

Synthesis and Stereochemistry of Bicyclo[6.2.1]undecane Derivatives. Acyloin Reactions of Esters of 1,3-Cyclopentanedipropionic Acids¹

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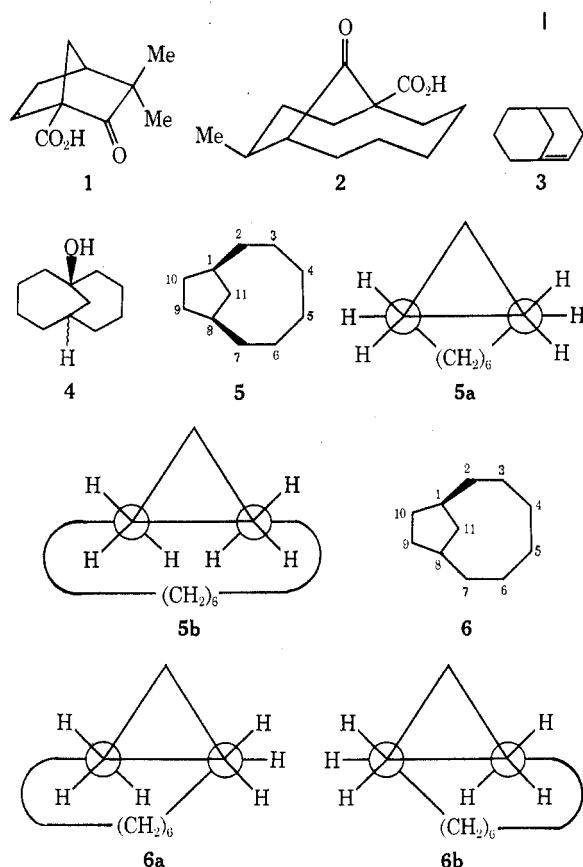
The stereochemical consequences of *cis*-*trans* bridgehead bonding in bridged bicyclic systems is discussed. Acyloin syntheses of *cis*- and *trans*-bridged bicyclic systems from esters of isomerically pure *cis*- and *trans*-1,3-cyclopentanedialkanoic acids were investigated. Reaction of dimethyl *cis*-1,3-cyclopentanedipropionate (**7b**) with sodium in dioxane gave a mixture of *cis*-bicyclo[6.2.1]undecan-4-ol-5-one (**8a**) and *cis*-bicyclo[6.2.1]undecane-4,5-dione (**8b**) in 43% yield. Dimethyl *trans*-1,3-cyclopentanedipropionate (**9b**) failed to undergo condensation to the corresponding strained *trans*-bicyclic products. Instead, a complex mixture of low yield products was obtained, the major component of which was identified as *trans*-1,3-cyclopentanedipropanol (**11**, 3% yield). Attempts to cyclize dimethyl *trans*-1,3-cyclopentanedibutyrate (**13d**) to the less strained *trans*-bicyclo[8.2.1]tridecane system **14** also resulted in the formation of abnormal minor products, and *trans*-1,3-cyclopentanedibutanol (**15**) was obtained in 7% yield.

There has been substantial interest in a variety of bicyclic systems because of their novel properties. The chemistry of the readily accessible small-ring bicyclic systems such as the bicyclo[2.2.1]heptanes has been studied extensively. Bicyclic systems containing medium and large rings, however, have received only minor attention.

Much of the unique chemistry of bicyclic compounds is related to their strain energy and is therefore markedly dependent on ring size. An example of the influence of ring size is provided by the well-known Bredt rule,³ which states that a double bond cannot exist at the bridgehead of a small-ring bicyclic system. Camphonic acid (**1**) and similar compounds can, therefore, be decarboxylated only with great difficulty because of an intermediate double-bonded bridgehead.⁴ In the medium-ring bicyclic acid **2**, however, decarboxylation occurs readily, since a bridgehead double bond can be accommodated without excessive additional strain.⁵ More recently, Marshall, Faubl, and Wiseman⁶ have demonstrated the existence of bicyclo[3.3.1]non-1-ene (**3**) in violation of Bredt's rule.

We wish to report here some of our investigations into related phenomena in the bicyclo[6.2.1]undecane system. Since, in the case of the larger ring bicyclic compounds, abnormal bonding situations may not be prohibited at the bridgeheads, a unique phenomenon must be taken into account when considering such systems, namely the possibility of *trans* bonding at the bridgehead. Dauben and Westman⁷ have shown through the isolation of two isomeric bicyclo[4.4.1]undecan-1-ols (**4**, H *cis* or *trans* to OH) that both *cis* and *trans* bonding at the bridgehead are possible in this molecule.

The possibility of *cis*-*trans* bonding at the bridgehead of bicyclo[6.2.1]undecane has some interesting consequences. Examination of Newman projections, **5a** and



5b, along the 10-1 and 9-8 carbon-carbon bonds of the molecule with *cis*-bridged bonding, **5**, reveals two possible conformational isomers. In one isomer (**5a**) the six-carbon bridge is bonded to the cyclopentane ring pseudodiaxially, and in the other isomer (**5b**) the bonding is pseudodiequatorial. Because of the restriction imposed by the six-carbon bridge, the bonding in **5** is probably pseudodiaxial. The two asymmetric bridgehead positions are of opposite absolute configuration and identically substituted; the molecule has a plane of symmetry and is an optically inactive meso form.

The *trans*-bridged bicyclo[6.2.1]undecane (**6**) also has two identically substituted bridgehead positions, but of the same absolute configuration. The bonding of the six-carbon bridge to the cyclopentane ring is pseudoaxial-equatorial. There are, examining Newman projections, **6a** and **6b**, two possible isomers of *trans*-bridged **6** which should be *optically active solely as the re-*

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(3) J. Bredt, *Justus Liebigs Ann. Chem.*, **437**, 1 (1924).

(4) F. S. Fawcett, *Chem. Rev.*, **47**, 219 (1950).

(5) (a) V. Prelog, L. Ruzicka, P. Barman, and L. Frenkiel, *Helv. Chim. Acta*, **31**, 92 (1948); (b) V. Prelog, P. Barman, and M. Zimmerman, *ibid.*, **32**, 1284 (1949).

(6) (a) J. A. Marshall and H. Faubl, *J. Amer. Chem. Soc.*, **89**, 5965 (1967);

(b) J. R. Wiseman, *ibid.*, **89**, 5966 (1967).

