67.5 ml. of toluene at 5° was added at two drops per second an ice-cold solution of 27 ml. of concentrated sulfuric acid in 67.5 ml. of water. After thirty minutes the reaction mixture was brought to 30°, and stirred at that temperature for forty-five minutes. The well-stirred solution was then gently refluxed for one hour. After cooling, the solvent layer was separated and the aqueous portion extracted with two 30-ml. portions of ether. The combined solvent layers were washed with 10 ml. of water, two 10-ml. portions of saturated sodium bicarbonate solution, then with small portions of water to neutrality. After drying over anhydrous calcium sulfate for two hours and then over anhydrous magnesium sulfate, the solvent was distilled at 60° under reduced pressure. A yellow oil setting to a mass of yellow crystals was obtained. After trituration with 10 ml. of petroleum ether (b. p. 30–60°) and storage overnight, XVIII was obtained, 2.48 g. (69.4%), m. p. 89–92°. An analytical sample, m. p. 92–93°, was recrystallized from ligroin (b. p. 60–90°).

Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29; mol. wt., 260.4. Found: C, 78.37; H, 9.31; mol. wt. (Rast, using camphor), 258.

Diethyldi-(4-keto-1-cyclohexenyl)-methane (XVIII) was found unstable on long standing even at 0°, and reacts immediately with dilute basic solutions to produce a brilliant green water-soluble dye, which is decolorized on acidification.

Diethyldi-(4-hydroxycyclohexenyl)-methane (XIX).—A solution of 0.260 g. (0.001 mole) of XVIII in 3 ml. of glacial acetic acid containing 0.016 g. of ferrous chloride dihydrate and 0.050 g. of prereduced Adams platinum catalyst was stirred in a microhydrogenator under one atmosphere of hydrogen pressure. After two hours and ten minutes 0.002 mole of hydrogen had been absorbed, and hydrogen uptake had practically ceased. After removal of the catalyst by filtration, the solvent was removed under reduced pressure, leaving a yellow oil (0.320 g.) that crystallized spontaneously. A portion of this crude material (0.225 g.) was triturated with 3 ml. of petroleum ether (b. p. 30–60°) and the slightly greenish residue was extracted with 10 ml. of boiling cyclohexane. The residue was recrystallized from 3 ml. of benzene. The long hair-like needles that separated from the cyclohexane and benzene solutions proved to be identical, and thus the product is one of the isomers of XIX, m. p. 140–142°. The total yield was 0.080 g. (43%). An analytical sample, after decolorization and recrystallization from benzene, melted sharply at 144°.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.11; H, 10.60.

Diethyldi-(4-hydroxy-1-cyclohexenyl)-methane reduces potassium permanganate in acetone, and does not give the green coloration in base characteristic of XVIII.

Summary

Several series of 4,4′-dihydroxy and diketo derivatives of hydrogenated dialkyldiphenylmethane have been synthesized for pharmacological testing.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

The Alkaline Cleavage of Desyl Thioethers

BY SYLVIA TEICH[1] AND DAVID Y. CURTIN

S-Desylthioglycolic acid (I) has been found to undergo ready cleavage when treated with boiling dilute aqueous sodium hydroxide.[2] The products isolated were desoxybenzoin and oxalic acid (as the calcium salt). The reaction has been extended to a number of related compounds.[2,3]

$$C_6H_5COCH(C_6H_5)SCH_2COOH \longrightarrow C_6H_5COCH_2C_6H_5 + HOOCCOOH$$

The mechanism proposed[2,3a] has involved as the initial step a displacement by hydroxyl ion on sulfur to give the conjugate base of desoxybenzoin (II) and a sulfenic acid derivative (III). III has been presumed to be converted to oxalate ion through a sequence of reactions which have not been further elucidated.

$$\underset{\text{II}}{C_6H_5COCHC_6H_5^-} \qquad \underset{\text{III}}{HOSCH_2COO^-}$$

An alternative path for the reaction could involve the initial removal of a proton from the carbon α to the carboxyl group by hydroxyl ion, this step either accompanied or followed by the elimination of the conjugate base of desoxybenzoin (II) as shown.

$$\text{I} + OH^- \longrightarrow C_6H_5CO\overset{\ominus}{CH}(C_6H_5)SCHCO\overset{\ominus}{O} \longrightarrow \text{II} + \underset{\text{IV}}{S{=}CHCOO^-}$$

$$\text{IV} + OH^- \longrightarrow {}^-OOCOO^-$$

That such a proton-removal is not impossibly slow even though it leads to a di-negatively charged ion is indicated by a study of the base-catalyzed racemization of the optically active α-phenylmercaptophenylacetic acid anion (V). The racemization has been reported[4] to have a half-time of five hours when carried out at 100° with an aqueous solution only 0.100 molar in V and 0.042 molar with respect to hydroxyl ion.

$$\underset{\text{V}}{C_6H_5CH(SC_6H_5)COO^-}$$

Evidence has been found by other workers that the sulfur atom in a sulfide can help to stabilize a negative charge on an adjacent carbon.[5]

We felt that the examination of the behavior toward alkali of certain compounds related to desylthioglycolic acid might aid in the choice

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[2] Behagel and Schneider, *Ber.*, **68**, 1588 (1935).

