0.329 g., m.p. 76–79.2°. The total yield was 44% from XXIII. The analytical sample of XXVI after two more sublimations at 70° (2 mm.) had m.p. 80.0–81.6°, ϵ_{212}^{EtOH} 1510; $\lambda_{max}^{CCl_4}$ 5.92, 7.95 μ; λ_{max}^{KBr} 8.05 μ.

Anal. Calcd. for $C_{11}H_{18}O_2$; C, 72.49; H, 9.96. Found: C, 72.73; H, 9.82.

Rearrangement of the chloroketone XXIII made from *trans*-2-chlorocrotonic acid was carried out separately and in the same manner as above, except that the benzyl ester was isolated (b.p. 114–116° (0.1 mm.), $n^{28}D$ 1.5158) before hydrolysis and submitted to hydrogenolysis to produce the corresponding acid, m.p. 65–72°. Sublimation and chromatography on silicic acid gave 20–28% of acid XXVI, m.p. 76.8–80.7°, undepressed on mixing with that described above.

Authentic *cis*-1,2,4,5-Tetramethyl-4-cyclohexenecarboxylic Acid (XXVII).—A mixture of 1.0 g. (0.101 mole) of tiglic acid and 2.0 ml. (0.0177 mole) of 2,3-dimethyl-1,3-butadiene was heated in a sealed tube at 180° for 24 hours, in the presence of a little hydroquinone. Distillation from an oil-jacketed flask yielded 1.25 g. of solid at a bath temperature of 110–120° (0.3 mm.). This had m.p. 78–86° and was a mixture of tiglic acid and adduct XXVII, as shown by ultraviolet measurement (tiglic acid has λ_{max}^{EtOH} 217 mμ, ϵ 9840). The mixture was chromatographed on 1:1 silicic acid–Celite and the resulting solid was sublimed twice to yield the analytical sample, m.p. 86.0–87.0° (depressed to 48–65° on admixture with XXVI); ϵ_{212}^{EtOH} 1890; $\lambda_{max}^{CCl_4}$ 5.92, 8.05μ; λ_{max}^{KBr} 8.05, 9.0 and 9.6 μ. The yield of acid XXVII was 45%.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.52; H, 9.89.

NEW YORK 27, N. Y.

[CONTRIBUTION FROM THE CHANDLER LABORATORY OF COLUMBIA UNIVERSITY, NEW YORK 27, N. Y.]

Synthesis and Reactions of Glycidonitriles. Transformation into α-Haloacyl Compounds and Aminoalcohols

BY GILBERT STORK, W. S. WORRALL AND J. J. PAPPAS

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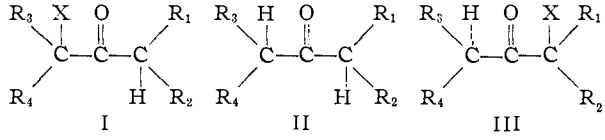
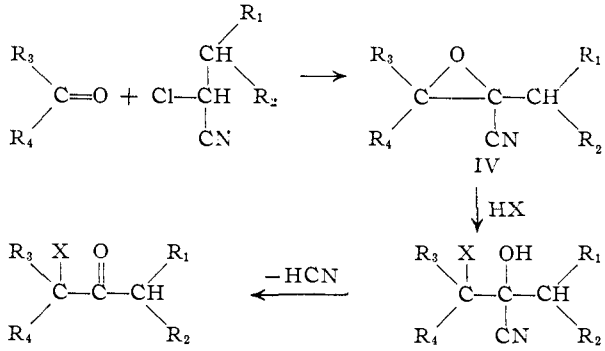
It is shown that the condensation of a ketone with an α-halonitrile is at least as general as the well-known Darzens glycidic ester synthesis. The glycidonitriles can be transformed into α-haloketones, α,β-unsaturated carbonyl compounds and aminoalcohols.

Studies in this Laboratory on the Favorskiĭ rearrangement[1] made it quite clear that the synthesis of haloketones of type I (R_1, R_2, R_3 = H or alkyl) is not at present very satisfactory. Direct halogenation of the parent ketone (*cf.* II) suffers from two major drawbacks: It is necessary to utilize a source of positive halogen which may not be compatible with the presence of certain functional groups in the molecule (*e.g.*, double bonds, phenolic rings), and although the *major* product is often predictable, mixtures of the two possible α-haloketones, I and III, often result.



I II III

This paper is concerned with the development of an alternative method which may be illustrated as follows: Should it be possible to synthesize glycidonitriles (IV) from ketones or aldehydes and α-



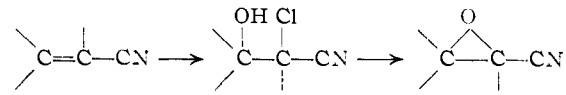
IV

halonitriles, opening of IV with HX would lead as usual to a chlorohydrin *which in this case would also be a cyanohydrin* and, consequently, could be transformed into the corresponding ketone by abstraction of the elements of hydrogen cyanide.[2] It will be noted that in this scheme the halogen can only appear on one specific carbon atom and that its source is actually a halide ion rather than an electrophilic halo compound.

We will now turn our attention to the synthesis of glycidonitriles. We first note that these substances are not new: they have been prepared previously by one of two methods. The reaction of many α-haloketones with cyanide ion leads to α-epoxynitriles.[3]

This particular synthesis is obviously of no interest for our purpose.

It has also been found possible in certain cases to add the elements of HOCl to α,β-unsaturated nitriles. Treatment with base then leads to glycidonitriles.[4]



This sequence suffers from the number of operations required and from the lack of a simple general synthesis of α,β-unsaturated nitriles.

(1) G. Stork and I. J. Borowitz, THIS JOURNAL, **82**, 4307 (1960).

(2) *Cf.* P. Delbaere, *Bull. soc. chim. Belg.*, **51**, 1 (1942).

(3) *Cf.* E. P. Kohler and F. W. Brown, THIS JOURNAL, **55**, 4299 (1933); R. Justoni and M. Terruzzi, *Gazz. chim. ital.*, **78**, 155 (1948).

(4) R. Gerbaux, *Acad. roy. Belg. Classe Sci., Mem.* **18**, No. **4**, 3 (1939); *Chem. Zentr.*, **113**, I, 1621 (1942); L. Moelants, *Bull. soc. chim. Belg.*, **52**, 53 (1943).

TABLE I

SYNTHESIS OF GLYCIDONITRILES USING POTASSIUM *t*-BUTOXIDE

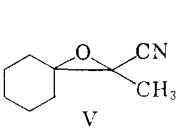
No.	Carbonyl compound	α-Chloronitrile	Recovery of starting material, %	Conversion, % (yield, %) of glycidonitrile	B.p., °C., (mm.)
1	Cyclohexanone	$ClCH_2CN$	[b]	79[c,a]	111–112 (19)
2	Cyclohexanone	CH_3CHCN | Cl	[b]	81[c,a]	105–107 (15)[d]
3	2,2-Dimethylcyclohexanone	$ClCH_2CN$	19	52 (64)	115–118 (13)
4	2,2-Dimethylcyclohexanone	CH_3CHCN | Cl	34	28 (42)	119–121 (15)
5	2,2,6-Trimethylcyclohexanone	$ClCH_2CN$	27	24 (33)	126–128 (17)
6	Cyclopentanone	$ClCH_2CN$	[b]	74[a]	95–97 (19)
7	Methyl isopropyl ketone	CH_3CHCN | Cl	[b]	67[a]	63–65 (8)
8	α-Tetralone	$ClCH_2CN$	16	65 (77)	103–104 (0.1)
9	Benzaldehyde	$ClCH_2CN$	[b]	49[a]	133–134 (16)

[a] These yields are based on total starting material and have not been corrected for recovered starting material. [b] No attempt was made to recover starting material. [c] Average of three runs. [d] Reported[6] b.p. 96.5–97.0° (12 mm.).