(7) W. G. Dauben and T. L. Westman, Abstracts, Fourth Biennial Organic Symposium, Chemical Institute of Canada, Edmonton, Alberta, 1960.

sult of asymmetric bridgehead bonding. Derivatives of **6** which have no axis of symmetry, such as the trans bicyclic acyloin **10a** do not have identically substituted bridgehead positions, and two *dl*-racemates should be possible as the result of asymmetry at the bridgehead carbon atoms. In addition, **10a** has an asymmetric center at position 5, and a total of eight isomers (2^3), four *dl*-racemates, is possible. In derivatives of **6** such as the trans-bicyclic diketones **10b** which have identically substituted bridgehead positions, the stereochemistry is the same as in **6** and only one *dl*-racemate is possible as the result of molecular dissymmetry.

An analogous phenomenon of molecular dissymmetry has recently been observed in trans-cyclic olefins by Cope and coworkers.⁸ A trans-cyclic olefin, such as *trans*-cyclononene, has an axis of symmetry but is optically active due to molecular dissymmetry.^{8b} In this respect, the trans-cyclic olefins are analogous to the hypothetical *trans*-bicyclo[6.2.1]undecane system (**6** and derivatives of **6** having identically substituted bridgehead positions).

Optically active *trans*-cyclononene is racemized upon heating due to rotation of the olefinic linkage.^{8b} This type of racemization could not occur in compound **6**, since it is sterically impossible for the five-membered ring to rotate through the nine-membered ring.⁹ Trans-bridged systems such as **6** should exhibit optical stability provided that neither bridgehead position is converted to a carbonium ion, anion, or radical species capable of inversion. Inversion of either bridgehead position would result in conversion of a trans-bicyclic system (**6**) into an optically inactive *cis*-bicyclic system (**5**). Inspection of models indicates that any equilibrium established between derivatives of **5** and **6** through bridgehead epimerization should lie far in the direction of **5**, which appears to be considerably less strained (as based upon bonding estimates).

It is well known that there exists a lower limit to the size of a ring required to accommodate a stable triple bond.¹⁰ Similarly, it is reasonable to postulate that for a homologous series of bicyclic compounds in which the size of one ring is constant, there exists a lower limit to the size of the second ring necessary to support trans-bridgehead geometry.

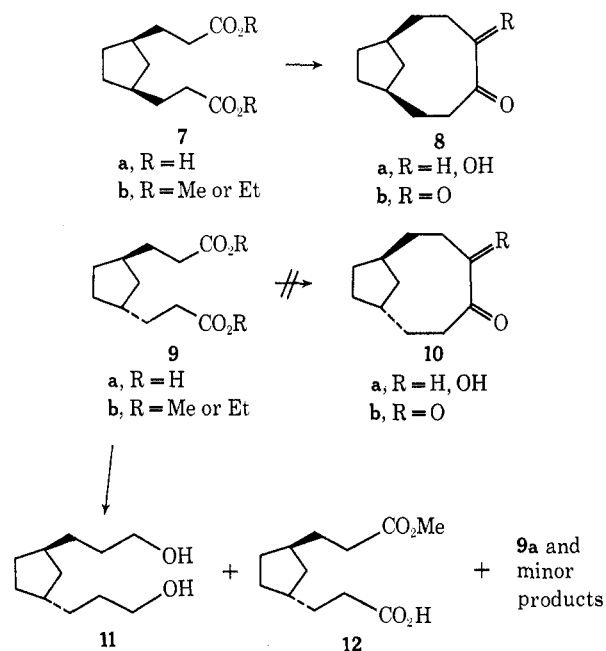
In initiating an investigation of the phenomena discussed above, we attempted the synthesis of the *cis*- (**8a** and **8b**) and trans-bridged (**10a** and **10b**) derivatives of bicyclo[6.2.1]undecane. Earlier we reported convenient syntheses of the *cis*- (**7a**) and *trans*-1,3-cyclopentanedipropionic (**9a**) acids.¹¹ Since it was necessary to form a nine-membered ring in synthesizing derivatives of **5** and **6**, acyloin condensation^{12,13} of the cyclopentanedipropionic esters, **7b** and **9b**, was believed to afford the greatest chance of success. Although we also considered the use of larger bicyclic systems derived from cyclohexanedipropionic acids,¹⁴ the cyclopentane deriv-

atives, **7a** and **9a**, were found to be more conveniently prepared and purified to isomerically pure compounds.

Results

The isomerically pure *cis*- and *trans*-1,3-cyclopentanedipropionic acids (**7a** and **9a**) were converted to the *cis* and *trans* diesters, **7b** and **9b**. Glpc analysis of the diesters **7b** and **9b**, purified either by distillation or column chromatography,¹⁵ revealed the presence of only one component in each case; however, subsequent results indicated some contamination of **9b** by **7b**.

The *cis* diester **7b** (R = Et) was allowed to react with sodium in xylene according to the acyloin condensation procedure of Cram and Steinberg.¹⁶ Distillation of the xylene, followed by column chromatography of the product, afforded *cis*-bicyclo[6.2.1]undecan-4-ol-5-one (**8a**) in 10% yield. The sample of **8a** showed the expected ir absorption bands at 3400 (OH) and 1690 cm⁻¹ (C=O), and the *p*-nitrobenzoate derivative gave the correct elemental analysis. Attempts to cyclize the *trans* diester **9b** (R = Et) by the same procedure resulted in the formation of a very small amount of a complex mixture, the components of which could not be identified.



The *cis*-bicyclic acyloin **8a** decomposed to the starting *cis* diacid **7a** upon standing at room temperature for several weeks. Because of the low yield and instability of **8a**, a method was sought by which it could be prepared in better yield and separated under milder conditions. Reaction of *cis* diester **7b** with sodium in dioxane at 50° gave a mixture of two products in 43% yield. The major component of the mixture (85%) was separated by glpc and identified as the *cis*-bicyclic acyloin **8a** by comparison of the ir spectrum with that of the sample of **8a** obtained in xylene. The minor component (10%) was identified as *cis*-bicyclo[6.2.1]undecane-4,5-

(8) (a) A. C. Cope, C. R. Ganellin, H. W. Johnson, Jr., T. V. Van Auken, and H. J. S. Winkler, *J. Amer. Chem. Soc.*, **85**, 3276 (1963); (b) A. C. Cope, K. Banholzer, H. Keller, B. A. Pawson, J. J. Whang, and H. J. S. Winkler, *ibid.*, **87**, 3644 (1965); (c) A. C. Cope and B. A. Pawson, *ibid.*, **87**, 3649 (1965); (d) A. C. Cope and M. W. Fordice, *ibid.*, **89**, 6187 (1967).