[3] (a) Behagel and Ratz, *Ber.*, **72**, 1257 (1939); (b) Holmberg, *Arkiv. Kemi. Minerol. Geol.*, **12A**, No. 9 (1939); (c) Schönberg and Iskander, *J. Chem. Soc.*, 90 (1942); (d) Behagel and Müller, *Ber.*, **68**, 2164 (1935).

[4] Ramberg and Hedlund, *Arkiv. Kemi. Mineral. Geol.*, **12A**, No. 12 (1936).

[5] Gilman and Webb, THIS JOURNAL, **62**, 987 (1940); Rothstein, *J. Chem. Soc.*, 1550, 1553, 1558 (1940); Woodward and Eastman, THIS JOURNAL, **68**, 2229 (1946).

TABLE I

S-DESYL ALKYL SULFIDES

Compound	Halide used in synthesis	Recrystallization solvent	Yield
Desyl ethyl sulfide (VI)[a,b]	Desyl chloride[c]	95% ethanol	80%
S-Desylthioglycolanilide (VII)[d]	Desyl chloride	Benzene	65%
S-Desyl-α-mercaptoisobutyric acid (VIII)[f]	Desyl chloride	Ethanol–water	. .
4-Methoxydesylthioglycolic acid (XV)	4-Methoxydesyl bromide[g]	Benzene–ligroin	45%
4′-Methoxydesylthioglycolic acid (XVI)	4′-Methoxydesyl bromide[g]	Benzene–ligroin	45%
4-Dimethylaminodesylthioglycolic acid (XVII)	4-Dimethylaminodesyl chloride[h]	Methanol	80%

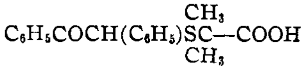
between the two schemes outlined above. We have prepared, therefore, desyl ethyl sulfide (VI), S-desylthioglycolanilide (VII) and S-desyl-α-mercaptoisobutyric acid (VIII). Their analyses, certain physical constants and derivatives are listed in Table I. In every case the sulfide was synthesized by the reaction of the required mercaptan with desyl chloride in aqueous ethanolic sodium carbonate and the structure confirmed by cleavage with Raney nickel to desoxybenzoin.

$C_6H_5COCH(C_6H_5)SCH_2CH_3$

VI

$C_6H_5COCH(C_6H_5)SCH_2CONHC_6H_5$

VII



$$C_6H_5COCH(C_6H_5)S\overset{CH_3}{\underset{CH_3}{C}}\text{—}COOH$$

VIII

The effect on the base-catalyzed cleavage of replacing the carboxyl group of desylthioglycolic acid by methyl was striking. Under conditions (treatment with 10% sodium hydroxide in boiling ethanol-water for thirty minutes) in which desylthioglycolic acid was converted to desoxybenzoin in a yield of 90%, 90% of the desyl ethyl sulfide employed could be recovered unchanged. When a longer time (five hours) was used, an alternative reaction occurred to give benzoic acid (93% yield) and benzyl ethyl sulfide (56% yield). Two per cent. of the starting material was recovered unchanged.

The behavior of desylthioglycolanilide toward dilute aqueous ethanolic sodium carbonate was examined. (Similar treatment was shown to convert desylthioglycolic acid to desoxybenzoin in a yield of 90%.) The interpretation of the result was complicated by the occurrence of a side reaction leading to a product which was not identified, as well as to thioglycolanilide disulfide (IX) in 12% yield. However, a 50% yield of desoxybenzoin and a 17% yield of benzoic acid were obtained. That the desylthioglycolanilide

$(\text{—}SCH_2CONHC_6H_5)_2$

IX

was not initially hydrolyzed to desylthioglycolic acid was indicated by a comparison run with thioglycolanilide which could be recovered to the extent of 93% after similar treatment.

When S-desyl-α-mercaptoisobutyric acid was subjected to the sodium carbonate treatment used above, no desoxybenzoin was obtained and 70% of the starting material was recovered.

These results seem most consistent with the mechanism which requires the presence of an acidic hydrogen on the carbon adjacent to the sulfur.