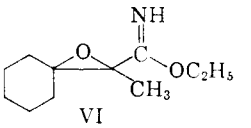
As we mentioned above, if the Darzens glycidic ester synthesis[5] could be extended to α-halonitriles, a simple solution would be at hand. That this possibility had not been explored before our work[6] is presumably because of the well-known propensity of α-halonitriles to self-condensation in the presence of basic catalysts. It is, therefore, of considerable interest that we found the condensation of carbonyl compounds with chloroacetonitrile and α-chloropropionitrile to be a general reaction and that it is less sensitive to steric hindrance than its Darzens counterpart. It will be seen from Table I that the reaction can be used successfully with a variety of carbonyl compounds. Of special interest is the fact that 2,2-dimethylcyclohexanone gives a 64% yield of glycidonitrile with chloroacetonitrile and that even 2,2,6-trimethylcyclohexanone still gives a 33% yield with the same reagent. In contrast, the similarly hindered 2,2,3-trimethylcyclohexanone and 2,2,3,6-tetramethylcyclohexanone give 20% yield and no reaction, respectively, in the Darzens glycidic ester synthesis, using methyl chloroacetate.[7]

Considerable attention was devoted to defining the most suitable procedure for the new reaction: the most generally applicable conditions involve the use of potassium *t*-butoxide in *t*-butyl alcohol solution at room temperature. It is under these conditions, which are more completely detailed in the Experimental section, that the yields of Table I were obtained.

It is interesting that the condensation of α-chloropropionitrile and cyclohexanone using sodium ethoxide as the base led not only to the expected epoxynitrile V but to the imido ester VI. The latter was obtained as the hydrochloride salt,

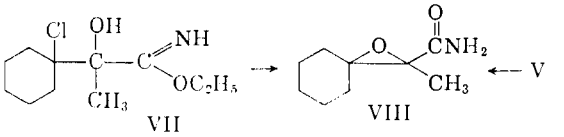


V



VI

m.p. 122–123°, of the corresponding chlorohydrin from the treatment of its mixture with V with anhydrous hydrogen chloride. The chlorohydrin salt could be converted by short treatment with cold, dilute base into the free chlorohydrin imido ester VII, m.p. 81–81.5°. More prolonged treatment with aqueous base transformed VII into the glycidic amide VIII, m.p. 185–186°, which was also formed when the epoxynitrile V was allowed to stand in the presence of aqueous base.



VII VIII

TABLE II

ANALYSES OF GLYCIDONITRILES IN TABLE I

No.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	$C_8H_{11}NO$	70.04	70.04	8.08	7.92	10.21	10.48
2	$C_9H_{13}NO$						
3	$C_{10}H_{15}NO$	72.69	72.55	9.15	9.37		
4	$C_{11}H_{17}NO$	73.70	73.59	9.56	9.59		
5	$C_{11}H_{17}NO$	73.70	73.59	9.56	9.21		
6	C_7H_9NO	68.27	68.33	7.37	7.57	11.37	11.26
7	$C_8H_{13}NO$	69.03	69.03	9.41	9.41		
8	$C_{12}H_{11}NO$	77.81	77.57	5.99	5.59		
9	C_9H_7NO	74.47	74.49	4.86	4.53		

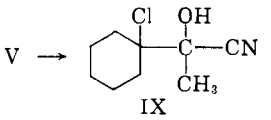
Synthesis of α-Haloketones.—With glycidonitriles readily available, attention could be turned to the opening with anhydrous halogen acids. Since chloroketones are in general more stable than their bromo analogs, we performed most of our experiments with anhydrous hydrogen chloride. Treatment with this reagent in anhydrous ether at 0° led to the chlorocyanohydrin IX, m.p. 79.5–

(5) M. S. Newman in "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 413.

(6) The first successful synthesis of epoxynitriles by this method was reported in the Ph.D. thesis of W. S. Worrall, Harvard, 1949. More recently, the method has been used by F. F. Blicke and J. A. Faust, THIS JOURNAL, **76**, 3156 (1954).

(7) E. C. Horning, M. C. Horning and E. J. Platt, *ibid.*, **71**, 1771 (1949).

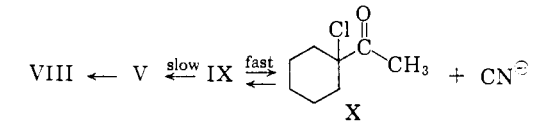
80.5°, from V. The cyanohydrin was quite stable



IX

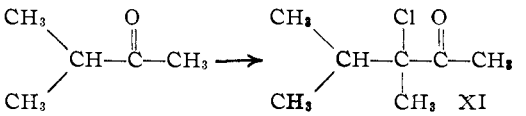
it could be recovered unchanged after refluxing in absolute ethanol for two hours and did not give a precipitate after standing at room temperature for twenty-four hours with 2,4-dinitrophenylhydrazine reagent. It was, however, possible to transform IX into the desired chloroketone, methyl-1-chlorocyclohexyl ketone (X), in 93% yield (54% over-all from cyclohexanone) by shaking with cold 5% sodium hydroxide solution for thirty seconds.

The interesting observation was made that if instead of extracting the mixture of cyanohydrin and dilute base immediately with ether, it was allowed to stand at room temperature for several days, the product was the epoxy amide VIII, a striking illustration of the difference between rate and equilibrium.

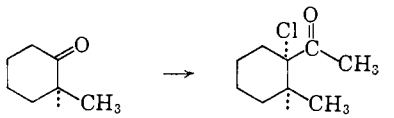


X

The same general procedure was used to make chloroketones XI, XII and XIII in 66, 56, and 59% yield, respectively, but in these cases it was necessary to use anhydrous zinc chloride as a catalyst for the opening of the epoxynitrile.



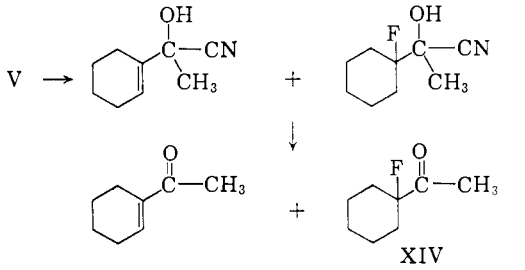
XI



XII

XIII

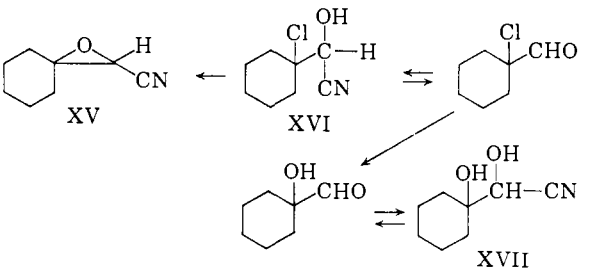
We made one further observation of considerable interest: the opening of glycidonitriles can be carried out in ether solution with boron trifluoride etherate.[8] Under these conditions the epoxynitrile V was converted to what was evidently a mixture of fluorohydrin and unsaturated cyanohydrin, since treatment with base produced the fluoroketone XIV in 55% yield (from V) accompanied by 25% of the α,β-unsaturated ketone, acetylcyclohexene. These two substances are easily separated by distillation and the yield of XIV could undoubtedly be



XIV

increased in the presence of added anhydrous hydrogen fluoride.

Glycidonitriles which are derived from chloroacetonitrile are also opened by anhydrous hydrogen chloride or by boron trifluoride etherate to the corresponding halocyanohydrins. The reaction of the latter with dilute aqueous base is, not unexpectedly, more complicated than with cyanohydrins derived from ketones. For instance, treatment of the chlorocyanohydrin XVI (from XV) with 5% sodium hydroxide solution at room temperature for thirty seconds produced only 18% of 1-chlorocyclohexanecarboxaldehyde, while 44% of the dihydroxynitrile XVII, m.p. 79.6–80.4°, was formed simultaneously (12% glycidonitrile XV and 9% recovered chlorohydrin XVI were also obtained from this particular reaction). The structure of XVII was proved by its analysis and cleavage to cyclohexanone by sodium periodate.

