pentane, m.p. 111–112°, whose composition agreed with the formula $(C_2H_2O)_n$. Seven fractionations of the remaining product yielded 26 g. (46%) of β-(N-methylacetamino)-ethyl thioacetate (III), b.p. 112–113° (1 mm.), $n^{20}D$ 1.5050.

*Anal.* Calcd. for $C_7H_{13}NO_2S$: C, 47.98; H, 7.48; N, 7.99. Found: C, 48.15; H, 7.60; N, 7.64; acetyl, 99% of theory.

**Bis-(N-acetyl-β-methylaminoethyl) Disulfide (Disulfide of IIIb).**—Bis-(β-methylaminoethyl) disulfide (6.7 g.) in 50 cc. of dry ether was treated with 8.1 g. of anhydrous powdered potassium carbonate, and 8 g. of acetyl chloride in 10 cc. of dry ether was added during 30 min., with refluxing for an additional 12 hr. The reaction mixture was filtered, concentrated *in vacuo* and the residue was distilled; the product (6 g.) was a colorless hygroscopic oil, b.p. 76° (0.9 mm.), $n^{20}D$ 1.5095.

*Anal.* Calcd. for $C_{10}N_{20}N_2O_2S_2$: C, 45.42; H, 7.63; N, 10.60; S, 24.25. Found: C, 45.99; H, 8.74; N, 10.74; S, 23.05.

The compound was also prepared by acetylation with ketene, but the analyses of material obtained in this way were less satisfactory.

**3-Aminopropyl Benzyl Sulfide (IVa).**—3-Aminopropyl chloride hydrochloride[14] (72 g.) in 200 cc. of absolute alcohol was added, after chilling, to an ice-cold stirred solution, prepared by dissolving (under dry nitrogen) 26.8 g. of sodium in a solution of 72.1 g. of benzyl mercaptan in 500 cc. of absolute ethanol. During the addition, which required 2 hr., nitrogen was passed over the mixture and the temperature was kept below 5°. The mixture was then refluxed by a heating mantle for 12 hr., with stirring to prevent bumping. The solvent was removed under water-pump vacuum on the steam-bath with stirring; 400 cc. of dry ether was added, the inorganic salts which precipitated were removed by filtration through Filter-cel, and the filtrate, combined with two 100-cc. ether washings of the inorganic material, was concentrated *in vacuo*. The residue, distilled through a helix-packed column, had the following properties: b.p. 97° (0.1–0.07 mm.), $n^{23}D$ 1.5645, wt. 81.6 g. (81%). Repeated analyses on material prepared in this way gave unsatisfactory analyses, being too low in carbon and sulfur; however, the following derivatives gave satisfactory analyses, although they required repeated recrystallization.

**The N-*p*-nitrobenzoyl** derivative was prepared by heating with *p*-nitrobenzoyl chloride in benzene; it melted crude at 103–103.5°, and, after seven recrystallizations from benzene, at 107–107.5°.

*Anal.* Calcd. for $C_{17}H_{18}N_2O_5S$: C, 61.80; H, 5.49; N, 8.48; S, 9.70. Found: C, 61.52; H, 5.40; N, 8.40; S, 9.68.

**The picrate** melted, after seven recrystallizations from absolute alcohol, at 118.5–119°; it gave a depression on mixed m.p. with picric acid.

*Anal.* Calcd. for $C_{16}H_{18}N_4O_7S$: C, 46.82; H, 4.42; N, 13.65; S, 7.81. Found: C, 46.91; H, 4.50; N, 13.43; S, 7.64.

