Ring-Opening Reactions of Certain 2-Carbonyl-Substituted Cyclopropylamines[1]

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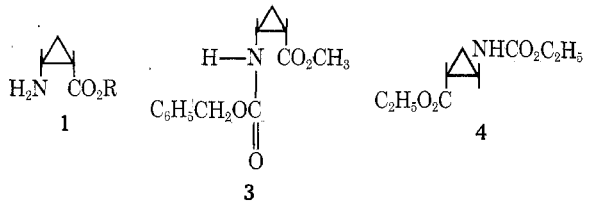
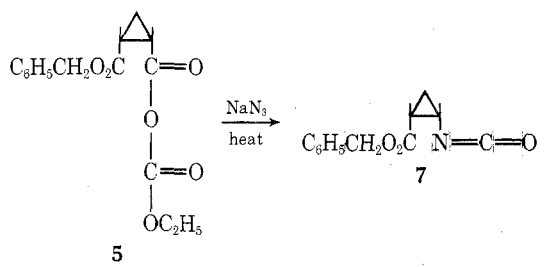
Aqueous acid treatment of *cis*- or *trans*-2-carbalkoxycyclopropyl isocyanates gives rise to the same ring-opened product, a β-formylpropionate ester corresponding to the ester group in the starting system. Experimental data and literature precedent are consistent with a reaction pathway involving initial hydration of the isocyanate group to a carbamate moiety, followed by decarboxylation of the carbamate group and ring opening to an immonium function which is immediately hydrolyzed to an aldehyde. This explanation can be invoked to rationalize literature reports of failures to achieve normal Hofmann hypohalite reactions on 2-carbalkoxy- and 2-carboxycyclopropanecarboxamides.

In the course of a continuing study of 1,2-difunctionalized cyclopropane systems, it was desired to obtain esters of *cis*-2-aminocyclopropanecarboxylic acid **1**. A Curtius reaction on *cis*-2-carbomethoxycyclopropanecarbonyl chloride (**2**) and treatment of the isocyanate product with benzyl alcohol permitted isolation of the carbamate **3** in 45% overall yield. Attempts to remove the *N*-benzyl group from **3** by hydrogenolysis failed; no identifiable organic nitrogen product could be isolated. Schroff, *et al.*,[2] reported that attempted acid-catalyzed hydrolysis of **4** gave polymeric material.



1 **3** **4**

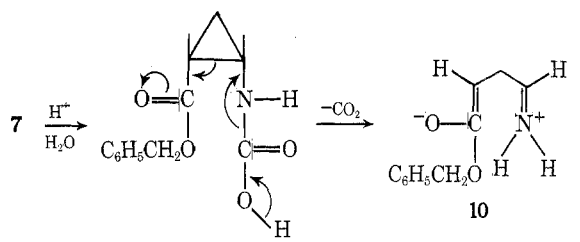
As an alternate approach, the mixed anhydride **5** was subjected to a modification[3] of the Curtius reaction to form **7**. Attempts to hydrolyze the isocyanate group of **7** and of



5 **7**

its trans isomer (**17**) with dilute hydrochloric acid led to the formation of the same distillable oil, which formed a 2,4-dinitrophenylhydrazone. The identity of this material (**8**) as benzyl β-formylpropionate was established by spectral and analytical data and was verified by conversion into a known compound, benzyl hydrogen succinate.

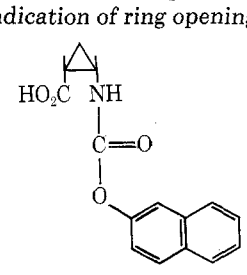
Walborsky and Ronman[4] have described a facile, base-catalyzed ring opening of 1-methyl-2,2-diphenylcyclopropylamine to a single product, 4,4-diphenyl-2-butanone. It was proposed by these workers that this ring opening may be expected of all primary cyclopropylamines, but that tertiary amines and salts are stable. In the present work, it is suggested that in an acidic aqueous environment, initial hydration of the isocyanate group is followed by decarboxylation and ring opening, analogous to a mechanism proposed by Rynbrandt and Dutton[5] for aminocyclopropyl sulfones.