(9) This type of racemization could conceivably occur in trans-bridged compounds in which one ring of the bicyclic system were very large.

(10) A. T. Blomquist and L. H. Liu, *J. Amer. Chem. Soc.*, **75**, 2153 (1953).

(11) T. L. Westman and A. E. Kober, *J. Org. Chem.*, **29**, 2448 (1964).

(12) V. L. Hansley, U. S. Patent No. 2,228,268 (Jan 14, 1941).

(13) V. Prelog, L. Frenkiel, M. Kobelt, and P. Barman, *Helv. Chim. Acta*, **80**, 1741 (1947).

(14) T. L. Westman, R. Paredes, and W. S. Brey, *J. Org. Chem.*, **28**, 3512 (1963).

(15) Initially, the diesters **7b** and **9b** were purified by distillation; however purification by column chromatography later proved to be just as efficient and more convenient.

(16) D. J. Cram and H. Steinberg, *J. Amer. Chem. Soc.*, **73**, 5702 (1951).

dione (**8b**) by comparison of its ir spectrum and 2,4-dinitrophenylhydrazone derivative with those of an analytical sample of **8b** obtained by bismuth trioxide oxidation¹⁷ of the cis-bicyclic acyloin **8a**.

Because of the instability of the cis-bicyclic acyloin **8a**, no attempt was made to separate it from the cis-bicyclic diketone **8b** on a large scale. Instead, the crude mixture of **8a** and **8b** was oxidized directly to the cis-bicyclic diketone **8b**, which was then purified using Girard's T reagent.¹⁸ This procedure gave **8b** in greater than 95% purity (glpc).

Glpc analysis of the reaction product of the trans diester **9b** with sodium in dioxane showed it to be a complex mixture in contrast to the results obtained with the cis isomer **7b**. Oxidation of the crude product with bismuth trioxide followed by column chromatography gave a compound with an ir spectrum identical with that of the cis-bicyclic diketone **8b**. The melting point (238–239° dec) of the 2,4-dinitrophenylhydrazone derivative of this material was identical with that of the 2,4-dinitrophenylhydrazone derivative of **8b**, and the mixture melting point was undepressed. This small amount of cis-bicyclic material apparently resulted from cyclization of contaminating cis isomer present in the starting trans diester **9b**. Additional purification of the starting trans diacid **9a** substantially reduced the amount of **8b** isolated from the reaction product (typically, 215 mg of **8b** was isolated from the reaction product of 19 g of **9b**).

Although a number of acyloin reactions were run on the trans diester **9b**, and a variety of separation techniques were employed, in no case was a trans-bicyclic product isolated. Glpc analysis of the neutral portion of the trans product revealed the presence of one major component other than unreacted trans diester **9b**.¹⁹ This compound was isolated by column chromatography and identified as *trans*-1,3-cyclopentanedipropanol (**11**; 3% yield) by comparison of its ir spectrum and *p*-nitrobenzoate derivative with those of an authentic sample of **11** prepared by lithium aluminum hydride reduction of the trans diacid **9a**.

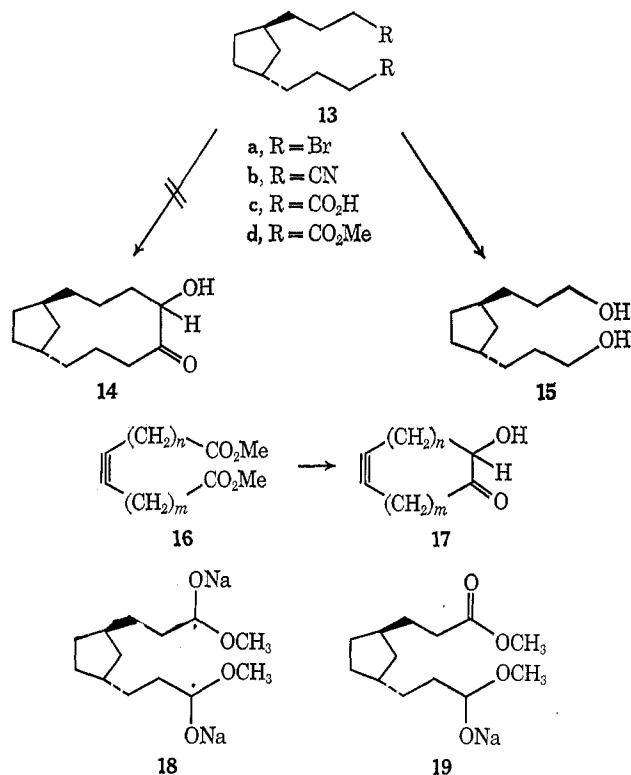
Acidic material was isolated from the crude trans product by extraction with sodium bicarbonate solution. Column chromatography of the recovered acids to remove trans diacid **9a**, followed by distillation, gave an analytical sample of *trans*-3-(β -carbomethoxyethyl)cyclopentylpropionic acid (**12**).

Since no trans-bicyclic products were isolated from the acyloin reaction product of **9b**, ring closure of dimethyl *trans*-1,3-cyclopentanedibutyrate (**13d**) to the less strained *trans*-bicyclo[8.2.1]tridecan-5-ol-6-one (**14**) was attempted.

Trans diacid **9a** was reduced to the trans-dipropanol **11** with lithium aluminum hydride,²⁰ and **11** was treated with phosphorus tribromide²¹ to obtain the trans dibromide **13a**. The trans dibromide **13a** reacted with potassium cyanide²² to give the trans-dibutyronitrile **13b**. Finally, **13b** was hydrolyzed to *trans*-1,3-cyclopenta-

nedibutyric acid (**13c**), which was recrystallized to analytical purity and converted to the dimethyl ester **13d**.

The reaction of the *trans*-dibutyric ester **13d** with sodium in dioxane was completely analogous to that of the *trans*-dipropionic ester **9b**, the major product being *trans*-1,3-cyclopentanedibutanol (**15**; 7% yield). The



trans-dibutanol **15** was characterized through its ir spectrum and *p*-nitrobenzoate derivative. As in the case of the *trans*-dipropionic ester **9b**, no *trans*-bicyclic products were isolated using Girard's T reagent, glpc, or column chromatography (no cis-bicyclic products were observed in this case).

Discussion

The failure of ordinary condensation reactions to give significant yields of cyclic products in the medium-ring range has been attributed to the high strain energy of the product and to the large entropy of activation to be overcome in bringing the ends of a long chain together.²³ The effects of ring strain and entropy apparently reach an unfavorable maximum for the formation of a nine-membered ring, as indicated by the minimum yield observed²⁴ for the formation of cyclononan-1-ol-2-one. It is not unexpected, therefore, that the cyclization even of the cis diester **7b** to a nine-membered ring is more difficult than that of the unsubstituted case because of the added restriction of the five-membered ring in the bicyclic product.

