A Study of the Lithium in Ammonia Reduction of 3-Ethoxycyclohexenone

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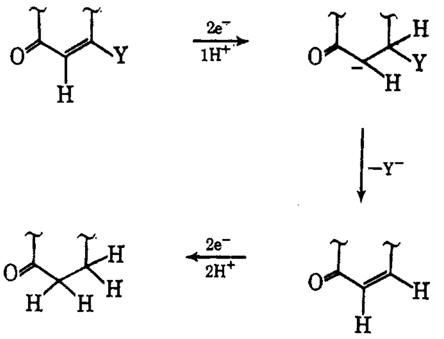
The composition of the product mixture from the reduction of 3-ethoxycyclohexenone (**1**) by lithium in ammonia under a variety of conditions has been determined. By appropriate choice of conditions, the predominant product can be made any of four compounds: cyclohexanone (**2**), cyclohexanol (**3**), 3-ethoxycyclohexanone (**4**), or *cis*-3-ethoxycyclohexanol (**5**). At −78°, products formed *via* elimination of ethoxide from enolate anion **9**, *viz.*, **2** and **3**, are not observed. At −33° this elimination has $t_{1/2}$ of *ca.* 7 min. Use at either temperature of absolute ethanol as a quenching reagent rather than ammonium chloride favors formation of the hydroxylic products **3** and **5**.

It has been clearly demonstrated that the reduction of α,β-unsaturated ketones with alkali metals in liquid ammonia proceeds *via* species with carbanionic character at the β position[2-4] to afford α-enolate anions which can be protonated, alkylated, or carbonated.[2] If the β position bears a potential leaving group, the α-enolate anion has a possible alternative to reaction with an electrophile, namely β elimination to form a new α,β-unsaturated ketone, which in turn should be susceptible to further reduction, as shown in Scheme I.

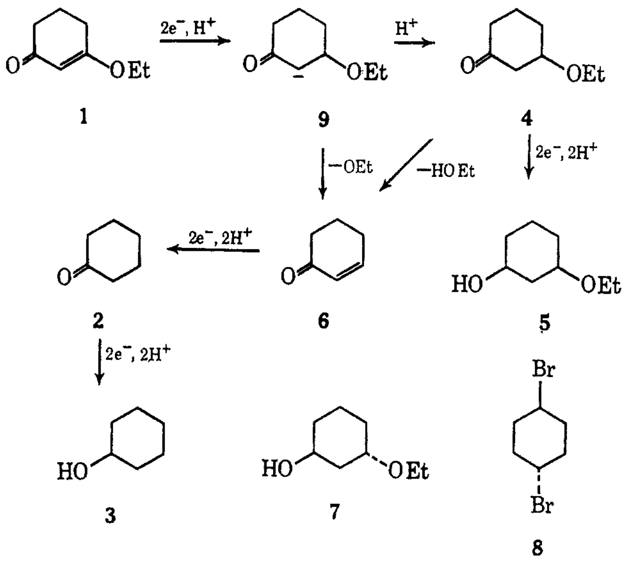
SCHEME I



Such elimination during the course of lithium–ammonia reduction of α,β-unsaturated ketones, while probably precedented,[5] had not been studied. In order to elucidate some of the factors relevant to its occurrence and to extend the versatility of the lithium–ammonia procedure, we have investigated the reduction of 3-ethoxycyclohexenone (**1**).

Identification of Products.—The compositions of crude products from lithium–ammonia reductions of **1** under the various conditions described below were determined by vpc as described in the Experimental Section. In addition to solvents and unreduced **1**, the five compounds **2**–**6** shown in Scheme II were detected, isolated by preparative vpc, and characterized.

SCHEME II



Cyclohexanone (**2**) and cyclohexanol (**3**) were identified by comparison of retention time and spectral properties with authentic samples. The previously unreported 3-ethoxycyclohexanone (**4**) was characterized by analysis, spectral properties, and conversion to the 2,4-dinitrophenylhydrazone of cyclohexenone (**6**).

The fifth product was identified as 3-ethoxycyclohexanol by analysis, spectral properties, and oxidation to **4**. Vpc on several columns and under different conditions showed only one peak, suggesting the presence of only one stereoisomer.[6] Although it was considered probable that the substance was the more stable *cis* isomer (**5**) rather than the *trans* isomer (**7**),[7] considerable effort was expended proving that this was indeed so. Attempted cleavage of the ether linkage with boron tribromide[8] to obtain the known *cis*-cyclohexane-1,3-diol[9] led to a 30% yield of *trans*-1,4-dibromo-

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[2] G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965).