9 **10**

A similar pathway may be proposed for the catalytic debenzylation of **3**. Further hydrolysis of **10** converts the immonium group into the aldehyde. This interpretation is consistent with our finding that hydrolysis of **7** with DCl in D_2O indicated that it had undergone deuteration of three succinate protons, but that it had retained the protons on the benzyl and the formyl groups. It is concluded that primary cyclopropylamines bearing a carbonyl substituent at position 2 and with a mobile electron pair on the nitrogen are highly prone to ring-opening processes, leading to replacement of the amino function by carbonyl. Kuehne and King[6] stated that protonation of the nitrogen of a cyclopropylamine prevents its assistance in ring opening and inhibits cyclopropane fission. In the case of **7**, acid treatment did not permit isolation of 2-carbobenzyloxycyclopropylamine. Failures to achieve normal Hofmann hypohalite reactions on 2-carboxy- or 2-carbalkoxycyclopropanecarboxamides[2,7] may be explainable on the basis of this type of ring opening.

Treatment of **7** with 2-naphthol gave a 2-naphthyl carbamate (**11**); hydrogenolysis of this product gave a carboxylic acid **12**, with no indication of ring opening.



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Experimental Section[8]

***cis*-2-Carbomethoxycyclopropanecarbonyl Chloride (2).** *cis*-2-Carbomethoxycyclopropanecarboxylic acid[2] (13 g, 0.09 mol) and 20 ml of $SOCl_2$ were stirred at room temperature for 4 hr. Excess $SOCl_2$ was removed by distillation and residual portions were azeotroped with anhydrous benzene. Distillation of the residue gave 12.2 g (85%) of product: bp 52–53° (0.35 mm); ir (film) 1790 (acyl chloride C=O), 1730 cm^{-1} (ester C=O); nmr (CCl_4) δ 1.20–2.80 (m, 4 H, ring H), 3.73 (s, 3 H, OCH_3).

Anal. Calcd for $C_6H_7ClO_3$: C, 44.32; H, 4.33; Cl, 21.80. Found: C,

44.53; H, 4.32; Cl, 21.59.

***cis*-2-Carbomethoxy-(*N*-carbobenzyloxy)cyclopropylamine (3).** A mixture of 5.4 g (0.0375 mol) of **2**, 2.7 g (0.0415 mol) of NaN_3, and 100 ml of Na-dried, redistilled toluene was refluxed for 8 hr, or until the ir spectrum of the reaction solution revealed no carbonyl chloride band at 1790 cm^{-1} and the presence of a strong isocyanate band at 2365 cm^{-1}. Benzyl alcohol (4.1 g, 0.039 mol) was added and the solution was refluxed for 1 hr. Removal of the toluene under reduced pressure gave a residue which was treated with excess Et_2O. The resulting solid was removed by filtration and the filtrate was evaporated to afford a solid which was recrystallized from hexane to give 3.7 g (45%) of **3**: mp 78.5–80°; ir (KBr) 3320 (NH), 1720 (ester C=O), 1690 cm^{-1} (carbamate C=O); nmr (CCl_4) δ 1.17 (t, 2 H, ring CH_2), 1.83 (q, 1 H, $CHCO_2R$), 3.36 (t, 1 H, CHN), 3.63 (s, 3 H, OCH_3), 5.03 (s, 2 H, CH_2Ph), 5.57 (broad, 1 H, NH), 7.25 (s, 5 H, ArH).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.63; H, 6.07; N, 5.62. Found: C, 62.32; H, 5.92; N, 5.85.