**γ-Acetaminopropyl Thioacetate (IV).**—To a stirred solution of 74 g. of 3-aminopropyl benzyl sulfide in 800 cc. of liquid ammonia was added, in small portions, sufficient sodium to produce a blue color which persisted for 45 min. After stirring for 2 hr., the blue color had faded, and the ammonia was removed *in vacuo* with a water-pump. The evacuated system was flooded with nitrogen, and 300 cc. of acetic anhydride was added in small portions with cooling. When the exothermic reaction had subsided, 150 cc. of acetyl chloride and 25 g. of powdered anhydrous sodium carbonate were added, and the mixture was refluxed with stirring under nitrogen for 2 hr. After stirring for an additional 24 hr. at room temperature, the inorganic salts were filtered off, and the filter cake was washed with two 100-cc. portions of hot ethyl acetate. The combined filtrate and washings were concentrated *in vacuo* at 40–50°, the brown oil which remained was extracted with four 200-cc. portions of boiling hexane, to remove 1,2-diphenylethane. The oil, after two distillations, weighed 52.8 g. (73%), b.p. 118.5–126° (0.1–0.3 mm.), $n^{21.5}D$ 1.5057. The product was prepared for analysis and for kinetic runs by three further fractionations *in vacuo;* the refractive index was unchanged.

*Anal.* Calcd. for $C_7H_{13}NO_2S$: C, 47.98; H, 7.48; N, 7.99; S, 18.30. Found: C, 48.33; H, 7.85; N, 8.04; S, 18.00; acetyl content, 99.4% of theory.

**Bis-(γ-acetaminopropyl) Disulfide (Disulfide of IVb).**—A sodium–liquid ammonia debenzylation on 81 g. of 3-aminopropyl benzyl sulfide, in which an attempt was made to isolate the intermediate 3-aminopropyl mercaptan, followed by treatment with acetic anhydride–sodium carbonate, yielded only the bis-(acetaminopropyl) disulfide. This weighed 39.0 g. (65%), m.p. 79–86°; it was dissolved in hot ethyl acetate, treated with Norite, and the product (32.0 g.) melted, after nine recrystallization from ethyl acetate, at 89.5–90°.

*Anal.* Calcd. for $C_{10}H_{20}N_2O_2S_2$: C, 45.42; H, 7.63; N, 10.60; S, 24.25. Found: C, 45.19; H, 7.46; N, 10.40; S, 24.12.

The product showed no absorption in the 230–240 mμ region or the 5.9–6.0 μ region, both of which are characteristic of thioesters.

**3-Phthalimidopropyl Benzyl Sulfide.**—To a solution of 23 g. of sodium and 124 g. of benzyl mercaptan in 400 cc. of absolute ethanol, under nitrogen, was added at 0°, a chilled solution of 268 g. of 3-bromopropylphthalimide[15] in a mixture of 500 cc. of absolute alcohol and 200 cc. of ether. The addition required 3 hr.; the reaction mixture was then refluxed with stirring for 12 hr., was cooled, and the sodium bromide was removed by filtration. The filtrate was concentrated *in vacuo*, and the resulting white solid melted, after crystallization from ethyl acetate, at 60.5–61°, wt. 142.5 g. The analytical sample after three crystallizations from hexane melted at 63–64°.

*Anal.* Calcd. for $C_{18}H_{17}NO_2S$: C, 69.42; H, 5.50; N, 4.50; S, 10.30. Found: C, 69.02; H, 5.23; N, 4.64; S, 10.39.

**N,S-Diacetylaletheine (V).**—β-Aminoethyl mercaptan[16] was converted to the disulfide dihydrochloride (Mills and Bogert, ref. 11) and this was acylated by N-carbobenzoxy-β-alanyl chloride, to yield bis-[N-(N-carbobenzoxy-β-alanyl)-2-aminoethyl] disulfide, according to Wittle, *et al.*[17]

To 18 g. of the disulfide in 500 cc. of liquid ammonia was added slowly with stirring enough sodium to maintain the blue color formed for about 45 min. Ammonium sulfate was then added in portions until the blue color was discharged and the ammonia was removed *in vacuo* with the water-pump. The grayish residue was extracted under nitrogen with six 100-cc. portions of hot absolute ethanol (dried by the diethyl phthalate–sodium method), and the combined extracts were concentrated *in vacuo* to a pale yellow oil. This was immediately treated with 150 cc. of acetic anhydride and 25 g. of anhydrous sodium carbonate, an atmosphere of dry nitrogen being maintained. There was an exothermic reaction with carbon dioxide evolution, and the mixture was stirred for 48 hr. at room temperature. The inorganic material was removed by filtration, was washed with hot ethyl acetate, and the combined filtrate and washings were concentrated at 40–45° (4–8 mm.). The white residue was dissolved in hot ethyl acetate, and the crude N,S-diacetylaletheine which resulted on cooling (13.3 g., 89%) melted at 107–121°. One crystallization from ethyl acetate yielded 11.3 g., m.p.[18] 137–139°. The material used in kinetic studies showed a constant m.p. of 142–143° after nine crystallizations from ethyl acetate, and showed 98.6% of the theoretical acetyl content.

