ozonized (0.055 mole of O_3/hr.) for 15 min. The solution was poured into water and the mixture was warmed on the steam bath for 30 min. After the usual work-up, the solution was concentrated and diluted with petroleum ether (b.p. 30–60°). The stable ozonide XV, m.p. 129–131°, was obtained in 83% yield (0.96 g.). The analytical sample, m.p. 130–131.5°, was obtained by recrystallization from benzene–petroleum ether.

Anal. Calcd. for $C_{21}H_{15}ClO_3$: C, 71.9; H, 4.2; Cl, 10.1. Found: C, 71.9; H, 4.3; Cl, 10.2.

There was no hydroxyl or carbonyl band in the infrared spectrum. The n.m.r. spectrum had a singlet at τ 4.73 (1H) and a multiplet with the largest peak at τ 2.56 (14H).

A solution of 4.0 g. of XV in 50 ml. of acetic acid containing 10 ml. of 48% hydrobromic acid was heated on a steam bath for 1 hr. The solvent was then removed on a rotary evaporator and the products were separated into acid and neutral fractions as usual. From the acid fraction 0.75 g. (54%) of benzoic acid was isolated. From the neutral fraction 1.3 g. (54%) of phenylphthalide, m.p. 115–117°, was obtained. Both products had infrared spectra identical with authentic spectra.

A solution of 10.0 g. of IX in 100 ml. of methylene chloride was ozonized (0.030 mole of O_3/hr.) for 4 hr. at Dry Ice–acetone temperature. The solvent was removed and the residue was crystallized from benzene–Skellysolve B to yield 8.9 g. (77%) of the ozonide XII, m.p. 138–140°. After two recrystallizations from benzene–Skellysolve B, the analytical sample, m.p. 138–140°, was obtained.

Anal. Calcd. for $C_{21}H_{15}ClO_3$: C, 71.9; H, 4.2; Cl, 10.1. Found: C, 71.8; H, 4.3; Cl, 9.9.

A solution of 1.75 g. of XII in 50 ml. of acetic acid was treated exactly as in the case of XV to yield 1.35 g. (91%) of 3,4-diphenylisocoumarin (XIV), m.p. 169–171°.

Ozonolysis. VII. Factors Controlling the Stability of *cis-* and *trans-*Molozonides of Straight-Chain Alkenes. Role of Nucleophilic Solvents in Alkene–Ozone Reactions

FRED L. GREENWOOD

Contribution No. 332, Chemistry Department, Tufts University, Medford, Massachusetts

Ozonation of *cis-* and *trans-*2-butene, 1-butene, and ethylene in ether solution at −110° followed by treatment with isopropyl Grignard reagent at this temperature gave propene, propane, and 2-propanol as reaction products. In addition, *cis-*2-butene gave 3-methyl-2-butanol, *trans-*2-butene gave 3-methyl-2-butanol and *dl-*butane-2,3-diol, 1-butene gave isobutyl alcohol, 2-methyl-3-pentanol, and butane-1,2-diol, and ethylene gave isobutyl alcohol. The data indicate that both a steric factor and a solvent effect are involved in the stability of the molozonide. One role a nucleophilic solvent may serve in ozonation reactions is to facilitate the rearrangement of the molozonide to the ozonide.

Previously,[1] it has been reported that ozonation of *trans-*3-hexene in ether solution at −110° and subsequent treatment of the ozonation mixture at −110° with isopropyl Grignard reagent gave rise to *dl-*hexane-3,4-diol. Similar treatment of *trans-*2-pentene and of 1-pentene produced *threo-dl-*pentane-2,3-diol and pentane-1,2-diol, respectively. From *cis-*3-hexene and *cis-*2-pentene no α-diol was obtained; the products in these instances were carbinols which would result from reaction of the Grignard reagent with the cleavage products of the ozonide of the alkene. Such carbinols also were found in minor amount in the reactions with the *trans-*alkenes and the 1-alkene. These facts were interpreted to indicate that the initial alkene–ozone adduct, the molozonide,[2] was stable in the case of a *trans-* or 1-alkene but not stable for steric reasons in the case of a *cis-*alkene. The various carbinols were attributed to reaction of the Grignard reagent with ozonide present in the ozonation mixture.