***cis*-2-Carbobenzyloxycyclopropanecarboxylic Acid (6).** *cis*-Cyclopropane-1,2-dicarboxylic acid anhydride[9] (33.6 g, 0.3 mol) and 35 g (0.322 mol) of benzaldehyde-free benzyl alcohol were stirred at 50–60° for 3 hr. Et_2O (15 ml) was added and the resulting mixture was cooled overnight. The resulting solid was recrystallized from Et_2O to give 60 g (90%) of product: mp 80–81.5°; ir (KBr) 3300–2500 (acid OH), 1730 (ester C=O), 1710 cm^{-1} (acid C=O); nmr ($CDCl_3$) δ 1.10–2.27 (m, 4 H, ring H), 5.14 (s, 2 H, CH_2Ph), 7.35 (s, 5 H, ArH), 10.40 (s, 1 H, CO_2H).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.64; H, 5.65.

***cis*-2-Carbobenzyloxycyclopropyl Isocyanate (7).** A procedure of Weinstock[3] was used. Compound **6** (33 g, 0.15 mol), 50 ml of H_2O, and 150 ml of Me_2CO were cooled to 0° and 16.1 g (0.16 mol) of triethylamine was added with stirring. Ethyl chloroformate (17.4 g, 0.16 mol) was added dropwise at 0° over 0.2 hr, and the resulting mixture was stirred for 1 hr. NaN_3 (16.2 g, 0.25 mol) in a minimum volume of H_2O was added dropwise with stirring at 0°. After 1 hr, 250 ml of ice–H_2O was added dropwise, and the resulting solution was extracted repeatedly with Et_2O. The combined extracts were washed with ice–H_2O and were dried ($MgSO_4$). Removal of volatiles under reduced pressure left the oily azide, to which was added 100 ml of Na-dried toluene, and the mixture was carefully refluxed for 3 hr. Removal of the toluene under reduced pressure left an orange oil which was distilled at 117–119° (0.1 mm) to give 21.8 g (75%) of product: ir (film) 2280 (NCO), 1730 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 1.05–1.67 (m, 2 H, ring CH_2), 1.90 (q, 1 H, $CHCO_2R$), 2.97 (q, 1 H, CHNCO), 5.24 (s, 2 H, CH_2Ph), 7.37 (s, 5 H, ArH).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10;, N, 6.44. Found: C, 66.26; H, 5.30; N, 6.38.

***trans*-Cyclopropane-1,2-dicarbonyl Chloride (13).** This was prepared from *trans*-cyclopropane-1,2-dicarboxylic acid[9] by the method of Gruen,[10] bp 50–60° (0.05 mm).

Dibenzyl *trans*-Cyclopropane-1,2-dicarboxylate (14). Benzyl alcohol (42 g, 0.39 mol) was added dropwise to a vigorously refluxing solution of 32.1 g (0.192 mol) of **13** in 400 ml of anhydrous Et_2O, and this mixture was refluxed for 8 hr. After repeated washing with 10% $NaHCO_3$, the organic layer was dried ($MgSO_4$), and the volatiles were removed. The residue was distilled at 177–180° (0.02 mm) to yield 46.3 g (78%) of product: ir (film) 1735 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.41 and 2.21 (sym t, 4 H, ring H), 5.10 (s, 4 H, CH_2Ph), 7.35 (s, 10 H, ArH).

Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.84. Found: C, 73.68; H, 5.85.

***trans*-2-Carbobenzyloxycyclopropanecarboxylic Acid (15).** A mixture of 13 g (0.1 mol) of *trans*-cyclopropane-1,2-dicarboxylic acid,[9] 15.6 g (0.05 mol) of **14**, 23 g (0.22 mol) of benzyl alcohol, and 5.2 ml of concentrated HCl was stirred and heated at 120–130° for 3 hr. An additional 5.2 ml of concentrated HCl was added and stirring was continued for 9 hr. The cooled reaction mixture was dissolved in 200 ml of Et_2O and was extracted with 10% $NaHCO_3$ until the washings were basic to litmus. The aqueous solution was acidified with 6 *N* HCl and was extracted with five 75-ml portions of Et_2O. The ethereal extract was dried ($MgSO_4$) and filtered, and the volatiles were removed to leave an oil which was treated with 10 ml of methylene chloride and cooled overnight. Crystals of *trans*-cyclopropane-1,2-dicarboxylic acid which separated were collected on a filter. The filtrate was evaporated to leave a viscous oil which was distilled at 158–160° (0.09 mm) to yield 7.9 g (36%) of **15**: ir (film) 3600–2350 (acid OH), 1735 (ester C=O), 1700 cm^{-1} (acid C=O); nmr ($CDCl_3$) δ 1.42 and 2.23 (2 m, 4 H, ring H), 5.10 (s, 2 H, CH_2Ph), 7.35 (s, 5 H, ArH), 10.86 (s, 1 H, CO_2H, exchanged with D_2O).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.27; H, 5.53.