[3] G. Stork and S. D. Darling, *ibid.*, **86**, 1761 (1964).

[4] M. Fetizon and J. Gore (*Tetrahedron Letters*, 471 (1966)) report β deuteration using $CH_3CH_2CH_2ND_2$ as solvent.

[5] (a) T. A. Spencer, K. K. Schmiegel, and W. W. Schmiegel (*J. Org. Chem.*, **30**, 1626 (1965)) report a reduction most easily rationalized as proceeding *via* δ elimination of acetate ion from the γ-enolate anion of an α,β-unsaturated ketone; (b) R. E. Ireland and J. A. Marshall (*J. Org. Chem.*, **27**, 1615 (1962)) report a sodium–ammonia reduction (of a 2-*n*-butylthiomethylenedecalone to a 2-methyldecalol) which can be rationalized as proceeding *via* β elimination of ⁻S-*n*-Bu.

[6] E. L. Eliel and T. J. Brett (*J. Org. Chem.*, **28**, 1923 (1963)) report that *cis*- and *trans*-3-methoxycyclohexanol have easily distinguishable retention times on a silicone QF-1 column.

[7] Dissolving metal reduction of unhindered, unstrained ketones usually affords the more stable alcohol (see H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 54, for a discussion of this topic).

[8] (a) E. Wenkert, A. Fuchs, and J. D. McChesney, *J. Org. Chem.*, **30**, 2931 (1965); (b) J. F. W. McOmie and M. L. Watts, *Chem. Ind.* (London), 1658 (1963); (c) T. G. Bonner, E. J. Bourne, and S. McNally, *J. Chem. Soc.*, 2929 (1960).

[9] (a) H. C. Brown and G. Zweifel, *J. Org. Chem.*, **27**, 4708 (1962); (b) M. F. Clarke and L. N. Owen, *J. Chem. Soc.*, 2103 (1950); (c) W. Rigby, *ibid.*, 1586 (1949).

cyclohexane (**8**).[10] Proof of stereochemistry was obtained, however, by preparation of both pure *cis*-cyclohexane-1,3-diol and pure *trans*-cyclohexane-1,3-diol[9b] and conversion of each of these with sodium and ethyl iodide to its monoethyl derivative. Authentic **5** thus prepared was identical in all respects with the material from the lithium–ammonia reductions, whereas the **7** thus prepared had distinctly different infrared and nmr spectra. Cyclohexenone (**6**), identified by comparison with an authentic sample, was observed infrequently and is assumed to have arisen by elimination of ethanol from **4** during work-up or vpc.[11]

The total actual yield of **2**–**6** rarely approached 100%, usually being about 60%. The remainder of the product has never been accounted for, despite extensive efforts to isolate or identify its constituents (see the Experimental Section).

Effects of Reaction Conditions on Product Composition.—When an ethereal solution of **1** was treated with excess lithium in ammonia[12] at its boiling point (−33°), the product composition depended on the time allowed for reaction and on the proton source ("quenching reagent") used to decompose the dark blue reducing medium. The results are shown in Table I for ammonium chloride as quenching reagent and in Table II for absolute ethanol as quenching reagent.

Table I

Relative Mole % of Products from Reduction of 3-Ethoxycyclohexenone (**1**) with Excess Lithium in Ammonia at −33°, Quenched with Ammonium Chloride

Time,[a] min	Products, mole %							Elimination, %
	2	3	2 + 3	4	5	4 + 5	1	
1	0	0	0	15	85	100	0	0
2.5	0	8	8	18	68	86	6	9
4	8	21	29	14	51	65	6	31
9	18	36	54	5	41	46	0	54
10	17	32	49	11	40	51	0	49
11	27	43	70	0	29	29	1	71
15	24	43	67	0	27	27	6	71
20	28	55	83	0	12	12	5	87
26	27	54	81	4	15	19	0	81
30	29	50	79	5[b]	5	10	11	88
31	34	52	86	2	10	12	2	88
40	21	57	79	0	12	12	9	87
41	27	57	84	1	5	6	10	93
60	46	47	93	0	4	4	3	95

[a] Time measured from start of addition of **1** to Li–NH_3 solution until blue color completely discharged after addition of quenching reagent (see Experimental Section for procedural details). [b] Includes 4% **6**, which was detected in this experiment only.