These studies have been extended to lower alkenes, and the reaction pattern follows the picture outlined above. *trans-*2-Butene gave rise to *dl-*butane-2,3-diol, methylisopropylcarbinol, isopropyl alcohol, propane, and propene. By vapor phase chromatography (v.p.c.) it was shown that if the diol contained any of the *meso* isomer, it contained something less than 10% of this isomer. The evidence would support the belief that the addition of ozone to *trans-*2-butene was a stereospecific process, as it was with *trans-*3-hexene and *trans-*2-pentene. With *cis-*2-butene no trace of an α-diol could be found; the crude reaction products remaining after the removal of solvent gave a negative test for α-diol with periodic acid. The reaction products in this instance were methylisopropylcarbinol, isopropyl alcohol, propane, and propene. A reaction with 1-butene gave as products butane-1,2-diol, ethylisopropylcarbinol, isopropylcarbinol, isopropyl alcohol, propane, and propene. The α-diols are presumed to have arisen from the reaction of the Grignard reagent with the molozonide. It has been established[3] that the various carbinols arose from interaction of the Grignard reagent with the ozonide.

There were some disturbing data among those reported above and in the earlier paper.[1] If steric factors only were involved in the stability of the molozonide, then one should expect the molozonide from an 1-alkene to be at least as stable, if not more so, than the molozonide from a *trans-*alkene. Yet, the facts were that 1-pentene and 1-butene gave considerably less α-diol than did the *trans-*alkenes. The ultimate experiment would be one using ethylene, for here we should obtain the parent molozonide, and steric factors should be at a minimum. Surprisingly, when this experiment was carried out, no trace of ethylene glycol could be detected in the reaction products; the identifiable products were isobutyl alcohol, isopropyl alcohol, propane, and propene. Clearly, factors other than steric must be involved in the stability of the molozonide. It would appear that a solvent effect is also involved.

(1) F. L. Greenwood, *J. Org. Chem.*, **29**, 1321 (1964).

(2) (a) H. Staudinger, *Ber.*, **58**, 1088 (1925). Direct evidence on the structure of the molozonide has yet to be obtained. (b) Like R. Criegee and G. Schröder [*Chem. Ber.*, **93**, 689 (1960)], we assign a 1,2,3-trioxolane structure to the molozonide.

(3) F. L. Greenwood and B. J. Haske, *J. Org. Chem.*, **30**, 1276 (1965).

The suggestion that a molozonide was the initial alkene–ozone reaction product was first made by Staudinger.[4] It was not until 1960 that firm experimental evidence for the existence of the molozonide appeared, when Criegee and Schröder[2b] reported the obtainment of a *threo-α*-diol by the reduction of a *trans*-di-*t*-butylethylene ozonation mixture. The *threo-α*-diol would indicate that the ozone made a synchronous addition to the carbon–carbon double bond. From the *cis*-alkene no trace of an α-diol could be obtained. Our work shows that this pattern is followed with several of the simpler *cis*- and *trans*-alkenes.

The various ozonations referred to above were carried out in ether, and solutions resulted. However, if an alkene–*n*-pentane solution was ozonized[5] at −110°, a white solid separated. This white solid was not an ozonide, and it was assumed to be the molozonide. Assuming the 1,2,3-trioxolane structure for the molozonide, a properly substituted molozonide should exhibit stereoisomerism, and if the addition of ozone to the

cis-molozonide   trans-molozonide
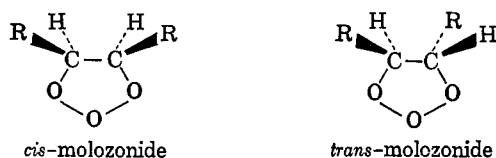
carbon–carbon double bond is indeed a synchronous process, then one might expect a *cis*-alkene to give rise to a *cis*-molozonide and a *trans*-alkene to form a *trans*-molozonide. A priori, one would expect the *cis*-molozonide to be less stable than the *trans*-molozonide, and the literature indicates that neither can be expected to be particularly stable.