In earlier procedures, the disulfide was reduced with sodium–liquid ammonia as described above, but precautions were not taken to protect the product from air. The acetylation was carried out by refluxing with acetic anhydride and a drop of sulfuric acid in the absence of nitrogen. The product consisted of 43% of N,S-diacetylaletheine, m.p. 134–140°, and 15% of the disulfide, N,N′-diacetylaletheine, m.p.,[19] after three crystallizations from methanol, 207.5–208°.

(14) Prepared by the action of thionyl chloride in chloroform on 3-aminopropanol, followed by precipitation with dry hydrogen chloride, and recrystallization from alcohol–ether; m.p. 146–148°.

(15) L. H. Amundsen and J. J. Sanderson, *Org. Syntheses*, **24**, 46 (1944).

(16) J. Baddiley and E. M. Thain, *J. Chem. Soc.*, 801 (1952).

(17) E. L. Wittle, *et al.*, THIS JOURNAL, **75**, 1697 (1953).

(18) Baddiley and Thain[16] report 139–140°.

(19) J. Baddiley and E. M. Thain, *J. Chem. Soc.*, 3425 (1951), report m.p. of 190°.

Several attempts to isolate aletheine as the oxalate, following the sodium–liquid ammonia reduction of bis-[N-(N-carbobenzoxy-β-alanyl)-2-aminoethyl] disulfide were unsuccessful.[20]

**Kinetic Runs.**—The kinetic runs were carried out essentially as described previously,[4] following the rate of the disappearance of the thioester group by measuring the ultraviolet absorption at 233 mμ with a Beckman DU spectrophotometer. It was shown that the thioesters obeyed Beer's law strictly; the $\epsilon \times 10^{-3}$ values at 233 mμ for the three thioesters were as follows: III, 4.51 ± 0.027; IV, 5.19 ± 0.082; V, 4.75 ± 0.032.

**Isolation of Products. A. From N,S-Diacetylaletheine (V).**—One gram of N,S-diacetylaletheine was hydrolyzed in 1 l. of 0.1 *M* sodium hydroxide at room temperature for 5 days, after which air was bubbled through the solution until no test for the thiol group was given using iodine–potassium iodide. The *p*H was brought to 3, with 1 *N* hydrochloric acid, the solution was reduced to dryness at 40°, with a water-pump, and the residue was extracted with 200 cc. of warm anhydrous methanol. The mixture was filtered, and the filtrate was evaporated to dryness with a water-pump. The white crystalline residue weighed 0.85 g. (m.p. 190–200°) and after two crystallizations from methanol yielded 0.80 g. (98%), m.p. 208–209°, of the expected disulfide, diacetylalethine (the disulfide derived from V, R = H); there was no depression on mixed m.p. with an authentic sample.

B. **From γ-Acetaminopropyl Thioacetate (IV).**—By essentially the above procedure, hydrolysis of 1 g. of IV and 0.1 *M* alkali yielded 97% of the expected disulfide (corresponding to IVb), m.p. and mixed m.p. 88.5–90°.

(20) T. E. King, C. J. Stewart and V. H. Cheldelin, THIS JOURNAL, **75**, 1290 (1953).