The isolation of cis-bicyclic products from the attempted condensations of the *trans* diester **9b** is readily explained by the presence of a small amount of contaminating cis isomer in the starting material. A less likely explanation is that *trans*-bicyclic products are formed

(17) A. T. Blomquist and C. J. Buok, *J. Amer. Chem. Soc.*, **81**, 675 (1959).

(18) A. Girard and G. Sandulesco, *Helv. Chim. Acta*, **19**, 1098 (1936).

(19) Polymeric material and at least seven unidentified minor reaction products were also present.

(20) R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **69**, 1197 (1947).

(21) J. B. Cloke, R. J. Anderson, J. Laehmann, and G. E. Smith, *ibid.*, **53**, 2791 (1931).

(22) F. H. Allen, "Organic Syntheses," Coll. Vol. I, Wiley, New York, N. Y., 1941, p 156.

(23) V. Prelog in "Perspectives in Organic Chemistry," A. R. Todd, Ed., Interscience, New York, N. Y., 1956, pp 96-133, and references cited therein.

(24) K. T. Finley, *Chem. Rev.*, **64**, 573 (1964), and references cited therein.

first but are then isomerized to the less strained *cis* system. This explanation is reasonable, since transannular participation is common in medium-sized rings²³ and since the removal of a hydrogen from either bridgehead position would result in conversion to the *cis* system. The fact that additional purification of the starting trans diacid **9a** greatly reduces the amount of *cis*-bicyclic products obtained indicates that isomerization is not the source of *cis* products. In addition, no *cis*-bicyclic products were isolated from the reaction of the expanded trans-dibutyric ester **13d**. In that case the ease of ring closure to trans-bicyclic products should have been greatly facilitated without reducing the probability of transannular participation.

A number of studies have been reported on the yields and lower limits of cyclization by the acyloin reaction.²⁴ For example, Cram and coworkers²⁵ have shown that acyloin condensation of the alkyne **16** to the acyloin **17** takes place readily when $m = n = 4$ but not at all when $m = n = 3$ or when $m = 3$ and $n = 4$. A triple bond has, however, been introduced into a preformed hydrocarbon ring of as few as eight carbon atoms.¹⁰ Similarly, the fact that the trans-bicyclic systems **10** and **14** could not be synthesized by the acyloin condensation reaction is not sufficient evidence that such compounds are incapable of existence. It is more reasonable to postulate that a large entropy barrier to cyclization and/or inherent product instability may be the reasons for the failure of the trans diesters **9b** and **13d** to cyclize.

Abnormal acyloin products analogous to those formed in the attempted condensations of the trans diesters **9b** and **13d** have been observed by others. In addition to normal condensation products, Machtinger²⁶ isolated 1,10-decanediol (3% yield) and sebacic acid (17% yield) from the acyloin reaction product of diethyl sebacate in xylene. In the present work yields of 3 and 7% were observed, respectively, for the trans diols **11** and **15**. The mixture of trans diacid **9a** and trans acid ester **12** was obtained in 7% yield.

The products observed by Machtinger and those isolated in the present work can be explained readily by a free-radical mechanism. By analogy with the mechanism proposed by Van Heyningen,²⁷ the sodium ketyls **18** and **19** are probably formed initially in the reaction of the trans diester **9b** with sodium. The ketyls **18** and **19** may then decompose and undergo further reactions by normal radical pathways to form a variety of products. The initially formed species apparently follow three major reaction pathways: (1) intramolecular reactions leading to cyclic products, (2) intermolecular reactions leading to linear products, (3) reactions with additional sodium or solvent. In previous work^{26,27} no effort was made to use a high dilution technique to minimize intermolecular reactions, and the formation of intramolecular products was not particularly unfavorable; therefore, a number of products resulting from both intra- and intermolecular reactions of the initial radicals were observed. In the case of the trans diester **9b** the entropy barrier to cyclization and the strain energy of the trans-bicyclic product make intramolecular reactions unfavorable, while the use of a high dilution technique renders intermolecular reactions unfavorable. The

only products observed in significant quantities are those which result from reactions of the initially formed radicals with additional sodium and solvent.

Experimental Section²⁸

Apparatus and Reagents.—The apparatus described by Cram and Steinberg¹⁶ was used with some modification. All glassware was dried overnight in an oven at 120° and protected by drying tubes during assembly. A Morton flask was equipped with a high-speed, stainless steel stirrer and a high-speed (20,000 rpm) stirrer motor.²⁹ In one of the necks of the flask was placed a Claissen adapter holding a West condenser directly over the flask and a 250-ml Hershberg dropping funnel in the outer arm. In the other neck of the flask was placed a second Claissen adapter, one arm of which was stoppered and one arm of which held a gas inlet. A gas outlet attached to a U-tube having a small head of mercury was placed in the top of the reflux condenser. The Claissen adapters were wired securely to the necks of the Morton flask. In order to remove the last traces of moisture, the entire system was heated with a flame while flushing with argon.

Reagent grade dioxane was further purified by refluxing over sodium metal for 12 hr under argon. The dry dioxane was then distilled under argon directly onto molecular sieve in an oven-dried bottle.

Isomerically pure *cis*- (**7a**) and *trans*-1,3-cyclopentanedipropionic (**9a**) acids were obtained as previously described.¹¹ The trans diacid **9a** (mp 96–97°) was further purified in the following manner before use. A sample of **9a** was dissolved in a minimum amount of tetrahydrofuran at room temperature. This solution was heated to boiling, and sufficient hexane was added to cloud the hot solution. Enough glacial acetic acid was then added to restore clarity, and the solution was filtered rapidly and allowed to cool to room temperature. The crystals which formed were separated and recrystallized two more times in the same manner. This procedure gave pure trans diacid **9a**, mp 100–101° (lit.¹¹ mp 100–101° for isomerically pure **9a**).

