ketoesters lowers the enol/keto ratio. Thus, ethyl α-bromoacetoacetate possesses 4% enol character.[12] It has also been shown[13] that α,γ-difluoroacetoacetate contains 5.2% enol.

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Methylenecyclopropane *via* Thermal Decomposition of Dimethylaminomethylcyclopropane *N*-Oxide[1,2]

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An earlier paper described the synthesis of bis-(dimethylaminomethyl) derivatives of cyclopropane by methylenecyclopropane.[2] Their preparation was of interest as they could possibly serve as precursors for the hydrocarbons dimethylenecyclopropane and trimethylenecyclopropane, provided their deamination could be achieved *via* either the Hofmann elimination method or the thermal decomposition of their *N*-oxides. However, some initial studies in this Laboratory on the deamination of bis(dimethylaminomethyl)cyclopropane, by the above routes, to produce dimethylenecyclopropane, have not been encouraging. It seemed desirable, therefore, to examine carefully the usefulness of deamination procedures in the synthesis of the known simple hydrocarbon methylenecyclopropane (I). Such a study might provide some information pertinent to the optimum experimental conditions for effecting deamination to introduce *exo*-unsaturation in cyclopropane systems.

Demjanow prepared the hydrocarbon I by the Hofmann elimination method[4] and most recently I was obtained in high yield by the decomposition of cyclobutanone tosylhydrazone.[5] Prior to the latter discovery the most convenient route to I was cyclization, by a modified Freund method, of 3-chloro(2-chloromethyl)-1-propene.[6] The most complete account of the properties of I are given in the report by the Ohio State University workers.[6]

For the present study dimethylaminomethylcyclopropane *N*-oxide (II) was obtained smoothly from dimethylaminomethylcyclopropane (III) by the procedure described by Cope.[7] The tertiary amine III was prepared by lithium aluminum hydride reduction of *N*,*N*-dimethylcyclopropanecarboxamide (IV). Preparation of IV from cyclopropanecarboxylic acid (V)[8] was straightforward.

Thermal decomposition of the *N*-oxide II was effected, over a range of temperature between 135–275°, in a nitrogen atmosphere at 3–5 mm., by slow, dropwise addition of an aqueous sirup of II onto a heated column packed with glass beads. The products formed were trapped as described in the Experimental Section. All olefinic products were initially adsorbed on alumina, then eluted and analyzed by vapor phase chromatography and by determinations of infrared and mass spectra. Three olefins were found as products: the hydrocarbon I together with isobutylene and 1,3-butadiene. Decomposition of the *N*-oxide II to the tertiary amine III was not observed. The three stated olefins were produced in low conversion and in yields which varied from *ca.* 4–12% with changes in pyrolysis temperatures. At best, the hydrocarbon I was obtained in *ca.* 6.5% yield at 210°. At this temperature, the optimum one for obtaining I, isobutylene and 1,3-butadiene were each produced in *ca.* 3% yield.[9] It was shown by an independent experiment that authentic I did not give either isobutylene or 1,3-butadiene under the pyrolysis conditions.

In conclusion it should be pointed out that the thermal decomposition of the amine oxide II contrasts sharply with similar decompositions of amine oxide derivatives of higher ring systems, *i.e.*, those with four through seven ring members.[10,11,12] In these systems amine oxide decompositions generally give 60–80% yield of olefin product.

EXPERIMENTAL

Materials. 1,3-Butadiene and isobutylene, obtained from The Matheson Co., were C.P. grade. Methylenecyclopropane, prepared as described earlier,[6] was found by vapor phase chromatography (VPC) analysis to contain 14% isobutylene.

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[1] This is the twelfth publication concerned with the chemistry of small carbon rings. For the preceding paper, see A. T. Blomquist and E. A. LaLancette, *J. Am. Chem. Soc.*, **83**, 1387 (1961).

[2] For a closely related paper see A. T. Blomquist and D. T. Longone, *J. Am. Chem. Soc.*, **81**, 2012 (1959).

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[7] A. C. Cope, N. A. LeBel, H.-H. Lee, and W. R. Moore, *J. Am. Chem. Soc.*, **79**, 4720 (1957).

