Structure of the 2:2 Condensation Product of Nitromethane and Cyclohexanone

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The 2:2 condensation product of nitromethane and cyclohexanone is shown by (1) appropriate degradative experiments, (2) the synthesis of the key degradation products XV and II, and (3) n.m.r. studies of the location of the double bond, to have structure I.

Isolation of a high-melting crystalline solid $C_{14}H_{20}N_2O_3$ (I) from condensation of nitromethane with cyclohexanone, catalyzed by secondary amines, has been reported from several sources.[2–7] Nightingale and her students have investigated the generality of formation of high-melting condensation products, analogous to I, from other aliphatic nitro compounds and cyclic ketones. Nitromethane is unique among the nitro compounds which were investigated, because nitroethane, 1-nitropropane, and phenylnitromethane gave no solid products with cyclohexanone analogous to I.[5] Compounds analogous to I are obtained, however, from condensations of nitromethane with cyclopentanone (8–24%)[5,7] cycloheptanone (51%),[7] and cyclooctanone (1%),[7] as well as with the substituted cyclohexanones, 3-methylcyclohexanone (1%)[4] (but not with 2-methylcyclohexanone[5]), 4-methylcyclohexanone (5–40%),[4,5,7] 4-isopropylcyclohexanone (40%),[7] 4-*sec*-butylcyclohexanone (23%),[7] 4-*t*-butylcyclohexanone (34%),[7] and 4-cyclohexylcyclohexanone (20%).[7] Secondary amines used as catalysts (with the yields given for formation of I from nitromethane and cyclohexanone) include piperidine[4] (8–14,[5] 20%[7]), piperazine (67%),[7] 2-methylpiperazine (27%),[7] pyrrolidine (23%),[7] morpholine (22%),[7] hexamethyleneimine (24%),[7] diethylamine (19%),[3] and di-*n*-propylamine,[5] but neither the primary amine, methylamine,[4] nor the tertiary amine, triethylamine,[7] nor tetramethylammonium hydroxide,[7] nor sodium ethoxide,[5] catalyzed the formation of I. Compound I also has been obtained from condensation of nitromethane with the other cyclohexanone reaction products,[3] 1-(nitromethyl)cyclohexanol (4%)[3,5] and 1-(nitromethyl)cyclohexene,[5] and with the enamines,[8] 1-piperidinocyclohexene (10%),[6] 1,4-bis(1-cyclohexenyl)piperazine (22%),[7] and 1-hexamethyleneiminocyclohexene (43%).[7]

In 1958 Nightingale, Reich, and Erickson reported an extensive study of the reactions of I, and proposed the partial structure $C_{13}H_{18}NO\cdot(C{=}O)NHOH$.[5] They suggested further that I contained a C=N group and a $-\overset{|}{C}{=}\overset{|}{C}-$ group, both of which are unconjugated. After the appearance of this publication, work aimed at a complete elucidation of the structure of I was begun in our laboratory. The results of the functional group determination and the proof of the atomic skeleton (structure I in Chart 1), which are described in detail here, have been presented previously in a Communication.[9] Shortly after submission of our Communication, we had established the location of the olefinic double bond, making it possible for Nightingale and her co-workers to utilize the complete structure of I in her most recent paper.[7] Recently, House and Magin[10] have reported independent degradative experiments which demonstrate the same atomic skeleton for I, but by a different and complementary route proceeding through selective reduction of the double bond (of IV). From n.m.r. data (on IV and IVa), they narrowed possible locations of the olefinic double bond to a single position in either cyclohexane ring; the final, correct choice was based on the difficulty of writing a rational mechanism to place the double bond in the other cyclohexane ring.[10]

The Functional Groups.—The acidic hydrolysis of I to $C_{14}H_{19}NO_3$(IV[11]), which corresponds to the hydrolysis of an oximino group, was previously formulated as the conversion of a hydroxamic acid to the corresponding carboxylic acid.[5] It followed then that the monomethyl derivative $C_{15}H_{21}NO_3$ (IVa), formed by action of potassium hydroxide and methyl iodide on IV, was the methyl ester of the carboxylic acid IV.[5] In the present work, methylation of IV to IVa (obtained as dimorphic forms both melting at 95–96°) has also been accomplished with diazomethane,[12] but attempted esterification of IV with methanol containing sulfuric acid gave only unchanged IV.[13] Failure of the acid-catalyzed esterification, and the low frequencies of infrared bands possibly attributable[5] to a carboxyl group in IV and to a methoxycarbonyl group in IVa, cast doubt on the presence of these functional groups.

Compounds IV and IVa, like compound I,[5] contain a carbon to carbon double bond, as shown by the olefinic band present in their infrared spectra, and by the two vinyl proton resonances present in the n.m.r. spectra of I and IVa. Catalytic hydrogenation of both IV and IVa over Raney nickel at two atmospheres gave the same neutral product $C_{14}H_{21}NO_2$ (XV), the conversion being carried out under much milder conditions than in the high-pressure hydrogenation previously

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[1] (a) National Science Foundation Graduate Fellow, June, 1960–June, 1962, and du Pont Summer Fellow, 1st Summer Session, 1962; (b) from the Ph.D. thesis of Richard J. Sundberg, University of Minnesota, August, 1962; *Dissertation Abstr.*, **24**, 85 (1963).

[2] N. C. Knight (with Dorothy V. Nightingale), M.S. thesis, University of Missouri, 1943; cited in ref. 5.

[3] A. Lambert and A. Lowe, *J. Chem. Soc.*, 1517 (1947).

[4] D. V. Nightingale, F. B. Erickson, and J. M. Shackelford, *J. Org. Chem.*, **17**, 1005 (1952).

[5] D. V. Nightingale, D. A. Reich, and F. B. Erickson, *ibid.*, **23**, 236 (1958).

[6] Z. Eckstein, A. Sacha, and W. Sobótka, *Bull. Acad. Polon. Sci.*, *Ser. Sci., Chim., Geol. Geograph.*, **7**, 295 (1959); *Roczniki Chem.*, **34**, 1329 (1960).

[7] D. V. Nightingale, S. Miki, D. N. Heintz, and D. A. Reich, *J. Org. Chem.*, **28**, 642 (1963).

[8] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

[9] W. E. Noland and R. J. Sundberg, *Tetrahedron Letters*, 295 (1962).

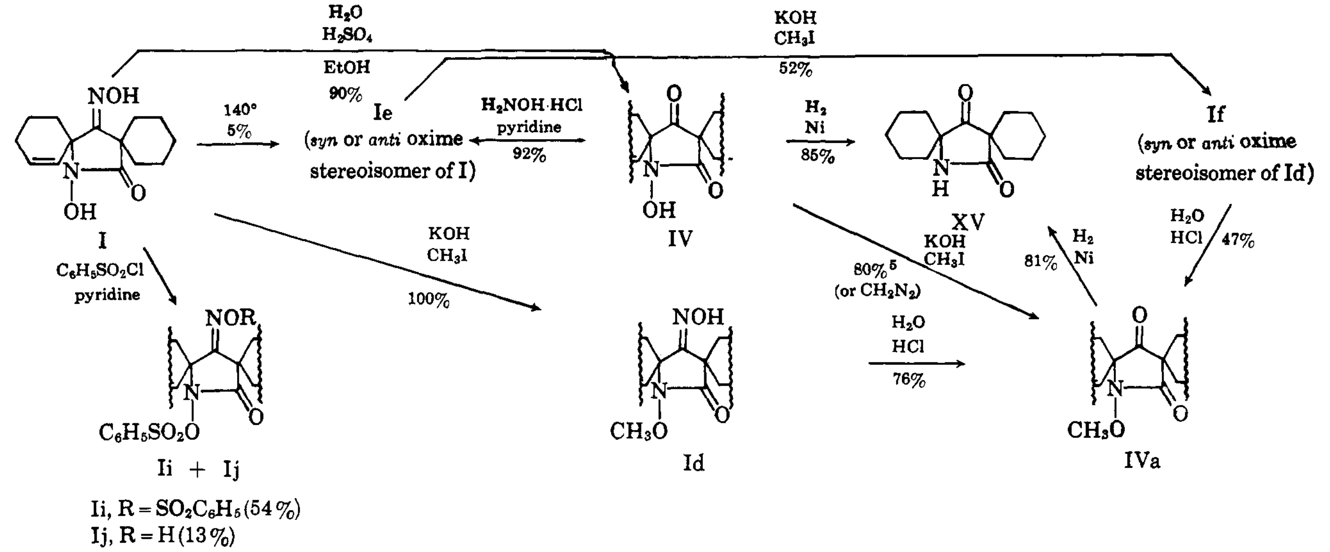
[10] H. O. House and R. W. Magin, *J. Org. Chem.*, **28**, 647 (1963).

[11] Wherever appropriate, our usage of roman numeral designations corresponds to that of Nightingale (ref. 5). With new compounds numbers have been chosen so as not to conflict with numbers already assigned to members of the Nightingale series.

[12] Experiment performed by Vernon D. Parker, University of Minnesota, 1959.

[13] Experiment performed by Allan M. Huffman, University of Minnesota, 1959.

CHART 1



employed.[5] Hydrogenolysis of the acidic hydroxyl group in IV and of the related methoxyl group in IVa under mild conditions is incompatible with the formulation of IV as a carboxylic acid and of IVa as its methyl ester. The acidity and ease of hydrogenolysis of the hydroxyl group, and the position of the amide carbonyl band in the infrared spectra, are all consistent, however, with the structure in I and IV of a five-membered ring N-hydroxylactam, which was resistant to hydrolysis. The remaining nitrogen and oxygen atom of I must then be a part of the oximino group which undergoes hydrolysis. The position of the oxime band in the infrared spectrum of I, and of the ketone carbonyl band in IV, in the methyl derivative IVa, and in the product XV, all indicate that a ketoxime group in I has undergone hydrolysis to a five-membered ring ketone.[14]

Catalytic hydrogenation of I over Raney nickel at two atmospheres and room temperature gave the primary aminolactam $C_{14}H_{24}N_2O$ (II) under much milder conditions than in the high-pressure hydrogenation previously employed.[5] This leaves a single oxygen atom in a five-membered ring amide carbonyl group. In some hydrogenation experiments, reduction stopped partially or completely before saturation of the carbon nitrogen double bond, giving as the product, the iminolactam $C_{14}H_{22}N_2O$ (IIg). Hydrogenation of IIg over fresh Raney nickel catalyst completed the reduction to II. Hydrolysis of IIg with aqueous ethanolic sulfuric acid gave the ketolactam XV. Oxidation of II with chromium trioxide in acetic acid, or with aqueous potassium permanganate, also gave XV. Conversely, XV was converted to II by oximation (to XVc, $C_{14}H_{22}N_2O_2$) and subsequent catalytic hydrogenation over Raney nickel at two atmospheres pressure.