In the tables the percentages of **2** and **3** are summed as products presumably formed *via* elimination of ethoxide ion from enolate anion **9**, whereas the percentages of **4**, **5**, and **6** are summed as nonelimination products (*cf.* Scheme II). Elimination of ethoxide ion from **9** is obviously a function of time and this is illustrated in Figure 1. The half-time for the presumed slow step **9** → **6** at −33° is about 7 min.[13]

Table II

Relative Mole % of Products from Reduction of 3-Ethoxycyclohexenone (**1**) with Excess Lithium in Ammonia at −33°, Quenched with Absolute Ethanol

Time,[a] min	Products, mole %							Elimination, %
	2	3	2 + 3	4	5	4 + 5	1	
1.5	0	15	15	0	85	85	0	15
2.5	0	25	25	0	75	75	0	25
4	16	33	49	0	51	51	0	49
10.5	2	69	71	0	29	29	0	71
15	17	66	83	0	17	17	0	83
19	0	81	81	0	19	19	0	81
22	0	79	79	0	15	15	6	84
25	0	66	66	0	25	25	5	69
30	0	94	94	0	6	6	0	94
35	0	87	87	0	5	5	3	90
40	0	100	100	0	0	0	0	100

[a] See Table I, footnote *a*.

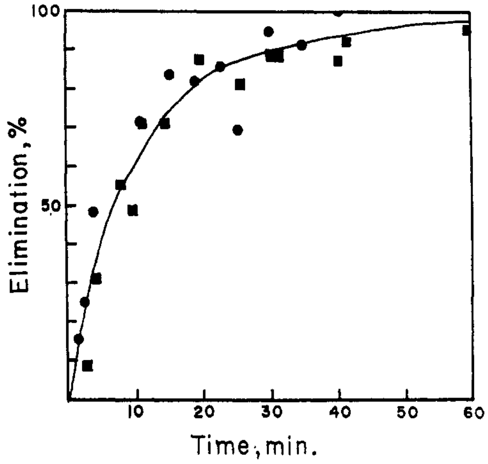

Figure 1.—Dependence on time of % elimination products (**2** + **3**) formed in the lithium–ammonia reduction of **1** at −33°, using ammonium chloride (■) or ethanol (●) quenching.

As expected, quenching with ethanol affords more of the hydroxylic products **3** and **5** than does quenching with ammonium chloride.[14] It is noteworthy, however, that ammonium chloride quenching at −33° affords a large fraction of hydroxylic products (even when the reaction times were so brief that the amount of "overreduction" can not be accounted for by protonation by ethanol derived from eliminated ethoxide).

The results can be dramatically changed by lowering the temperature of the reaction with a Dry Ice–acetone bath to about −78°.[15] The product compositions from a series of reductions of **1** at −78° with ammonium

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[10] *Cf.* H. L. Goering and L. L. Sims, *J. Am. Chem. Soc.*, **79**, 6270 (1957), for the conversion of 1-chlorocyclohexene to **8** by hydrogen bromide and ferric chloride.

[11] Conversion of **4** to **6** upon vpc was demonstrated by injection of pure samples of **4**. On a virgin column, elimination was negligible, but it increased as the column was used (*cf.* footnote *b* of Table III).

[12] In most runs, the ammonia was used directly from its container without purification. Several reductions using ammonia distilled from lithium gave results indistiguishable from those obtained using unpurified ammonia under the same conditions. Nonetheless, the use of unpurified ammonia from different containers added another uncertainty to the complex system and is regrettable.

[13] The data of Tables I and II do not give a good straight line in an Arrhenius plot for an assumed first-order slow step of **9** → **6**. In view of the imprecisely controlled reaction conditions, this is not surprising. A straight line calculated by the method of least squares gives $t_{1/2}$ = 7.2 min.

[14] See, for example, "Steroid Reactions," C. Djerassi, Ed., Holden Day, Inc., San Francisco, Calif., 1963, Chapter 7, for consideration of this point and references to specific cases. The reasons for the differences in quenching behavior between methanol or ethanol and ammonium chloride or *t*-butyl alcohol are obscure.

[15] The temperatures of the cooling bath or the reaction mixtures themselves were not measured; −78° is the usual approximation for the temperature of mixtures cooled by solid carbon dioxide, mp −78.8°.

chloride quenching and ethanol quenching are given in Tables III and IV, respectively.