***trans*-2-Carbobenzyloxycyclopropanecarbonyl Chloride (16).** Compound **15** (5.5 g, 0.025 mol) was stirred with 40 ml of $SOCl_2$ at room temperature for 5 hr. Excess $SOCl_2$ was removed by azeotroping with benzene under reduced pressure. The residue was distilled at 128–130° (0.3 mm) to give 4.9 g (83%) of product: ir (film) 1888 cm^{-1} (acyl chloride C=O); nmr ($CDCl_3$) δ 1.66 (m, 2 H, ring H), 2.52 (m, 2 H, ring H), 5.17 (s, 2 H, CH_2Ph), 7.40 (s, 5 H, ArH).

Anal. Calcd for $C_{12}H_{11}ClO_3$: C, 60.38; H, 4.64; Cl, 14.85. Found: C, 60.16; H, 4.46; Cl, 15.11.

***trans*-2-Carbobenzyloxycyclopropyl Isocyanate (17).** NaN_3 (6.5 g, 0.1 mol) in 30 ml of H_2O was added dropwise to a cooled (0°) solution of 23.8 g (0.1 mol) of **16** in 200 ml of anhydrous diglyme. After stirring for 0.5 hr, the reaction mixture was extracted with Et_2O and the organic layer was washed with H_2O and dried ($MgSO_4$). Removal of the volatiles under reduced pressure left an oil which was refluxed with 100 ml of Na-dried toluene for 2 hr. Evaporation of the toluene left an oil: bp 116–119° (0.3 mm); yield 16.8 g (78%); ir (film) 2280 (NCO), 1728 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.00–1.60 (m, 2 H, ring H), 1.73–2.08 (m, 1 H, $CHCO_2R$), 3.13–3.40 (m, 1 H, CHNCO), 5.13 (s, 2 H, CH_2Ph), 7.39 (s, 5 H, ArH).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.44. Found: C, 66.02; H, 5.14; N, 6.70.

Benzyl β-Formylpropionate (8). The hydrolysis procedure of Weinstock[3] was used. Compound **7** or **17** (2.7 g, 0.0125 mol) was added with vigorous stirring to 10 ml of 20% HCl (0.0125 mol), and the resulting solution was stirred for 10 hr. The reaction mixture was extracted with four 50-ml portions of Et_2O. The combined extracts were dried ($MgSO_4$), and filtered, and the Et_2O was removed to leave an oil which distilled at 89–92° (0.05 mm) to yield 1.15 g (48%) of product: ir (film) 2730 (CHO), 1730–10 cm^{-1} (ester, aldehyde C=O); nmr ($CDCl_3$) δ 2.72 (t, 4 H, CH_2 CH_2), 5.13 (s, 2 H, CH_2Ph), 7.37 (s, 5 H, ArH), 9.78 (s, 1 H, CHO, no D_2O exchange).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.56; H, 6.29.

Concentration of the aqueous solution from the Et_2O extraction and addition of anhydrous EtOH to the residue afforded 0.55 g (78%) of a white solid which gave a positive test for chloride with $AgNO_3$ and which liberated NH_3 upon addition of NaOH; nmr (D_2O) revealed no C–H signals.

Benzyl Hydrogen Succinate (18). Compound **8** (1 g, 0.0052 mol) was allowed to stand exposed to the air with periodic agitation for 30 days. Distillation gave 0.2 g of unchanged **8**, bp 89–95° (0.05 mm), followed by 0.55 g (52%) of **18**, bp 131–133° (0.05 mm), which crystallized on standing, mp 117–119°. An authentic sample[11] of **18** (mp 117–119°) gave an identical nmr spectrum to that of the product of the reaction described.