An attempt to reconvert the ketone IV to the oxime I by oximation gave, instead, Ie ($C_{14}H_{20}N_2O_3$) the *syn* or *anti* stereoisomer of I. Partial isomerization of I to Ie was effected by refluxing I in xylene. A small amount of Ie, along with I, was also isolated from an incomplete oxidation of I with aqueous potassium permanganate at 95°. That the isomerization of I to Ie during the oxidation is not due solely to action of the alkali generated is suggested by the quantitative recovery of I from an aqueous 10% potassium hydroxide solution at room temperature. Catalytic hydrogenation of Ie under the conditions used for I also gave the aminolactam II, proving that I and Ie have the same atomic skeleton. Methylation of I and Ie with potassium hydroxide and methyl iodide gave isomeric methyl derivatives $C_{15}H_{22}N_2O_3$, Id and If, respectively. Both isomers were hydrolyzed with aqueous hydrochloric acid to IVa, proving that the difference between Id and If (and, thus, of their parent compounds I and Ie) must lie in the stereochemistry of the oxime group. Completion of the series of transformations described previously confirmed that I is an unsaturated, five-membered ring ketoxime N-hydroxylactam.

The Atomic Skeleton: by Degradation.—For degradation, the primary aminolactam II, obtained by low-pressure hydrogenation of I, was chosen as a subject for study. Dimethylation of II with formaldehyde and formic acid[15] gave an N,N-dimethylaminolactam $C_{16}H_{28}N_2O$ (IId), which was converted to its methiodide IIe ($C_{17}H_{31}N_2OI$). Application of the Hofmann degradation to IIe produced a displacement product, $C_{14}H_{23}NO_2$ (XIV), in which the trimethylammonium group has been replaced by a hydroxyl group. The product XIV had been obtained previously by Nightingale, Reich, and Erickson[5] by high-pressure hydrogenation of the keto N-methoxylactam IVa. In the present work the same transformation has been effected *via* the sodium borohydride reduction of XV. Application of the Hofmann degradation to IIe in ethylene glycol also produced a displacement product, $C_{16}H_{27}NO_3$ (IIf), in which the trimethylammonium group has been replaced by a 2-hydroxyethoxyl group derived from ethylene glycol. The fact that application of the Hofmann degradation to IIe did not result in formation of an olefinic elimination product, but produced instead the displacement products XIV and

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(14) In the infrared spectra of the ketolactams IV, IVa, and XV (as well as of M-IVa, IVc-e, IVg-j) the five-membered ring ketone carbonyl band at 1736-1767 cm.$^{-1}$ is of medium intensity, always much less intense than the strong lactam carbonyl band in the region of 1650-1701 cm.$^{-1}$. This marked intensity difference is reminiscent of that in anhydrides and imides, and led to the infrared evidence for the five-membered ring ketone carbonyl group being overlooked in the original work (ref. 5).

(15) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

CHART 2

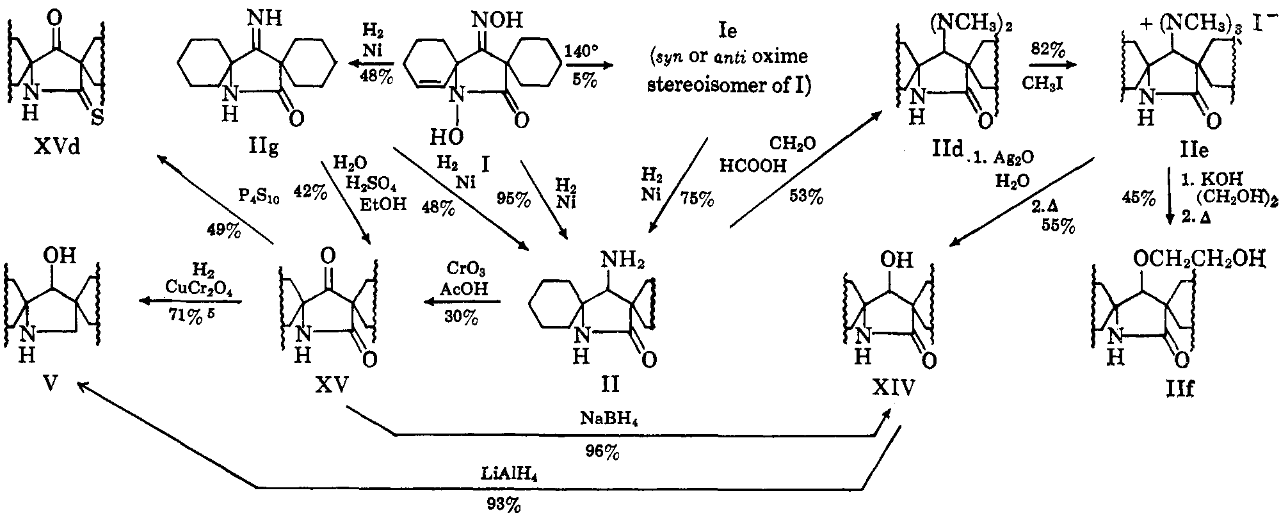
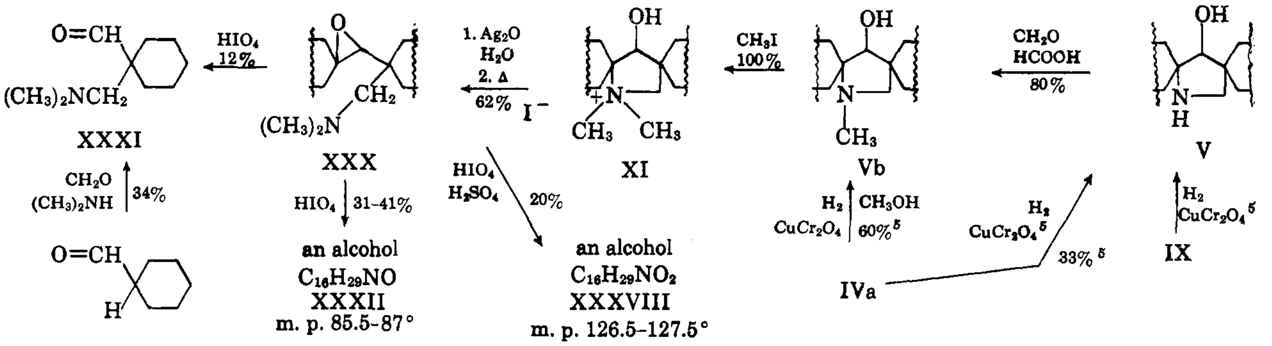


CHART 3



IIf, strongly suggests that the carbon bearing the trimethylammonium group in IIe (and, correspondingly, the carbon bearing the hydroxyl group of XIV and the amino group of II and IId) is attached to carbons bearing no hydrogens.

Attention was then turned to degradative procedures involving the second nitrogen of II, the nitrogen atom still present in the lactam group of XIV and XV. Lithium aluminum hydride reduction of XIV gave the hydroxyamine $C_{14}H_{25}NO$ (V), in which the lactam group has been reduced to an amino group. The product V had been obtained previously by Nightingale, Reich, and Erickson[5] by high-pressure hydrogenation of XV, of IVa, and of the unsaturated hydroxyamine $C_{14}H_{23}NO$ (IX). Methylation of V with formaldehyde and formic acid[15] gave the hydroxy-N-methylamine $C_{15}H_{27}NO$ (Vb). Compound Vb has been obtained previously by Nightingale, Reich, and Erickson[5] by high-pressure hydrogenation of IVa in methanol solution, in which the methanol apparently acted as a methylating agent. Conversion of Vb to its known methiodide $C_{16}H_{30}NOI$ (XI)[5] and application of the Hofmann degradation produced a colorless oil, the epoxy-N,N-dimethylamine $C_{16}H_{29}NO$ (XXX), an intramolecular displacement product. Formation of epoxides by intramolecular displacement under Hofmann degradation conditions is characteristic of β-hydroxyamine methiodides.[16a] Consequently, in XI and its precursors V and Vb, the hydroxyl group corresponding to the primary amino group of II must be beta to the amino nitrogen.

