dino) according to the preceding method gave the diamine IV (NR₂ = pyrrolidino) in an 82.5% yield, m.p. 51–54°. The product was purified by recrystallization from Skellysolve B (petroleum ether, b.p. 63–68°), m.p. 54–55° (large prisms).

Anal. Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63. Found: C, 81.52; H, 8.49.

2,2-Diphenyl-3-piperidinopropylamine (IV, –NR₂ = piperidino).—This compound was prepared from the corresponding nitrile in the above manner. The distilled product was obtained in a 71% yield in the form of a very viscous oil, $n^{23}D$ 1.577, boiling over a wide temperature range. A pure dihydrochloride could not be prepared. A monoformate was obtained, m.p. 148–149° (from methanol–ether).

Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29. Found: C, 74.65; H, 8.08.

The once-distilled product was used in the preparation of amine derivatives (Table I).

Attempts to prepare the ethylated diamine IV (R = C_2H_5) were unsuccessful. The reduction product distilled over a wide temperature range and isolation of pure derivatives failed.

N-Tetramethyl-2,2-diphenyl-1,3-propanediamine.—A mixture of 10.16 g. (0.04 mole) of the diamine IV (R = CH₃), 80 cc. of 90% formic acid and 3.0 g. of paraformaldehyde was refluxed for five hours after which time the formic acid was removed by distillation *in vacuo*. The residual oil was dissolved in water and reprecipitated by the addition of excess 20% sodium hydroxide. The oil was taken up in ether, washed with water and dried over anhydrous magnesium sulfate. Filtration followed by removal of the ether and vacuum distillation of the residue gave 9.1 g. of colorless, viscous, completely methylated diamine, b.p. 110–114° (0.1 mm.), $n^{25}D$ 1.5579.

Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28. Found: C, 80.71; H, 9.24.

The monomethiodide was prepared by treatment of the base with excess methyl iodide in dry ether, m.p. 148–149° (dec.) (from methanol–ether).

Anal. Calcd. for $C_{20}H_{29}N_2I$: C, 56.60; H, 6.89; N, 6.60. Found: C, 56.87; H, 6.96; N, 6.60.

The dimethiodide was prepared by treating the base with excess methyl iodide in dry methanol, m.p. 203–204° (dec.) (from methanol).

Anal. Calcd. for $C_{21}H_{32}N_2I_2$: C, 44.53; H, 5.70. Found: C, 44.35; H, 5.50.

N-Substituted Derivatives of the Propanediamines IV.—The derivatives of the three diamines IV (–NR₂ = $N(CH_3)_2$, pyrrolidino and piperidino) are listed in Table I. The N-formyl derivatives were prepared by the action of ethyl formate on the diamines according to the elegant procedure of Human and Mills.[9] They were isolated as the free bases and recrystallized from Skellysolve B or Skellysolve C (petroleum ether, b.p. 88–98°).

The other acylated amines were prepared by ordinary methods involving use of the acid anhydrides or acid chlorides. Whenever the reagent was readily available, it was used in excess as a solvent, the product was isolated in the form of the free base and recrystallized from a Skellysolve. In other cases benzene was used as a solvent with the acid chloride, and if the hydrochloride of the product precipitated in filterable condition, it was isolated in that form, and recrystallized from an alcohol–ether mixture. The carbamates were all prepared in this manner, using methyl or ethyl chloroformate in solvent benzene.

The ureides were prepared by the action of potassium cyanate on the neutral aqueous solutions of the diamine hydrochlorides.[10] They were isolated as the free bases and purified by recrystallization from alcohol or alcohol–water mixtures.

(9) J. P. E. Human and J. A. Mills, *J. Chem. Soc.*, 1457 (1948).

(10) W. J. Hickinbottom, "Reactions of Organic Compounds," 2nd Ed., Longmans, Green and Co., London. 1948, p. 298.

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A Further Study of the Course of Ring-opening of Unsymmetrical Epoxides with Nucleophilic Reagents

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Styrene oxide and butadiene monoxide react with cyanacetic ester to yield α-cyano-γ-phenyl-γ-butyrolactone and α-cyano-γ-vinyl-γ-butyrolactone, respectively. Fractional crystallization and fractional distillation were used to separate what were subsequently shown to be diastereoisomers in both cases. The significance of these results relating to the mechanisms of epoxide ring-opening is discussed.

A substantial literature concerning the mechanism of epoxide ring-opening has been accumulated. There have been important exceptions to the generalizations formerly used to explain the mechanics of ring-opening. We should note that the opening of saturated unsymmetrical epoxides appears to be straight-forward, that is, occurring at the primary carbon atom; but exceptions are seen to occur in cases involving unsaturated members possessing allylic resonance within the epoxide itself.