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[9] Under the pyrolysis conditions described *N*,*N*-dimethylbutylamine *N*-oxide gave consistently 90–95% pure 1-butene.

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Cyclopropanecarbonyl chloride,[13] b.p. 46–48° (64 mm.) and n_D^{20} 1.4475, was prepared in a standard way by reaction of thionyl chloride with cyclopropanecarboxylic acid,[8] b.p. 64–65° (3.8 mm.) and n_D^{20} 1.4382, which had been prepared from γ-chlorobutyronitrile[14] of b.p. 104–107° (60–62 mm.).

N,N-Dimethylbutylamine,[15] b.p. 93–95° (745 mm.) and n_D^{20} 1.3970, was prepared from *n*-butylamine (Distillation Products Ind.) by a described methylation procedure.[16] The tertiary amine formed a picrate derivative of m.p. 95°,[15] a methiodide derivative of m.p. 230°,[17] and an *N*-oxide whose picrate had m.p. 107.5–108°.

Anal. Calcd. for $C_{12}H_{18}N_4O_8$: C, 41.62; H, 5.24. Found: C, 41.81; H, 5.42.

Instruments. Infrared spectra were determined with 10-cm. gas cells with potassium bromide windows and used in Perkin-Elmer Spectrophotometers, Models 21 and "Infracord." All VPC work was done at room temperature with a Perkin-Elmer Vapor Fractometer, Model 154 B, fitted with an aluminum column, 2 m. × 4 mm., packed with dinonyl phthalate (30% by weight) on "Chromasorb W" (Johns-Manville). Mass spectra were determined with a Consolidated Engineering Corp. Mass Spectrometer, Model No. 21-401, and with a spectrometer specially designed and built by Dr. Richard F. Porter of Cornell.

N,N-Dimethyl cyclopropanecarboxamide (IV). Anhydrous dimethylamine (The Matheson Co.) was passed with stirring, into a solution of 43.0 g. (0.42 mole) of cyclopropanecarbonyl chloride in 300 ml. of benzene, cooled with an ice bath, until precipitation of dimethylamine hydrochloride was complete. From the filtered, dried benzene solution there was obtained 36.5 g. (77%) of the amide IV; b.p. 55° (1.5 mm.), n_D^{20} 1.4640.

Anal. Calcd. for $C_6H_{11}NO$: C, 63.60; H, 9.78; N, 12.38; mol. wt. 113. Found: C, 63.58; H, 9.85; N, 12.42; mol. wt. 115.

Dimethylaminomethylcyclopropane (III). To 4.36 g. (0.12 mole) of lithium aluminum hydride in 60 ml. of anhydrous ether, which had been refluxed 3 hr. with stirring, 17.0 g. (0.15 mole) of the amide IV in 60 ml. of ether was added in 30 min. The mixture was refluxed 3 hr., cooled with an ice bath, and excess hydride decomposed by careful addition of 25 ml. of saturated ammonium chloride solution. From the filtered, dried ether solution there was obtained 9.12 g. (61%) of the amine III; b.p. 99–100° (750 mm.), n_D^{20} 1.4194.[4]

The *picrate and methiodide derivatives* of the amine III, m.p.'s 100–101°[4] and 180–181°,[4] respectively, were prepared by standard procedures. The *N-oxide derivative* of the amine III (II) was prepared by reaction of the amine, in two to three times its volume of methanol, with 50% excess 35% hydrogen peroxide. After this mixture had stood at room temperature for 24 hr. excess peroxide was destroyed by the portionwise addition of small amounts of platinum black.[7] The filtered solution of the *N*-oxide II, concentrated to a sirup under an air stream, was assayed by conversion of an aliquot to the *N*-oxide *picrate derivative,* m.p. 131–131.5°.

Anal. Calcd. for $C_{12}H_{16}N_4O_8$: C, 41.86; H, 4.69. Found: C, 41.96; H, 4.63.