A crude and inelegant type of experiment to test these ideas would be to ozonize alkene–*n*-pentane solutions at −110°, then permit the mixture to warm slowly after placing a thermometer into it and to determine the temperature at which rapid decomposition occurred. Such experiments indicated that the molozonide was extremely pressure sensitive and exploded with great violence. When raising an ozonation flask containing a thermometer and about 2.5 mmoles of molozonide from the cooling bath the mixture exploded with sufficient violence to blow out the bottom of the flask. Apparently, the thermometer bulb crushed some solid on the bottom of the flask and this pressure was sufficient to cause explosion. A flask containing some 20 mmoles of molozonide on explosion shattered not only the reaction flask, but the dewar flask containing the cooling bath as well.

The results of experiments of the above-described type supported the existence of *cis*- and *trans*-molozonides, and of decreased stability in the *cis*-molozonide. *cis*-2-Butene and *cis*-2-pentene gave molozonides which decomposed rapidly at −95 and −90°, respectively, whereas molozonides from *trans*-2-butene and *trans*-2-pentene underwent rapid decompositon at −68 and −60°, respectively. The molozonides from ethylene and 1-pentene might be expected to exhibit stability

comparable to that of *trans*-alkenes; this was indeed the case, with the ethylene molozonide decomposing rapidly at −68° and the 1-pentene molozonide decomposing at −66°. The picture with 3-hexene became somewhat troublesome. *trans*-3-Hexene molozonide decomposed rapidly at −67°, an expected temperature. The molozonide from *cis*-3-hexene, however, decomposed rapidly at −70°, and repetition of this experiment gave a value of −68°. These were unexpected values, and they suggested that *cis*-3-hexene did not give a *cis*-molozonide but formed in fact a *trans*-molozonide. If this be true, then the addition of ozone to the carbon–carbon double bond may not always be a synchronous process. The addition may occur stepwise with the ozone first adding to one of the unsaturated carbon atoms, and steric factors may necessitate rotation about what was the carbon–carbon double bond before the molozonide ring can be closed.

The white solids designated as molozonides in the preceding paragraph are not ozonides. Ozonides of these alkenes have been reported[6] in the literature; they are much more stable compounds, for they have been subjected to vacuum distillation and have been well characterized. It is possible that many of the explosions which in the literature have been attributed to ozonides have been caused in fact by the molozonide. This view is strengthened when one finds that the ozonation was carried out in methyl chloride solution at −70 to −80° with 7–10% ozone.

The above evidence would indicate that an alkene molozonide is a reasonably stable species, and the question then arises as to why *cis*-alkenes and ethylene gave no α-diol, and why 1-alkenes gave considerably less α-diol than did the *trans*-alkenes reported above. One must realize that in these experiments some 5 hr. elapsed from the beginning of the ozonation and the beginning of the addition of the Grignard reagent to the ozonation mixture.

It occurred to us some years ago that the way in which a nucleophile which is present in an ozonation mixture becomes involved in the reaction is by nucleophilic attack on the molozonide. Indeed, this view has been published by Bailey, *et al.*[7] If the nucleophilic atom carries a hydrogen atom, the cleavage species (I) undergoes proton transfer to give a type of hydroperoxide. A recent example of this type of cleavage has been reported by Thompson,[8] and other examples
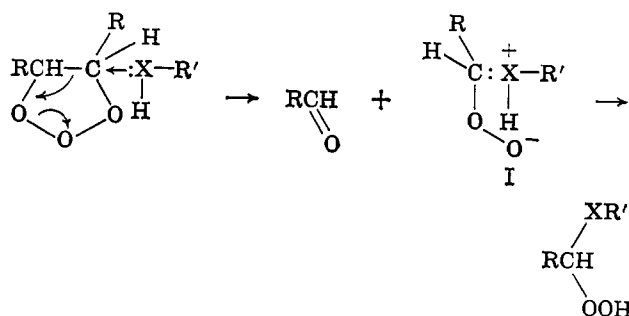
(4) Staudinger[2a] introduced the trivial name, molozonide; it was adequately defined, it is as meaningful as any trivial name, and it is our suggestion that it be used for this adduct.

(5) (a) F. L. Greenwood and S. Cohen, *J. Org. Chem.*, **28**, 1159 (1963); (b) F. L. Greenwood and B. J. Haske, *Tetrahedron Letters*, **No. 11**, 631 (1965).