Some presently held conceptions regard the major influences to be steric factors and the allylic resonance within the epoxide. The steric factors are of two types: first, the relative "bulkiness" of the attacking anion; and, secondly, the size and configuration of the unsymmetrical epoxide. Let us consider malonic, acetoacetic and cyanacetic esters as typical nucleophilic reagents and study them in order of decreasing size of their anions.

Russell and VanderWerf,[1] in their study of the condensation of styrene oxide and butadiene monoxide with malonic ester, demonstrated that attack in both of these cases occurred solely at the primary carbon atom. The conclusion was that the phenyl group pushes electrons into the benzylic position so as to permit attack at only the primary carbon. A group in this department[2] working with 3,4-dihydronaphthalene-1,2-oxide and ethyl methylmalonate demonstrated that in this case attack occurred exclusively at the benzylic position, despite the fact that steric factors of *both* epoxide and nucleophilic reagent are greater here than was the case with styrene oxide and malonic ester. In the case of the 3,4-dihydronaphthalene-1,2-oxide con-

(1) R. R. Russell and C. A. VanderWerf, THIS JOURNAL, **69**, 11 (1947).

(2) E. E. van Tamelen, G. Van Zyl and G. D. Zuidema, *ibid.*, **72**, 488 (1950).
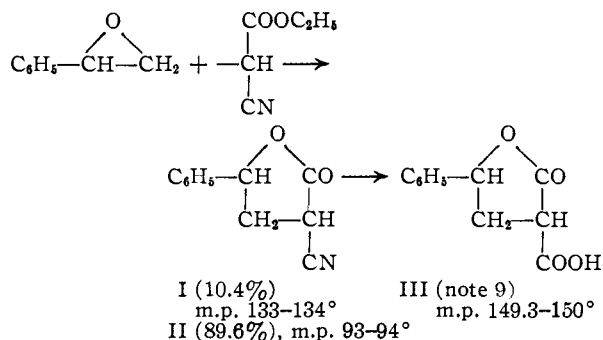
densation steric factors are equivalent for both epoxide carbons and electrical factors governed the course of the reaction.

In the case of addition of styrene oxide to acetoacetic ester, Adams and VanderWerf[3] demonstrated that attack was entirely at the primary carbon. However, butadiene monoxide[3] was found to undergo attack both at primary and secondary carbons in approximately equal amounts. They attributed the attack at the primary carbon in the styrene oxide addition as being directed by steric factors. In the latter case, however, the allylic resonance was thought to outweigh steric factors to cause considerable attack at the secondary carbon. Studies of the addition of saturated epoxides with the above anion[4–6] led without exception to attack at the primary carbon atom.

Studies involving the addition of unsymmetrical epoxides to cyanacetic ester have dealt with saturated epoxides. Glickman and Cope[7] selected cyclohexene oxide, propylene oxide and isobutylene oxide for their work. They found that using molar equivalent amounts of sodium, attack occurred at the primary carbon. However, using 0.1 molar catalytic amounts, the reaction took a different course to yield enamines.

It was decided to put the above theoretical considerations to further test. By selecting a nucleophilic reagent anion smaller than that of acetoacetic ester it might be possible to demonstrate attack at the secondary carbon as well as the primary with both styrene oxide and butadiene monoxide. The ethyl cyanoacetate anion was selected and molar equivalents of sodium were used throughout to assure comparable conditions.

The addition of styrene oxide to cyanacetic ester yielded two crystalline products. The first (I) melting 133–134° was present to the extent of 10.4%; while the second (II) melting 93–94° made up 89.6%. The total yield was 91.5%. Both compounds analyzed correctly for $C_{11}H_9O_2N$. I was shown to be α-cyano-γ-phenyl-γ-butyrolactone by alkaline hydrolysis to the known compound, α-carboxy-γ-phenyl-γ-butyrolactone (III) m.p. 149–151°, originally described by Van Zyl and van Tamelen.[8] A mixed melting point determination with

an authentic sample showed no depression. Alkaline hydrolysis of II also yielded III, m.p. 149–151°, and a mixed melting point determination with an authentic sample was not depressed. This conclusively demonstrates that cyanacetic ester attacks styrene oxide at the primary carbon and that the two crystalline products isolated were diastereoisomers.

The addition of butadiene monoxide to cyanacetic ester produced a high boiling liquid in good yield (65–74%). One hundred-fifty grams was fractionated in a Todd column of 36 theoretical plates using a reflux ratio of 12 to 1. A fraction of 15.5 g. (10.9%) (IV) material boiling 146–148° (2 mm.) was collected. An intermediate fraction of 7.0 g. boiling 148–150° (2 mm.) was taken, followed by 120.0 g. (84.5%) (V) boiling 150–152° (2 mm.). Both IV and V analyzed correctly for $C_7H_7O_2N$. Infrared analysis of IV and V shows that these compounds are not identical and that good separation was achieved by distillation.

