Anodic Decarboxylation of Glycidic Acids

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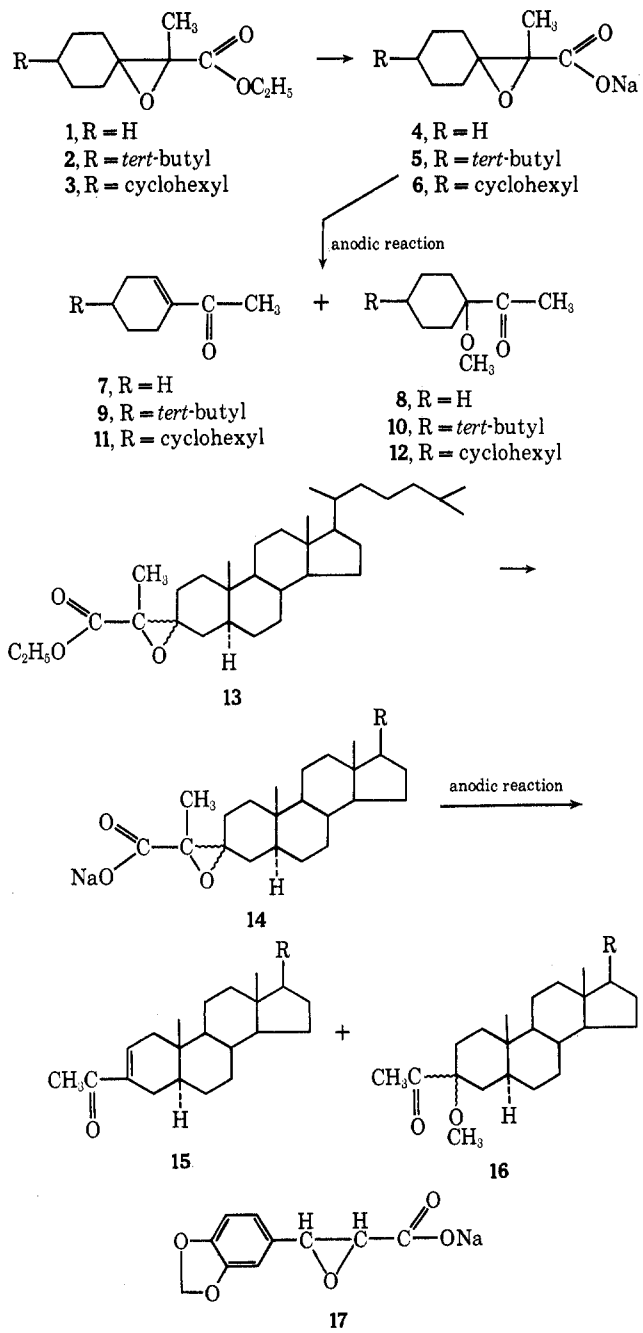
Electrolytic oxidation of sodium glycidates **4**, **5**, and **6** in methanol at a platinum electrode gave α,β-unsaturated ketones **7**, **9**, and **11** and α-methoxy ketones **8**, **10**, and **12**, respectively. Steroidal glycidate **14**, derived from 5α-cholestan-3-one, gave 3-acetyl-5α-cholest-2-ene (**15**) and 3ξ-acetyl-3ξ-methoxy-5α-cholestane (**16**) in 32 and 11% yields, respectively. Anodic oxidation of the aromatic glycidate **17** gave a low yield of neutral material consisting of numerous compounds. The mechanism of the decarboxylation and epoxide ring opening is discussed.

During the past decade several laboratories[1-9] have reported on the anodic decarboxylation of various carboxylic acids in which the products obtained were derived from carbonium ion intermediates. These intermediates are the result of further oxidation of free radicals formed in the normal Kolbe electrochemical process.[10,11] We became interested in studying what effect this process would have on the α,β-epoxy group present in glycidic acids, a class of carboxylates which has not been studied by the electrochemical method. However, the photochemical decarboxylation[12] of sodium glycidates has recently been reported.

Methods and Results

The α-methyl glycidic esters **1–3** were prepared by the Darzens synthesis[13] in 60–70% yields from the parent ketone and ethyl α-bromopropionate. The esters were converted directly into analytically pure sodium salts **4–6** using a slight excess of base according to the method of Claisen.[14a] No attempt was made to isolate the unstable free glycidic acids.