(6) C. Harries and R. Koetschau, *Ber.*, **42**, 3305 (1909); A. Rieche, R. Meister, and H. Sauthoff, *Ann.*, **553**, 187 (1942); R. Criegee, G. Blust, and H. Zinke, *Chem. Ber.*, **87**, 766 (1954); R. Criegee, A. Kerchow, and H. Zinke, *ibid.*, **88**, 1878 (1955); ref. 5b.

(7) P. S. Bailey, S. B. Mainthia, and C. J. Abshire, *J. Am. Chem. Soc.*, **82**, 6136 (1960).

(8) Q. E. Thompson, *J. Org. Chem.*, **27**, 4498 (1962).

have been cited by Bailey.[9] If the nucleophilic atom does not carry a hydrogen atom, then the nucleophile will simply assist the molozonide in rearranging to the ozonide.
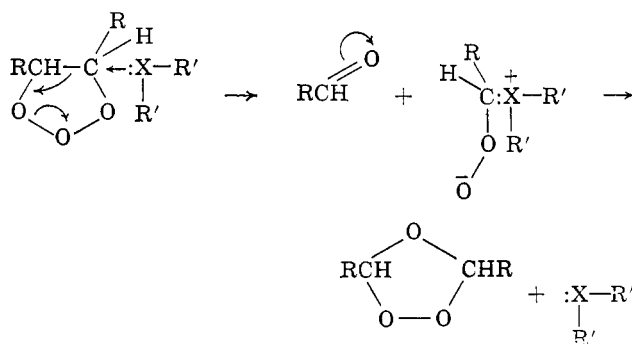
The lack of α-diol from the cis-alkene reactions may be explained by the inherent instability of a cis-molozonide coupled with ether-facilitated rearrangement of the molozonide to the ozonide in the period between the onset of ozonation and the treatment of the ozonation mixture with the Grignard reagent. The reasonable yield of α-diol from trans-alkenes may be explained by the greater stability of the trans-molozonide and the hindrance to nucleophilic attack by ether at the secondary carbon atom of the molozonide. With 1-alkenes we have a "stable" molozonide, but now there is a primary carbon atom at which nucleophilic attack by ether occurs more readily; rearrangement of the molozonide to the ozonide is facilitated and less α-diol is found than with trans-alkenes. In the case of ethylene a "stable" molozonide is formed; however, ether can exert its nucleophilic attack at two primary carbon atoms, the molozonide rearranges rather readily to the ozonide, and no glycol is found in the reaction products.

The above-described picture receives some support from the literature. Streitwieser and Andreades[10] and, more recently, Weiner and Sneen[11] have reported evidence which indicated that an ether may become involved as a nucleophile in the solvolysis of esters of primary and of secondary alcohols.

There are reports in the ozonolysis literature which may be interpreted to support the view that the function of a nucleophilic solvent is to facilitate the rearrangement of the molozonide to the ozonide, and thereby to minimize the diversion of the molozonide to polymer, etc. Fischer, et al.,[12] when studying the catalytic hydrogenation of ozonides, preferred ethyl acetate as the ozonation solvent, for in this solvent no polymeric material was formed and the hydrogenations were much more successful. The Upjohn workers[13] found that ozonation of several trans-22-unsaturated sterols in methylene chloride–pyridine solution followed by a reductive work-up procedure gave yields of the desired aldehyde which were markedly superior to those obtained when the pyridine was omitted. Ozonation of a trans-alkene in a nonnucleophilic solvent gave poly-

mer almost exclusively. An explanation of the Upjohn workers' results may be that with pyridine present, more ozonide and less polymer was obtained, and one would expect the ozonide to be reduced to the aldehyde more effectively than would polymeric material. Ipatieff, et al.,[14] reported a 40% yield of nopinone from the ozonation of β-pinene in carbon tetrachloride solution, whereas Conia and Leriverend[15] obtained the ketone in some 70% yield by conducting the ozonation of the β-pinene in methylene chloride–pyridine solution. The explanation here may be the same as that cited above.

Experimental

Chemicals.—n-Pentane, ethyl ether, and isopropyl bromide were from the same sources as described previously.[1]

cis- and trans-2-butene, 1-butene, and ethylene were research grade materials (Phillips Petroleum Co.).

cis- and trans-2-pentene and cis- and trans-3-hexene were API standard samples (Carnegie Institute of Technology).