The pure diacids **7a** and **9a** were converted to their dimethyl or diethyl esters **7b** and **9b** by the method of Vogel.³⁰ Distillation of the crude diethyl esters gave pure diethyl *cis*-1,3-cyclopentanedipropionate (**7b**, R = Et) [bp 121–123° (0.25 mm), n_D^{20} 1.4505] and diethyl *trans*-1,3-cyclopentanedipropionate (**9b**, R = Et) [bp 121–123° (0.15 mm), n_D^{20} 1.4509]. The diesters were found to be more conveniently purified by column chromatography because of their high boiling points. Accordingly, pure dimethyl *cis*-1,3-cyclopentanedipropionate (**7b**, R = Me, n_D^{20} 1.4568) and dimethyl *trans*-1,3-cyclopentanedipropionate (**9b**, R = Me, n_D^{20} 1.4572) were obtained by elution from a column of activity grade I alumina with petroleum ether. Pure **7b** and **9b** were stored over molecular sieve after removal of the petroleum ether at reduced pressure.

Acyloin Condensation of *cis* Diester **7b (R = Et). Xylene Method.**—The acyloin condensation in xylene followed the procedure of Cram and Steinberg.¹⁶ Xylene (125 ml), dried over sodium, was placed in a 250-ml Morton flask prepared as described above. The last traces of moisture were removed from the solvent by distilling a small amount through the condenser which was temporarily placed in distilling position. During the distillation the air in the flask was replaced by argon. The condenser was replaced in reflux position, and 4.9 g (0.21 g-atom) of freshly cut sodium metal was added through the top of the reflux condenser under a stream of argon. After reheating the xylene to reflux, the stirrer was started, and the molten sodium was dispersed by stirring at an estimated 2000 rpm for 15 min. Addition of a solution of 13.9 g (0.052 mol) of **7b** in 25 ml of dry xylene to the sodium dispersion was completed in 45 hr. The reaction mixture was heated with continued stirring for an additional 3 hr. After cooling in an ice bath,

(28) Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Glpc analyses were made with an Aerograph A-90-P gas chromatograph using an 8 ft by 0.25 in. column packed with 20% Silicone GE SF-96 on firebrick. The analyses were made at a column temperature of 235° using helium (60 cc/min) as an eluent gas. All melting points and boiling points are uncorrected.

(29) A Lab-Line Stir-O-Vac high-speed stirrer and a Premier Dispersator (Premier Mill Corp., Geneva, N. Y.) were used.

(30) A. I. Vogel, "A Text-Book of Practical Organic Chemistry," Longmans, Green and Co., London, 1957, p 381.

(25) (a) D. J. Cram and N. L. Allinger, *J. Amer. Chem. Soc.*, **78**, 2518 (1956); (b) D. J. Cram and L. K. Gaston, *ibid.*, **82**, 6386 (1960).

(26) D. Machtinger, *Bull. Soc. Chim. Fr.*, 1341 (1961).

(27) E. Van Heyningen, *J. Amer. Chem. Soc.*, **74**, 4861 (1952).

14 g (0.24 mol) of glacial acetic acid was added dropwise to decompose excess sodium. During the addition of acetic acid it was necessary to add an additional 50 ml of xylene to suspend the sodium acetate formed. Sodium acetate was removed by vacuum filtration and returned to the reaction flask with 50 ml of fresh xylene. After stirring vigorously for several minutes, the solid was again filtered, and the xylene filtrates were combined. The xylene solution was washed with water and dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Xylene was removed by distillation through a 10-cm Vigreux column. Additional product was recovered by dissolving the sodium acetate in 200 ml of water and extracting with ether several times. The washed, dried ethereal extract afforded a residue upon evaporation of the solvent, the ir spectrum of which was identical with that of the residue from the xylene distillation. The two samples were combined (4.1 g total) and chromatographed on a 14 × 1.5 cm column of activity grade V Woelm neutral alumina. Evaporation of the benzene eluate gave 0.9 g (10% yield) of crude acyloin product.

cis-Bicyclo[6.2.1]undecan-4-ol-5-one (8a).—The crude acyloin product (300 mg) prepared by the xylene method was rechromatographed on activity grade I Woelm neutral alumina to obtain a pure sample for characterization. The residue (100 mg) from the methanol eluate of the column was pure cis-bicyclic acyloin **8a**: ir (film) 1690 (C=O) and 3400 cm⁻¹ (OH). A pure sample of the *p*-nitrobenzoate derivative of **8a** (mp 140–141°) was obtained after several recrystallizations from acetone–water.

Anal. Calcd for C₁₃H₂₁NO₅: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.40; H, 6.32; N, 4.26.

Acyloin Condensation of cis Diester 7b (R = Me). Dioxane Method.—Pure, dry dioxane (300 ml) was siphoned under argon into a 1-l. Morton flask prepared as described above. Freshly cut sodium (5.7 g, 0.25 g-atom) was added to the flask through the top of the reflux condenser, and after heating the dioxane to reflux, the molten sodium was dispersed by stirring at an estimated 8000 rpm for 15 min. A solution of the pure cis diester **7b** (15.0 g, 0.062 mol) in 150 ml of dioxane was added to the refluxing dispersion for 1 hr. Heating was then stopped, and the rate of stirring was decreased somewhat. Addition of the solution of **7b** was completed in 40 hr, after which stirring was continued for an additional 48 hr. At the end of this time, the excess sodium was decomposed at 0° by the addition of 17.0 g (0.28 mol) of glacial acetic acid dropwise with continued stirring. When it was certain that the sodium had been completely destroyed,³¹ the reaction mixture was poured into 1 l. of ice and water, and the product was extracted with several portions of ether. Some solid, insoluble material separated at this point and was removed by filtration. The ether solution was washed several times with water and dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Removal of the solvent gave 12.5 g of an oil. The crude product was placed on a 2 × 25 cm column of Florex and eluted with benzene. Evaporation of the benzene eluate afforded 4.8 g (43% yield) of crude acyloin product. Glpc analysis of this material revealed the presence of two major components which appeared at retention times of 6.5 and 8 min under the analysis conditions (starting cis diester **7b** had a retention time of 9.5 min). A sample of the component with a retention time of 8 min (estimated to be 85% of the crude product) was collected. The ir spectrum of this material was identical with that of the cis-bicyclic acyloin **8a**. The other component of the crude product (estimated to be 10% of the sample) with a retention time of 6.5 min was later identified as the cis-bicyclic diketone **8b** by comparison with an authentic sample.