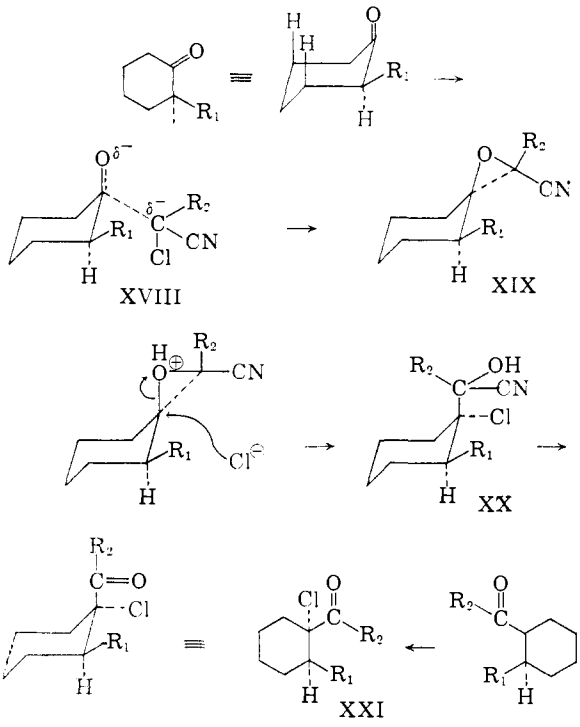


XV XVI XVII

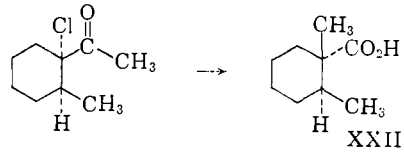
Stereochemistry of the Haloketones.—The formation of a glycidonitrile from an unsymmetrical ketone and a substituted α-chloropropionitrile leads to the formation of two new asymmetric centers. One of these, at the cyano-bearing carbon, needs not concern us here since it is removed in the process of conversion to haloketones. The other is of interest as it is involved in determining the stereochemistry of the halohydrins, and consequently of the derived haloketones. We will illustrate the anticipated result with a 2-substituted cyclohexanone: The bulky halonitrile carbanion can only be involved in a transition state in which it is essentially equatorial as shown in XVIII. The subsequent step (formation of epoxide) does not involve any change in the stereochemistry of the ring C–O bond. Opening of the epoxide, XIX → XX, could *a priori* take place on either of two carbon atoms: the electron-withdrawing effect of the cyano group is such as to prevent stretching of the C–O bond contiguous to it in the transition state for the hydrogen chloride opening, and it is the ring carbon which becomes somewhat positive. Inversion now takes place with the attachment of the chloride ion to give XX in which the chlorine atom is *cis* to the hydrogen on the adjacent sub-

(8) The opening of certain epoxides to fluorohydrins with boron trifluoride etherate has been described, *inter alia*, by H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4765 (1957), and H. O. House and H. L. Wasson, THIS JOURNAL, **78**, 4394 (1956).

stituted carbon. Since there is no further change at the halogenated center in conversion of the cyanohydrin to a carbonyl group, this is also the stereochemistry in the final haloketone (XXI).

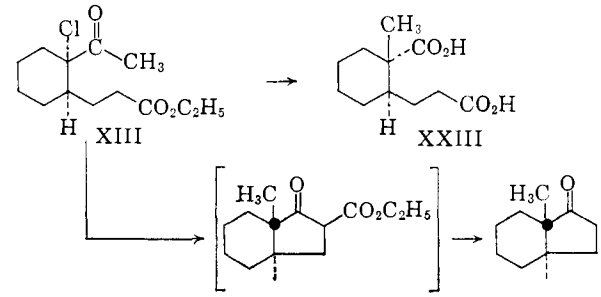


The final haloketone from this sequence should then have the *same stereochemistry* that would have resulted from direct halogenation of the enol of the parent ketone. The assumptions above were verified starting with 2-methylcyclohexanone: the final haloketone (XII = XXI, $R_1 = R_2 = CH_3$) was subjected to Favorskiĭ rearrangement and gave the acid XXII, thus establishing the stereochemistry indicated in XXI.[1]

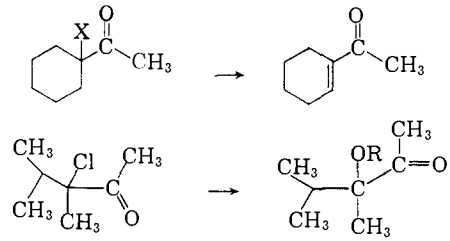


Similarly, the final haloketone expected from ethyl 2-cyclohexanonepropionate should be XIII and its Favorskiĭ rearrangement should lead to *trans* - 2 - methyl - 2 - carboxycyclohexanepropionic acid (XXIII). This was in fact obtained and represents a possible construction of the typical precursor of the *trans*-8-methylhydrindanone system which is present in the steroids.[9] As a matter of fact, since the same reagent (alkoxide ion) may be used for the Favorskiĭ rearrangement and the cyclization of the resulting diester, treatment of the chloroketone XIII with excess sodium methoxide, followed by aqueous acid hydrolysis transforms it albeit in unspectacular yield, into *trans*-8-methylhydrindanone.

(9) *Cf.* (a) W. E. Bachmann and S. Kushner, THIS JOURNAL, **65**, 1963 (1943); (b) W. S. Johnson, *ibid.*, **66**, 215 (1944).

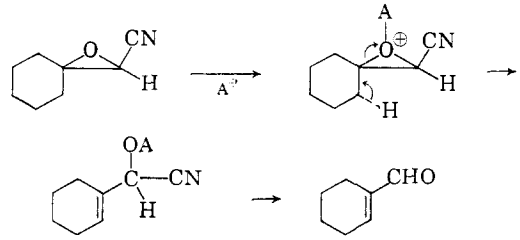


α,β-Unsaturated Ketones and Aldehydes from Glycidonitriles.—Since α-haloketones can be converted to α,β-unsaturated ketones, it is evident that the synthesis which we have just described can be used for the synthesis of the latter. For instance, treatment of 1-chlorocyclohexyl methyl ketone with semicarbazide acetate in aqueous ethanol[10] gave the semicarbazone of cyclohexenyl methyl ketone in 91% yield. It is also worth noting that the corresponding fluoroketone XIV gave the dinitrophenylhydrazone of the same unsaturated ketone in 95% yield.[11]



The chloroketone XI gave the semicarbazone of the corresponding ethoxy or hydroxy ketone in the presence of aqueous ethanol and aqueous dioxane, respectively.[12]

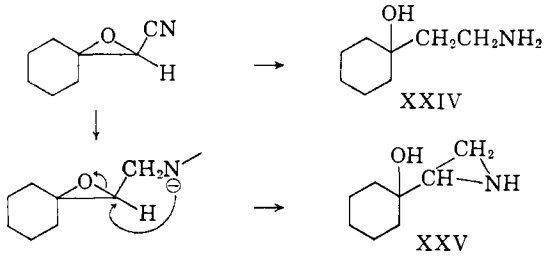
We mentioned earlier that α-chloroaldehydes are not satisfactorily prepared by our epoxynitrile synthesis. It is, therefore, of considerable interest that α, β-unsaturated aldehydes can be synthesized directly from epoxynitriles. For instance, the glycidonitrile XV from cyclohexanone and chloroacetonitrile is transformed by anhydrous aluminum chloride in ether, at room temperature, into about 40% yield of 1-cyclohexenecarboxaldehyde. This reaction is obviously capable of generalization to the synthesis of α, β-unsaturated ketones: we found, in preliminary experiments, that V gives a good yield of 1-acetylcyclohexene under these conditions.



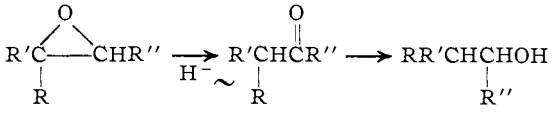
Other Lewis acids can presumably be found that are more efficient than aluminum chloride in this reaction.

(10) *Cf.* W. F. McGuckin and E. C. Kendall, *ibid.*, **74**, 5811 (1952).
(11) *Cf.* V. R. Mattox and E. C. Kendall, *ibid.*, **70**, 882 (1948).
(12) *Cf.* F. Ramirez and A. F. Kirby, *ibid.*, **75**, 6026 (1953); **74**, 4331 (1952).