1-Pentene was from the source specified earlier.[1]

dl-Butane-2,3-diol was prepared from cis-2-butene by the method of Emmons, et al.,[16] b.p. 50° (1 mm.), n^{25}D 1.4311 [lit. b.p. 176° (760 mm.), n^{24}D 1.4318,[17] and b.p. 54° (2 mm.), $n^{19.4}$D 1.4320[18]].

meso-Butane-2,3-diol was prepared from trans-2-butene by the method of Emmons, et al.,[16] b.p. 45° (1 mm.), n^{25}D 1.4372 [lit.[17] b.p. 60–61° (2 mm.), n^{24}D 1.4372].

Butane-1,2-diol was prepared from 1-butene by the method of Emmons, et al.,[16] b.p. 56° (1 mm.), n^{25}D 1.4365 [lit. b.p. 96–97° (10 mm.),[19] n^{20}D 1.4378[20]].

The **ozonation procedure** was the same as that described earlier.[1] The ozonizer produced about 550 mg. of ozone/hr.

General Reaction Procedure.—In the experiments with cis- and trans-2-butene and with 1-butene the alkene was measured into a gas buret, and the alkene was dissolved in 400 ml. of ether which had been cooled to −110°. To the alkene solution was added 90% of the theoretical amount of ozone. During the ozonation of ethylene (b.p. −104°) the alkene and ozone were bubbled simultaneously into 400 ml. of ether which was cooled to −110°. After standing for 30 min. while the oxygen of the ozonizer was displaced with nitrogen, the reaction mixture was purged of oxygen by bubbling nitrogen through it for 1 hr. The ozonation mixture was treated with excess isopropyl Grignard reagent, and the reaction mixture was worked up as previously[1] outlined. The gas evolved from the ozonation mixture–Grignard reagent reaction was analyzed by mass spectrometry.[21]

trans-2-**Butene.**—Alkene used was 45.2 mmoles; ozone introduced was 40.7 mmoles; Grignard reagent reacted was 150 m-moles. Refluxing the ozonation mixture–Grignard reagent reaction mixture gave 23.5 mmoles of propene and 39.0 mmoles of propane. The more volatile material (3.86 g.) was analyzed by v.p.c. (5% cyanosilicone on hexamethyldisilazane-treated Chromosorb W column) and found to contain isopropyl alcohol, 32.1 mmoles, and methylisopropylcarbinol, 23.3 mmoles. The high-boiling material (1.50 g.) was analyzed by v.p.c. (30% phenyldiethanolamine succinate on hexamethyldisilazane-treated Chromosorb W column) and found to contain dl-butane-2,3-diol, 14.0 mmoles, and unidentified material, 0.10 g. A mixture of authentic dl- and meso-butane-2,3-diol was not separated completely by this column; however, the dl-diol peak obtained on v.p.c. of a mixture containing 10% of the meso-diol (longer retention time) had a very marked shoulder caused by the meso-diol. V.p.c. of the diol obtained from the trans-2-butene gave a

(9) P. S. Bailey, Chem. Rev., 58, 925 (1958).

(10) A. Streitwieser, Jr., and S. Andreades, J. Am. Chem. Soc., 80, 6553 (1958).

(11) H. Weiner and R. A. Sneen, ibid., 87, 287 (1965).

(12) F. G. Fischer, H. Düll, and L. Ertel, Ber., 65, 1467 (1932).

(13) D. A. Shepherd, et al., J. Am. Chem. Soc., 77, 1212 (1955); G. Slomp, Jr., et al., ibid., 77, 1216 (1955); G. Slomp, Jr., and J. L. Johnson, ibid., 80, 915 (1958).

(14) V. N. Ipatieff, G. J. Czajkowski, and H. Pines, ibid., 73, 4098 (1951).

(15) J. M. Conia and P. Leriverend, Compt. rend., 250, 1078 (1960).

(16) W. D. Emmons, A. S. Pagano, and J. P. Freeman, J. Am. Chem. Soc., 76, 3472 (1954).

(17) J. Dale, J. Chem. Soc., 910 (1961).