The anodic reaction of sodium glycidates **4**, **5**, and **6** in methanol gave neutral mixtures in 46–65%[14b] yields, from which α,β-unsaturated ketones **7**, **9**, and **11** and α-methoxy ketones **8**, **10**, and **12**, respectively, were obtained by fractional distillation or extensive preparative tlc. To illustrate the general reaction, sodium glycidate **6** was electrolyzed using smooth platinum electrodes for 6 hr at 155–160 mA at 11–12 V which gave a neutral mixture in 45% yield. After repeated continuous development preparative tlc, α-methoxy ketone **12** was obtained in 7% yield. The nmr spectrum of **12** (see Experimental Section) gave conclusive proof that both the acetyl and methoxy groups were attached to the same carbon atom and hence no rearrangement occurred during the anodic process. The major product, α,β-unsaturated ketone **11**, was obtained as an oil in 24% yield.



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Electrolysis of glycidates **4** and **5** gave reaction products **7–10**, analogous to ketones **11** and **12**. Compounds **8** and **9** were not isolated in a pure state but gave definitive spectral data similar to their respective analogs.

In a kinetic experiment, the oxidation of **6** was easily followed by the appearance of uv absorption of **11**, which reached a constant OD at 4 hr. This time interval was used as a basis for the other anodic reactions.

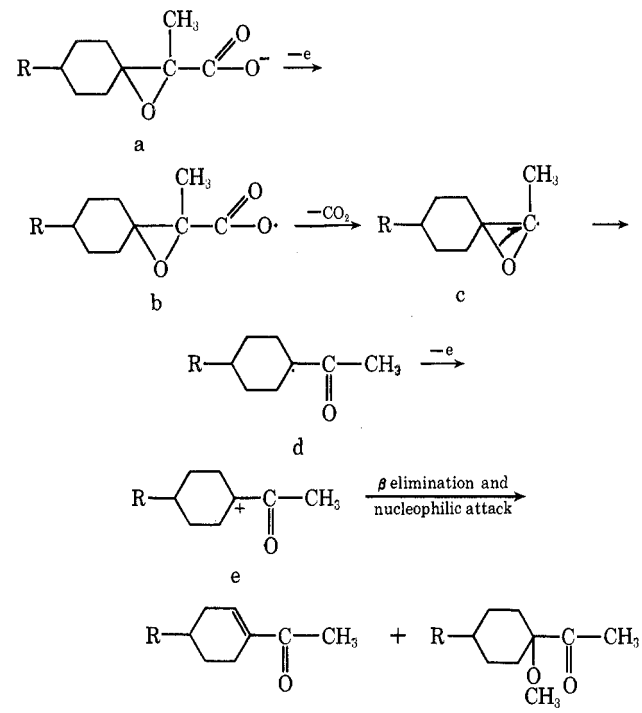
This reaction was applied successfully to steroidal compounds by preparation of glycidate **13** derived from 5α-cholestan-3-one. An excellent yield of **13** was obtained by carrying out the Darzens condensation for 2 days at room temperature, followed by removal of minor impurities by column chromatography over alumina. Anodic reaction of sodium glycidate **14** in the usual manner gave a neutral mixture in 90% yield. Preparative tlc gave 3-acetyl-5α-cholest-2-ene (**15**).[15] The minor component, 3ξ-acetyl-3ξ-methoxy-5α-cholestane (**16**), was obtained as colorless flakes.

The anodic reaction of the aromatic glycidate, *i.e.*, piperonal glycidate **17**, was unsuccessful. During the initial phases of the electrolysis, the solution darkened and a neutral mixture was obtained in a 10% yield which consisted of numerous products as indicated by tlc. The reaction was not further investigated.

Discussion

The anodic decarboxylation of glycidic acids to α,β-unsaturated and α-methoxy ketones contrasts with the classical method of decarboxylation in the presence of acid[13] and the recent photochemical process,[12] both of which give saturated ketones or aldehydes as principal products. The mechanism of the acid-catalyzed decarboxylation has received considerable attention.[16–18] Recently some unusual rearrangements of these acids under acidic conditions have been reported.[19]