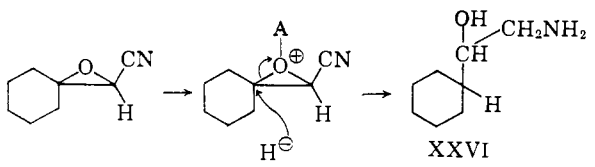
Amino Alcohols from Glycidonitriles.—We have briefly studied the reduction of glycidonitriles with lithium aluminum hydride. Reduction of XV with the latter reagent in ether led to two products which were easily separated because of their considerable difference of solubility in ligroin. The ligroin-soluble product, formed in about 50% yield, was shown to be the 1,3-aminoalcohol 1-(2-aminoethyl)-cyclohexanol (XXIV). This was identified by its acetyl derivative, m.p. 126.5–127.5°, identical with a sample prepared by lithium aluminum hydride reduction of 1-hydroxycyclohexaneacetamide, followed by acetylation. The ligroin-insoluble substance was soluble in water, in which it gave a strongly basic solution ($pH > 10$), and melted at 91–92.6° after vacuum sublimation. The monomeric substance (isothermal distillation) had the empirical formula $C_8H_{15}NO$ and gave cyclohexanone on cleavage with sodium periodate. These facts have led us to assign to it the ethylene imine structure XXV. The stability of ethylene imines to lithium aluminum hydride has been noted previously.[13]



It may be mentioned that the isomeric 1,2-amino alcohol XXVI may be obtained by carrying out the reduction of the epoxide in the presence of aluminum chloride. The structure of the amino alcohol was proved by comparison with an unambiguously synthesized sample. Although not especially good, (20% yield only) this reaction may be of some use since the same epoxynitrile can lead to either a 1,2- or 1,3-amino alcohol and some of these substances may be of physiological interest. It would appear further that this particular system reduces in the presence of aluminum chloride by a path different from that followed in the cases investigated by Eliel who showed that the normal course is as[14]



In our case, the path was more likely the alternative one since aluminum chloride does not appear to produce the α-ketonitrile (see above).



(13) N. G. Gaylord, "Reductions with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p. 819.

(14) E. L. Eliel and D. W. Delmonte, THIS JOURNAL, **80**, 1744 (1958).

Experimental

α-Chloropropionamide.—To 273.2 g. (2.00 moles) of ethyl α-chloropropionate, cooled to 0–5°, was added with vigorous stirring 224 ml. of chilled concentrated (sp. gr. 0.9) aqueous ammonia. The reaction mixture was stirred for 15 minutes and the temperature was kept at 0–5°. During this period two layers remained. An additional 228 ml. of concentrated aqueous ammonia was added and the stirring continued at 5–10° for 1.5 hours. The reaction mixture became clear and homogeneous. A portion of the solvent was removed under vacuum keeping the temperature below 10°. The mixture was then cooled to −15° in a methanol–ice-bath for 20 minutes. White crystals formed which upon filtration gave 147.6 g. (69%) of the amide, m.p. 77–79° (reported[15] m.p. 80°).

α-Chloropropionitrile.—An intimate mixture of 77.5 g. (0.72 mole) of α-chloropropionamide and 109.2 g. (0.77 mole) of phosphorus pentoxide was heated in an oil-bath maintained at 210–220°. A fraction boiling at 115–120° was collected over a 2-hour period. Redistillaton of this material from approximately 10 g. of phosphorus pentoxide afforded 40.4 g. (63%) of the nitrile, b.p. 119–122° (reported[15] b.p. 121–122°).

General Procedure for the Synthesis of Glycidonitriles Using Potassium *t*-Butoxide.—To a 2-l. round-bottomed flask equipped with reflux condenser was added 850 ml. of *t*-butyl alcohol (dried and distilled over calcium hydride). The system had been previously dried and filled with nitrogen. To the *t*-butyl alcohol was added 1.03 gram-atoms of freshly cut potassium and the mixture was allowed to reflux under nitrogen until all the potassium had reacted. Complete dissolution usually required 5 to 10 hours. After cooling to room temperature the solution of potassium *t*-butoxide was rapidly transferred to a 1-l. addition funnel with a side-arm for equalizing pressure and used immediately.

To a mixture of 1.0 mole of ketone or aldehyde and 1.0 mole of α-chloronitrile was added, with stirring and under nitrogen, the above solution of potassium *t*-butoxide. The temperature was kept at 15–20° during the addition which required 1 hour. The mixture was then allowed to stir overnight at room temperature. The solvent was removed under vacuum (20 mm.) up to a temperature of 50°. To the residue were added ether and water. In some cases where an appreciable amount of polymer was present, it was more convenient to filter off any insoluble material in order to facilitate subsequent work-up. The water layer was separated and extracted again with ether. The ether layers were washed thoroughly with water, dried and evaporated and the glycidonitrile was then distilled.

Condensation with Sodium Ethoxide. Formation of Imido Ester.—Dry sodium ethoxide prepared from 18 g. (0.78 g. atom) of sodium was added slowly with stirring to a solution of 72 ml. (68 g., 0.70 mole) of cyclohexanone, 62 g. (0.70 mole) of α-chloropropionitrile and 200 ml. of absolute ether cooled to −80°. The temperature was allowed to rise slowly to room temperature. The rate of addition of sodium ethoxide and the rate of rise in temperature had to be carefully controlled in order to prevent the reaction from becoming too vigorous. The color of the reaction mixture became tan. The mixture was refluxed for 5 hours, 300 ml. of water was added, and the mixture was extracted with three 100-ml. portions of ether. The combined ether fractions were dried and the ester was evaporated. Distillation yielded 87.1 g. of a mixture of the glycidic nitrile V and its imino ethyl ester VI, b.p. 94–97.5° (11 mm.). The infrared spectrum showed a band at 6.0 μ.

Anal. Calcd. for $C_9H_{13}ON$ (the glycidic nitrile (V)): C, 71.49; H, 8.66. Calcd. for $C_{11}H_{19}O_2N$ (the imido ethyl ester (VI)): C, 66.95; H, 9.73. Found: C, 69.97; H, 8.68.

A solution of 18.8 g. of a mixture of the glycidic nitrile V and its imido ester VI in 156 ml. of 1.6 *N* hydrogen chloride etherate (about 2 equivalents), was allowed to stand at room temperature for 24 hours during which time white crystals separated. Filtration yielded 6.6 g. of crystals. These were shaken with absolute ether and filtered giving 6.5 g. of the hydrochloride of ethyl 2-hydroxy-2-(1-chlorocyclohexyl)-propionimidate (VII), m.p. 122–123°, with gas evolution.

Anal. Calcd. for $C_{11}H_{21}O_2Cl_2N$: C, 48.87; H, 7.84. Found: C, 49.36; H, 8.12.

(15) H. Backunts and R. Otto, *Ber.*, **9**, 1592 (1876).

The solvent was evaporated from the filtrate, yielding a solid crystalline residue mostly of 2-hydroxy-2-(1-chlorocyclohexyl)-propionitrile (IX). This residue was shaken with water to remove any imido ethyl ester hydrochloride leaving 14.2 g. of the chlorohydrin nitrile IX, m.p. 73–75°. Recrystallization from ligroin raised the m.p. to 79.5–80.5°. This was identical with authentic material (see below).

The hydrochloride of the imido ethyl ester VII is soluble in water and insoluble in ether. The hydrochloride (6.0 g.) was shaken with 5% sodium hydroxide for a few seconds and filtered immediately yielding crystals which were washed with water yielding 2.0 g. of ethyl 2-hydroxy-2-(1-chlorocyclohexyl)-propionimidate (VII), m.p. 79.0–80.0°. Recrystallization from acetone and water raised the m.p. to 81.0–81.5°. The infrared spectrum has a band at 6.0 μ.

Anal. Calcd. for $C_{11}H_{20}O_2ClN$: C, 56.50; H, 8.64. Found: C, 56.74; H, 8.67.

The chlorohydrin imido ester VII was added to 5% sodium hydroxide and allowed to stand at room temperature. The crystals gradually changed to an oil within 15 minutes and the oil slowly dissolved. Within several hours colorless crystals of 2-methyl 1-oxaspiro[2.5]octane-2-carboxamide (VIII), m.p. 185–186°, separated out of solution; mixed m.p. with an authentic sample (see below) 185–186°.

2-Hydroxy-2-(1-chlorocyclohexyl)-propionitrile (IX).—Anhydrous hydrogen chloride was rapidly bubbled for one hour through a solution of 15.0 g. of 2-methyl-1-oxaspiro [2.5] octane-2-carbonitrile (V) in 200 ml. of anhydrous ether cooled in an ice-bath. The ether was evaporated under vacuum leaving a crystalline residue. An additional 50 ml. of ether was added and evaporated to remove all hydrogen chloride. Crystallization of the solid from 45 ml. of ligroin yielded 13.4 g. (72%) of the chloro cyanohydrin IX, m.p. 78–79°.

The chloro cyanohydrin IX did not give a precipitate with 2,4-dinitrophenylhydrazine reagent on standing at room temperature for 24 hours (acetone cyanohydrin reacts in 1 hour). No derivative could be obtained on reacting with either semicarbazide acetate or semicarbazide hydrochloride in refluxing pyridine. It was also recovered unchanged after refluxing in absolute ethanol for 2 hours.