TABLE III

RELATIVE MOLE % OF PRODUCTS FROM REDUCTION OF 3-ETHOXYCYCLOHEXENONE (1) WITH EXCESS LITHIUM IN AMMONIA AT −78°, QUENCHED WITH AMMONIUM CHLORIDE

Time,[a] min	Products, mole %			
	2 + 3	4 + 6[b]	5	1
1.5	0	71	23	6
2.5	0	80	6	14
5	0	91	4	5
6	0	69	20	11
10	0	83	16	1
10	0	77	7	16
10	0	58	8	34
15	0	88	8	4
18	0	74	9	17
25	0	77	16	7
25	0	91	4	5
28	0	77	0	23
30	0	57	26	17
37	0	67	19	14
120	0	74	26	0
Av	0	76	13	11

[a] See Table I, footnote *a*. [b] The amount of **6** detected in some of these experiments was quite high, probably because of decomposition of **4** on aging, contaminated vpc columns.

TABLE IV

RELATIVE MOLE % OF PRODUCTS FROM REDUCTION OF 3-ETHOXYCYCLOHEXENONE (1) WITH EXCESS LITHIUM IN AMMONIA AT −78°, QUENCHED WITH ABSOLUTE ETHANOL

Time,[a] min	Products, mole %			
	2 + 3	4 + 6[b]	5	1
10	0	0	100	0
10	0	0	72	28
15	0	0	78	22
16	0	0	100	0
21	0	0	100	0
30	0	0	100	0
30	0	20	54	26
60	0	17	83	0
Av	0	5	86	9

[a] See Table I, footnote *a*. [b] See Table III, footnote *b*.

The most striking observation is that *there is no elimination product* (**2** *or* **3**) *observed even after 120 min.*[16] When ethanol was used as quenching agent at −78°, *cis*-3-ethoxycyclohexanol (**5**) was in several instances the only product detected by vpc. In a preparative run, 46% of redistilled **5** was obtained. When ammonium chloride was used as quenching agent, 3-ethoxycyclohexanone (**4**) became the predominant product (Table III). Ammonium chloride quenching at −78° afforded the smallest amount of hydroxylic products of any conditions tested. This fact suggested that reduction at −33°, followed by ammonium chloride quenching at −78°, would afford cyclohexanone (**2**) as the major product. The results shown in Table V confirm this expectation.

Thus, by appropriate manipulation of experimental conditions, it is possible to obtain any of the four primary products **2**, **3**, **4**, or **5** as the predominant one.

TABLE V

RELATIVE MOLE % OF PRODUCTS FROM REDUCTION OF 3-ETHOXYCYCLOHEXENONE (1) WITH EXCESS LITHIUM IN AMMONIA AT −33°, QUENCHED AT −78° WITH AMMONIUM CHLORIDE

Time,[a] min	Products, mole %				
	2	3	4 + 6[b]	5	1
20	37	14	22	15	12
28	68	11	8	0	13
45	65	5	10	1	19
46	49	0	12	0	39

[a] See Table I, footnote *a*. [b] See Table III, footnote *b*.

Elimination of ethoxide ion can be suppressed by lowering the reaction temperature and undesired reduction of ketone groups can be suppressed by quenching the reaction with ammonium chloride at low temperature. All the results are consistent with Scheme II, with the initial reduction process being very rapid even at −78° and the unimolecular elimination **9** → **6** being relatively slow.

Finally, the small and unpredictably variable amount of unreacted starting material **1** found in most reaction products deserves consideration. In an attempt to ensure complete reduction of **1**, 1 equiv of *t*-butyl alcohol was added to the reaction medium under several different sets of experimental conditions.[17] No significant change in product composition was observed and the average amount of unreduced **1** (4%) was the same as in the runs without added *t*-butyl alcohol.

Experimental Section[18]

General Procedure for Lithium in Ammonia Reductions.—To a 1-l. three-necked flask fitted with a Dry Ice–acetone condenser, a stopper, and an inlet tube was added 170 ml of ammonia.[13] To the magnetically stirred ammonia was added 0.50 g (7.19×10^{-2} mole) of lithium metal ribbon (Alfa Inorganics, Inc.). The mixture was allowed to stir for *ca.* 10 min. To this deep blue solution was added a solution of 1.50 g (1.07×10^{-2} mole) of 3-ethoxycyclohexenone (**1**), bp 72–74° (1 mm), in 50 ml of anhydrous ether from a dropping funnel. The starting material (**1**) was added to the lithium–ammonia solution over a 2-min period. In the reductions which have reaction times less than 4 min, the starting material (**1**) was added over a 15-sec period. The reaction time was the interval measured from initiation of addition of **1** to complete discharge of the blue color.