In our study, anodic oxidation of glycidic acids, represented by a, produces the epoxy radical c *via* the normal Kolbe electrochemical process. The oxirane then opens to give the keto radical d. Bond breakage at this stage is analogous to the formation of similar epoxy radicals *via* peroxide-catalyzed reactions[20] or by photochemical pathways.[21,22] Although further anodic oxidation of the α carbon radical *c* cannot, *a priori*, be disregarded, one would expect attack by methanol on the resulting carbonium ion. However, the formation of α-methoxy α,β-oxiranes was not observed. Further oxidation of the radical d at the electrode to the tertiary carbonium ion e is in accordance with previous studies.[1–9] This radical–carbonium ion transformation is extremely fast (*ca.* 10^{-15} sec)[8b] and is especially favored in alkaline solution.[23] Finally, β elimination (predominant) and secondary nucleophilic attack of the carbonium ion by solvent to produce α,β-unsaturated ketones and α-methoxy ketones, respectively, would be expected to occur in an extremely rapid fashion to overcome the electrostatic repulsion of adjacent positive charges[24,25a] present in the keto carbonium ion e (partial positive carbonyl carbon). The limited kinetic data (Experimental Section) for the disappearance of carboxylate **6** (as judged by appearance of α,β-unsaturated ketone **11**) suggests a first-order reaction (plot of ln OD *vs.* time) for this anodic oxidation. However, additional data are required to delineate this proposal.



Group migrations which accompany the photochemical[22] or acid-catalyzed[24] opening of oxiranes was obviated in this study when both β positions were substituted by the cyclohexyl ring system or the steroidal ring A.

Stereospecific β elimination (to the Δ^2 position as opposed to the Δ^3 position) was observed in the electrolysis of the steroidal glycidate **14**, which exclusively gave 3-acetyl-5α-cholest-2-ene (**15**).

Failure to obtain products from the electrolysis of piperonal glycidate **17** analogous to those from the saturated glycidates may be due to the fact that aromatic compounds oxidize at anode potentials less than those required for carboxylate oxidation.[25b] Apparently polymers are predominantly formed from the aromatic ring oxidation of **17**.

Experimental Section

Apparatus.—Melting points were taken on a Kofler block and are corrected. The infrared spectra were measured on a Perkin-Elmer spectrometer (Model 21) in carbon disulfide. The uv spectra were obtained on a Cary 15 spectrophotometer in ethanol. The nmr spectra were obtained on a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as internal standard. Electrolysis apparatus I consisted of two smooth plati-

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num electrodes (sheet), 9 mm wide and 40 mm long. The electrodes, placed parallel to each other 3-4 mm apart, were immersed 20–25 mm into the magnetically stirred solutions. Glass beakers were used as electrolysis vessels. Apparatus II consisted of 25 × 60 mm platinum electrodes which were immersed 50 mm into the solutions.

Ethyl α-methyl-α,β-epoxycyclohexylideneacetate (1) was prepared in a manner similar to that described for the corresponding methyl ester,[13] namely from 50 g (0.5 mol) of cyclohexanone, 145 g (0.8 mol) of ethyl 2-bromopropionate, and 47.2 g of sodium methoxide in 200 ml of ether. There was obtained 69.1 g (70%) of the desired ester 1, bp 92–95° (3 mm), as a colorless oil, lit.[26] bp 154–156° (40 mm).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.40; H, 9.03.

Ethyl α-methyl-α,β-epoxy-4-*tert*-butylcyclohexylideneacetate (2) was prepared from 25.0 g (0.16 mol) of 4-*tert*-butylcyclohexanone, 43.5 g (0.24 mol) of ethyl α-bromopropionate, and 20.4 g (0.3 mol) of sodium ethoxide in 150 ml of anhydrous ether. Work-up in the usual manner, followed by two fractional distillations, gave the desired glycidic ester, bp 100–103° (0.38–0.43 mm).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.86; H, 10.18.

Ethyl α-methyl-α,β-epoxy-4-cyclohexylcyclohexylideneacetate (3) was prepared in the usual manner from 46.1 g (0.25 mol) of 4-cyclohexylcyclohexanone[27] and 72.5 g (0.40 mol) of ethyl 2-bromopropionate. Ester 3 was obtained as a colorless liquid (42.2 g, 60%), bp 130–132° (0.12 mm).

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 73.02; H, 9.96.

Sodium α-Methyl-α,β-epoxycyclohexylideneacetate (4).—To 10.4 g (0.052 mol) of ester 1 was added 3.3 g of sodium hydroxide in 65 ml of methanol. The mixture was refluxed for 2 hr under nitrogen. Approximately two-thirds of the solvent was evaporated, ether was added, and the white solid which precipitated was collected by filtration and washed with ether. The yield was 5.1 g (51%). The analytical sample was recrystallized two times from methanol–ether.

Anal. Calcd for $C_9H_{13}O_3Na$: C, 56.24; H, 6.82. Found: C, 55.98; H, 6.97.

Sodium α-methyl-α,β-epoxy-4-*tert*-butylcyclohexylideneacetate (5) was prepared in analogy to 6.