***cis*-2-Carbobenzyloxy(*N*-carbo-2-naphthyloxy)cyclopropylamine (11).** The method used for **7** was repeated, utilizing 19 g (0.086 mol) of **6**, 50 ml of H_2O, 80 ml of Me_2CO, 8.8 g (0.088 mol) of triethylamine, 12.6 g (0.11 mol) of ethyl chloroformate, and 8.0 g (0.125 mol) of NaN_3 in a minimum amount of H_2O. The azide thermolysis was conducted in refluxing toluene for 2 hr; then 12 g (0.0832 mol) of 2-naphthol was added and refluxing was continued for 2 hr. The reaction mixture was permitted to stand at room temperature overnight, and the volatiles were removed under reduced pressure to leave a brown solid. This was taken up in $CHCl_3$ and was washed with three 50-ml portions of 5% NaOH and then repeatedly with H_2O until the washings were neutral to litmus. The organic solution was dried ($MgSO_4$) and the solvent was removed to give a solid which was recrystallized from toluene to yield 22 g (70%) of a white powder: mp 178–179.5°; ir (KBr) 3280 (NH), 1728 (ester C=O), 1710 cm^{-1} (carbamate C=O); nmr ($CDCl_3$) δ 1.35 (t, 2 H, ring CH_2), 2.04 (q, 1 H, $CHCO_2R$), 3.55 (m, 1 H, CHN), 5.23 (s, 2 H, CH_2Ph), 5.92 (m, 1 H, NH), 7.38 (s, 5 H, ArH), 7.15–8.00 (m, 7 H, 2-naphthyl).

Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.11; H, 5.29; N, 3.87. Found: C, 73.26; H, 5.39; N, 4.02.

***cis*-[2-(*N*-Carbo-2-naphthyloxy)amino]cyclopropanecarboxylic Acid (12).** Compound **11** (9 g, 0.025 mol) in 100 ml of EtOAc was hydrogenated in a Parr shaker apparatus in the presence of 1 g of 5% Pd/C at 75° and an initial pressure of 55 psig. The reaction was complete in 3 hr. The hot reaction mixture was filtered through a Celite pad and upon removal of the solvent from the filtrate, a solid was formed which was recrystallized from tolu-

ene to afford 5.3 g (78%) of **12**: mp 169–172° (dec); ir (KBr) 3320 (NH), 1710 (carbamate C=O), 1685 cm^{-1} (acid C=O); nmr (DMSO-d_6) δ1.32 (t, 2 H, ring CH_2), 1.85 (q, 1 H, $CHCO_2R$), 3.10 (m, 1 H, CHN), 7.10–8.10 (m, 7 H, 2-naphthyl).

Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.71; H, 4.95; N, 4.90.

Registry No.—**2**, 53229-56-4; **3**, 53229-57-5; **6**, 53229-58-6; **7**, 53229-59-7; **8**, 53229-60-0; **11**, 53403-91-1; **12**, 53229-62-2; **13**, 6860-35-1; **14**, 53229-63-3; **15**, 53229-64-4; **16**, 53229-65-5; **17**, 53229-66-6; **18**, 103-40-2; $SOCl_2$, 7719-09-7; *cis*-2-carbomethoxycyclopropanecarboxylic acid, 31420-47-0; *cis*-cyclopropane-1,2-dicarboxylic acid anhydride, 5617-74-3; benzyl alcohol, 100-51-6; *trans*-cyclopropanedicarboxylic acid, 696-75-3.