After the reaction had proceeded for about 2 min less than the desired "time" of reaction, *ca.* 15 g of ammonium chloride or *ca.* 60 ml of anhydrous ethanol was added in order to discharge the blue color. The ammonium chloride was added at one time, but the ethanol had to be added more slowly because of boiling of the ammonia. The quenching period (until the blue color was gone) usually required about 2 min irrespective of quenching reagent. An additional 200 ml of anhydrous ether was then added. A drying tube containing sodium hydroxide was attached after removal of the Dry Ice–acetone condenser. The flask was allowed to stand at room temperature until the ammonia had evaporated.

The ether solutions of the reactions quenched with ammonium chloride were filtered. The salts were crushed and washed with two 50-ml portions of anhydrous ether. The combined ether

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[16] The large observed retardation of, presumably, **9** → **6** upon lowering the temperature 45° corresponds to reasonable values of thermodynamic activation parameters estimated from the approximate $t_{1/2}$ at −33° and maximum possible rates at −78°. However, other factors such as insolubility of lithium enolate at the lower temperature could well be involved.

[17] The equivalent of *t*-butyl alcohol might by hypothesized to assist in reduction of **1** by serving as an efficient proton source for the initially formed highly basic β-carbanionic species which otherwise could abstract a proton from **1** to give an enolate anion which might survive until work-up.

[18] Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were taken in open capillaries and were not corrected. Infrared spectra were determined on a Perkin-Elmer Model 21 double beam recording spectrometer. Ultraviolet spectra were determined on a Bausch and Lomb Spectronic 505 spectrometer. Nmr spectra were determined in carbon tetrachloride containing tetramethylsilane on a Varian DA-60-IL spectrometer. Vapor phase chromatography was done on a Wilkens A-700 chromatograph.

solutions were evaporated at aspirator pressure with gentle heating to afford the crude product.

The ether solutions of the reactions quenched with ethanol were added to 200 ml of water. The ether layer was separated and the aqueous layer was extracted with three 50-ml portions of ether. The combined ether layers were dried over magnesium sulfate, filtered, and evaporated to afford the product.

In several cases, 1 equiv of *t*-butyl alcohol was mixed with the ethereal solution of **1** before its addition to the reducing medium. Under conditions designed to optimize the yields of **2–5**, the *t*-butyl alcohol had no significant effect on the product composition. For example, reductions run at −78° and quenched with ammonium chloride still afforded 3-ethoxycyclohexanone (**4**) as the predominant product. In particular, the *t*-butyl alcohol failed to eliminate the small amount of **1** found in most products. The average amount of **1** in reductions run in the presence or absence of *t*-butyl alcohol was 4%.

General Procedure for the Analysis of Reduction Products.—Vapor phase chromatography (vpc) was used to analyze the products of the reductions. A Wilkens A-700 chromatograph was used with a 9-ft 7.5% Carbowax 20 M column at 150° with helium as a carrier gas at a flow rate of 60 ml/min. The injector and detector were equilibrated at 190 and 205°, respectively. The retention times of the reduction products follow: cyclohexanone (**2**), 2 min; cyclohexanol (**3**), 2.5 min; cyclohexenone (**6**), 4.5 min; 3-ethoxycyclohexanone (**4**), 8 min; *cis*-3-ethoxycyclohexanol (**5**), 10 min; and 3-ethoxycyclohexenone (**1**), 25 min. In reductions worked up with ammonium chloride, ethanol (retention time, 1 min) was observed in those cases where elimination products were found.

The method of analysis depended upon the linear relationship between the volume of an injected sample and the weight of the chart paper peak produced by this injection. A graph of the weight of paper *vs.* the volume injected was constructed for each of the reaction components by injecting authentic samples of known volume. It was then possible to inject a known volume of reduction product, to weigh the peaks produced on the recorder, and to convert these weights to volumes. Once the volume of an individual component in the injected sample was known, the total volume of the component in the product could be calculated by a simple proportion. Knowing the density and molecular weight of each pure component, the total number of moles of the component in the product were calculated. Relative mole percentages and actual yields were also calculated. This method of analysis assumes that there is insignificant volume change upon mixing. Analyses of mixtures of known composition were accurate usually to within 1% and never erred by more than 2%, so the assumption is acceptable. In several cases, the amount of starting material (**1**) in the products was determined by ultraviolet spectroscopy. All calculations were performed on a General Electric GE-235 computer at Dartmouth.