Thermal decomposition of the N-oxide II. The procedure used was generally based on one described by Cope.[7] All experiments were done at temperatures which were varied from 135° to 275° and with sirups of the *N*-oxide which contained 0.01–0.07 mole of the compound II.

Apparatus. Thermal decompositions were done in a heated, vertical Pyrex tube (2 cm. O.D.) packed with 3-mm. glass beads over a 45 cm. length. Amine oxide solutions were introduced at the top of the tube through a fitted funnel whose stem extended 5–10 cm. into the column packing. Also attached to the top of the column was a nitrogen inlet line, fitted with a sulfuric acid bubbler to allow observation of rate of flow. Attached to the bottom of the pyrolysis tube was a series of six traps ultimately joined to a vacuum system. The six traps comprised the following: two traps at *ca.* −16° for the collection of nonolefinic liquid products; a U-tube at *ca.* −65° packed centrally with 40 g. of activated alumina (Alcoa F-20) and at each end with Drierite; a 2.5 × 30 cm., indented olefin trap cooled in liquid nitrogen; finally two additional traps cooled in liquid nitrogen.

Procedure. Prior to the addition of *N*-oxide solutions, the entire apparatus was evacuated to 3–5 mm. pressure while maintaining a constant nitrogen atmosphere, the pyrolysis tube was brought to the desired temperature for a particular experiment, and all traps were cooled. The entire apparatus was then kept at a constant state of readiness for 1 hr. Finally, before decomposition of the *N*-oxide of the amine was done, a check experiment was carried out on the decomposition of a known quantity of *N,N*-dimethylbutylamine *N*-oxide to make certain that the apparatus was in proper working order. In all such check experiments 90–98% of pure 1-butene was obtained, as indicated by VPC analysis.

The *N*-oxide of the amine, as a sirup, was then added dropwise to the evacuated heated column at a rate such that decomposition of each drop was complete before more material was added. This was ascertained by observation of the nitrogen flow rate. After addition of all material was complete, 0.5 to 1 hr., the column was kept at the prescribed temperature for one more hour. Then the vacuum system was disconnected and the apparatus brought to atmospheric pressure by the continued flow of nitrogen. With the flow of nitrogen through the system continued, the first two traps were allowed to warm to room temperature and the U-tube trap was heated to 70° for 6 hr. This procedure released the olefinic products which then condensed in the still cooled olefin trap.

The olefin trap was separated from the system and attached to a gas burett and the total volume of gaseous olefins determined. The mixture of gaseous olefins was then transferred to a 50-ml. flask for handling in subsequent analysis.

Product analysis. The gaseous olefinic products were analyzed by VPC and by the methods of infrared and mass spectrophotometry. Nonolefinic products which remained on the column and collected in the first two traps were analyzed by chemical methods.

Infrared analysis of the olefinic products, determined in samples at 100–200 mm. pressure in a gas cell, showed that the mixture comprised isobutylene, 1,3-butadiene, and methylenecyclopropane. VPC analysis confirmed this observation and also gave quantitative information about the relative amounts of the three hydrocarbons; the relative amounts varied depending upon the pyrolysis temperature. The VPC studies were confirmed by similar studies made with authentic specimens of the three hydrocarbons named. The mass spectra of pyrolysate samples, corrected for the known quantity of isobutylene and 1,3-butadiene present[18] as determined by VPC data, agreed at all a.m.u. (29–54) with the spectrum of authentic methylenecyclopropane. Finally, the infrared spectrum of methylenecyclopropane,[19] isolated by preparative VPC, was identical with that of an authentic specimen.

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Treatment with ethanolic picric acid of the nonolefinic material which collected in the first two traps gave no insoluble picrate derivatives characteristic of the tertiary amine III or its *N*-oxide II. From an ethanolic wash of the column itself, however, the picrate derivative of the original amine *N*-oxide II was obtained.

Thermal stability of methylenecyclopropane. A typical sample of olfinic pyrolysate was observed by VPC analysis to be unchanged in composition after standing at room temperature for two weeks. It was observed also, by VPC analysis, that authentic methylenecyclopropane underwent no change when passed through the complete pyrolysis apparatus at 210° as was done with the amine *N*-oxide II.