Decomposition of the Crude cis-Acyloin Product.—Upon standing at room temperature for several days, the crude cis-acyloin product began to solidify. The mixture was dissolved in ether and extracted with several portions of dilute sodium bicarbonate solution. The basic extract was acidified and extracted with several portions of ether. Removal of the solvent from the dried ethereal extract afforded an oil which solidified and had mp 97.5–99° after two recrystallizations from water–acetic acid. The mixture melting point with pure cis diacid **7a** (mp 98–99.5°) was undepressed, and the ir spectra of the two samples were identical. The ir spectrum of the washed cis-

acyloin product was identical with that of the freshly prepared material but glpc analysis showed this sample to be enriched in the cis-bicyclic diketone **8b** (6.5 min).

cis-Bicyclo[6.2.1]undecane-4,5-dione (8b).—The crude cis-acyloin product (dioxane method) was oxidized with bismuth trioxide according to the procedure of Blomquist and Buck.¹⁷ The crude cis product (2.6 g 1.4 mmol) and 2.6 g (5.6 mmol) of bismuth trioxide were refluxed in 20 ml of glacial acetic acid for 30 min with stirring. The hot acetic acid solution was filtered to remove metallic bismuth and poured into 60 ml of cold water. The mixture was extracted with several portions of benzene, and the combined benzene extracts were washed with water and dilute sodium bicarbonate solution. The benzene extract was dried over anhydrous magnesium sulfate and evaporated to give 2.1 g of crude cis bicyclic diketone **8b**. The crude product was dissolved in 75 ml of a solution of exactly 10% by weight of acetic acid in absolute ethanol. Girard's T reagent¹⁸ (4.0 g, 12.0 mmol) was added and the mixture was refluxed for 1.5 hr. The reaction product was cooled and poured into 450 ml of ice water containing 4.31 g of sodium carbonate (final pH 5–6). The aqueous solution was extracted repeatedly with ether to remove unreacted, nonketonic material. When necessary, enough extra ethanol was added to break the emulsion which formed. The final aqueous solution was filtered to remove a small amount of suspended material, and its volume was measured. Enough concentrated hydrochloric acid was added to give a 0.8 N solution, and the solution was allowed to stand at room temperature to regenerate **8b**. After standing for 1.5 hr, the cloudy, aqueous solution was again extracted repeatedly with ether. The combined ethereal extracts of **8b** were washed with several portions each of water and dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Removal of the solvent afforded 1.7 g (65% yield based on crude cis acyloin) of the cis-bicyclic diketone **8b**. Glpc analysis revealed a single component having a retention time of 6.5 min comprising greater than 95% of the sample. Distillation in a micro-Hickman still at 110° (0.5 mm) gave an analytical sample of the cis-bicyclic diketone **8b**: *n*_D²⁰ 1.5011; ir (film) 1700 (C=O), 3400 (OH, weak), and 760 (C=C, weak) cm⁻¹.

Anal. Calcd for C₁₁H₁₆O₂: C, 73.30; H, 8.95. Found: C, 73.34; H, 9.03.

The 2,4-dinitrophenylhydrazone derivative of **8b** was prepared. An analytical sample was obtained by elution of the crude derivative from a column of activity I Woelm neutral alumina with chloroform. The derivative had mp 238–239° dec after two recrystallizations from dioxane–water.

Anal. Calcd for C₂₃H₂₄N₆O₈: C, 51.11; H, 4.48; N, 20.74. Found: C, 50.98; H, 4.52; N, 20.56.

Reactions of trans Diester 9b (R = Me) with Sodium in Dioxane.—The dioxane condensation method described above was employed without modification.³² A solution of 19 g (0.078 mol) of pure trans diester **9b** in 175 ml of dioxane was added to a dispersion of 7.2 g (0.31 g-atom) of sodium in 400 ml of dioxane. The crude acyloin product was placed on a 2 × 25 cm column of Florex and eluted with 600 ml of petroleum ether (7.2 g, fraction A), 850 ml of benzene (2.6 g, fraction B), and 400 ml of ether (1.6 g, fraction C). The sodium bicarbonate wash of the ethereal solution of crude product was acidified and extracted with ether in order to recover 1.1 g of acidic products (fraction D).

Identification of trans-Acyloin Fraction A.—*trans*-Acyloin fraction A (7.2 g) was dissolved in 50 ml of petroleum ether and filtered through a column of 50 g of activity grade I Woelm neutral alumina. The column was washed with additional petroleum ether until evaporation of a sample of the eluate left no residue. The ir spectrum of the petroleum ether residue was identical with that of the starting trans diester **9b**. Continued elution with acetone gave an additional small amount of **9b** which contained increasing amounts (ir analysis) of another component. This component was eluted from the column in a relatively pure state with methanol: ir (film) 1690 (C=O) and 3400 cm⁻¹ (OH). The methanol fractions were combined and treated with 2,4-dinitrophenylhydrazine. The crude derivative was eluted from activity grade I Woelm neutral alumina with chloroform. Recrystallization of the residual orange oil from dioxane–water several times gave an analytical sample,

(31) Considerable caution must be exercised at this point. Sodium particles may become coated and remain unreacted in the product if sufficient time is not allowed for their decomposition.

(32) Several condensations were also attempted in xylene; however, no significant yield of any product was observed.

mp 234–235° dec. The ir spectrum of this compound was identical with that of the 2,4-dinitrophenylhydrazone of cis-bicyclic diketone **8b**: ir (KBr) 1600 (C=N) and 3300 cm⁻¹ (NH).

Anal. Calcd for C₂₅H₂₄N₂O₈: C, 51.11; H, 4.48; N, 20.74. Found: C, 51.38; H, 4.60; N, 21.00.

Identification of trans-Acyloin Fraction B.—A sample of trans-acyloin fraction B (0.6 g) was oxidized with bismuth trioxide by the procedure described for the preparation of the cis-bicyclic diketone **8b**. The crude oxidation product (0.5 g) was placed on a 1.5 × 15 cm column of silica gel (Fisher S-662). Elution of the column with 5:1 petroleum ether:chloroform afforded a small amount of an oil (50 mg) upon removal of the solvent. The ir spectrum of this fraction was essentially identical with that of the pure cis-bicyclic diketone **8b**. The 2,4-dinitrophenylhydrazone derivative of this material had mp 233–234° dec after two recrystallizations from chloroform-ethanol. The ir spectrum was identical with that of the 2,4-dinitrophenylhydrazone derivative of **8b**, and the mixture melting point was undepressed. Elution of the silica gel column with more polar solvents gave a second component: ir (film) 1100–1300 (ester), 1700 (C=O), 1740 (ester C=O), and 3400 cm⁻¹ (OH, weak). It could not be determined whether this material was a single pure compound or a mixture of the starting trans diester **9b** with another compound. Efforts to fractionate this material further using Girard's T reagent, distillation, or column chromatography were unsuccessful, and no solid derivatives could be prepared.