Compounds **1–6** accounted for, on the average, 60% of the reduction product. Numerous efforts to detect the unidentified material failed. Six different vpc columns (7.5% Carbowax 20 M, 20% SE-30, 10% Ucon Polar, 10% Apiezon L, 10% NPGS, and 5% silicone rubber on CM-BS-P) at varied temperatures and flow rates did not reveal a peak corresponding to anything other than compounds **1–6**. Infrared, ultraviolet, and nmr spectra of crude products disclosed no information about the unidentified material. Elution chromatography on acid-washed alumina also failed to reveal any new compounds.

3-Ethoxycyclohexenone (**1**).—According to the procedure of Gannon and House,[19] 53.0 g of dihydroresorcinol afforded 43.2 g (65%) of pure **1**: bp 72–74° (1 mm) (lit.[19] bp 66–68.5° (0.4 mm)); $\lambda_{\max}$ 6.05 and 6.25 μ; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 250 mμ (ε 16,900) (lit.[19] $\lambda_{\max}^{\mathrm{EtOH}}$ 250 mμ (ε 17,200)); $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 1.37 (3 H, t, $\mathrm{C}\mathit{H}_3\mathrm{CH_2O}$–), 3.56 (2 H, q, $\mathrm{CH_3C}\mathit{H}_2\mathrm{O}$–), and 5.17 ppm (1 H, s, $=\mathrm{C}\mathit{H}$—).

Δ^2-Cyclohexenone (**6**).—According to the procedure of Gannon and House,[20] **1** was converted to **6**, which was purified by vpc on a 5-ft 20% Apiezon L column at 140°. The 2,4-dinitrophenylhydrazone derivative of **6**, prepared in the usual manner, had mp 164–166° (lit.[21] mp 164.5°).

3-Ethoxycyclohexanone (**4**).—To a solution of 0.50 g (7.2 × 10^{-2} mole) of lithium in 170 ml of liquid ammonia cooled in a Dry Ice–acetone bath was added a solution of 1.50 g (1.07 × 10^{-2} mole) or **1** in 50 ml of anhydrous ether. After 25 min the reaction was quenched with *ca.* 15 g of ammonium chloride. After evaporation of the ammonia, the ether solution was filtered and evaporated to afford 1.49 g of yellow oil. Vpc showed that the actual yield of **4** was 53%. Vpc-purified **4** had $\lambda_{\max}$ 5.80 μ and $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 1.15 (3 H, t, $\mathrm{C}\mathit{H}_3\mathrm{CH_2O}$–) and 3.45 ppm (2 H, q, $\mathrm{CH_3C}\mathit{H}_2\mathrm{O}$–).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.29; H, 9.75.

A 2,4-dinitrophenylhydrazone derivative was prepared from **4** with an acidified ethanolic solution of 2,4-dinitrophenylhydrazine and had, after two recrystallizations from absolute ethanol, mp 164.8–165.5°. The infrared spectrum of this material was identical with that of the 2,4-dinitrophenylhydrazone of **6** and the mixture melting point of the derivatives was 163.6–166°.

***cis*-3-Ethoxycyclohexanol** (**5**).—To a solution of 3.3 g (4.75 × 10^{-1} mole) of lithium in 450 ml of liquid ammonia cooled in a Dry Ice–acetone bath was added 10.0 g (7.13 × 10^{-2} mole) of **1** in 50 ml of anhydrous ether. After the reaction had run for 14 min, the blue color was dispelled by the addition of *ca.* 60 ml of anhydrous ethanol. After the ammonia had completely evaporated, 200 ml of water was added. The ether layer was separated; the aqueous layer was extracted with three 100-ml portions of ether. The combined ether layers were dried over magnesium sulfate, filtered, and evaporated to give 8.13 g of dark yellow oil. Vpc showed that the actual yield of **5** was 54%. The product was distilled under vacuum to afford 4.73 g (46%) of clear liquid, bp 68–72° (1.25 mm), which was >99% pure **5** by vpc. Vpc-purified **5** had $\lambda_{\max}$ 2.95 μ; $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 1.16 (3 H, t, $\mathrm{C}\mathit{H}_3\mathrm{CH_2O}$–), 3.45 (2 H, q, $\mathrm{C_3HC}\mathit{H}_2\mathrm{O}$–), and 3.72 ppm (1 H, broad s, *H*O–, removable by deuteration).

Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.48; H, 11.24.

Oxidation of 4.14 g of **5** with Jones reagent[22] afforded 4.02 g of oil. Vpc showed one major peak which was collected and identified as 3-ethoxycyclohexanone (**4**) by comparison of infrared spectra.