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# The Effect of Ring Size on the Rate of Acetolysis of the Cycloalkyl *p*-Toluene and *p*-Bromobenzenesulfonates[1]

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A number of cycloalkyl tosylates (4-, 5-, 6-, 7-, 8-, 9-, 11-, 12-, 13-, 14-, 15- and 17-ring members) have been synthesized and the rates of acetolysis measured at several temperatures in order to ascertain the effect of ring size on reactivity. The behavior of several brosylates (5-, 6- and 7-) was also examined. In the common rings, the cyclopentyl and cycloheptyl derivatives exhibit an enhanced reactivity attributed to the de-eclipsing of bonds in the ionization stage. On the other hand, the decreased reactivity of the cyclohexyl derivatives is attributed to an increase in bond opposition in the ionization stage. A further increase in reactivity is observed in the medium rings (8- to 12-) followed by a decrease in the large rings (13- to 17-) to rates of reactions similar to those observed in open-chain compounds. The maximum in reactivity in the medium rings is attributed to a relief of strain accompanying the loss of a bond in the ionization stage. For the strained rings (5- to 11-members) a simple relationship exists between the association constants for cyanohydrin formation and the rate constants for acetolysis of the tosylates.

Ring compounds exhibit a remarkable change in chemical reactivity with ring size.[3–6] It has been proposed that the changes in chemical reactivity can be correlated with the changes in internal strain accompanying the formation or breaking of a bond to the ring atom in the rate-determining stage.[5–7]

The available data are too few to permit a rigorous test of the utility of the proposed explanation. In order to obtain data of this kind we are currently examining the effect of ring size on the reactivity of ring derivatives in a few representative reactions. The present paper reports a study of the effect of ring size on the acetolysis of cyclic tosylates[8] and certain selected brosylates.

## Results

The *p*-toluenesulfonates of cyclobutanol, cyclopentanol, cyclohexanol, cycloheptanol, cyclooctanol, cyclononanol, cycloundecanol, cyclododecanol, cyclotridecanol, cyclotetradecanol, cyclopentadecanol, cycloheptadecanol and the *p*-bromobenzenesulfonates of cyclopentanol, cyclohexanol and cycloheptanol were prepared by treating the alcohol with *p*-toluenesulfonyl or *p*-bromobenzenesulfonyl chloride in dry pyridine, essentially according to the method described by Tipson.[9]

The *p*-toluenesulfonates of cycloheptanol, cycloöctanol, cyclononanol and cycloundecanol were relatively unstable, the cycloheptyl compound undergoing decomposition after several days at room temperature and the others undergoing decomposition after several days at 0–10°. The product obtained by treatment of cyclodecanol with *p*-toluenesulfonyl chloride in dry pyridine decomposed rapidly at room temperature upon removal of the ether with which it had been extracted. Before the preparation could be repeated, it was learned that the compound had been synthesized in another laboratory and its rate of acetolysis measured.[8] Accordingly no attempt was made to repeat this preparation.

The properties of the cyclanols and the aryl-

(1) Chemical Effects of Steric Strains. XII.

(2) Research assistant on a contract supported by the Office of Naval Research and a grant provided by the National Science Foundation.

(3) V. Prelog, *J. Chem. Soc.*, 420 (1950).

(4) J. D. Roberts and V. C. Chambers, THIS JOURNAL, **73**, 5034 (1951).

(5) H. C. Brown, R. S. Fletcher and R. B. Johannesen, *ibid.*, **73**, 212 (1951).

(6) H. C. Brown and M. Borkowski, *ibid.*, **74**, 1894 (1952).

(7) P. D Bartlett, *Bull. soc. chim.*, C100 (1951).

(8) In the course of discussions with Professor V. Prelog during the Fourteenth International Congress of Pure and Applied Chemistry in Zurich, July 21–27, 1955, it was learned that Professor Prelog and Dr. R. Heck had carried out a similar study of the acetolysis of the cycloalkyl tosylates (6-, 7-, 8-, 9-, 10-, 11-, 12- and 20-ring members). These results have since been published: R. Heck and V. Prelog, *Helv. Chim. Acta*, **38**, 1541 (1955). The present study includes data on certain tosylates (4-, 5-, 13-, 14-, 15- and 17-ring members) and brosylates (5-, 6- and 7-) not included in the investigation by Heck and Prelog. Moreover, it should be of interest to compare the agreement realized in a closely similar study in two different laboratories. Consequently, we are reporting all of our results even where these duplicate those obtained by Heck and Prelog.

(9) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).