Anal. Calcd for $C_{13}H_{21}O_3Na$: C, 62.86; H, 8.54. Found: C, 63.00; H, 8.73.

Sodium α-methyl-α,β-epoxy-4-cyclohexylcyclohexylideneacetate (6) was prepared in a manner similar to that described by Claisen.[14a] To 14.0 g (0.05 mol) of glycidic ester 3 was added 4.0 g (0.075 mol) of sodium methoxide in 43 ml of absolute methanol. After slight warming of the mixture to bring the ester into solution, 2.7 ml (0.15 mol) of water was added, whereupon the sodium salt immediately precipitated. An additional 40 ml of methanol was added and the thick mixture was stirred for 15 min. The colorless solid (9.3 g, 68%) was removed by filtration and washed with methanol and then ether. An analytical sample was recrystallized two times from methanol.

Anal. Calcd for $C_{15}H_{23}O_3Na$: C, 65.67; H, 8.45. Found: C, 65.77; H, 8.33.

Anodic Reaction of Sodium α-Methyl-α,β-epoxycyclohexylideneacetate (4).—A solution of 7.1 g (0.037 mol) of sodium salt 4 in 350 ml of methanol was electrolyzed with apparatus II at 1.1 A and 12–14 V for 6 hr. Methanol was added periodically to maintain the original volume. The temperature of the solution was maintained at 24.5–27° by an evaporating acetone bath. Most of the solvent was then distilled from the reaction mixture at atmospheric pressure using a 250-mm Vigreux column. To the residue was added 75 ml of ether. The ethereal extract was washed with 10 ml of sodium carbonate (5%), 10 ml of water, and 10 ml of saline solution and then dried over sodium sulfate. The ether was distilled off at atmospheric pressure. The yellow, oily product was distilled under reduced pressure using a micro distillation apparatus. The five fractions collected were as follows: (1) 0.83 g at 23–26° (17 mm); (2) 0.4 g at 81–86° (16 mm); (3) 0.44 g at 86–88° (16 mm); (4) 0.42 g at 90–96° (16 mm); (5) 0.51 g at 72–103.5° (5 mm). Total distillate was 2.6 g. Fraction 4 contained a high percentage of α,β-unsaturated ketone 7 on the basis of ir, nmr, and uv. Fractions 1–3 also contained ketone 7 but were contaminated by unidentified anodic oxidation by-products.

Fraction 4 was converted to the semicarbazone with sodium acetate as buffer to give 338 mg of colorless solid, mp 182–200°. After six recrystallizations from dilute ethanol the semicarbazone of 7 had mp 217–219° dec. The compound was identical (mixture melting point, ir, uv) with the semicarbazone of 1-acetyl-1-cyclohexene,[28] prepared by the method of Ruzicka[29] from cyclohexene and acetyl chloride.

The nmr of fraction 5 indicated that it contained a high percentage of α-methoxy ketone 8 with prominent bands at 2.18 (CH_3C–) and 3.18 ppm (–OCH_3). The compound was not isolated in pure form.

Anodic Reaction of Sodium α-Methyl-α,β-epoxy-4-*tert*-butylcyclohexylideneacetate (5).—A solution of 699 mg (2.8 mmol) of sodium glycidate 5 in 50 ml of methanol was electrolyzed for 6 hr at 150 mA (8–10 V) with apparatus I. Work-up of the reaction mixture gave 457 mg of neutral product. Preparative tlc of the reaction mixture gave 90 mg (15%) of non-uv absorbing material, which on additional tlc purification and recrystallization from hexane gave 1-acetyl-1-methoxy-4-*tert*-butylcyclohexane (10) as colorless needles, mp 58–58.5°.

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.74; H, 11.30.

The α,β-unsaturated ketone 9 was present in the reaction mixture, as indicated by uv (232 nm), in 22% yield of the neutral mixture. The compound was not isolated in a pure state.