Samples of IV and V were converted to the α-carboxylactones via alkaline hydrolysis and decarboxylated by distillation to yield VI and VII, respectively. Comparison of the infrared spectra of VI with an authentic sample of γ-vinyl-γ-butyrolactone (VIII) reveals that VI is identical with VIII, proving that IV must have been α-cyano-γ-butyrolactone. In the same manner, VII is shown to be identical with VIII, proving conclusively that V also must have been α-cyano-γ-vinyl-γ-butyrolactone. This observation provides substantial proof to support the infrared data which originally indicated that IV and V were not identical and that in all probability IV and V represent diastereoisomers.
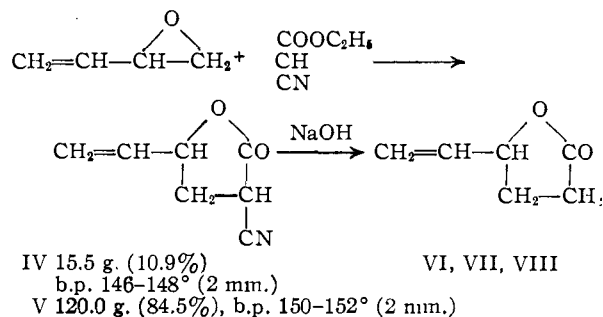
IV 15.5 g. (10.9%)   VI, VII, VIII
b.p. 146–148° (2 mm.)
V 120.0 g. (84.5%), b.p. 150–152° (2 mm.)

TABLE I

INFRARED ABSORPTION MAXIMA OF COMPOUNDS IV THROUGH VIII

| α-Cyano-γ-vinyl-γ-butyrolactone | | γ-Vinyl-γ-butyrolactone | | |
IV	V	VI	VII	VIII
3.42	3.42	3.44	3.39	3.38
4.42	4.42	..[a]	..[a]	..[a]
5.62	5.62	5.64	5.64	5.64
6.10	6.10	6.10	6.10	6.10
6.72	6.72	6.74	6.74	6.74
6.90	6.90	6.88	6.90	6.84
7.0	6.98	7.04	7.04	7.02
7.23	7.22	7.26	7.26	7.24
7.52	7.48	7.48	7.50	7.52
7.70	7.70	7.70	7.70	7.70
8.14	8.14	8.14	8.14	8.14
8.58	8.58	8.56	8.58	8.56

I (10.4%)   III (note 9)
m.p. 133–134°   m.p. 149.3–150°
II (89.6%), m.p. 93–94°

(3) R. M. Adams and C. A. VanderWerf, ibid., 72, 4368 (1950).

(4) W. Traube and E. Lehman, Ber., 34, 1971 (1901).

(5) T. L. Knunyantz, G. V. Chelintzev and E. D. Osetrova, Compt. rend. acad. sci., U. S. S. R., 1, 315 (1934).

(6) G. V. Chelintzev and E. D. Osetrova, J. Gen. Chem. (U. S. S. R.), 7, 2373 (1937).

(7) S. A. Glickman and A. C. Cope, THIS JOURNAL, 67, 1012 (1945).

(8) G. Van Zyl and E. E. van Tamelen, ibid., 72, 1357 (1950).

[a] Absence of C≡N group after hydrolysis.

These results are not consistent with those expected from the above-mentioned work by Adams and VanderWerf.[3]

It is obvious from the above evidence that steric factors and allylic resonance within the epoxide are not the only factors in determining direction of S_N2 ring-opening. For example, Sexton and Britton,[9] and more recently ourselves,[10] have shown that in the reaction of phenols with propylene oxide and hexene-1,2-oxide the presence of an alkaline catalyst directs ring-opening to give secondary alcohol ethers, whereas with an acid catalyst both primary and secondary ethers are obtained. Previously, Chitwood and Freure[11] had shown this to be similarly true with alkyl alcohols and epoxides. These observations suggest that the relative acidity of the nucleophilic reagent involved might play a role in determining the direction of ring-opening, as well as the influence of steric factors and allylic resonance, although the above experimental evidence does not lend itself to any definite conclusion in this respect. At any rate, this study demonstrates that there are still unknown factors to be elucidated in the mechanism of epoxide ring-opening.

Experimental

α-Cyano-γ-phenyl-γ-butyrolactone (I and II).—Twenty-three grams of metallic sodium was dissolved in 375 ml. of absolute ethyl alcohol in a one-liter, three-neck flask equipped with a stirrer, thermometer, dropping funnel and reflux condenser, with a calcium chloride drying tube attached. The solution was cooled to 10° and 113.1 g. (1 mole) of ethyl cyanoacetate was added during 10 minutes. After stirring a few minutes, 120.1 g. (1 mole) of styrene oxide was added slowly dropwise. The mixture was allowed to come to room temperature during 30 minutes and was warmed to 50° in another 30 minutes. The temperature was maintained at 60° for 16 hours. If an exothermic reaction occurs, it may be controlled by external cooling.