***trans*-1,4-Dibromocyclohexane** (**8**).—To a solution of 1.00 g (6.92 × 10^{-3} mole) of **5** in 10 ml of anhydrous methylene chloride was added dropwise 5.4 g (2.1 × 10^{-2} mole) of boron tribromide (Matheson Coleman and Bell, 99+% pure) in 10 ml of anhydrous methylene chloride. The mixture was stirred for 2 hr and the solvent was removed on a rotary evaporator. Water (30 ml) was added. The mixture was extracted with two 25-ml portions of ether. The ether layers were washed with 25 ml of brine and dried over magnesium sulfate. The ether was stripped to afford 1.36 g of oil which was chromatographed twice on acid-washed alumina. The crystals thus obtained were recrystallized once from ether–hexane to afford 0.51 g (30%) of *trans*-1,4-dibromocyclohexane (**8**): mp 108–110° (lit.[10] mp 112°); $\lambda_{\max}^{\mathrm{CS_2}}$ 8.59, 10.10, 11.30, 11.50, 13.55, and 13.75 μ (lit.[10] $\lambda_{\max}^{\mathrm{CS_2}}$ 8.6, 10.1, 11.3, 11.5, 13.5, and 13.7 μ); $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 2.05 (8 H, m, $-\mathrm{C}\mathit{H}_2-$) and 4.26 ppm (2 H, m, $-\mathrm{CH_2C}\mathit{H}\mathrm{BrCH_2}-$).

Anal. Calcd for $C_6H_{10}Br_2$: C, 29.78; H, 4.17. Found: C, 30.06; H, 4.18.

cis **and** *trans*-**Cyclohexane-1,3-diol.**—According to the procedure of Clarke and Owen,[9b] 100 g of resorcinol afforded 37.6 g (36%) of a mixture of *cis*- and *trans*-cyclohexane-1,3-diol, bp 126–132° (5 mm) (lit.[9b] bp 130–140° (6 mm)). The *cis* and *trans* isomers were separated by fractional crystallization of the dibenzoate derivatives.[9b] Saponification afforded pure *cis*-cyclohexane-1,3-diol, mp 82–83.5° (lit.[9b] mp 85.5°) and a very small amount of *trans*-cyclohexane-1,3-diol, mp 113–114° (lit.[9b] mp 115.5°).

Conversion of ***cis*-Cyclohexane-1,3-diol to 5.**—A solution of 0.95 g (8.2 × 10^{-3} mole) of *cis*-cyclohexane 1,3-diol, mp 82–83.5°, and 0.42 g (1.8 × 10^{-2} mole) of sodium in 75 ml of anhydrous dimethoxyethane was refluxed for 18 hr. Ethyl iodide (10 ml) was added and the mixture was refluxed for an additional 12 hr. Water (25 ml) was added; the solution was extracted with three 25-ml portions of ether. The ether solution was dried over magnesium sulfate, filtered, and evaporated to give 1.09 g of oil. Vpc on a 7.5% Carbowax 20 M column at 150° showed only one major peak (retention time, 9 min) which was collected. This product had infrared and nmr spectra identical with those of **5** isolated from lithium–ammonia reductions.

Conversion of ***trans*-Cyclohexane-1,3-diol to 7.**—A solution of 0.067 g (4.65 × 10^{-4} mole) of *trans*-cyclohexane-1,3-diol, mp 113–114°, and 0.065 g (2.8 × 10^{-3} mole) of sodium in 50 ml

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[19] W. F. Gannon and H. O. House, *Org. Syn.*, **40**, 41 (1960).

[20] W. F. Gannon, and H. O. House, *ibid.*, **40**, 14 (1960).

[21] K. Dimroth and K. Resin, *Ber.*, **75B**, 322 (1942).

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of anhydrous dimethoxyethane was refluxed for 12 hr. Ethyl iodide (10 ml) was added and the mixture was refluxed for an additional 18 hr. Water (25 ml) was added; the solution was extracted with two 25-ml portions of ether. The ether solution was dried over magnesium sulfate, filtered, and evaporated to give 0.030 g of yellow oil. Vpc on a 7.5% Carbowax 20 M column at 150° showed only one major peak (retention time, 9.75 min) which was collected. This vpc-purified **7** had λ_{max} 2.95 μ in an infrared spectrum markedly different from that of **5**; $\delta_{TMS}^{CCl_4}$ 1.26 (t, CH_3CH_2O-), 1.64 (s, $-CH_2-$), and 3.50 ppm (q, CH_3CH_2O-). Note that in contrast to the methylene protons of **5**, which appear as a multiplet from 1.2 to 2.2 ppm, those of **7** appear as a broad singlet at 1.64 ppm, most likely as a result of rapid conformational flipping in the *trans* isomer. The methylene regions in the nmr spectra of the dibenzoate derivatives of *cis*- and *trans*-cyclohexane-1,3-diol show an analogous difference.