Anodic Reaction of Sodium α-Methyl-α,β-epoxy-4-cyclohexylcyclohexylideneacetate (6).—A solution of 685 mg (2.5 mmol) of sodium salt 6 in 50 ml of methanol was electrolyzed (apparatus I) for 6 hr at 155–160 mA (11–12 V). The temperature of the solution was maintained at 15–18°. Most of the methanol was removed under reduced pressure. To the resulting solid was added 40 ml of ether and the mixture was extracted with sodium bicarbonate solution (5%), water, and then with saline solution. The ethereal solution was dried over sodium sulfate and evaporated to yield 317 mg of a neutral fraction, which was subjected to preparative tlc (2 plates, silica gel G, 1 mm thick) and developed continuously with hexane–ether (92:8) for 3 hr. Inspection of the plates under shortwave uv light indicated distinct bands at the upper portion of the plates, which were eluted with acetone to give 147 mg of oil. Polar material which stayed at the origin accounted for 33% of the neutral fraction. The eluted material (147 mg) was further purified by continuous preparative tlc in the usual manner to give two pure compounds. The least polar compound, mp 34–37°, was methoxy ketone 12 (7% yield of neutral mixture), as indicated by spectral and analytical data: ir 1715 (C=O) and 1082 cm^{-1} (–OCH_3); nmr 2.16 (s, CH_3C=O) and 3.16 ppm (s, OCH_3).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.63; H, 10.80.

The oxime of 12, prepared by the pyridine method, was obtained as colorless flakes, mp 112–112.5°.

Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74. Found: C, 71.28; H, 10.60.

The second pure compound, obtained as an oil in 24% yield, was α,β-unsaturated ketone 11: ir 1675 (O=CC=C) and 1645 cm^{-1} (>C=CH); nmr 2.27 (s, CH_3C=O) and 6.90 ppm (m, >C=CH); λ_{max} 232 nm (ε 12,500).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.76; H, 10.49.

The semicarbazone of 11 was obtained as colorless needles from dilute ethanol, mp 213.5–215° dec, λ_{max} 260 nm (ε 26,300).

Anal. Calcd for $C_{15}H_{25}N_3O$: C, 68.40; H, 9.57. Found: C, 68.58; H, 9.63.

Rate of Anodic Decarboxylation of 6.—A solution of 981 mg of sodium salt 6 in 50 ml of methanol was electrolyzed in the above manner and the rate of the reaction was followed by the appearance of the 232-nm uv band of 11. Aliquots (0.1 ml) of the reaction were removed every 30 min and diluted to 10 ml with ethanol and the uv recorded (minimum, OD): 0, 0.0; 30, 0.69; 90, 1.14; 120, 1.42; 150, 1.59; 180, 1.84; 210, 1.86; 240, 1.88.

Glycidic Ester of 5α-Cholestan-3-one (13).—To a stirred solution of 5.0 g (0.013 mol) of 5α-cholestan-3-one and 4.7 g (0.026 mol) of ethyl α-bromopropionate in 50 ml of anhydrous ether

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was added 1.8 g (0.026 mol) of sodium ethoxide in small portions over a period of 30 min. The resulting mixture was stirred for 2 days at room temperature, after which 14 ml of dilute hydrochloric acid was added. The ether layer was separated and washed with water, 5% sodium bicarbonate, water, and saline water and then dried over sodium sulfate. The solvent and excess ethyl α-bromopropionate were evaporated under reduced pressure. Tlc of the reaction mixture indicated the presence of the desired steroidal glycidic ester and three minor impurities. The mixture was chromatographed on 150 g of alumina (Woelm, neutral grade 2). Elution with petroleum ether (bp 30–60°) and benzene gave 5.05 g of **13** as a colorless semisolid which was homogeneous by tlc. Repeated efforts to obtain a satisfactory elemental analysis of this compound failed, apparently due to residual amounts of solvent present in the semisolid. However, mass spectral analysis gave a correct molecular ion peak of M^+ 486 for $C_{32}H_{54}O_3$, ir 1728 and 1755 cm^{-1} (carbonyl stretching of glycidic ester),[30] nmr 4.22 ppm (q, CH_2CH_3).

Sodium Glycidate of 5α-Cholestan-3-one (14).—To a solution of 957 mg (0.002 mol) of glycidic ester **13** in 5 ml of absolute ethanol was added 200 mg (0.003 mol) of sodium ethoxide and then 0.09 ml (0.005 mol) of water. The mixture was allowed to stand at room temperature for 30 min, during which time the sodium salt precipitated. An additional 5 ml of ethanol was then added and the mixture was refluxed for 1 hr. After cooling, 843 mg (88%) of pale yellow solid was collected by filtration. An analytical sample of **14** was obtained as a colorless solid after two recrystallizations from methanol.

Anal. Calcd for $C_{30}H_{49}O_3Na$: C, 74.95; H, 10.27. Found: C, 74.91; H, 10.08.