Reaction of the epoxide XXX with periodic acid gave, in addition to an isomeric rearrangement product XXXII and an oxidation product $C_{16}H_{29}NO_2$ (XXXVIII), the known cleavage product, 1-dimethylaminomethylcyclohexanecarboxaldehyde[17] (XXXI). The identity of the cleavage product XXXI was established by comparison of its methiodide (XXXIa) with the methiodide of a synthetic sample prepared by a Mannich reaction[17] from cyclohexanecarboxaldehyde. Isolation of XXXI as a cleavage product proves the structure of the epoxyamine (see XXX), if the plausible assumption is made that the remaining six carbons not present in the cleavage fragment XXXI were part of a second cyclohexane ring. Such an assumption is consistent with the already established fact that the hydroxyl carbon atom in XIV must be attached only to quaternary carbons. The second of the quaternary carbons, not present in XXXI, can, therefore, be part of a cyclohexane ring connected through a spiro junction to the hydroxyl carbon and the nitrogen atom of XIV.[18] This conclusion is strongly supported by the n.m.r. spectrum of the precursor XV, which contains a

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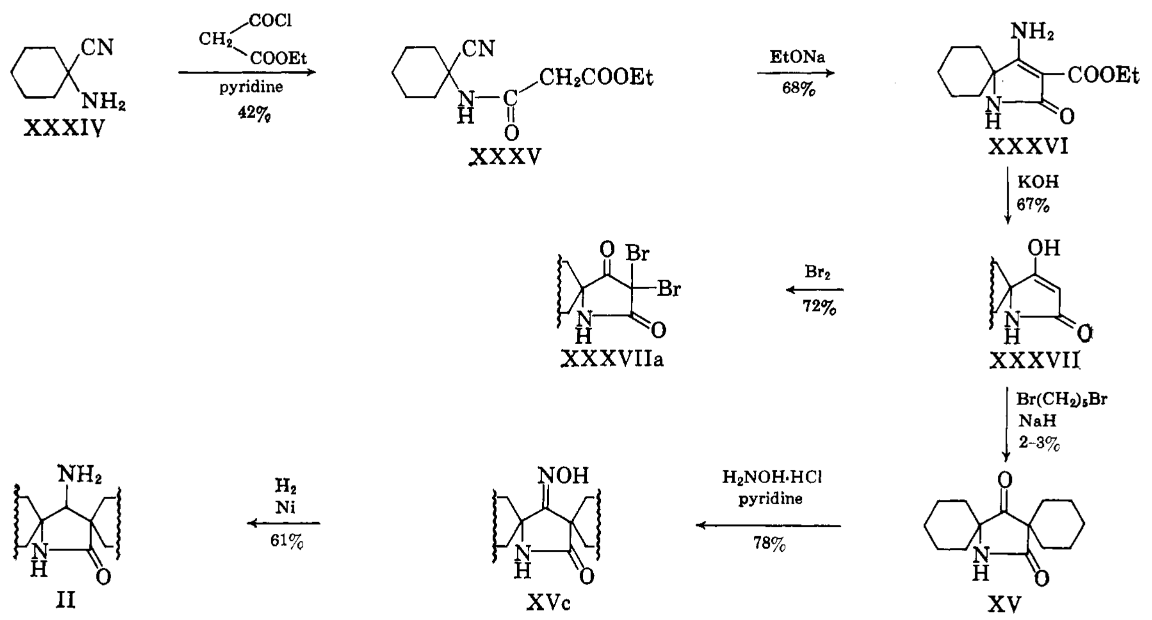
[16] (a) A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 352 (1960); (b) 380 (1960).

[17] C. Mannich, B. Lesser, and F. Silten, *Ber.*, **65**, 378 (1932).

[18] Cleavage of XXX with periodic acid would be expected to yield cyclohexanone as well as XXXI, but all attempts to isolate cyclohexanone from the reaction as its 2,4-dinitrophenylhydrazone were unsuccessful. When cyclohexanone was treated under the conditions of the periodic cleavage, an attempt to isolate it as its 2,4-dinitrophenylhydrazone was equally unsuccessful. It is assumed, therefore, that under the conditions of the periodic acid cleavage cyclohexanone undergoes iodination or further oxidation.

Chart 4

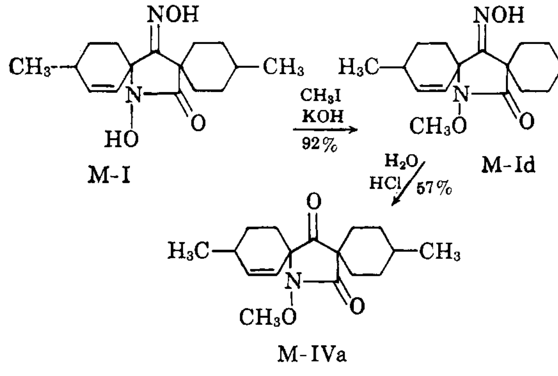


single large peak at 8.31 τ, attributed to the twenty essentially equivalent methylene protons of the two cyclohexane rings. Assignment of structure XXX to the epoxyamine permits assignment of structural formulas to its precursors XI, Vb, V, XIV, and the key compounds XV and II, as well as to their derivatives XVc, IId, IIe, IIf, and IIg (see Charts 2–4).

The Atomic Skeleton: by Synthesis of XV and II.—The ketolactam XV was chosen as the target compound for a synthetic proof of the atomic skeleton of I. The synthesis began with 1-aminocyclohexanecarbonitrile (XXXIV), obtained by action[19] of ammonia on cyclohexanone cyanohydrin. Acylation with ethyl chloroformylacetate in pyridine gave XXXV (see Chart 4) as an oil, which was cyclized with sodium ethoxide to XXXVI (isolated in dimorphic forms).[20] Alkaline hydrolysis of XXXVI, with accompanying decarboxylation, gave XXXVII.[20,21] Dialkylation of XXXVII with 1,5-dibromopentane, catalyzed by sodium hydride in N,N-dimethylformamide,[26] gave XV in 2–3% yield.[27,30] The synthetic sample of XV was identical, as shown by mixture melting point and infrared comparison, with the sample obtained by degradation of I. As XV has been converted to II, synthesis of XV also constitutes a total synthesis of II (Chart 4). Since II is derivable from I under mild conditions by low-pressure hydrogenation, it is assumed that the atomic skeleton proved to be present in II is also present in I.

Location of the Olefinic Double Bond: the Complete Structure of I.—Action of strong alkali at 200° on IV gave cyclohexanecarboxylic acid, also characterized as its amide. This acid cleavage of the β-ketolactam group (and subsequent hydrolysis of the N-hydroxyamide linkage) proves that the olefinic double bond is not present in the right-hand cyclohexane ring of IV and its precursor I (as written in Chart 1). To differentiate between the two possible positions in the left-hand ring, the n.m.r. spectrum of the more soluble derivative IVa was compared with that

Chart 5



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[19] R. A. Jacobson, *J. Am. Chem. Soc.*, **67**, 1996 (1945).

[20] The Nujol infrared spectra of the two dimorphs of XXXVI show that they are in the enol form in the solid state. Likewise, XXXVII is largely but not entirely enolized in the solid state. This is shown by the presence in the Nujol infrared spectrum of a weak five-membered ring ketone carbonyl band at 1764 and a medium inflection at 1677 cm.$^{-1}$, attributed to an unconjugated lactam carbonyl band; and strong conjugated lactam and conjugated double bond bands at 1655 and 1595 cm.$^{-1}$, which are attributed to the enol form. The ultraviolet spectra of XXXVI and XXXVII show that the two compounds also exist as enols in ethanol solution; the ultraviolet spectra compare favorably with those of related enolic tetramic[22] and tetronic[23,24] acids. In agreement with its enolic structure, compound XXXVII reacts almost instantaneously with bromine in water to form a dibromide XXXVIIa, as does the related γ,γ-dimethyltetramic acid, 4-hydroxy-5,5-dimethyl-3-pyrrolin-2-one.[25]

[21] Synthesis of XXXVII has analogy in the synthesis of 3,4-dihydroxy-2-pentenoic acid γ-lactone (γ-methyltetronic acid), in which the 1-(ethoxycarbonyl)ethyl ethyl ester of malonic acid was cyclized by the action of sodium in toluene, with accompanying loss of the ethoxycarbonyl group: L. J. Haynes and A. H. Stanners, *J. Chem. Soc.*, 4103 (1956).

[22] R. N. Lacey, *ibid.*, 850 (1954).

[23] E. R. H. Jones and M. C. Whiting, *ibid.*, 1419 (1949).

[24] R. N. Lacey, *ibid.*, 832 (1954).

[25] S. Gabriel, *Ber.*, **47**, 3033 (1914).

[26] H. E. Zaugg, D. A. Dunnigan, R. J. Michaels, L. R. Swett, T. S. Wang, A. H. Sommers, and R. W. DeNet, *J. Org. Chem.*, **26**, 644 (1961).

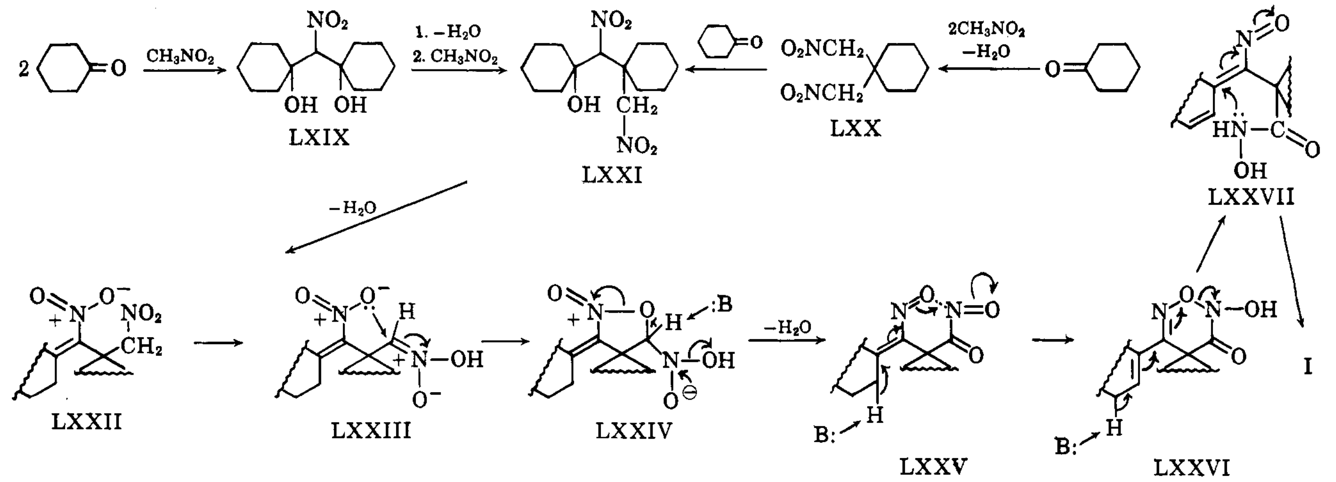
[27] The low solubility and high crystallinity permitted XV to be isolated without difficulty. The low yield may be due in part to intermolecular dialkylation, leading to polymerization, and in part to O-alkylation. O-Alkylation occurs to the exclusion of C-alkylation in methylation with dimethyl sulfate of a related ambident anion,[28] the sodium salt of 3,4-dihydroxy-2-methyl-2-butenoic acid γ-lactone (the sodium salt of α-methyltetronic acid).[29]

[28] N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955).