References and Notes

(1) This investigation was supported by Grant No. NS-06100, National Institute of Neurological Diseases and Stroke. Abstracted from a portion of a thesis submitted by J.E.G. in partial fulfillment of the requirements for the Ph.D. degree, University of Iowa, 1974.
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Carbon-13 Nuclear Magnetic Resonance Spectroscopy Quantitative Correlations of the Carbon Chemical Shifts of Simple Epoxides[1]

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Fourier transform carbon-13 nuclear magnetic resonance spectra have been obtained for 42 simple epoxides. A set of additivity parameters have been developed which allow the calculation of the expected chemical shift of the carbon atoms of the epoxide functional group. The effect of adjacent unsaturation is also discussed.

Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectroscopy has become an extremely important research tool in the structural elucidation of organic compounds.[4] To interpret the ^{13}C nmr spectra of any particular compound it is usually required to examine the ^{13}C nmr spectra of closely related compounds containing similarly substituted carbons. A number of methods have been developed to aid in the assignment of the carbon resonances. One method in particular has proved to be quite useful for the assignment of carbon resonances. Using least-squares analyses, a system of substituent parameters has been developed for a number of compound types. These parameters are then used to predict the carbon chemical shifts of related compounds. This method has been most successfully applied by Grant,[5] Roberts,[6] and Djerassi.[7] We have extended this method to aliphatic epoxides and obtained a series of empirical substituent parameters which should prove very useful in the assignment of structure to molecules containing the epoxide functionality.

Experimental Section

A. Preparation of the Epoxides. The epoxides were either obtained commercially or synthesized by peracetic acid oxidation of the appropriate olefin. The structures of the epoxides were confirmed by proton magnetic resonance spectroscopy.

B. ^{13}C Spectra. The carbon-13 chemical shifts were obtained on a Bruker HX-90-E instrument equiped with a Bruker-Nicolet Data System, Model B-NC-12. The spectra were recorded at 22.6 MHz with 5-μsec pulse widths applied at 1-sec intervals. All of the chemical shifts were measured relative to 10% internal TMS using 45% $CDCl_3$ as solvent. At these concentrations 1000 pulses were used to obtain a reasonable signal-to-noise ratio. Complete proton decoupling was used to obtain the chemical shifts and single-frequency-off-resonance decoupled spectra were used to assign the resonances of the epoxy carbons in questionable cases. No attempts were made to assign the other carbons in the molecules.

C. Least-Squares Solutions. The least-squares solutions were obtained by using a modification of the BMD03R[8] regression analysis program for the CDC 3151 computer at California State University, Los Angeles. The program computed the least-squares empirical value for the substituent parameter, the 96% confidence limits for the parameters, the deviation between each calculated and experimental chemical shift, the standard error of prediction, and the multiple correlation coefficient.[9]

Results and Discussion

Recently several papers have appeared on the subject of the ^{13}C spectra of epoxides. Tori and Komeno[10] have studies the conformational effects in steroidal epoxides. Anet and Servis have investigated the conformational analysis of cycloheptane oxide by ^{13}C spectroscopy[11] and Anet has also studied the ^{13}C spectra of a series of di-, tri-, and tetraepoxides[12] and assigned additivity parameters to these classes of polyepoxides. However, there has not been a detailed study of simple epoxides. We now wish to report such a study.

In calculating the chemical shifts of the epoxy carbon atoms, substituent effects shown in Chart Ia were used. These are defined in the same manner as those defined by Roberts in his study of acyclic alkenes.[6] Using this method, the substituent effects for carbon 3 of *trans*-3,4-epoxy-5-methylheptane are given as $\alpha + \beta + \alpha' + 2\beta' + \gamma'$ (Chart Ib). In addition to the substituent parameters α, β, γ, α', β', and γ', it was found that better results were obtained if a cis correction factor was included when α and α' were located cis to one another. Finally a gem correction factor was also included when a system contained two α parameters. Thus the substituent effects of carbon 4 of *cis*-4,5-epoxy-4-methyloctane are given as $2\alpha + \beta + \gamma + \alpha' + \beta' + \gamma'$ + gem factor + cis factor (Chart Ic). The ^{13}C nmr shift of any epoxide can be calculated by addition of the appropriate substituent parameters to the chemical shift of ethylene oxide. The values obtained for the substituent parameters are given in Table I.