Anodic Reaction of the Sodium Glycidate of 5α-Cholestan-3-one (14).—A solution of 744 mg (1.5 mmol) of sodium glycidate **14** in 50 ml of methanol was electrolyzed (apparatus I) for 6 hr at 150 mA (14–17 V) with the solution temperature maintained at 14.5–16°. Work-up in the usual manner gave 668 mg of a neutral fraction, tlc of which showed the presence of two compounds, one of which absorbed short-wave uv light. The neutral products were chromatographed on two preparative tlc plates (silica gel, 1 mm thick) and developed continuously for 3 hr in hexane–ether (92:8). Elution of the uv absorbing zone from each plate gave a total of 207 mg (32%) of product. Approximately one-half of this was crystallized from methanol–acetone to give 73 mg of 3-acetyl-5α-cholest-2-ene (**15**) as clusters of colorless needles, mp 90–92°. The analytical sample had mp 92–92.5°, $[\alpha]^{20}D$ +91.2° ($CHCl_3$) [lit.[15] mp 90–91°, $[\alpha]^{15}D$ +93.8° ($CHCl_3$)]; ir 1670 ($CH_3C{=}O$) and 1642 cm^{-1} (>C=CH–); nmr 2.25 (s, $CH_3C{=}O$) and 6.80 ppm (m, >C=CH–).

Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.59; H, 11.96.

The material lacking uv absorption eluted from the plates (215 mg) was impure and was rechromatographed on a 1-mm preparative tlc plate, from which 106 mg of pure material was obtained. The solid was recrystallized from acetone to give 56 mg (11%) of 3ξ-acetyl-3ξ-methoxy-5α-cholestane (**16**) as colorless flakes: mp 100–101° (a second recrystallization from the same solvent raised this to 101–101.5°); $[\alpha]^{20}D$ +21.9° ($CHCl_3$); *ir 1712 cm^{-1}* ($CH_3C{=}O$); *nmr 2.16* (s, $CH_3C{=}O$) and 3.12 ppm (s, $-OCH_3$).

Anal. Calcd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 81.07; H, 11.94.

Attempted Anodic Reaction of the Sodium Glycidate of Piperonal (17).—A solution of 714 mg of sodium glycidate **17**, prepared in the usual two-step synthesis, in 50 ml of methanol was electrolyzed with apparatus I for 6 hr in the usual manner. The solution turned red immediately at the outset of electrolysis and was deep purple after 10 min. Work-up of the reaction gave only 80 mg of a neutral fraction, which consisted of numerous products on the basis of tlc. The reaction was not further investigated.

Registry No.—**1**, 31045-09-7; **2**, 31045-10-0; **3**, 31107-22-9; **4**, 31045-11-1; **5**, 31045-12-2; **6**, 31045-13-3; **7**, 932-66-1; **7** semicarbazone, 7499-13-0; **8**, 15174-91-1; **10**, 31045-17-7; **11**, 31107-23-0; **11** semicarbazone, 31044-94-7; **12**, 31044-95-8; **12** oxime, 31044-91-4; **13**, 31107-17-2; **14**, 31044-92-5; **15**, 2310-32-9; **16**, 31045-21-3.

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Notes

Reductions of Thio Acids with Lithium Aluminum Hydride and Sodium Borohydride

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In a recent study on the reduction of certain organosulfur compounds,[1] it was reported that reduction of thiobenzoic acid with lithium aluminum hydride produced primarily benzyl mercaptan (90%) and a very small amount of benzyl alcohol. In contrast to this report, during a brief study of the reduction of thiobenzoic acid and thioheptanoic acid with lithium aluminum hydride, we observed that significant amounts of both alcohol and thiol were obtained. Therefore, we decided to make a systematic study of the reduction of thio acids, in order to determine how the relative amounts of sulfur and oxygen displacement (*i.e.*, alcohol and thiol formation, respectively) would be affected by the following factors: (1) nature of the group attached to the thiocarboxylate function, (2) type of metal hydride used, (3) method of reagent addition, and (4) presence of Lewis acid catalysts. The effect of the latter was of particular interest since it has been shown that lithium aluminum hydride reduction of thiol esters in the presence of boron fluoride[2] or aluminum chloride[3] occurs with oxygen displacement (thioether formation) as opposed to the sulfur displacement (alcohol and thiol formation) which occurs with lithium aluminum hydride alone. Similarly, hydrogenolysis of hemithioacetals and hemithioketals with lithium aluminum hydride–aluminum chloride results exclusively in cleavage of the carbon–oxygen bond.[4]

Results and Discussion

Table I shows the composition of the alcohol–thiol mixtures obtained by reduction of a series of thio acids

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