[29] L. J. Haynes and J. R. Plimmer, *Quart. Rev.* (London), **14**, 309 (1960).

[30] Synthesis of spiro systems from enolate anions by dialkylation has also been accomplished previously: M. Mousseron, R. Jacquier, and H. Christol, *Bull. soc. chim. France*, 346 (1957).

CHART 6



of M-IVa, its 3,11-dimethyl homolog. For this purpose, M-I[31] (Chart 5), formed by condensation of nitromethane with 4-methylcyclohexanone was methylated (to M-Id) and then hydrolyzed to M-IVa, analogous to the conversion of I to Id to IVa.

The n.m.r. spectrum of M-IVa shows clearly that the double bond is not in the 10,11-position, as such a structure would contain only one vinyl proton, rather than the two seen to be present. The n.m.r. spectra of I, IVa, and M-IVa all contain two doublets (J = 9–10.7 c.p.s.), a simple one centered at 4.67–4.75 τ (C-9 olefinic proton, which has no adjacent aliphatic protons) and a more complex one centered at 3.84–4.01 τ (C-10 olefinic proton). The C-10 proton is coupled to two C-11 protons in I and IVa, accounting for the complexity of the doublet. With M-IVa, in which the C-10 proton is coupled to the single C-11 proton, each member of the C-10 proton doublet is itself a finely split doublet (J = 3.1 c.p.s.). The similarity of the vinyl proton region in the n.m.r. spectra of I, IVa, and M-IVa shows that the double bond is in the same position in all three compounds, and cannot have rearranged during the acid hydrolysis of I to IV, or during the alkaline methylation of IV to IVa. With location of the double bond in the 9,10-position, it is now possible to assign complete structural formulas to I, IVa, and M-IVa, and to their unsaturated derivatives, including Id, Ie, If, IV, IX, M-I, and M-Id (Charts 1, 5, 7). By analogy with the structure of I, it is assumed that similar structures may be assigned to the related condensation products of nitromethane with cyclopentanone,[5,7] cycloheptanone,[7] cyclooctanone,[7] and 3-[32] and 4-alkylsubstituted[5,7,32] cyclohexanones.

A Plausible Mechanism for Formation of Compound I.—Formation of I from nitromethane and cyclohexanone probably proceeds (Chart 6) through the key intermediate LXXI, which could be formed either (1) *via* the 2:1 condensation product LXX (which has been isolated from a reaction in which I was also formed[3]), or (2) *via* the 1:2 adduct LXIX. From LXXI there would follow a series of steps (possibly proceeding in the order LXXII–LXXVII shown[33]), involving intramolecular oxygen transfer, dehydration, and oxidation–reduction, culminating in a second key intermediate LXXVII, which could readily isomerize to I. Transformation of the nitromethyl group of LXXI to the hydroxamic acid group of LXXVII is seen to be an example of the Victor Meyer reaction, which usually occurs under strongly acidic conditions.[34,35]

Ancillary Degradative Experiments.—Reduction of IV with lithium aluminum hydride gave diastereoisomeric amino alcohols $C_{14}H_{23}NO$, IXa (isolated as dimorphic forms, m.p. 129–131° and 133–134°) and IXb (m.p. 150–152°), and a reduction intermediate $C_{14}H_{21}NO_2$, the nitrone IXc (Chart 7), analogous to the saturated derivative recently described by House and Magin.[10] Diastereoisomer IXa is assigned the structure in which the 7-hydroxyl group and the 9,10-double bond are attached *cis* to the central pyrrolidine ring (Chart 8). The n.m.r. spectrum of IXa differs from that of IXb in (1) the 0.18 τ relative deshielding in IXa of the two 9,10-double bond protons by the *cis* 7-hydroxyl group, (2) the 0.07 τ relative deshielding in IXb of the *cis* C–H proton (at 6.59 τ) of the secondary alcohol by the C-9 double bond proton, and (3) the difference in chemical shift in IXa between the two C-15 methylene protons, which gives rise to a 4-peak AB pattern (J = 11.3 c.p.s.) centered at 7.15 τ, while IXb gives only a single sharp peak at 7.15 τ. It is likely that IXc is stereochemically related to IXb, since with reduction under more vigorous conditions the yield of IXc decreased from 21 to 4% while that of IXb increased from 20 to 33%, but the yield of IXa changed only slightly, from 15 to 13%. Comparison of the infrared spectra shows that the reduction product IX,[5] m.p. 140–141°, of Nightingale and Reich[36] consisted predominantly of the less soluble diastereoisomer IXb.

Methylation of a crude mixture of diastereoisomers IX with formaldehyde and formic acid[15] gave a corresponding mixture of the methyl derivatives (IXg). The separate diastereoisomers IXa and IXb were methylated with methyl iodide to the corresponding methiodides IXe and IXd, both of which showed a marked tendency to crystallize as 2:1 complexes with

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[31] Formerly designated as compound XXI (ref. 5); now compound M-I (ref. 7).

[32] D. V. Nightingale, F. B. Erickson, and J. M. Shackelford, *J. Org. Chem.*, **17**, 1005 (1952).

[33] We wish to thank a referee for suggesting the sequence LXXIII–LXXVI.

[34] H. B. Hass and E. F. Riley, *Chem. Rev.*, **32**, 373 (1943).

[35] W. E. Noland, *ibid.*, **55**, 137 (1955).

[36] Donald A. Reich, Ph.D. thesis (with Dorothy V. Nightingale), University of Missouri, June, 1956, p. 34; *Dissertation Abstr.*, **16**, 2313 (1956).

CHART 7

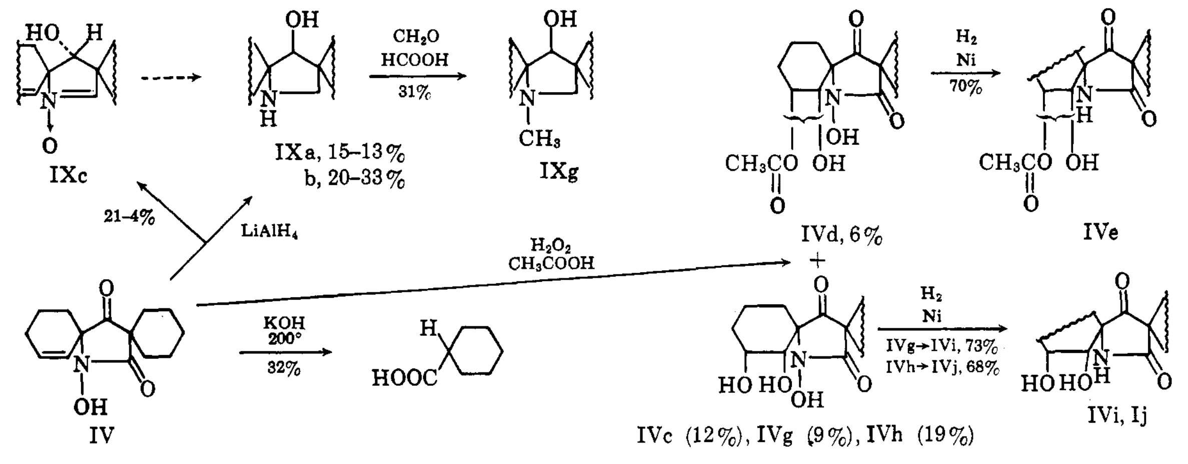
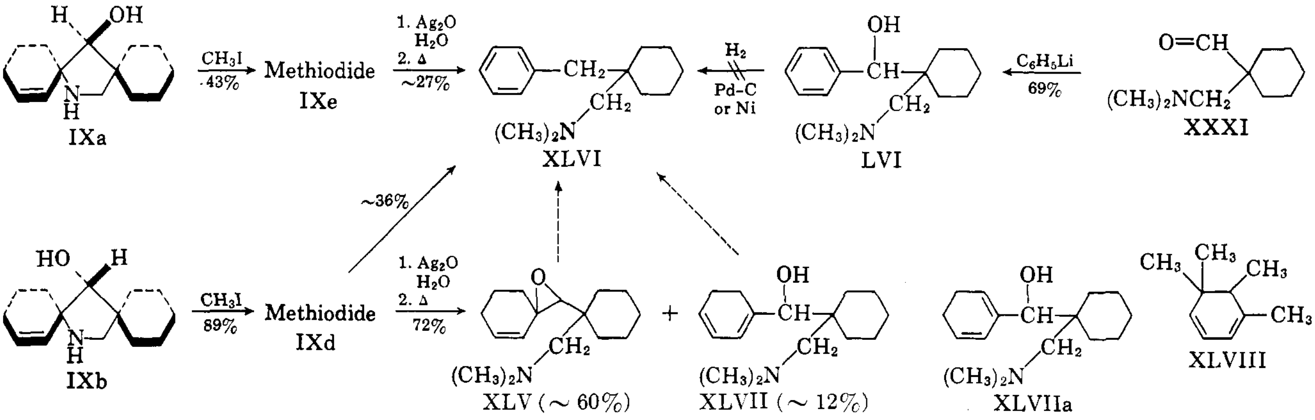


CHART 8



benzene from ethanol–benzene solution. Pyrolysis of the methohydroxide of IXd gave on one occasion a distillable oil $C_{16}H_{27}NO$, which, from the n.m.r. and infrared spectra, appears to consist largely of the epoxide XLV (Chart 8), with a small amount of the isomeric conjugated diene alcohol XLVII (or, less likely, the isomer XLVIIa). The ultraviolet spectrum of the oil, using α-pyronene (XLVIII) as a model,[37] indicates the presence of 16% conjugated diene. Pyrolysis on other occasions of the methohydroxides of IXd and IXe gave in the distillate impure oils, having aromatic ultraviolet spectra and identical infrared spectra. The oils, purified through the crystalline picrate (XLVIa), were shown to consist largely of the aromatized product $C_{16}H_{25}N$ (XLVI) assumed to result from pyrolytic dehydration of the intermediates XLV and XLVII. The aromatic ultraviolet spectrum of XLVI agrees well with those of toluene[38] and 1-(1-dimethylaminomethylcyclohexyl)-1-phenylmethanol (LVI), prepared by action of phenyllithium on 1-dimethylaminomethylcyclohexanecarboxaldehyde (XXXI). Attempts to provide an independent synthesis of XLVI by converting LVI to XLVI were unsuccessful; highly sterically hindered benzyl alcohols are reported to resist hydrogenolysis.[39]

Additional Derivatives.—Action of benzenesulfonyl chloride in pyridine on I gave both a monobenzenesulfonyl derivative $C_{20}H_{24}N_2O_5S$ (Ij), and a dibenzenesulfonyl derivative $C_{26}H_{28}N_2O_7$ (Ii) analogous to the diacetyl derivative Ia.[3,5] The monobenzenesulfonyl derivative is assigned the N-hydroxylactam benzenesulfonate structure (Ij in Chart 1) on the basis of the position of the hydroxyl band in the infrared spectrum, and the fact that it was recovered unchanged (76%) from attempted reaction with hydrochloric acid under conditions known to effect Beckmann rearrangement of oxime sulfonate esters.[40] Reaction of II with nitrous acid gave $C_{14}H_{20}N_2O_2$ (VII), which has a strong, conjugated ultraviolet spectrum, and OH or NH bands as well as an amide carbonyl band in the infrared spectrum. Fusion of XV with tetraphosphorus decasulfide gave a monothioamide $C_{14}H_{21}NOS$ (XVd, Chart 2), as shown by the five-membered ring ketone carbonyl band in the infrared spectrum.