(18) L. Fishbein, J. Am. Chem. Soc., 79, 2959 (1957).

(19) W. Reppe, et al., Ann., 596, 65 (1955).

(20) K. A. Clendenning, J. F. Macdonald, and D. E. Wright, Can. J. Res., B28, 608 (1950).

(21) The author is indebted to the Texas Research Laboratories, Beacon, N. Y., for the mass spectrometric analyses.

dl-diol peak which had no trace of a shoulder. Hence, if this *dl*-diol was not completely free of *meso* isomer, it surely contained considerably less than 10% of this isomer. The high-boiling material gave the bis(4-nitrobenzoate), m.p. and m.m.p. 129.0–129.5°, lit.[17] m.p. 128°. After distillation of the high-boiling material a residue of 0.25 g. remained.

cis-2-Butene.—Alkene used was 41.5 mmoles; ozone introduced was 39.4 mmoles; Grignard reagent reacted was 147 mmoles. Refluxing the ozonation mixture–Grignard reagent reaction mixture gave 15.6 mmoles of propene and 30.4 mmoles of propane. After removal of the solvent the reaction products gave a negative test for α-diol with periodic acid. The more volatile material (6.27 g.) was found to contain by v.p.c. isopropyl alcohol (28.5 mmoles), methylisopropylcarbinol (49.3 mmoles), and unidentified material (0.04 g.). There was a distillation residue of 0.26 g.

1-Butene.—Alkene used was 45.3 mmoles; ozone introduced was 40.8 mmoles; Grignard reagent reacted was 155 mmoles. Refluxing the ozonation mixture–Grignard reagent reaction mixture gave 20.5 mmoles of propene and 39.7 mmoles of propane. The more volatile material (4.63 g.) was found by v.p.c. to contain isopropyl alcohol (31.6 mmoles), isobutyl alcohol (14.2 mmoles), ethylisopropylcarbinol (17.9 mmoles), and unidentified material (0.19 g.). The high-boiling material was analyzed by v.p.c. and found to contain butane-1,2-diol (9.0 mmoles) and unidentified material (0.35 g.). The bis(4-nitrobenzoate) of the high-boiling material was prepared and had m.p. and m.m.p. 95–96°.

Anal.[22] Calcd. for $C_{18}H_{16}N_2O_8$: C, 55.7; H, 4.2; N, 7.2. Found: C, 56.3; H, 4.4; N, 7.3.

There was a distillation residue of 0.04 g.

Ethylene.—Ozone introduced was 40.0 mmoles; Grignard reagent reacted was 144 mmoles. Refluxing the ozonation mixture–Grignard reagent reaction mixture gave 19.9 mmoles of propene and 37.3 mmoles of propane. After removal of solvent the reaction products gave a negative test for α-diol with periodic acid. The more volatile material (4.15 g.) was found by v.p.c. to contain isopropyl alcohol (21.9 mmoles), isobutyl alcohol (38.5 mmoles), and unidentified material (0.41 g.). There was a distillation residue of 0.42 g.

(22) By S. M. Nagy, Massachusetts Institute of Technology Microchemical Laboratory.

Detection of ethylene glycol in the aqueous layer was attempted by v.p.c. (10% Ethofat on Fluoropak column), but none could be detected either in the initial aqueous layer or after it had been concentrated to 75 g. on a rotary evaporator. Control experiments showed that the glycol could be detected without difficulty in a 0.5 wt. % aqueous solution, and that this solution could be concentrated on a rotary evaporator without loss of the glycol.

Preparation of Molozonides in *n*-Pentane.—The alkene (7.0–10 mmoles) was dissolved in 75 ml. of *n*-pentane. The solution was cooled to −110° and 2.50 mmoles of ozone was added to the solution. Ethylene was introduced simultaneously with the ozone into the *n*-pentane. The ozone–oxygen stream contained about 1.5 vol. % of ozone. All of the ozone was retained by the reaction mixture. With the C_2, C_4, and C_5 alkenes solid material separated in the reaction mixture from the very early stages of the ozonation. The C_5 molozonides were sufficiently soluble in the pentane to necessitate a reduction of the volume of *n*-pentane to 50 ml. The molozonides of the *trans* C_4 and C_5 alkenes were more soluble than were those from the corresponding *cis*-alkenes.