1-Chlorocyclohexyl Methyl Ketone (X).—A solution of 13.4 g. (0.083 mole) of the chloro cyanohydrin IX was shaken with 100 ml. of 5% sodium hydroxide for 30 seconds. The aqueous layer was separated immediately and extracted with ether. The ether layers were washed, dried and evaporated. Distillation gave 10.6 g. (93%) of the chloro ketone X, b.p. 75–76° (8 mm.) (reported[16] b.p. 87–89° (15 mm.)).

With 2,4-dinitrophenylhydrazine reagent there was obtained the 2,4-dinitrophenylhydrazone of 1-acetylcyclohexene, m.p. 205–207° (reported[17] m.p. 202°).

When the chlorohydrin nitrile IX was allowed to stand in 5% sodium hydroxide at room temperature for a week, white crystals of 2-methyl-1-oxaspiro[2.5]octane-2-carboxamide (VIII) appeared, m.p. 179–185°; mixed melting point with an authentic sample of the glycidic amide (VIII), 182–186°.

2-Methyl-1-oxaspiro[2.5]octane-2-carboxamide (VIII).—A mixture of 2-methyl-1-oxaspiro[2.5]octane-2-carbonitrile (V) and 5% sodium hydroxide was kept at room temperature for several hours when white crystals of 2-methyl-1-oxaspiro [2.5]octane-2-carboxamide (VIII) separated. Recrystallization from 95% ethanol yielded the analytical sample, m.p. 185–186°.

Anal. Calcd. for $C_9H_{15}O_2N$: C, 63.88; H, 8.94. Found: C, 64.07; H, 8.72.

The glycidic nitrile V was refluxed with 0.64 *N* potassium hydroxide for 2 hours. No ammonia could be detected and after standing overnight white crystals of the glycidic amide were present. Titration showed that none of the potassium hydroxide had been used to form the salt of a weak acid.

3-Chloro-3,4-dimethyl-2-pentanone (XI).—A solution of 10.0 g. (0.072 mole) of 2,3-epoxy-2,3,4-trimethylvaleronitrile (Table I, no. 7) and 11.8 g. (0.086 mole) of anhydrous zinc chloride in 200 ml. of anhydrous ether was cooled in an ice-bath. A stream of gaseous hydrogen chloride was passed through the solution for 3 hours. The solution was allowed to stand at room temperature for 12 hours. The reaction mixture was washed with water until the water layer was neutral. The ether layer was then shaken with 300 ml. of 5% sodium hydroxide solution for 30 seconds, washed thoroughly with water, dried and evaporated. Distillation of the chloro ketone XI yielded 6.7 g. (66%), b.p. 77–80° (52 mm.), $n^{25}D$ 1.4347.

Anal. Calcd. for $C_7H_{13}ClO$: C, 56.56; H, 8.81; Cl, 23.85. Found: C, 56.58; H, 8.89; Cl, 23.75.

***cis* 1-Acetyl-1-chloro-2-methylcyclohexane (XII):** (This synthesis and the following rearrangement were carried out by I. J. Borowitz).—The glycidonitrile (XIX, R_1 and R_2 = CH_3) prepared from 2-methylcyclohexanone and α-chloropropionitrile had b.p. 90–92° (4.5 mm.), $n^{25}D$ 1.4621.

Anal. Calcd. for $C_{10}H_{15}ON$: C, 72.69; H, 9.15. Found: C, 72.60; H, 9.16.

On treatment with anhydrous hydrogen chloride–fused zinc chloride, in the manner described above for the preparation of XI, 4.0 g. of the glycidonitrile above gave 56% of *cis*-1-acetyl-1-chloro-2-methylcyclohexane (XII), b.p. 57–60° (1.2 mm.), $n^{28.5}D$ 1.4723–1.4734. The infrared spectrum (carbon tetrachloride) was identical with that of XII which had been prepared previously[1] by sulfuryl chloride chlorination of 1-acetyl-2-methylcyclohexane. Redistillation gave the analytical sample, $n^{28}D$ 1.4731.

Anal. Calcd. for $C_9H_{15}OCl$: C, 61.88; H, 8.66. Found: C, 62.08; H, 8.30.

Favorskiĭ Rearrangement of XII.—Rearrangement with sodium benzyloxide, as described by Stork and Borowitz,[1] and hydrogenolysis of the distilled benzyl ester, b.p. 107° (0.01 mm.), gave in 53% yield *cis* 1,2-dimethylcyclohexanecarboxylic acid (XXII) which distilled at a bath temperature of 150° (1.2 mm.).

The anilide, m.p. 112.9–113.6°, formed in 63% yield from the acid was identical with an authentic sample.[1]

Ethyl 2-Chloro-2-acetylcyclohexanepropionate (XIII).—The epoxynitrile was prepared from ethyl 2-oxocyclohexanepropionate[18] before the potassium *t*-butoxide method had been developed: To a mixture of 97 g. of the keto ester and 44 g. (1 equiv.) of α-chloropropionitrile kept under nitrogen at room temperature was added slowly and with stirring 11.8 g. of sodium hydride (1 equiv.). After standing overnight at room temperature, the mixture was heated to 50–60° for 5 hours and finally to 80° for another hour. Addition of water (300 ml.), extraction with ether (5 × 100 ml.), drying and distillation of the ether extracts produced the glycidonitrile XIX (R_2 = CH_3, R = $CH_2CH_2CO_2C_2H_5$) in 67% yield, b.p. 144–151° (2 mm.) and $\lambda_{max}^{CCl_4}$ 4.50 (weak) and 5.85μ.

Anal. Calcd. for $C_{14}H_{21}O_3N$: C, 66.89; H, 8.44. Found: C, 66.68; H, 8.02.

One isomer of the epoxyamide acid corresponding to the epoxynitrile ester could be obtained by refluxing 2.0 g. of the epoxynitrile with 1.9 g. of sodium hydroxide in 20 ml. of 95% ethanol for 3.5 hours. Most of the solvent was removed *in vacuo*, 30 ml. of water was added and the solution was acidified with 10% hydrochloric acid. Extraction with two 30-ml. portions of ether, drying of the combined ether layers and evaporation left a crystalline residue which was recrystallized from a benzene–ligroin mixture giving 0.5 g. of white crystals (A), m.p. approximately 130–162°. The solvent was evaporated leaving 0.7 g. of a crystalline residue (B); (B) upon one recrystallization from ethyl acetate had a m.p. of 177–180°. Three more recrystallizations from ethyl acetate raised the m.p. to 181.2–181.9°. This glycidic amide is soluble in water. One recrystallization of (A) from ethyl acetate raised the m.p. to 165–175°.

Anal. Calcd. for $C_{12}H_{19}O_4N$: C, 59.72; H, 7.95. Found: C, 59.92; H, 7.68.

The epoxynitrile described above (26.0 g., 0.109 mole) was dissolved in 300 ml. of anhydrous ether and shaken for 2 hours with 17 g. (0.125 m.) of freshly fused zinc chloride. After the mixture had stood at room temperature an additional 12 hours, anhydrous hydrogen chloride was bubbled in for 90 minutes until only one phase was left. Addition of ice-water was followed by extraction with ether and the ether layer was repeatedly washed with water to remove dissolved acid. The ether solution was shaken for 30 seconds with 150 ml. of 5% sodium hydroxide and then washed with water, with dilute hydrochloric acid and again with water.

(16) B. Tchoubar and O. Sackur, *Compt. rend.*, **208**, 1020 (1939).

(17) F. Burton and P. F. G. Praill, *Chemistry & Industry*, 75 (1954).

(18) G. Stork and H. K. Landesman, THIS JOURNAL, **78**, 5128 (1956).

Drying and distillation gave 16.7 g. (59%) of ethyl 2-chloro-2-acetylcyclohexanepropionate (XIII), b.p. 121–126° (0.1 mm.). The sample for analysis had $n^{22}D$ 1.4809 and $\lambda_{max}^{CCl_4}$ 5.82 (ester) and 5.86 μ (ketone).

Anal. Calcd. for $C_{13}H_{21}O_3Cl$: C, 59.87; H, 8.12; Cl, 13.60. Found: C, 60.00; H, 8.07; Cl, 13.62.