Oxidation[41] of IV with peracetic acid has been reported[5] to yield a compound $C_{16}H_{23}NO_7$, m.p. 219–221°. Working with a larger ratio of hydrogen peroxide and acetic acid, we isolated instead a hydroxy acetate $C_{16}H_{23}NO_6$ (IVd, m.p. 242–246°) and three isomeric glycols $C_{14}H_{21}NO_5$ (Chart 7): IVc (m.p. 220–221°), IVg (m.p. 235–237°), and IVh (m.p. 240–243°, sublimes). As IVg and IVh were isolated after alkaline saponification, one of them may be derived from IVd; IVh was

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(37) λ_{max} in isoöctane: 263 mμ (log ε 3.76); R. T. O'Connor and L. A. Goldblatt, *Anal. Chem.*, **26**, 1726 (1954).

(38) (a) E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **71**, 84 (1949); (b) T. W. Campbell, S. Linden, S. Godshalk, and W. G. Young, *ibid.*, **69**, 880 (1947).

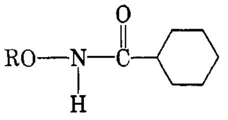
(39) W. H. Hartung and R. Simonoff, *Org. Reactions*, **7**, 268 (1953).

(40) L. G. Donaruma and W. Z. Heldt, *ibid.*, **11**, 1 (1960).

(41) We have found that ozonolysis of IV and IVa in ethyl acetate solution, followed by oxidation with hydrogen peroxide, gave oils which failed to crystallize.

most readily isolated as a sodium salt monohydrate (IVf). Oxidation of IV with performic acid gave, after saponification, IVg and IVh (as IVf). Formation of a total of three glycols implies that, unless double bond migration[42] or skeletal rearrangement has occurred, in addition to the expected two *trans* isomers, one of the *cis* forms was also obtained, a fact which can be rationalized in terms of anchimeric assistance by the neighboring N-hydroxyl group. Catalytic hydrogenation of IVd, IVg, and IVh over Raney nickel at two atmospheres and room temperature gave the hydrogenolysis products IVe, IVi, and IVj, containing one less oxygen atom, analogous to the conversion of IV to XV.

During the course of this work cyclohexanehydroxamic acid (LXXIX) and its methyl derivative (LXXX) were prepared for examination as model compounds.



LXXIX, R = H
LXXX, R = CH_3

Experimental

Melting points were determined on a calibrated Kofler micro hot stage. Where not specified, the drying agent used for organic solutions was anhydrous magnesium sulfate.

14-Hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione, 7-Oxime, Isomer 1 (I).—The procedure used was essentially that of Nightingale, Reich, and Erickson,[5] except that the reflux period was increased from 30 to 72 hr., and the catalyst, piperidine, was added occasionally during the reflux period. The product consisted of small white needles, m.p. 271–274° sublimes (29%), lit.[7] 24%; lit.[3] m.p. 270–271°, lit.[7] 273–274° dec. (sublimes); ν_{OH} 3180 m infl., 3080 m, 2650 m, (KBr), 3070 s, 2650 w (Nujol), $\nu_{C=N}$ 1690 m (KBr), 1693 m (Nujol), $\nu_{C=O,\ C=C}$ 1655 s, 1639 s (KBr), 1654 s, 1641 s (stronger) cm.$^{-1}$ (Nujol).[13] The n.m.r. spectrum of a saturated solution in N,N-dimethylformamide[43a] contains the most intense absorption (in τ; 1 τ = 56.44 c.p.s.) in the aliphatic methylene proton region as a complex with a major peak at 8.35 and a lesser peak at 8.13. In the vinyl proton region there is a doublet (4.78, and stronger peak at 4.61; J = 9.6 c.p.s.) centered at 4.70, and a more complex multiplet having its strongest peak at 4.01. In a 1:1 solution of chloroform-*d* and dimethyl sulfoxide-d_6[43b] (in τ; 1 τ = 100 c.p.s.) there is a central peak at 8.19, with side peaks at 8.39 and 7.89 (16.4 protons). The two vinyl protons appear as a doublet (4.77, and stronger peak at 4.68; J = 9 c.p.s.) centered at 4.73, and a more complex doublet (stronger peak at 3.96, and 3.87; J = 9 c.p.s.) centered at 3.94, and the two hydroxyl protons appear as sharp singlets at +0.56 and −0.67.

Anal.[13] Calcd. for $C_{14}H_{20}N_2O_3$ (264.32): C, 63.61; H, 7.63; N, 10.60. Found: C, 63.83; H, 7.71; N, 10.52.

Diacetyl Derivative of I: 14-Acetoxy-14-azadispiro[5.1.5.2]-pentadec-9-ene-7,15-dione, 7-Acetyloxime (**Ia**).[3,12]—A solution of I (2.00 g., 0.00756 mole) in acetic anhydride (50 cc., 0.53 mole) was refluxed for 10 min., and the excess acetic anhydride was evaporated under aspirator pressure. The white residue was recrystallized from ethanol–water, yielding white crystals (2.15 g., 82%), m.p. 129–130°; lit.[3,5] m.p. 128–129°; ν_{OH} none, $\nu_{C=O,\ C=N}$ 1804 s and 1790 s (doublet), 1733 s, $\nu_{C=C}$ 1655 mw cm.$^{-1}$ (Nujol).

Anal.[13] Calcd. for $C_{18}H_{24}N_2O_5$ (348.39): C, 62.05; H, 6.94; N, 8.04. Found: C, 62.28; H, 7.08; N, 8.03.

Benzenesulfonyl Derivatives of I.—Action of benzenesulfonyl chloride (10 cc., 0.079 mole) on I (2.00 g., 0.00756 mole) in refluxing pyridine (100 cc.) gave a mixture of benzenesulfonyl derivatives as a brown oil, which was dissolved in 1:1 benzene–methylene chloride (8 cc.) and chromatographed on alumina. Elution with benzene removed a clear yellow oil which quickly solidified to a white solid (Ii, 2.22 g., 54%), m.p. 125–127°. Elution with methylene chloride removed an orange crystalline solid (Ij, 0.41 g., 13%), m.p. 190°.

Two recrystallizations of Ii from ethanol–water yielded **14-benzenesulfonyloxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione, 7-benzenesulfonyloxime** (**Ii, dibenzenesulfonyl derivative of I**) as a granular white solid, m.p. 124–125°; ν_{OH} none, $\nu_{C=O}$ 1745 m, ν_{OSO_2} 1381 s, 1195 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{26}H_{28}N_2O_7S_2$ (544.63): C, 57.33; H, 5.18; N, 5.14; S, 11.78. Found: C, 57.35; H, 5.19; N, 4.80; S, 12.14.

Four recrystallizations of Ij from methanol–water yielded **14-benzenesulfonyloxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione, 7-oxime** (**Ij, monobenzenesulfonyl derivative of I**) as white prisms, m.p. 184–187° dec.; ν_{OH} 3290 m, $\nu_{C=O}$ 1727 s, $\nu_{C=N}$ 1647 m, ν_{OSO_2} 1389 s, 1190 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{20}H_{24}N_2O_5S$ (404.47): C, 59.39; H, 5.98; N, 6.93; S, 7.93. Found: C, 59.74; H, 5.90; N, 6.79; S, 8.39.

Methyl Derivative of I: 14-Methoxy-14-azadispiro[5.1.5.2]-pentadec-9-ene-7,15-dione, 7-Oxime, Isomer 1 (**Id**).—Methyl iodide (28 g., 0.197 mole) was added to a solution of I (37.0 g., 0.140 mole) and potassium hydroxide (9.25 g., 0.165 mole) in methanol (350 cc.), and the resulting solution refluxed for 2.5 hr. The solution was then concentrated by distilling methanol (~150 cc.), and diluted with boiling water (350 cc.). Fine white needles (39.3 g., 100%), m.p. 183–185°, crystallized. Two recrystallizations from methanol–water yielded fine white needles, m.p. 185–186°; ν_{OH} 3210 ms, 3060 m, $\nu_{C=N,\ C=O}$ 1689 s, $\nu_{C=C}$ 1647 ms cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{15}H_{22}N_2O_3$ (278.34): C, 64.72; H, 7.97; N, 10.07. Found: C, 64.67; H, 7.98; N, 10.22.