The reactions with dilute sodium hydroxide of a number of examples of molecules with structure X have been reported. The reaction generally

$ArCOCH(C_6H_5)SAr'$

X

observed is not analogous to that of desylthioglycolic, but instead leads to XI and XII.[2,3a,3c] Two examples have been examined, however, in which unreported amounts of the corresponding desoxybenzoin (XIII) were isolated.[3a] In these cases it is obvious that the proton-removal mechanism is impossible. The rates of cleavage seem to be of a different order of magnitude from the rate of cleavage of desylthioglycolic acid and the two reactions may well proceed by different mechanisms.

$ArCOOH$	$C_6H_5CH_2SAr'$	$ArCOCH_2C_6H_5$
XI	XII	XIII

S-Desyl-β-mercaptopropionic acid (XIV) has also been reported to undergo a slow reaction to give a 15% yield of desoxybenzoin.[3c] The interpretation of this result is complicated by the possibility that the first step may be an elimination reaction to give desylmercaptan and acrylic acid. Eliminations which are somewhat analogous have been reported[3a,6] and desylmercaptan has been found to undergo a complicated change which leads to desoxybenzoin, hydrogen sulfide and sulfur.[3c]

$C_6H_5COCH(C_6H_5)SCH_2CH_2COOH$

XIV

In connection with other work 4-methoxydesylthioglycolic acid (XV), 4′-methoxydesylthioglycolic acid (XVI) and 4-dimethylaminothioglycolic acid (XVII) were prepared and their structures confirmed by cleavage with Raney nickel to the corresponding unsymmetrical desoxybenzoin. In each case cleavage with dilute sodium hydroxide gave the same desoxybenzoin as that obtained in the reaction with Raney nickel. This fact precludes rearrangement during the course of the former reaction.

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(6) Nicolet, THIS JOURNAL, 53, 3066 (1931).

TABLE I (*Continued*)

M. p.	Formula	Carbon		Hydrogen		Sulfur		Neutral equivalent	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
78.5–79°	$C_{16}H_{16}OS$	74.9	74.9	6.3	6.1	12.5	12.6	...	...
123–124° (112–113°)[e]	$C_{22}H_{19}NO_2S$	73.1	73.4	5.3	5.5	8.9	8.9	...	...
129–130°	$C_{16}H_{18}O_3S$	68.8	68.4	5.8	5.7	10.2	9.7	...	...
115–116° (93.5–94.5°)[h]	$C_{17}H_{16}O_4S$	64.5	64.3	5.1	5.3	10.1	10.1	316	317
108–109°	$C_{17}H_{16}O_4S$	64.5	64.4	5.1	5.1	10.1	10.0	316	316
190–191°	$C_{18}H_{19}NO_3S$	65.6	65.7	5.8	5.7	9.7	9.3	...	...

[a] *Oxime*, recrystallized from ligroin, m. p. 117.5–118°. *Anal.* Calcd. for $C_{16}H_{17}NOS$: C, 70.8; H, 6.3. Found: C, 71.0; H, 6.2. [b] *Sulfone*, prepared by oxidation with 2% potassium permanganate, recrystallized from ethanol, m. p. 166–166.5°. *Anal.* Calcd. for $C_{16}H_{16}O_3S$: C, 66.6; H, 5.6. Found: C, 67.0; H, 5.6. [c] See reference 11. [d] Thioglycolanilide was prepared from aniline and thioglycolic acid in a yield of 80% by the method of Hellstrom and Lauritzson, *Ber.*, **69**, 1999 (1936). [e] This compound resolidified on further heating and remelted at 123–124°. If the bath was heated slowly only the m. p. 123–124° was observed. The lower melting point was apparently not due to hydrate formation since material having the behavior described above gave the correct analysis with no further drying. [f] α-Mercaptoisobutyric acid was prepared by the method of von Braun, *Ber.*, **35**, 3385 (1902). It was not isolated but treated directly with desyl chloride in the solution in which it was prepared. [g] Jenkins, THIS JOURNAL, **56**, 682 (1934). [h] A second melting point was also observed at 93.5–94.5°; the melting point behavior was similar to that discussed in note (e). [i] See experimental.

Experimental[7]

The S-desyl alkyl sulfides (Table I) were prepared by the reaction of the proper α-haloketone with the mercaptan in sodium bicarbonate solution in an atmosphere of nitrogen following the procedure of Behagel and Ratz.[3a]

Raney Nickel Cleavage.—The sulfides in Table I were cleaved to the corresponding desoxybenzoins by treatment with Raney nickel in 70% aqueous ethanol[8] in yields of 35–55% or with Raney nickel which has been previously deactivated by refluxing in acetone by the procedure of Spero, McIntosh and Levin[9] in yields of 55–90%.