Identification of trans-Acyloin Fraction C.—A 200-mg sample of fraction C was placed on a 1.5 × 15-cm column of silica gel and eluted with 1:1 benzene:acetone. Initial fractions were contaminated with an ester, possibly the unidentified component of fraction B. Continued elution of the column with the same solvent afforded several fractions in which the carbonyl absorption was negligible: ir (film) 1060 (OH) and 3400 cm⁻¹ (OH). This compound was identified as *trans*-1,3-cyclopentanedipropanol (**11**) by comparison of its ir spectrum and *p*-nitrobenzoate derivative with those of an authentic sample of **11**. The mixture melting point of this derivative (mp 86–87°) with the *p*-nitrobenzoate of **11** (mp 87–88°) was undepressed, and the ir spectra of the two samples were identical.

Identification of trans-Acyloin Fraction D.—The acidic fraction D from the bicarbonate wash of the trans-acyloin product deposited crystals upon standing in the cold. This solid, recrystallized from water, had mp 99–100° and an ir spectrum identical with that of the pure trans diacid **9a** (mp 100–101°). The mixture melting point with **9a** was undepressed. The liquid portion of the acidic fraction (from the filtrate) was placed on a 1.5 × 15-cm column of Florex and washed with 60 ml of benzene. Elution of the column with ether, followed by distillation of the residue in a micro-Hickman still at 175° (0.15 mm), gave an analytical sample of *trans*-3-(β-carbomethoxyethyl)cyclopentylpropionic acid (**12**): ir (film) 1100–1300 (ester), 1705 (acid C=O), 1740 (ester C=O), and 2500–3500 cm⁻¹ (acid); *n*_D²⁰ 1.4680.

Anal. Calcd for C₁₂H₂₀O₄: C, 63.13; H, 8.83. Found: C, 62.98; H, 8.97.

Gpc Analysis and Yields of trans Products.—Gpc analysis of the trans-acyloin fractions A–D was used to obtain an estimate of the distribution and yields of the various products. The composition of each fraction was estimated from the relative areas of the chromatogram peaks and was only an approximation, since the extent of decomposition of the components under the analysis conditions could not be determined. Starting trans diester **9b** (R = Me), purified either by distillation or column chromatography, gave a single peak comprising 98+ % of the sample at a retention time of 10 min,²⁸ and a known sample of the trans-dipropanol **11** had a retention time of 8 min. Two major components other than **9b** and **11** were detected in the fractions. Component I appeared at a retention time of 6.5 min and was identified as the cis diketone **8b** by collection of a small sample and comparison of its ir spectrum and 2,4-dinitrophenylhydrazone derivative with those of an authentic sample of **8b**. The total amount of cis diketone **8b** in the fractions was estimated at 215 mg. Component II, which had a retention time of 5.5 min, was not present in sufficient quantity to be isolated and identified. This peak appears only in the gpc analysis of fraction B and may be due to the unidentified component observed during column chromatography of that fraction. The total amount of trans-dipropanol **11** in fraction C was estimated to be 540 mg (3.3% yield). In addition to I and II, at least seven

minor components having retention times of less than 4 min were present in the product.

trans-1,3-Cyclopentanedipropanol (11).—The procedure of Nystrom and Brown²⁰ was used to reduce the trans diacid **9a** to the trans-dipropanol **11**. To a slurry of 12.0 g (0.31 mol) of lithium aluminum hydride in 600 ml of anhydrous ether was added 26.9 g (0.125 mol) of fused trans diacid **9a** in 500 ml of anhydrous ether. Evaporation of the solvent after work-up of the product gave 20.6 g (88% yield) of crude trans-dipropanol **11**: *n*_D²⁰ 1.4767; ir (film) 1060 (OH) and 3400 cm⁻¹ (OH). The *p*-nitrobenzoate derivative of **11** was prepared, and an analytical sample was obtained by four recrystallizations from 95% ethanol (mp 87–88°).

Anal. Calcd for C₂₅H₂₈N₂O₈: C, 61.97; H, 5.83; N, 5.78. Found: C, 61.73; H, 5.77; N, 5.59.

trans-1,3-Cyclopentanedibromopropane (13a).—The trans-dibromide **13a** was prepared by the method of Cloke and co-workers.²¹ The crude trans-dipropanol **11** (18.6 g, 0.1 mol) was added dropwise with stirring to 27.1 g (0.1 mol) of phosphorus tribromide. The chloroform extract of crude product was washed with several portions of concentrated sulfuric acid, followed by water and dilute sodium bicarbonate solution. Evaporation of the dried solution gave 25.4 g (82% yield) of trans dibromide **13a**: *n*_D²⁰ 1.5066; ir (film) 1220 and 1260 cm⁻¹.

trans-1,3-Cyclopentanedibutyronitrile (13b).—Following the procedure of Allen,²² 25.0 g (0.08 mol) of the trans dibromide **13a** was allowed to react with 13.7 g (0.2 mol) of KCN in ethanol-water solvent. The crude reaction product was purified by chromatography on a column of Florex (60 g). Upon evaporation of the ether eluate, 15.7 g (96% yield) of trans-dinitrile **13b** (*n*_D²⁰ 1.4698) was obtained. Gpc (280°) was used to obtain a pure sample of **13b**: *n*_D²⁰ 1.4708; ir (film) 2250 cm⁻¹ (CN).

trans-1,3-Cyclopentanedibutyric Acid (13c).—The trans-dinitrile **13b** (6 g, 0.03 mol) was heated with 30 ml of 75% sulfuric acid at 90° for 3 hr. The reaction mixture was cooled and poured into 150 ml of ice and water. The product was isolated by extraction with several portions of ether, and the combined ethereal extracts were washed once with water then extracted with 100 ml of 10% aqueous KOH. The basic, aqueous extract was boiled to remove dissolved ether, filtered through Celite, then cooled, and added slowly to a cold, stirred solution of 20 ml of concentrated HCl in 50 ml of water. The precipitate was filtered and dried to give 5.8 g (82% yield) of crude trans-dibutyric acid **13c**. Three recrystallizations of the acid from a large volume (250 ml/g) of 5% acetic acid afforded an analytical sample (mp 118–120°) of trans-dibutyric acid **13c**: ir (KBr) 1705 (acid C=O) and 2500–3600 cm⁻¹ (acid).

Anal. Calcd for C₁₃H₂₂O₄: C, 64.44; H, 9.15. Found: C, 64.26; H, 9.23.