14-Hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione, 7-Oxime, Isomer 2 (**Ie**). (A) **From Oximation of IV.**—A solution of IV (6.07 g., 0.0244 mole) and hydroxylamine hydrochloride (4.0 g., 0.057 mole) in pyridine (25 cc.) and absolute ethanol (25 cc.) was refluxed for 36 hr. At fourteen convenient intervals during the reflux period, one-fourteenth of each of the following was added: hydroxylamine hydrochloride (28.0 g., 0.403 mole), pyridine (140 cc.), and absolute ethanol (140 cc.). At the end of the reflux period, the solvents were evaporated in a stream of air. The residual mushy solid was extracted successively with water and chloroform, leaving behind nearly pure crystalline solid (5.93 g., 92%). Recrystallization from ethyl acetate–light petroleum ether (b.p. 60–68°) yielded fine needles, m.p. 262–264°, having an infrared spectrum different from that of I; ν_{OH} 3360–2360 ms (very broad), $\nu_{C=N}$ 1696s, $\nu_{C=O}$ 1673s, $\nu_{C=C}$ 1655 ms infl. cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{20}N_2O_3$ (264.32): C, 63.61; H, 7.63; N, 10.60. Found: C, 63.57; H, 7.58; N, 10.44.

(B) **From Partial Thermal Isomerization of I in Xylene.**—A mixture of I (2.0 g.) and xylene (80 cc.) was refluxed for 72 hr., but remained heterogeneous throughout the period. Then the hot mixture was quickly filtered, removing unchanged I (1.53 g., 76%), m.p. 276–278°, identified by its infrared spectrum (Nujol). Upon being cooled overnight, the filtrate deposited a mixture of I and Ie (0.11 g., 5%), m.p. 250–256° dec., the presence of Ie being shown in particular by the shape of the carbonyl band, and of the doublet in the 950–900-cm.$^{-1}$ region.

(C) **From Partial Thermal Isomerization of I in Xylene in the Presence of Chloranil.**—A mixture of I (3.0 g.), chloranil (5.6 g.), and xylene (150 cc.) was refluxed for 13 hr., and then filtered while hot. The filtrate deposited a dark brown solid (1.17 g.) after a time. This solid was dissolved in aqueous potassium hydroxide and the mixture filtered to remove an insoluble black tar. The filtrate was treated with charcoal, and then acidified, causing precipitation of a light tan powder (1.13 g., 38%), m.p. 260–262° (sublimes above 200°), having an infrared spectrum (Nujol) indicating it to be predominantly Ie. Fractional crystallization from ethyl acetate–light petroleum ether (b.p. 60–68°) separated unchanged I (0.34 g., 11% recovery) and Ie (0.14 g., 5%), as shown by their infrared spectra (Nujol). Recrystallization of the Ie from ethyl acetate–light petroleum ether yielded small white needles, m.p. 262–263° dec. (sublimes above 200°), having an infrared spectrum (Nujol) identical with that of the sample prepared by oximation of IV.

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[42] Double bond migration in acetic acid is unlikely, because it did not occur during the hydrolysis of I to IV in aqueous ethanolic sulfuric acid.

[43] Spectrum determined (a) by George B. Bodem, University of Minnesota, August 5, 1959; (b) by LeRoy F. Johnson, Varian Associates, Palo Alto, Calif., November 27, 1962.

Anal. Found: C, 63.25; H, 7.79; N, 10.52.

Methyl Derivative of Ie: 14-Methoxy-14-azadispiro[5.1.5.2]-pentadec-9-ene-7,15-dione, 7-Oxime, Isomer 2 (**If**).—Methylation of Ie (0.22 g., 0.00083 mole) essentially as described previously for methylation of I to obtain Id gave white crystals (0.12 g., 52%), m.p. 184–186° sublimes. Recrystallization from methanol–water yielded a white powder, m.p. 185–186°; ν_{OH} 3210 m, 3080 vw, $\nu_{C=N,\ C=O}$ 1692 s, $\nu_{C=C}$ 1658 m cm.$^{-1}$ (Nujol). The infrared spectrum is different from that of Id.

Anal. Calcd. for $C_{15}H_{22}N_2O_3$ (278.34): C, 64.72; H, 7.97; N, 10.07. Found: C, 64.75; H, 8.05; N, 10.23.

14-Hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (IV).—The compound was prepared essentially according to the procedure of Nightingale, Reich, and Erickson,[5] except that the reflux period was decreased from 53 to 24 hr., and ethanol was added in order to decrease the solvent volume required. The crystalline product was dissolved in methylene chloride (in which any unchanged I is insoluble), and the solution was dried, treated with charcoal, and concentrated. Dilution with hot light petroleum ether (b.p. 60–68°) yielded white crystals (90%), m.p. 174–175°; lit.[5] 91%, m.p. 170–172°; ν_{OH} 3060 m, 2690 w (KBr), 3060 m, 2690 w, 3360–2200 m (very broad) in Nujol, 3040 m, 2660 w (halocarbon oil), $\nu_{C=O}$ 1755 ms, 1676 s (KBr), 1752 m, 1676 s (Nujol), 1750 ms, 1675 s (halocarbon oil), $\nu_{C=C}$ 1648 ms (KBr), 1646 m (Nujol), 1645 ms cm.$^{-1}$ (halocarbon oil).[13]

Anal.[13] Calcd. for $C_{14}H_{19}NO_3$ (249.30): C, 67.44; H, 7.68; N, 5.62. Found: C, 67.67; H, 7.75; N, 5.71; neut. equiv., 232, 242.

14-Methoxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (IVa). (A) **From Methylation of IV with Potassium Hydroxide and Methyl Iodide.**—The preparation of IVa in 80% yield by methylation of IV with potassium hydroxide and methyl iodide has been described by Nightingale, Reich, and Erickson.[5] These authors report that IVa, like I and IV, gives a purple color with ferric chloride solution. In our hands IVa, like Id, does not give a positive ferric chloride test. The positive reaction previously observed with IVa may possibly have been due to the presence of unmethylated IV as a contaminant in the IVa.

(B) **From Methylation of IV with Diazomethane.**[12]—An ethereal solution of diazomethane[44] was prepared by adding N-nitroso-N-methylurea (10.3 g., 0.100 mole) to a mixture of aqueous 50% potassium hydroxide solution (30 cc.) and ether (100 cc.) at 5°. The distilled ethereal solution of diazomethane was added to IV (2 g., 0.0080 mole), with swirling, until no more gas evolution was observed. The ether was evaporated and the grayish residue was recrystallized from methanol–water, yielding white platelets, m.p. 89–91°, having an infrared spectrum (Nujol) which showed the product to be IVa.

(C) **From Acidic Hydrolysis of Id.**—Compound Id (0.32 g., 0.00115 mole) was stirred with a solution of concentrated hydrochloric acid (14 cc.) in water (86 cc.) at 90° on a steam bath. After 3.5 hr. the mixture had become homogeneous, but stirring and heating were continued for 1 more hr. The solution was then allowed to cool to room temperature, and long needles crystallized (0.23 g., 76%), m.p. 86–90°, having an infrared spectrum (Nujol) identical with that of a sample prepared by methylation of IV as described in part A. Recrystallization from methanol–water yielded a sample, m.p. 92–94°, which gave no depression in m.m.p., 92–94°, with a sample of m.p. 95–96° prepared by methylation of IV as described in part A; lit.[5] m.p. 95–96°.

(D) **From Acidic Hydrolysis of If.**—Hydrolysis of If (0.20 g., 0.00072 mole) as described for Id in part C gave needles (0.09 g., 47%), m.p. 95–95.5°, which gave no depression in m.m.p., 95–96°, with a sample of m.p. 95–96° prepared by methylation of IV as described in part A.[5] The infrared spectra of the two samples (Nujol) were identical.

(E) **Dimorphism of IVa.**—Compound IVa was obtained in two dimorphic forms, both melting at 95–96°, but having different infrared spectra (Nujol). The spectrum of dimorph A is characterized by three sharp bands of relative intensity (going toward lower frequency) m, s, s around 735 cm.$^{-1}$, while dimorph B has sharp bands of relative intensity m, s, m in the same region.

Dimorph A, m.p. 95–96°, was obtained by crystallization from ethanol–water; $\nu_{C=O}$ 1751 ms, 1701 s; $\nu_{C=C}$ 1650 m cm.$^{-1}$ (Nujol).[12] The n.m.r. spectrum of a 10% solution in carbon tetrachloride contains the most intense absorption (in τ; 1 τ = 56.44 c.p.s.) in the aliphatic methylene proton region, as a complex with a major peak at 8.34 and lesser declining peaks at 8.06 and 7.88. There is a sharp peak at 6.15 (14-methoxyl group protons). The two vinyl protons appear as a doublet (4.76, and stronger peak at 4.58; J = 10.1 c.p.s.) centered at 4.67, and a more complex doublet (stronger peak at 3.94, and 3.75; J = 10.7 c.p.s.) centered at 3.85.

Anal.[12] Calcd. for $C_{15}H_{21}NO_3$ (263.33): C, 68.41; H, 8.04; N, 5.32. Found: C, 68.63; H, 8.01; N, 5.35.

Dimorph A, upon recovery from refluxing in acetic anhydride, crystallized as dimorph B, m.p. 95–96°,[12] thus constituting dimorph interconversion in one direction. Recrystallization of IVa, prepared as described in part A,[5] from methanol–water also gave dimorph B, m.p. 95–96°[13]; $\nu_{C=O}$ 1748 m, 1698 s (Nujol, halocarbon oil); $\nu_{C=C}$ 1643 mw cm.$^{-1}$ (Nujol, halocarbon oil).

Anal. Found: C, 68.39; H, 8.03; N, 5.43.

7-Amino-14-azadispiro[5.1.5.2]pentadecan-15-one (II). (A) **From Low-Pressure Hydrogenation of I.**—Compound I (8.58 g., 0.0324 mole) in ethanol (250 cc.) was hydrogenated over Raney nickel at 2 atm. and room temperature. Compound I was not completely soluble in the original solution, but dissolved completely as the hydrogenation proceeded. Hydrogen uptake ceased after 43 hr. of shaking, when the pressure drop corresponded to 123% of the calculated amount, but shaking was continued for an additional 24 hr. The catalyst was filtered off and washed with hot 95% ethanol. The combined ethanol filtrate and washings were concentrated and diluted with hot water, causing crystallization of clusters of fine white needles (7.3 g., 95%), m.p. 193–195°. Several recrystallizations from ethanol–water yielded fine white needles, m.p. 195–196°, lit.[5] m.p. 192–193°; ν_{NH} 3160 m, 3040 mw (KBr), 3150 m, 3050 mw (Nujol), 3130 and 3030 mw (halocarbon oil), $\nu_{C=O}$ 1676 s (KBr), 1678 s (Nujol), 1673 s cm.$^{-1}$ (halocarbon oil).