Alkaline Cleavage of Desyl Ethyl Sulfide (VI), (a) for Thirty Minutes.—When 0.7 g. of VI in 15 cc. of 95% ethanol and 15 cc. of 20% aqueous sodium hydroxide were heated under gentle reflux for thirty minutes 0.6 g. (90%) of the starting material could be recovered. Desylthioglycolic acid under similar conditions gave a 90% yield of desoxybenzoin, m. p. 55–56°.

(b) **For Five Hours.**—A solution of 3.0 g. (0.012 mole) of VI in 40 cc. of 95% ethanol and 40 cc. of 20% sodium hydroxide were heated under gentle reflux for five hours in an atmosphere of nitrogen. The acidic fraction of the product gave, after sublimation, 1.3 g. (93%) of benzoic acid melting at 121°. The neutral fraction was distilled to give recovered VI, m. p. 78° (2%) and a liquid fraction (1.1 g., 56% yield), b. p. 216° (reported for benzyl ethyl sulfide,[10] 214–216°). It was further characterized by oxidation to the corresponding sulfone, m. p. 84° (reported,[11] 84°).

Alkaline Cleavage of S-Desylthioglycolanilide (VII).—The sulfide (VII) (4.0 g., 0.011 mole) in 110 cc. of ethanol was heated under reflux with 180 cc. of 10% sodium carbonate solution for two hours in an atmosphere of nitrogen. The reaction mixture was diluted with 100 cc. of water and the desoxybenzoin which precipitated was collected and purified by sublimation (1.1 g., 50% yield, m. p. 55°, mixed with authentic sample, m. p. 55°). From the acid fraction of the residue, benzoic acid was obtained in the usual way and purified by sublimation. The purified acid (0.23 g., 17% yield) was characterized by m. p. (121–122°) and mixed m. p. with an authentic sample. Fractional precipitation from ether of the residue gave 0.2 g. (12%) of thioglycolanilide disulfide (IX) which after one recrystallization from ethanol melted at 161–162° and gave no depression when mixed with an authentic sample of the disulfide prepared from the reaction of thioglycolanilide and iodine.[12]

For comparison, thioglycolanilide was treated with sodium carbonate as described above. The starting material (93%) was recovered unchanged.

When desylthioglycolic acid was subjected to the same treatment a yield of 90% of desoxybenzoin was obtained.

Attempted Cleavage of S-Desyl-α-mercaptoisobutyric Acid (VIII).—When subjected to the sodium carbonate treatment (VIII) (0.15 g.) was recovered unchanged (0.10 g., 70% recovery).

4-Dimethylaminodesyl chloride was prepared in a yield of 50% by the method previously described for desyl chloride.[13] The compound, after recrystallization from methanol, melted at 123–123.5° with decomposition.

Anal. Calcd. for $C_{16}H_{16}ClNO$: C, 70.2; H, 5.9; N, 5.1. Found: C, 70.1; H, 6.1; N, 5.2.

Alkaline Cleavage of Desylthioglycolic Acids.—The methoxy- and dimethylaminodesylthioglycolic acids (XV–XVII) were cleaved with excess boiling 10% sodium hydroxide by the procedure of Behagel and Schneider.[2] In each case the desoxybenzoin was identical with that obtained in the Raney nickel cleavage and the yield was 90% or greater.

Summary

A new mechanism for the base-catalyzed cleavage of desylthioglycolic acids has been proposed. In order to test the effect on the reaction of variation in the structure of the thioglycolic acid portion of the molecule, desyl ethyl sulfide, S-desylthioglycolanilide and S-desyl-α-mercaptoisobutyric acid have been prepared and their behavior toward alkali has been examined.

The facts now available seem most consistent with the new mechanisms.

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(7) All melting points are corrected. Analyses were carried out by Miss Lois May and the Clark Microanalytical Laboratories.

(8) Bougault, Cattelain and Chabrier, *Bull. soc. chim.*, **7**, 781 (1940); Mozingo, Wolf, Harris and Folkers, THIS JOURNAL, **65**, 1013 (1943).

(9) Spero, McIntosh and Levin, *ibid.*, **70**, 1907 (1948).

(10) Märcker, *Ann.*, **140**, 86 (1866).

(11) Böhme and Fischer, *Ber.*, **75**, 1310 (1942).

(12) Beckurts and Frerichs, *J. prakt. Chem.*, [2] **66**, 172 (1902).

(13) "Organic Syntheses," Coll. Vol. II, p. 159.