Rearrangement of the Chloroketone XIII to *trans*-2-Methyl-2-carboxycyclohexanepropionic Acid (XXIII).—To a suspension of dry sodium ethoxide (from 0.5 g. of sodium) in 50 ml. of absolute ether, kept under nitrogen, was added in one portion, 5.6 g. of the chloroketone XIII dissolved in a little ether. The mixture was refluxed for 3 hours, decomposed with water and the ether layer was separated. Combination of the ether layer and the ether extracts of the aqueous layer, drying and distillation gave 2.9 g. of impure diester of XXIII, b.p. 95–100° (0.05 mm.). The "diester" was hydrolyzed by refluxing 0.86 g. with 25 ml. of concentrated hydrochloric acid for 24 hours. Cooling gave 0.250 g. of *trans*-2-methyl-2-carboxycyclohexanepropionic acid m.p. 173–176°, and an oil which could not be crystallized. Recrystallization of the acid from ethyl acetate raised the melting point to 179.8–180.0° (reported[9b] m.p. 179–180°). The melting point was undepressed on admixture with authentic material kindly supplied by Professor W. S. Johnson.

***trans*-8-Methylhydrindanone-1 from the Chloroketone XIII.**—The chloroketone XIII was refluxed for 3 hours with seven equivalents of dry sodium ethoxide in anhydrous ether, the ether was then replaced by dry benzene and the mixture was refluxed for an additional 2 hours. Removal of the benzene *in vacuo* was followed by refluxing 4 hours with 10% aqueous hydrochloric acid. The solution was extracted with ether, the ether layer was washed with 5% sodium hydroxide solution, dried and distilled. *trans*-8-Methylhydrindanone-1 was obtained in about 30% yield from the chloroketone XIII. It was characterized by its semicarbazone, m.p. 237–238°, after recrystallization from alcohol (reported m.p. of semicarbazone of *trans*-8-methylhydrindanone-1, 242–243°[9b]; of *cis*-224.5–225.5°[19]; of a mixture, 206–208°[9b].)

1-Chloro-α-hydroxycyclohexaneacetonitrile (XVI).—Anhydrous hydrogen chloride was bubbled rapidly for 1 hour through a solution of 10.0 g. (0.073 mole) of 1-oxaspiro[2.5]octane-2-carbonitrile (XV) in 200 ml. of anhydrous ether cooled in an ice-bath. The ether was removed and the residue distilled. A fraction with b.p. 96–103° (0.1 mm.) was collected and weighed 10.2 g. The infrared spectrum showed no absorption in the carbonyl region. This material partially crystallized and melted approximately between 15 and 30°. Great difficulty was encountered in the recrystallization of this compound especially if it had not been previously distilled. Recrystallization from benzene–ligroin in a cold room gave 7.1 g. (56%) of the chlorocyanohydrin XVI, m.p. 40–43°. An analytical sample had m.p. 43.0–43.6°.

Anal. Calcd. for $C_8H_{12}ClNO$: C, 55.33; H, 6.96. Found: C, 55.41; H, 7.19.

The chlorocyanohydrin XVI was recovered unchanged after heating at 200° for 1 hour. No derivatives could be obtained with either semicarbazide or 2,4-dinitrophenylhydrazine. It did not exchange its hydrogen cyanide when heated with pyruvic acid.

Reaction of 1-Chloro-α-hydroxycyclohexaneacetonitrile (XVI) with Sodium Hydroxide.—A solution of 5.94 g. (0.0342 mole) of pure chloro cyanohydrin XVI in 100 ml. of ether was shaken with 50 ml. of 5% sodium hydroxide at room temperature for 30 seconds. The layers were separated and the ether was washed several times with water. The water layers were saved. The ether layers were dried and evaporated. The residue, which weighed 3.58 g., was distilled into three distinct fractions.

The first fraction with b.p. 47–50° (6 mm.) was **1-chlorocyclohexanecarboxaldehyde.** The yield was 0.90 g. (18%). The infrared spectrum showed two characteristic peaks, a weak one at 3.75 μ and the carbonyl peak at 5.83μ. With 2,4-dinitrophenylhydrazine reagent a yellow precipitate formed which when heated on the steam-bath turned dark red. Recrystallization gave the 2,4-dinitrophenylhydrazone of 1-cyclohexene-1-carboxaldehyde, m.p. 220–221° (reported[20] m.p. 219–220°).

Anal. Calcd. for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86. Found: C, 54.06; H, 5.06.

The second fraction with b.p. 75–80° (6 mm.) was substantially pure **1-oxaspiro[2.5]octane-2-carbonitrile (XV)**, contaminated with a small amount of 1-chlorocyclohexanecarboxaldehyde and weighed 0.55 g. (12%).

The third fraction, b.p. 130–132° (6 mm.), solidified and had m.p. 41–42°. It did not depress the melting point of the starting **chlorohydrin XVI.** Recovery was 0.54 g. (9%).

The alkaline water layers from above were acidified with concentrated hydrochloric acid and extracted thoroughly with ether. The ether layers were washed with saturated sodium chloride solution, dried and evaporated. A viscous oil was obtained which crystallized upon standing in the refrigerator for several days. There was obtained 2.34 g. (44%) of the **hydroxy cyanohydrin XVII**, m.p. 73–76°. Several recrystallizations from benzene gave an analytical sample, m.p. 79.6–80.4°.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44, N, 9.03; mol. wt., 155. Found: C, 61.98; H, 8.57; N, 8.88; mol. wt., 193 (Rast), 179 (isothermal distillation).

The hydroxy cyanohydrin XVII, 103 mg., was treated with 400 mg. of periodic acid and 400 mg. of sodium bicarbonate in 4 ml. of water. The system was put under high vacuum (0.1 mm.) and the volatile fraction collected in a Dry Ice trap. To the distillate was added 2,4-dinitrophenylhydrazine reagent. There was obtained 72 mg. (39%) of the 2,4-dinitrophenylhydrazone of cyclohexanone, m.p. 160–161°, undepressed by an authentic sample.

1-Fluorocyclohexyl Methyl Ketone (XIV).—To 250 ml. of absolute ether were added 5.00 g. (0.0331 mole) of 2-methyl-1-oxaspiro[2.5]octane-2-carbonitrile (V) and 50 ml. of boron trifluoride etherate. The solution was allowed to stand at room temperature for 36 hours (1-hour standing gave total recovery of starting material). The mixture was poured onto ice and extracted with ether. The ether layer was washed thoroughly with water and then treated for 1 minute with 150 ml. of 5% sodium hydroxide. The layers were separated and the ether washed with water, dried and evaporated. The infrared indicated the presence of saturated and unsaturated ketone with the former predominating. Distillation afforded two distinct fractions.

The first fraction, with b.p. 50–51° (8 mm.), $n^{25}D$ 1.4272–1.4282, was 1-fluorocyclohexyl methyl ketone (XIV). It absorbed in the infrared at 5.84μ. The yield was 2.63 g. (55%).

Anal. Calcd. for $C_8H_{13}FO$: C, 66.63; H, 9.08; F, 13.17. Found: C, 67.13; H, 9.29; F, 10.44, 15.18.

The purity of this compound was demonstrated by gas chromatography. The compound was passed through a silicone column and showed only a single peak at either 128° or 144°. In addition, the fluoro ketone (0.50 g.) reacted with 2,4-dinitrophenylhydrazine reagent to give a yellow precipitate which on being refluxed for 2 hours on the steam-bath changed into a red precipitate. Filtration yielded 1.00 g. (95%) of the 2,4-dinitrophenylhydrazone of 1-acetylcyclohexene, m.p. 202–204°.

The second fraction from the distillation of the boron fluoride reaction products consisted of 1.03 g. (25%) of **1-acetylcyclohexene**, b.p. 83–97° (water pump vacuum) (reported b.p. 86–92° (25 mm.)). It reacted with 2,4-dinitrophenylhydrazine to give an instantaneous red precipitate which on purification had m.p. 205–207°.

Reaction of 1-Oxaspiro[2.5]octane-2-carbonitrile (XV) with Boron Trifluoride Etherate.—A solution of 5.00 g. (0.0364 mole) of the glycidonitrile XV and 50 ml. of boron trifluoride etherate in 250 ml. of anhydrous ether was allowed to stand at room temperature for 1 hour. The ether was washed many times with water, dried and evaporated. Distillation of the residue gave 0.20 g. (5%) of **1-cyclohexene-1-carboxaldehyde**, b.p. 28–30° (0.2 mm.) (identified by its 2,4-dinitrophenylhydrazone, m.p. 220–221°), and 4.06 g. of a fraction, b.p. 97° (0.2 mm.). A sample of this latter fraction was analyzed.