Anal. Calcd. for $C_{14}H_{24}N_2O$ (236.35): C, 71.14; H, 10.24; N, 11.85. Found: C, 70.95; H, 10.18; N, 11.89.

(B) **From Low-Pressure Hydrogenation of Ie.**—Compound Ie (1.00 g., 0.00378 mole) dissolved in absolute ethanol (200 cc.) was hydrogenated as described in part A. After filtration of the catalyst, the combined ethanol filtrate and washings were evaporated to dryness, and the residue was dissolved in chloroform. The chloroform solution was extracted with dilute hydrochloric acid, and the acid extract made alkaline with sodium hydroxide. Extraction with chloroform, drying, and evaporation of the chloroform gave a hard white solid (0.67 g., 75%), m.p. 193–195°, which gave no depression in m.m.p., 193–195°, with a sample of m.p. 193–196° prepared from I. The infrared spectra (Nujol) of the two samples were identical.

(C) **From Low-Pressure Hydrogenation of IIg.**—Compound IIg (0.45 g., 0.00192 mole) was hydrogenated and the reaction mixture worked up essentially as described in part B, giving white needles (0.22 g., 48%), m.p. 193–196°, having an infrared spectrum (Nujol) identical with that of a sample prepared from I.

(D) **From Low-Pressure Hydrogenation of XVc.**—Compound XVc (1.00 g., 0.00400 mole) in ethanol (200 cc.) was hydrogenated and the reaction mixture worked up as described in part B, giving a hard white solid (0.58 g., 61%), m.p. 192–194°. Recrystallization from ethanol–water gave a sample which gave no depression in m.m.p., 193–196°, with a sample of m.p. 193–196° prepared from I. The infrared spectra (Nujol) of the two samples were identical.

Monoacetyl Derivative of II: 7-Acetamido-14-azadispiro-[5.1.5.2]pentadecan-15-one (**IIa**).[5,45]—A solution of II (0.90 g., 0.00380 mole) in acetic anhydride (25 cc., 0.265 mole) was heated on a steam bath for 20 min. The solution was then poured into ice water and the precipitated white solid filtered off. One recrystallization from ethanol–water yielded colorless plates (0.58 g., 55%), m.p. 277–278°, lit.[5] m.p. 271–272°; ν_{NH} 3330 m, 3140 m, 3040 m, $\nu_{C=O}$ 1683 s, 1651 s cm.$^{-1}$ (Nujol).

Diacetyl Derivative of II: 7-Diacetylamino-14-azadispiro-[5.1.5.2]pentadecan-15-one.[5,45]—A solution of II (1.07 g., 0.00453 mole) in acetic anhydride (25 cc., 0.265 mole) was refluxed for 3 hr. After the solution had cooled to room temperature and had been kept for 2 days, the white crystals, m.p. 226–227°, were filtered off. Addition of water to the filtrate caused separation of most of the product (total 0.50 g., 34%); lit.[5] m.p.

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(44) (a) A. I. Vogel, "Practical Organic Chemistry," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 969–971; (b) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

(45) Experiment first performed by Roger D. Johnson, National Science Foundation Undergraduate Research Participant, University of Minnesota, summer, 1959, with support from NSF Grant G-8179.

224.5–226°; ν_{NH} 3310 ms, 3100 mw, $\nu_{C=O}$ 1728 s, 1703 s, 1644 s cm.$^{-1}$ (Nujol).

Action of Nitrous Acid on II: Preparation of VII.—Sufficient hydrochloric acid was added to a mixture of II (3.00 g., 0.0127 mole) and water (375 cc.) to dissolve completely the solid. The pH was then adjusted to 4–5 by addition of aqueous potassium hydroxide solution. The solution was cooled in an ice bath and a cold solution of sodium nitrite (2.63 g., 0.0381 mole) in water (375 cc.) was added gradually. The solution was stirred at room temperature for 30 hr. and then filtered, giving a yellow solid (2.41 g.), having an infrared spectrum (Nujol) very similar to that of the analytical sample. Two crystallizations from methanol–water, and a final recrystallization from ethanol–water, yielded white crystals, m.p. 261–262° dec. (sealed capillary); λ_{max} mμ (log ϵ) in 95% ethanol: 225 (4.15), 277 (3.95); $\nu_{NH\ or\ OH}$ 3330 m, 3190 w, 3110 m, $\nu_{C=O}$ 1681 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{20}N_2O_2$ (248.32): C, 67.71; H, 8.12; N, 11.28. Found: C, 67.79; H, 8.30; N, 10.98.

Incomplete Hydrogenation of I: Preparation of 14-Azadispiro[5.1.5.2]pentadecane-7,15-dione, 7-Imine (IIg).—Compound I (10.0 g., 0.0378 mole) in ethanol (250 cc.) was hydrogenated over Raney nickel at 2 atm. and room temperature. Hydrogen uptake ceased after 72 hr. of shaking, but the pressure drop corresponded to only 93% of the calculated amount. The hydrogenation solution, which contained a white precipitate, was heated to boiling to dissolve the precipitate. Then the catalyst was filtered off and the filtrate concentrated, diluted with hot water, and allowed to cool to room temperature. The resulting white crystalline precipitate (4.28 g., 48%), m.p. 214,° was recrystallized twice from ethanol–water, and then twice from methylene chloride–light petroleum ether (b.p. 60–68°), yielding white needles, m.p. 209–210° sublimes; ν_{NH} 3130 ms, 3040 m, $\nu_{C=O}$ 1698 s, $\nu_{C=N}$ 1661 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{22}N_2O$ (234.33): C, 71.75; H, 9.46; N, 11.96. Found: C, 71.75; H, 9.27; N, 11.32.[46]

14-Azadispiro[5.1.5.2]pentadecane-7,15-dione (XV). (A) From Low-Pressure Hydrogenation of IV.[45]—Compound IV (10.0 g., 0.0401 mole) in 95% ethanol (200 cc.) solution was hydrogenated over Raney nickel at 2 atm. and room temperature for 6 hr. The hydrogenation solution, which contained precipitated product, was heated to boiling to dissolve the precipitate. Then the catalyst was filtered off and washed with hot ethanol. Concentration and cooling of the combined filtrate and washings gave colorless needles (8.06 g., 85%), m.p. 238–239°. Three recrystallizations from ethanol–water yielded glistening white needles, m.p. 244–245°, lit.[5] m.p. 233–234°; ν_{NH} 3150 m, 3060 m, $\nu_{C=O}$ 1754 m, 1695 s cm.$^{-1}$ (Nujol). The n.m.r. spectrum of a 3% solution in deuteriochloroform contains a single, large peak at 8.31 ± 0.01 τ.

Anal. Calcd. for $C_{14}H_{21}NO_2$ (235.32): C, 71.45; H, 9.00; N, 5.95. Found: C, 71.60; H, 9.22; N, 5.91.

(B) From Low-Pressure Hydrogenation of IVa.—Compound IVa (0.18 g., 0.00068 mole) in methanol (100 cc.) solution was hydrogenated over Raney nickel at 2 atm. and room temperature for 42 hr. The mixture was then heated to 55° and the catalyst filtered off. The filtrate was concentrated to about 15 cc. and diluted with water, causing precipitation of a white solid (0.13 g., 81%) in two crops, m.p. 225–236° and 235–237°. The infrared spectrum (Nujol) is identical with that of a sample prepared from IV. Recrystallization of the white solid from ethanol–water gave a sample, m.p. 235–237°, which gave no depression in m.m.p., 241–243°, with a sample of m.p. 243–244° prepared from IV.

(C) From Oxidation of II with Chromium Trioxide.—Chromium trioxide (2.7 g., 0.027 mole) was stirred with glacial acetic acid (80 cc.). The resulting violet-brown solution was decanted from a small amount of undissolved residue and added over a period of 1 hr., with occasional warming on a steam bath, to a solution of II (2.0 g., 0.0085 mole) in glacial acetic acid (30 cc.). Then the resulting solution was diluted with water until it became cloudy, and cooled overnight. The resulting precipitate was crystallized from ethanol–water, giving a solid (0.60 g., 30%) in two crops, m.p. 238–240° and 230–237°. One recrystallization from ethanol–water gave a sample, m.p. 236–238°, which gave no depression in m.m.p., 236–238°, with a sample of m.p. 240–241° prepared from IV. The infrared spectra of the two samples (Nujol) were identical.

Oxidation of II (2.0 g.) with refluxing aqueous potassium permanganate solution added in portions also gave XV (16%), along with unchanged II (36%).

(D) From Acidic Hydrolysis of IIg.—A mixture of IIg (1.00 g., 0.00427 mole) and a solution of concentrated sulfuric acid (10 cc.) in ethanol (20 cc.) and water (30 cc.) was refluxed for 20 hr. The mixture remained inhomogeneous throughout the reflux period. The hot mixture was filtered. After the filtrate had cooled, white needles precipitated (0.286 g.,), m.p. 235–237°. Additional solid (0.14 g.; total, 0.426 g., 42%) was obtained by recrystallization of the filtered solid from ethanol–water. The infrared spectrum (Nujol) is identical with that of a sample prepared from IV.

Oxime of XV: 14-Azadispiro[5.1.5.2]pentadecane-7,15-dione, 7-Oxime (XVc).—Compound XV (3.0 g., 0.0128 mole) and hydroxylamine hydrochloride (2.0 g., 0.029 mole) in pyridine (15 cc.) and absolute ethanol (15 cc.) was refluxed for 37 hr. At seven convenient intervals during the reflux period, one seventh of each of the following was added: hydroxylamine hydrochloride (7.0 g., 0.101 mole), pyridine (35 cc.), and absolute ethanol (35 cc.). At the end of the reflux period the solvents were evaporated in a stream of air. The residual solid was extracted with water to dissolve salts, and the remaining solid was refluxed with 3 25-ml. portions of 90% ethanol to extract unchanged XV. The residue (2.50 g., 78%) was recrystallized twice from dioxane–ethanol–water, yielding a white powder, m.p. 320–322° uncorrected (sealed tube); ν_{OH} 3240 m infl., ν_{NH} 3140 m, 3050 m, $\nu_{C=O}$ 1698 s, $\nu_{C=N}$ 1667 ms cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{22}N_2O_2$ (250.33): C, 67.17; H, 8.86; N, 11.19. Found: C, 67.18; H, 8.90; N, 11.01.