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Bicyclic Bases. I. 2-Hydroxymethyl-2-phenyl-3-pyrrolidinylmethyl-5-norbornene

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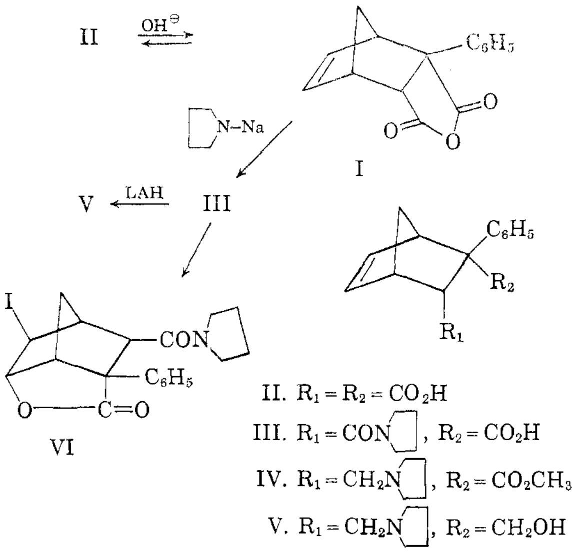
In considering structures that could have analgesic activity, we were attracted to the possibility that compounds such as the norbornene derivatives IV and V might be of interest. In addition to fulfilling the well known structural requirements for analgesic activity,[1] compounds such as IV and V might fit Beckett's proposed "analgesic receptor site"[2] although the "cavity" between the "flat place" and "anionic site" would have to be rather large to accommodate the bulk of the norbornene ring. Some advantage might be gained also by having functional groups fixed in space through their attachment to a rigid bicyclic system which would make any study of the relationship between conformation and pharmacological activity more precise.

Synthesis of these structures was approached through the cyclopentadiene-phenylmaleic anhydride[3] Diels-Alder adduct I. Anhydride I was first prepared by Miller and Mann[4] who characterized their product by saponification to the crystalline dicarboxylic acid II, which was obtained in 51.5% yield. No sterochemical assignment was made to this product. Subsequently, Winternitz, Mousseron, and Rouzier[5] reported that cyclopentadiene and phenylmaleic anhydride reacted to give a noncrystalline product which upon hydrolysis gave 55% of a crystalline mixture of diacids. The French workers concluded on the basis of the isolation of a bromo acid lactone after bromination of their diacid that their crystalline diacid was 70% *cis-exo* and 30% *cis-endo* (II).

In our hands, the reaction of cyclopentadiene and phenylmaleic anhydride under conditions very similar to those reported[4,5] led directly to 69% of pure crystalline *endo*-anhydride I, m.p. 69-70°. We first obtained the crystalline anhydride by saponification of the crude adduct to the pure acid II (66% yield, m.p. 171-172°) followed by cyclization with acetyl chloride to the pure anhydride (87% yield). Proof for the *endo*-configuration of I is given below.



Opening the anhydride ring of I with secondary amines proved to be surprisingly difficult. In 25% aqueous dimethylamine at 55° for many hours as well as in anhydrous dimethylamine in a sealed tube at 60°, I was uneffected and recovered unchanged. The anhydride was also returned in good recovery after heating eighteen hours under reflux in pyrrolidine. However, by dissolving three equivalents of sodium hydride in a large excess of pyrrolidine and allowing the anhydride to stir in the resulting suspension of pyrrolidine salt at room temperature, the desired amide acid was obtained in 87% yield. Structure III is most probable for this product. The *endo*-sterochemistry of the carboxyl group was proved by conversion to an iodolactone VI. This iodolactonization also proves the *endo*-configuration for anhydride function and carboxyl groups of I and II. The position of the amide function in III is inferred from the expected attack of the pyrrolidine amide anion at the less hindered carbonyl group attached to the 3- position of the norbornene ring. Only one sharp-melting amide acid was obtained, indicating definite selectivity. Support for this assignment of the acid and amide functions in III is gained by analogy with the reaction of phenylsuccinic anhydride with ammonia and

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