Anal. Calcd. for $C_8H_{12}FNO$: C, 61.12; H, 7.69; N, 8.91; F, 12.08. Calcd. for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21; F, 0.00. Found: C, 62.18; H, 7.88; N, 9.31; F, 15.60.

(19) W. E. Bachmann, W. Cole and A. L. Wilds, THIS JOURNAL, **62**, 824 (1940).

(20) I. Heilbron, E. R. H. Jones, R. W. Richardson and F. Sondheimer, *J. Chem. Soc.*, 737 (1949).

It would appear that the mixture consists essentially of the desired **fluorohydrin** (85 to 90%) together with some (10 to 15%) **cyanohydrin of cychohexenecarboxaldehyde.** Attempts to obtain the fluorohydrin pure were unsuccessful. Treatment with dilute base gave a mixture of 1-fluorocyclohexanecarboxaldehyde and cyclohexenecarboxaldehyde on the basis of the infrared spectrum of the mixture.

Dehydrochlorination of 1-Chlorocyclohexyl Methyl Ketone (X) with Semicarbazide Acetate.—A solution of semicarbazide acetate was made by dissolving 10.0 g. of semicarbazide hydrochloride and 11.7 g. of sodium acetate in 25.0 ml. of water and 42.0 ml. of absolute ethanol. The final volume was 75.1 ml.

A mixture of 1.00 g. (0.0062 mole) of chloro ketone X and 10.4 ml. (0.0124 mole of semicarbazide hydrochloride) of the above solution was refluxed for 1 hour. After cooling to room temperature water was added to precipitate the derivative. Filtration and thorough washing with water yielded 1.03 g. (91%) of the semicarbazone of **1-acetylcyclohexene,** m.p. 220–222° (reported[17] m.p. 221°).

Reaction of 3-Chloro-3,4-dimethyl-2-pentanone (XI) with Semicarbazide Acetate. (a) In Aqueous Ethanol.—A solution of 0.50 g. (0.0034 mole) of 3-chloro-3,4-dimethyl-2-pentanone (XI), 0.83 g. (0.0074 mole) of semicarbazide hydrochloride, 0.63 g. of sodium acetate in 2.5 ml. of water and 4.0 ml. of ethanol was allowed to stand at room temperature for 48 hours. After addition of 8 ml. of water the solution was cooled in an ice-bath. The crystals of the semicarbazone of **3,4-dimethyl-3-ethoxy-2-pentanone** were filtered off, washed and dried. This material weighed 0.43 g. (59%) and had m.p. 156–158°. An analytical sample had m.p. 158.6–160.2°.

Anal. Calcd. for $C_{10}H_{21}N_3O_2$: C, 55.79; H, 9.83. Found: C, 56.08; H, 10.06.

(b) In Aqueous Dioxane.—A solution of 0.50 g. (0.0034 mole) of chloro ketone XI, 0.83 g. (0.0074 mole) of semicarbazide hydrochloride, 0.63 g. of sodium acetate in 2.5 ml. of water and 4.0 ml. of dioxane was refluxed on the steam-bath for 1 hour and then allowed to stand at room temperature for 12 hours. The dioxane was removed under vacuum and the crystals of the semicarbazone of **3,4-dimethyl-3-hydroxy-2-pentanone** which formed were filtered. The semicarbazone weighed 0.32 g. (50%) and had m.p. 191–194°. An analytical sample had m.p. 199.8–201.2°.

Anal. Calcd. for $C_8H_{17}N_3O_2$: C, 51.31; H, 9.15. Found: C, 51.28; H, 9.01.

1-Cyclohexenecarboxaldehyde from 1-Oxaspiro[2.5]octane-2-carbonitrile (XV).—A mixture of 10.0 g. (0.073 mole) of glycidonitrile XV and 58.4 g. (0.438 mole) of anhydrous aluminum chloride in 500 ml. of anhydrous ether was allowed to stand at room temperature for 1 hour. Ice-water was cautiously added with cooling. The two layers were separated. The ether was washed, dried and evaporated. Distillation yielded 3.14 g. (39%) of 1-cyclohexene-1-carboxaldehyde, b.p. 64–70° (10 mm.) (reported[20] b.p. 70° (13 mm.)).

The 2,4-dinitrophenylhydrazone had m.p. 220–221° undepressed by an authentic sample.

Under the same conditions, 1-acetylcyclohexene was formed from V.

Reduction of 1-Oxaspiro[2.5]octane-2-carbonitrile (XV) with Lithium Aluminum Hydride.—To 4.14 g. (0.109 mole) of lithium aluminum hydride slurried in 414 ml. of anhydrous ether was added over 1 hour 5.00 g. (0.0364 mole) of the glycidonitrile XV. The heat of reaction caused a slight amount of refluxing. The reaction mixture was allowed to stir at room temperature overnight. Saturated sodium sulfate solution (16.6 ml.) was added dropwise over a 1-hour period and the mixture was stirred an additional 5 hours in order to obtain a more granular precipitate. The aluminum hydroxide was filtered off and washed thoroughly with ether. The ether was dried and evaporated. The crude product weighed 4.92 g. and had m.p. 70–85°. Upon recrystallization from ligroin 1.99 g. (39%) of **2-(1-hydroxycyclohexyl)-aziridine (XXV),** m.p. 88–90°, was obtained. Several recrystallizations from ligroin and sublimation at 75° (0.2 mm.) gave an analytical sample, m.p. 91.0–92.6°.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92; mol. wt., 141. Found: C, 67.86, 68.20; H, 10.97, 10.79; N, 10.10, 9.78; mol. wt., 180, 190 (Rast), 165 (isothermal distillation, with either acetone or benzene as solvent).

A mixture of 52.3 mg. (0.00037 mole) of the ethylene imine XXV, 200 mg. of periodic acid and 200 mg. of sodium bicarbonate in 2 ml. of water was allowed to stand at room temperature for 1 hour. The system was put under vacuum (0.2 mm.) and the volatile material was collected in a Dry Ice trap. The distillate had an ammoniacal odor. It reacted with 2,4-dinitrophenylhydrazone reagent to give 28.3 mg. (28%) of a derivative, m.p. 159–160°. Mixed melting point with the 2,4-dinitrophenylhydrazone of cyclohexanone did not depress the melting point of this derivative.

The mother liquors from the recrystallizations of the ethylene imine XXV were concentrated further to remove the small amount of ethylene imine in the mixture. This was not entirely successful since the mixture still reacted with periodic acid to give a small amount of cyclohexanone (identified through its 2,4-dinitrophenylhydrazone). There was obtained in this manner 2.56 g. (49%) of **1-(2-aminoethyl)cyclohexanol (XXIV),** infrared identical in all respects with the infrared of an authentic sample (see below). A small portion was distilled, b.p. 120° (17 mm.), $n^{25}D$ 1.4934, and analyzed.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.09; H, 11.96. Found: C, 66.65; H, 12.23.

The amino alcohol XXIV was monoacetylated in the following manner. A solution of 0.97 g. (0.0068 mole) of amino alcohol XXIV and 0.87 g. (0.0085 mole) of acetic anhydride in 9.7 ml. of methanol was allowed to stand at room temperature for 18 hours. The solvent was completely removed and the crude product was recrystallized three times from benzene. This afforded 0.64 g. (51%) of pure N-acetyl-1-(2-aminoethyl)-cyclohexanol, m.p. 126.0–127.5°. The melting point was undepressed on admixture with an authentic sample (see below).

When the reduction of the glycidonitrile XXIV was carried out in refluxing ether for 36 hours, the identical products were isolated in approximately the same yields.

Authentic 1-(2-Aminoethyl)-cyclohexanol (XXIV).—A mixture of 61.6 g. (0.33 mole) of ethyl 1-hydroxycyclohexaneacetate[21] and 500 ml. of concentrated ammonia was vigorously stirred at room temperature for 7 days. After that period of time most of the ester had reacted and gone into solution. The solution was then concentrated to approximately 100 ml. and extracted with petroleum ether. Upon evaporation of the petroleum ether layer there was recovered 11.7 g. (19%) of starting material. The water layer was concentrated further. The crystals which formed were filtered off and dried, m.p. 118–120°. One recrystallization from benzene yielded 15.7 g. (30%) of **1-hydroxycyclohexaneacetamide,** m.p. 121.0–122.5°. The melting point did not change on further recrystallization.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62. Found: C, 61.43; H, 9.74.