The ozonation flask was removed from the apparatus, and a thermometer (precooled in liquid nitrogen) was placed carefully into the reaction mixture. In the case of *cis*-2-pentene the thermometer went into the reaction mixture with a sizzling noise, and when the thermometer bulb touched the bottom of the reaction flask one could hear and feel a small explosion at the end of the thermometer. In this first experiment the reaction mixture exploded as the reaction flask was being raised from the cooling bath. This was attributed to the thermometer bulb crushing some of the solid on the bottom of the reaction flask. Thereafter, the cooling bath was lowered carefully from the reaction flask. The reaction mixture was allowed to warm slowly, and the temperature was noted when the warming rate increased rapidly. At this point the white solid in the reaction mixture disappeared rapidly. The temperatures at which these rapid decompositions began for the various alkene molozonides follow: ethylene, −68°; *cis*-2-butene, −95°; *trans*-2-butene, −68°; *cis*-2-pentene, −90°; *trans*-2-pentene, −60°; 1-pentene, −66°; *cis*-3-hexene, −70 and −68°; and *trans*-3-hexene, −67°.

The Synthesis of 4,1-Benzothiazepines and 5,1-Benzothiazocines

M. Uskoković, G. Grethe, J. Iacobelli, and W. Wenner

Department of Chemical Research, Research Division of Hoffmann-La Roche Inc., Nutley, New Jersey

Synthesis of 3,5-dihydro-4,1-benzothiazepin-2(1H)-one (V) and 1,3,4,6-tetrahydro-2H-5,1-benzothiazocin-2-one (XI) are described. Lithium aluminum hydride reduction of V and XI gave 1,2,3,5-tetrahydro-4,1-benzothiazepine and 2,3,4,6-tetrahydro-1H-5,1-benzothiazocin, respectively.

The first report on a compound with a benzothiazepine structure appeared about 40 years ago. Mayer and Horst[1] reacted β-chloropropionic acid with *o*-nitrothiophenol and the resulting β-(*o*-nitrophenylmercapto)propionic acid was then reduced to its amino analog, which, when heated, cyclized to 2,3-dihydro-1,5-benzothiazepin-4(5H)-one.[2,3] This compound was reduced by lithium aluminum hydride to 2,3,4,5-tetrahydro-1,5-benzothiazepine.[4] Several alternative approaches to this class of compounds have been developed. They are based upon the condensation of *o*-aminothiophenol with α,β-unsaturated acids,[5] α,β-unsaturated esters,[6] α,β-unsaturated ketones,[7–9] acetoacetic ester, or diketene.[10] The significance of the substituted derivatives of 2,3-dihydro-1,5-benzothiazepin-4(5H)-one and 1,5-benzothiazepin-4(5H)-one as pharmacologically useful agents was brought to light by the work of Krapcho and his co-workers.[11–13] The isomeric 1,4-benzothiazepine structure was ob-

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(2) N. Cagnoli, A. Ricci, and N. Fedi, *Ann. Chim.* (Rome), **47**, 606 (1957).

(3) C. Finzi, Atti del congresso nazionale di chimica pura ed applicata, 2nd Congress, 1926, pp. 1312–1315.

(4) O. E. Fancher and G. Nichols, U. S. Patent 3,029,251 (1962).

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(6) L. K. Mushkalo and N. Y. Kozlova, *Ukr. Khim. Zh.*, [8] **28**, 960 (1962).

(7) L. K. Mushkalo, *ibid.*, **19**, 193 (1953).

(8) L. K. Mushkalo, *J. Gen. Chem. USSR*, **28**, 498 (1958).

(9) L. K. Mushkalo, *ibid.*, **28**, 723 (1958).

(10) W. Ried and W. Marx, *Chem. Ber.*, **90**, 2683 (1957).

(11) J. Krapcho, A. Szabo, and J. Williams, *J. Med. Chem.*, **6**, 214 (1963)

(12) J. Krapcho, E. R. Spitzmiller, and C. F. Turk, *ibid.*, **6**, 544 (1963).

(13) J. Krapcho, U. S. Patents 3,075,967, 3,075,968, and 3,089,872 (1963).