Reaction of trans-Dibutyric Ester **13d with Sodium in Dioxane.**

—The pure trans-dibutyric acid **13c** was converted to the dimethyl ester **13d** and purified by column chromatography. Pure trans-dibutyric ester **13d** (*n*_D²⁰ 1.4579, 4.4 g, 0.16 mol) in 70 ml of dioxane was allowed to react with 1.5 g (0.065 g-atom) of sodium metal dispersed in 150 ml of dioxane. The crude product (500 mg) was placed on a 1.5 × 15 cm column of Florex and eluted with petroleum ether, benzene, and ether. Only a trace of material was eluted by petroleum ether. Evaporation of the benzene eluate gave 50 mg of fraction B, and 400 mg of fraction C was recovered from the ether eluate. The ir spectrum of fraction B [ir (film) 1700–1740 (C=O) and 3400 cm⁻¹ (OH)] was quite similar to that of the corresponding fraction from the reaction of the trans diester **9b**. Oxidation of B with bismuth trioxide failed to alter the ir spectrum, and this fraction remained unidentified as did the corresponding fraction from **9b**.

Fraction C was separated into ketonic and nonketonic material with Girard's T reagent. Fraction C (400 mg) was allowed to react with 660 mg (4.0 mmol) of Girard's T reagent according to the procedure described for the purification of the cis diketone **8b**. Work-up, as previously, gave 25 mg of ketonic material and 250 mg of nonketonic material. The ir spectrum of the ketonic fraction was essentially identical with that of fraction B. An attempt to prepare the 2,4-dinitrophenylhydrazone derivative was unsuccessful. The ir spectrum of the nonketonic portion was very similar to that of the trans-dipropanol **11**. The sample (250 mg, 7% yield) was purified by distillation at 120° (0.2 mm) in a micro-Hickman still to give the *trans*-1,3-cyclo-

pentanedibutanol (15): n_D^{20} 1.4798; ir (film) 1060 (OH) and 3400 cm^{-1} (OH). The *p*-nitrobenzoate derivative of 15 was prepared, and an analytical sample (mp 83.5–84.5°) was obtained after several recrystallizations from 95% ethanol.

Anal. Calcd for $\text{C}_{27}\text{H}_{32}\text{O}_2\text{N}_2$: C, 63.27; H, 6.29; N, 5.47. Found: C, 63.41; H, 6.10; N, 5.31.

Registry No.—7b, R = Et, 26269-16-9; 8a, 26269-17-0; 8a, *p*-nitrobenzoate, 26269-18-1; 8b, 26269-19-2; 8b

2,4-DNP, 26269-20-5; 9b, 26269-21-6; 12, 26269-22-7; 13a, 26269-23-8; 13b, 26269-24-9; 13c, 26269-25-0; 15, 26269-26-1; 15 *p*-nitrobenzoate, 26269-27-2.

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The Pyrolysis of Some Cyclobutanone Benzenesulfonylhydrazones

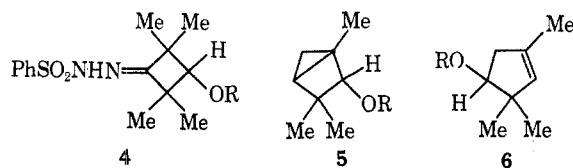
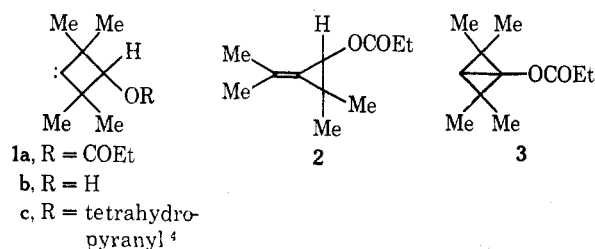
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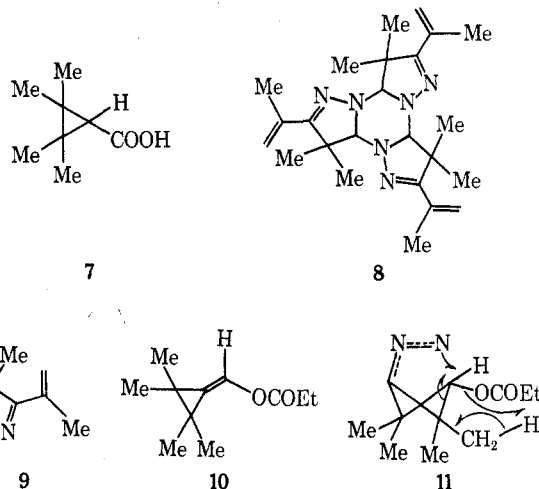
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Some related 4-substituted 2,2,3,3-tetramethylcyclobutanone benzenesulfonylhydrazones have been pyrolyzed in a modified Bamford–Stevens reaction. Products were isolated and identified which suggested that the main reaction proceeds *via* the diazo compounds to the corresponding carbenes which undergo methyl insertion to form 2-substituted 1,3,3-trimethylbicyclo[2.1.0]pentanes. Some transformation products of these bicyclopentanes are described. In particular, the 2-propionyloxy derivative underwent homoallylic rearrangement to give 4-propionyloxy-1,3,3-trimethylcyclopentene. Unpredictable products also obtained from these pyrolyses included a novel nitrogen heterocycle.

The carbene 1 has been the reported intermediate^{2–5} in attempts, finally successful,⁵ to obtain the cyclopropane 2,^{5–8} once thought to be the cockroach sex attractant.⁷ We prepared 1a and examined some of its numerous transformation products in the hope of finding the bicyclobutane 3.⁶



A plausible route to 7 is from 2 *via* the isomeric methylenecyclopropane 10 (more stable than a cyclopropene¹¹) which can then hydrolyze and oxidize (air) to the acid.



Starting from the hydrazone 4a we thus obtained the known bicyclic ester 5a^{5a} and the unsaturated ester 6a, already reported,^{3a,5a} and in addition we also isolated isobutyronitrile, the acid 7,⁹ and a trimer¹⁰ presumed to be 8 of the Schiff's base 9.

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The production of 9 must involve transannular attack of the "hot" diazo group with loss of propionic acid accompanied by ring opening. A radical reaction in the gas phase is contemplated and a tentative mechanism 11 proposed.

When we generated the carbene 1b from 4b, it gave mainly the stable bicyclopentane alcohol 5b. The latter on propionylation underwent homoallylic rearrangement to ester 6b.

We found further indication for the intermediacy of a bicyclopentane when we pyrolyzed the dry salt of 12, obtained using sodium methoxide. The carbene generated gave the known ester 14¹² as major product, presumably *via* the ketone 13 and derived ketene which picked up residual methanol. This reaction is homol-

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