Registry No.—**1,** 5323-87-5; **4,** 13619-73-3; **5,** 13618-81-0; **7,** 13618-82-1; **8,** 13618-83-2.

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Heterocyclic Syntheses Involving Acetylenedicarboxylate Adducts of Thiosalicylic Acid Derivatives

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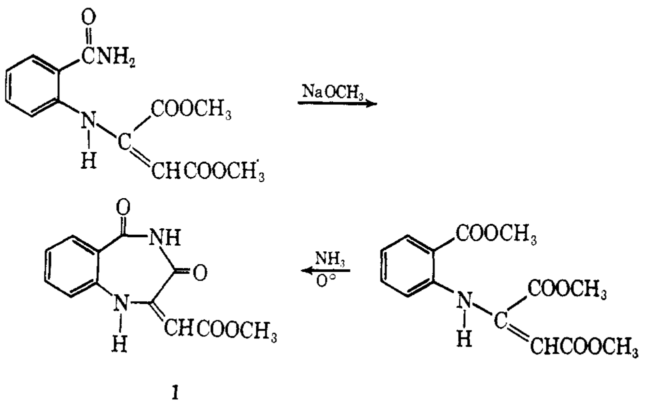
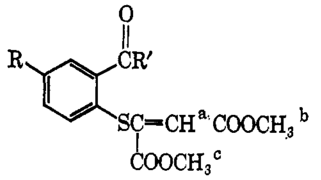
Adducts prepared by the nonanionic addition of thiosalicylates or mercaptobenzamide to dimethyl acetylenedicarboxylate have been shown to possess fumarate geometry. These adducts undergo facile cyclization to 3-hydroxybenzo[*b*]thiophenecarboxylate and benzothiazinone derivatives, respectively.

Recent reports of the utility of dimethyl acetylenedicarboxylate as a heterocyclic ring-forming reagent with amino, mercapto, and hydroxyl groups adjacent to electrophilic centers[1,2] prompt us to report our results in some related thiophenol derivatives. One of us has demonstrated the facile synthesis of benzodiazepinediones (**1**) by base-catalyzed cyclization of the Michael adducts of dimethyl acetylenedicarboxylate (**2**) and *o*-aminobenzamides and by controlled ammonolysis of similar adducts of **2** with methyl anthranilates.[3] In the event that an analogous reaction course is attained with *o*-mercaptobenzamide adducts and methyl thiosalicylate adducts of **2**, a new and direct route to the benzothiazepine ring system would be achieved. Members of both the benzodiazepine[4] and the benzothiazepine[5] systems have come under recent scrutiny for their tranquilizer and muscle-relaxant potential.



1

TABLE I[a]



	H^a	$CH_3{}^b$	$CH_3{}^c$	R′ = OCH_3	R′ = OH
6a (R′ = OCH_3; R = H)					
Maleate	6.05	3.68	3.68	3.90	...
Fumarate	6.80	3.45	3.80	3.90	...
6b (R′ = OCH_3; R = Cl)	6.81	3.46	3.78	3.92	...
6c (R′ = OCH_3; R = Br)	6.83	3.46	3.75	3.93	...
6d (R′ = OH; R = H)	6.84	3.48	3.80	...	10.95
6e (R′ = NH_2; R = H[b])	6.74	3.43	3.80	...	...

[a] All spectra were run in $CDCl_3$ against tetramethylsilane (TMS) and are reported in parts per million. [b] Run in dimethyl sulfoxide-d_6 owing to lack of solubility in $CDCl_3$.

The *o*-mercaptobenzamide (**3**) underwent a spontaneous and mildly exothermic reaction with **2** which resulted in formation of the adduct **6e**. Absence of SH absorption in the infrared and nmr spectra of the product and the retention of the amide NH_2 bands clearly defined the adduct as an S-substituted species. Furthermore, benzamide was inert to reaction with **2** under these conditions, but thiophenol formed an adduct. The nmr spectrum of **6e** (see Table I) allowed the structural assignment of fumarate geometry to the diester portion. This adduct required a catalytic quantity of sodium methoxide to effect ring closure and the resulting product was not the expected benzothiazepinedione but 2-carbomethoxymethyl-2-carbomethoxy-1,3-

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