The excess alcohol was removed by distillation at 15–20 mm., after which 200 ml. of benzene was added to the oily residue. Then a mixture of 100 ml. of concentrated hydrochloric acid and 200 g. of ice was added with shaking. The aqueous layer was extracted with four 100-ml. portions of benzene. The benzene solutions were combined and on standing a white crystalline precipitate appeared. This was removed by filtration by suction (18.0 g., 1) and the filtrate was evaporated at 15–20 mm. to remove more benzene. The mixture was then cooled and filtered by suction. One hundred and fifty-three grams (II) (89.6% of total yield) of crude material was obtained. The total crude material was 171.0 g. (91.5%). Recrystallization of 1 from 95% alcohol yielded 13.0 g. melting 133–134°.

Anal. Calcd. for $C_{11}H_9O_2N$: C, 70.58; H, 4.85; N,

(9) A. R. Sexton and E. C. Britton, THIS JOURNAL, 70, 3606 (1948).
(10) Unpublished data.
(11) H. C. Chitwood and B. T. Freure, THIS JOURNAL, 68, 680 (1946).

7.48. Found: C, 70.84; H, 4.91; N, 7.25 (10.4% of total yield).

Recrystallization of II yielded 131.0 g. melting at 92–93°. *Anal.* Calcd. for $C_{11}H_9O_2N$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.87; H, 4.86; N, 7.33.

α-Carboxy-γ-phenyl-γ-butyrolactone (III) from I and II.— Ten grams of α-cyano-γ-phenyl-γ-butyrolactone (I) was refluxed with 125 ml. of 3 N NaOH until evolution of ammonia ceased (10 hours). The alkaline solution was cooled and 50 ml. of ice-cold 12 M hydrochloric acid was added slowly until acid to congo red. The cloudy solution was placed in the cold overnight. The mixture was filtered by suction and the precipitate was recrystallized from hot water to free it of sodium chloride. The melting point of the compound after drying for three hours at 60° is 147–148°. After recrystallization from alcohol, 4.7 g. melting at 149–150° was obtained. No melting point depression was observed when the compound was mixed with an authentic sample of α-carboxy-γ-phenyl-γ-butyrolactone.[9]

Hydrolysis of II yielded the same carboxy lactone, III, as was obtained by hydrolysis of I. A mixed melting point with an authentic sample showed no depression.

α-Cyano-γ-vinyl-γ-butyrolactone (IV and V).—IV and V were prepared by the same method as was used for the corresponding γ-phenyl compound. After the reaction was complete, the excess alcohol was removed at 15–20 mm., and 200 ml. of benzene was added. This mixture was then added to a mixture of 100 ml. of 12 M hydrochloric acid and 150 g. of ice. The aqueous layer was extracted four times with benzene. The combined benzene solution was washed with 50 ml. of water and twice with 50-ml. portions of saturated sodium carbonate solution, again washed with water, and dried over anhydrous sodium sulfate. After removal of the benzene at 20 mm., the product was distilled at 2 mm. The yields of crude material varied from 65–74%, boiling at 140–155°. Fractionation with a Todd column at a reflux ratio of 12 to 1 was carried out. One hundred-fifty grams of crude product yielded 15.5 g. boiling at 146–148° (2 mm.), 7.0 g. boiling at 148–150° (2 mm.) and 120.0 g. boiling at 150–152° (2 mm.).

Anal. Calcd. for $C_7H_7O_2N$: C, 61.12; H, 5.15; N, 10.22. Lower boiling fraction (IV), found: C, 61.24; H, 5.10; N, 10.28. Higher boiling fraction (V), found: C, 61.16; H, 5.05; N, 10.13.

γ-Vinyl-γ-butyrolactone (VI and VII).—Twenty-nine grams (0.2 mole) of IV was refluxed with 300 ml. of 3 N sodium hydroxide until the evolution of ammonia ceased. After cooling in an ice-box, the solution was acidified to congo red with 12 M hydrochloric acid, filtered, and nearly all the water removed by distillation at reduced pressure. The residue was extracted repeatedly with ether which was then dried over anhydrous sodium sulfate, b.p. 68–70° (1 mm.).

Anal. Calcd. for $C_6H_8O_2$: C, 64.28; H, 7.14. Found for IV: C, 64.35; H, 6.93.

The above procedure was also carried out for the hydrolysis of V to VII. Material boiling 68–70° (1 mm.) was recovered. *Anal.* Calcd. for $C_6H_8O_2$: C, 64.28; H, 7.14. Found for V: C, 64.27; H, 7.01.

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