The mother liquors were concentrated to dryness, triturated with benzene, filtered and dried. The crude hydroxy amide thus obtained weighed 17.2 g. and had m.p. 100–108°.

To a slurry of 4.52 g. (0.119 mole) of lithium aluminum hydride in 100 ml. of anhydrous ether was added 5.00 g. (0.0318 mole) of the above hydroxy amide slurried in 300 ml. of ether. The addition required 2 hours. About 50 ml. of ether was passed through the addition funnel to carry along any hydroxy amide which was left behind on the sides of the funnel. The mixture was then refluxed for 14 hours. After cooling, 18 ml. of saturated sodium sulfate solution was added cautiously over a period of an hour. Stirring was continued for 6 more hours. The aluminum hydroxide was filtered off and washed with ether. The ether was dried, and evaporation yielded 4.45 g. of a semi-crystalline mass to which ligroin was added. The crystalline compound that did not dissolve was filtered off. In this way there was recovered 1.60 g. (32%) of starting material, m.p. 116–118°. The filtrate was evaporated. The infrared spectrum indicated that there was practically no hydroxy amide in this fraction. Distillation afforded 1.65 g. (36%) of amino alcohol XXIV, b.p. 115–117° (10 mm.), $n^{25}D$ 1.4950. This compound solidified on standing to a waxy solid with a very unsharp melting point between 43 and 46°.

(21) R. L. Shriner, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 17.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.09; H, 11.96. Found: C, 67.36; H, 11.73.

The N-acetyl derivative was prepared by allowing a solution of 640 g. (0.00447 mole) of the amino alcohol XXIV and 541 mg. (0.00530 mole) of acetic anhydride in 6.4 ml. of absolute methanol to stand at room temperature for 18 hours. After removal of the solvent the amide was recrystallized from benzene to yield 790 mg. (95%) of an analytical sample, m.p. 126.5–127.5°.

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34. Found: C, 64.74; H, 10.68.

Reduction of 1-Oxaspiro[2.5]octane-2-carbonitrile (XV) with Lithium Aluminum Hydride in the Presence of Aluminum Chloride.—To 1.38 g. (0.0364 mole) of lithium aluminum hydride dissolved in 150 ml. of absolute ether was added 19.42 g. (0.1456 mole) of aluminum chloride. Stirring was commenced and 5.00 g. (0.0364 mole) of glycidonitrile XV in 50 ml. of absolute ether was added over a 15-minute period. The reaction mixture was allowed to stir for 12 hours at room temperature. Decomposition of the reaction mixture was accomplished by dropwise addition of water and then addition with cooling of 110 ml. of 10% sulfuric acid. The solution was extracted with ether, the ether layer was washed with water and the combined water layers were saved for further processing. The ether extract was dried and evaporated yielding 1.02 g. of neutral material. The infrared spectrum indicated the presence of hydroxyl (3.0 μ) and carbonyl (5.85 μ) groups. Treatment of this mixture with 2,4-dinitrophenylhydrazine reagent yielded after several recrystallizations a 2,4-dinitrophenylhydrazone, m.p. 171–172°. It was shown to be identical with the 2,4-dinitrophenylhydrazone of cyclohexanecarboxaldehyde (reported[20] m.p. 172°) by mixed melting point.

The combined aqueous acid fractions were made basic with concentrated sodium hydroxide solution and extracted with ether. The ether was washed with saturated sodium chloride solution, dried and evaporated. The crude product weighed 4.04 g. Distillation yielded 1.11 g. (21%) of **α-(aminomethyl)-cyclohexanemethanol (XXVI)**, b.p. 130–133° (12 mm.), and a residue which could not be distilled up to 190°. The amino alcohol solidified and had m.p. 55–70°. On recrystallization from ligroin 0.95 g. was obtained with m.p. 80–85°. The melting point was not depressed by admixture with an authentic sample of XXVI, prepared as described later on.

The N-acetyl derivative was formed by the reaction of 0.17 g. (0.0012 mole) of XXVI and 0.15 g. (0.0015 mole) of acetic anhydride in 2 ml. of absolute methanol. After standing overnight at room temperature the solvent was removed and the crude amide was recrystallized three times from benzene to yield 0.17 g. (77%) of pure **N-acetyl-α-(aminomethyl)-cyclohexanemethanol**, m.p. 107–108°. Mixed melting point with an authentic sample (see below) gave no depression.

Authentic α - (Aminomethyl) - cyclohexanemethanol (XXVI).—To a stirred solution of 28.1 g. (0.460 mole) of nitromethane and 0.93 ml. of 10 *N* sodium hydroxide solution in 25.5 ml. of absolute ethanol kept at 30–35° was added 51.5 g. (0.467 mole) of 3-cyclohexene-1-carboxaldehyde. After the addition of approximately two-thirds of the aldehyde over a 1-hour period, 0.93 ml. of 10 *N* sodium hydroxide and 3.4 ml. of water were added. The remainder of the aldehyde was added over a half-hour. The mixture was then stored at 37° for 5 days. Concentrated hydrochloric acid (1.5 ml.) was added and the reaction mixture was shaken vigorously. After discarding the aqueous layer the solution was extracted with ether and the ether layer was washed three times with saturated sodium chloride solution. The ether was dried and evaporated. Distillation yielded 39.9 g. (51%) of **1-(3-cyclohexen-1-yl)-2-nitroethanol**, b.p. 116–126° (1 mm.).

A solution of 10.0 g. (0.058 mole) of the above nitro alcohol in 5 ml. of glacial acetic acid and 100 ml. of absolute ethanol was hydrogenated under a pressure of two atmospheres in the presence of 1.0 g. of 10% palladium-on-charcoal. There was an uptake of 4 moles of hydrogen. The solution was filtered to remove the catalyst and was concentrated to dryness. The residue was taken up in water and extracted with ether. The water layers were concentrated practically to dryness, made basic with 40% sodium hydroxide solution, and extracted with ether. The ether was washed with a small amount of water, dried and evaporated. There was obtained 5.9 g. (72%) of the amino alcohol **α-(aminomethyl)-cyclohexanemethanol (XXVI)**, m.p. 73–82°. On recrystallization from ligroin the melting point remained in the range 70–80°. Only when heated at 70° for several hours did the melting point gradually rise to 85–86°. On crystallization from ligroin the melting point again dropped to 70–80°. The compound is probably dimorphic. A sample, sublimed twice at 100° (15 mm.), had m.p. 85–86°.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 66.81; H, 11.90; N, 9.78.

The N-acetyl derivative was prepared by allowing a mixture of 1.00 g. (0.0070 mole) of α-(aminomethyl)-cyclohexanemethanol (XXVI), 0.71 g. (0.0070 mole) of acetic anhydride and 10 ml. of absolute methanol to stand at room temperature for 18 hours. The solvent was removed and the residue was dissolved in chloroform. The chloroform was extracted with dilute hydrochloric acid, washed with water, dried and evaporated. The crude product weighed 1.03 g. (79%) and had m.p. 107–108°. Several recrystallizations from benzene gave an analytical sample, m.p. 107.5–108.0°.

Anal. Calcd. for $C_{10}C_{19}NO_2$: C, 64.83; H, 10.34. Found: C, 64.62; H, 10.57.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE UNIVERSITY, AMES, IOWA]

Stereochemistry of Hydrogen Halide Addition to 1,2-Dimethylcyclopentene

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Addition of hydrogen chloride to 1,2-dimethylcyclopentene gives predominantly (perhaps exclusively) *trans*-1,2-dimethylcyclopentyl chloride. The product isomerizes, even in pentane solution, to a mixture which is richer in the *cis*-chloride. Addition of hydrogen bromide to the same alkene gives mixtures which are apparently equilibrated. This is attributed to instability of the halide, which is evidenced by the fact that elimination of hydrogen bromide occurs rapidly in non-polar solvents.

In an earlier study of the addition of hydrogen bromide to 1,2-dimethylcyclohexene in pentane or glacial acetic acid, the product was shown to be *trans*-1,2-dimethylcyclohexyl bromide.[2] Because of the flexibility of cyclohexene systems the mechanistic significance of the *trans*-addition is slightly clouded. Assumption of diaxial attack on the double bond leads to the conclusion that hydrogen and bromine are widely separated at the time they enter the molecule. The first product of such an addition would be I, the stable conformer of *trans*-1,2-dimethylcyclohexyl bromide.

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(2) G. S. Hammond and T. D. Nevitt, THIS JOURNAL, **76**, 4121 (1954).