Action of Tetraphosphorus Decasulfide on XV: 14-Azadispiro[5.1.5.2]pentadecan-7-one-15-thione (XVd).—Compound XV (0.50 g., 0.00212 mole) and tetraphosphorus decasulfide (0.75 g., 0.00169 mole) were fused over a small flame. Additional tetraphosphorus decasulfide (0.25 g., 0.00056 mole) was added and the fusion was repeated. After the fused mass had cooled, it was crushed and stirred with dilute hydrochloric acid. The undissolved solid was dissolved in ethanol, and the solution treated with charcoal and filtered. The filtrate deposited brownish needles (0.26 g., 49%), m.p. 240–250°. Three recrystallizations from absolute ethanol yielded colorless needles, m.p. 248–249°; ν_{NH} 3130 m, $\nu_{C=O}$ 1748 m, 1669 w, $\nu_{C=S}$ 1512 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{21}NOS$ (251.38): C, 66.88; H, 8.42; N, 5.57. Found: C, 66.39; H, 8.06; N, 5.73.

7-Dimethylamino-14-azadispiro[5.1.5.2]pentadecan-15-one (IId).—For the purpose of methylation,[15] a solution of II (5.7 g., 0.0241 mole), aqueous 35% formaldehyde solution (14 cc., 0.16 mole), and aqueous 88% formic acid (14 cc., 0.33 mole) was refluxed for 15 hr. The solution was then concentrated by passing a stream of air over the heated solution. The residual white solid was dissolved in dilute hydrochloric acid and the acidic solution extracted with chloroform. The acidic aqueous layer was made alkaline with sodium hydroxide and extracted with chloroform. The extract was dried and evaporated to dryness. Recrystallization of the residual white solid from light petroleum ether (b.p. 60–68°) gave white crystals (3.4 g., 53%) in two crops, m.p. 152–156° and 150–153°. Four more recrystallizations from light petroleum ether yielded fine white needles, m.p. 156–158°; ν_{NH} 3150 m, 3050 w, $\nu_{C=O}$ 1684 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{28}N_2O$ (264.40): C, 72.68; H, 10.67; N, 10.60. Found: C, 72.59; H, 10.47; N, 10.04, 10.21.

Methiodide (IIe) of IId.—Compound IId (7.1 g., 0.0268 mole) and methyl iodide (23 g., 0.162 mole) in benzene (100 cc.) were refluxed for 44 hr. During this time additional methyl iodide (46 g., 0.324 mole) was added in two portions. Filtration of the reaction mixture gave IIe (4.51 g.), m.p. 222–228°. Filtration of the reaction mixture after additional reflux periods of 48 and 24 hr. gave more IIe (4.43 g.; total, 8.94 g., 82%), m.p. 216–226°. Three recrystallizations from absolute ethanol yielded white needles, m.p. 226–230°; ν_{NH} 3270 m, $\nu_{C=O}$ 1695 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{17}H_{31}N_2OI$ (406.35): C, 50.24; H, 7.69; N, 6.89. Found: C, 50.28; H, 7.68; N, 6.21, 6.28.

7-Hydroxy-14-azadispiro[5.1.5.2]pentadecan-15-one (XIV). (A) From the Displacement Reaction of Hydroxyl Ion on IIe.—Silver oxide, freshly prepared[16b] from silver nitrate (2.17 g., 0.128 mole) and sodium hydroxide (0.55 g., 0.137 mole), was added to a solution of IIe (2.17 g., 0.00534 mole) in aqueous 10% methanol (100 cc.). The resulting mixture was stirred for 1.5 hr. and

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(46) The compound gave low and erratic nitrogen analyses.

filtered. The filtrate was concentrated by distillation of the water under reduced pressure, taking precautions to avoid excessive foaming, and then was distilled under reduced pressure to dryness at about 100°. The brown residue was extracted with a mixture of water and chloroform. The chloroform layer was washed with dilute hydrochloric acid, dried, and evaporated, giving a clear, colorless, viscous oil, which soon crystallized. Recrystallization from chloroform–light petroleum ether (b.p. 60–68°) gave a white solid (0.70 g., 55%), m.p. 200–208°. One more recrystallization of part of the crystals from chloroform–light petroleum ether yielded XIV as white prisms, m.p. 215–217° sublimes, lit.[5,47] m.p. 190–191°; ν_{OH} 3360 m, ν_{NH} 3170 m, 3050 vvw infl., $\nu_{\mathrm{C=O}}$ 1686 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{23}NO_2$ (237.33): C, 70.85; H, 9.77; N, 5.90. Found: C, 70.69; H, 9.69; N, 5.84.

The major portion of the original crystals, m.p. 200–208°, and an oily residue isolated from the mother liquors were combined, dissolved in chloroform, and chromatographed on alumina. Elution with 1:1 benzene–chloroform removed an unidentified white semisolid (0.06 g.). Elution with chloroform removed a solid which, after recrystallization from chloroform–light petroleum ether (b.p. 60–68°), gave XIV (0.43 g., 34%), m.p. 218–219° sublimes.

(B) **From Reduction of XV with Sodium Borohydride.**—A solution of sodium borohydride (3.0 g., 0.0079 mole) in absolute ethanol (100 cc.) was added dropwise to a suspension of XV (37.9 g., 0.161 mole) in absolute ethanol (1000 cc.). The mixture was refluxed for 0.5 hr. and then additional sodium borohydride (3.0 g., 0.0079 mole) in absolute ethanol (50 cc.) was added, and refluxing was continued for an additional 1.75 hr. The volume of the solution was reduced by distillation to about 300 cc. and hot 2% hydrochloric acid (275 cc.) was added. The resulting solution was decanted from a gummy white solid, and the solution concentrated and cooled, giving white prisms (36.5 g., 96%), m.p. 216–217° sublimes,[47] which gave no depression in m.m.p., 216–218° sublimes, with a sample of m.p. 215–217° sublimes, prepared from IIe (part A). The infrared spectra (Nujol) of the two samples were identical, and were also identical with the infrared spectrum of a sample[48] of m.p. 198–199° sublimes[47] prepared by hydrogenation of IVa at 177 atm. and 230° over copper chromium oxide.[5]

7-(2-Hydroxyethoxy)-14-azadispiro[5.1.5.2]pentadecan-15-one (IIf).—In an attempt to effect a Hofmann elimination reaction,[49] a solution of IIe (4.25 g., 0.0104 mole) and potassium hydroxide (42.0 g., 0.75 mole) in ethylene glycol (225 cc.) and water (42 cc.) was refluxed for 6 hr. The solution was cooled, diluted with water, and extracted with ether. The ether extract was washed with dilute hydrochloric acid, dried, and evaporated, leaving a yellow oil which soon crystallized, giving a gray solid (1.31 g., 45%), m.p. 146–150°. Two recrystallizations from ethanol-water yielded fine white needles, m.p. 150–157°; ν_{OH} 3390 mw, ν_{NH} 3180 m, 3050 w, $\nu_{\mathrm{C=O}}$ 1692 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{27}NO_3$ (281.38): C, 68.29; H, 9.67; N, 4.98. Found: C, 68.34; H, 9.76; N, 5.02.

7-Hydroxy-14-azadispiro[5.1.5.2]pentadecane (V).—A solution of XIV (36.5 g., 0.154 mole) in anhydrous tetrahydrofuran (500 cc.) was added dropwise to a suspension of lithium aluminum hydride (7.9 g., 0.208 mole) in ether (950 cc.), and then the mixture was refluxed, with stirring, for 26 hr. The excess lithium aluminum hydride was decomposed by addition of absolute ethanol, and then water (150 cc.) was added dropwise with vigorous stirring, causing formation of a heavy white precipitate. The ether–tetrahydrofuran solution was decanted, and the residual precipitate was washed twice with ether. The combined decanted ether solution and washings were extracted with dilute hydrochloric acid, and the acidic extract was made alkaline with sodium hydroxide and cooled. The resulting white crystalline precipitate was filtered and dried, giving a solid (32.0 g., 93%), m.p. 169–170°. Sublimation at 130° (4 mm.) yielded fine white needles, m.p. 166.5–167.5°, lit.[5,47] m.p. 162–163°; $\nu_{\mathrm{NH,\,OH}}$ 3390 s, 3320 w (3500–3200, very broad) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{25}NO$ (223.35): C, 75.28; H, 11.28; N, 6.27. Found: C, 75.01; H, 11.25; N, 6.36.

7-Hydroxy-14-methyl-4-azadispiro[5.1.5.2]pentadecane (Vb).—For the purpose of methylation,[15] a mixture of V (32.0 g., 0.144 mole), aqueous 35% formaldehyde, and aqueous 88% formic acid was stirred at 90° for 17 hr. Concentrated hydrochloric acid (30 cc.) was added, and the solution was concentrated by distillation until the residue became viscous. The residue was then dissolved in water and washed with ether. The water layer was made alkaline with sodium hydroxide and kept for several hr., with occasional stirring, during which time an oil separated. The mixture was extracted with light petroleum ether (b.p. 60–68°), and the extract dried and evaporated, leaving a clear oil. The oil was dissolved in an equal volume of light petroleum ether (b.p. 30–60°), and solution cooled for several hours in a freezer, causing crystallization of a hard white solid (27.6 g., 80%), m.p. 75–78°, lit.[5] m.p. 79–81°; ν_{OH} 3150 s, 2680 w cm.$^{-1}$ (Nujol).

Methiodide (XI) of Vb.—Compound XI has been prepared previously in unstated yield in absolute ethanol solution.[5] In the present work, the use of ether as solvent resulted in precipitation of the product in quantitative yield. A solution of Vb (10.0 g., 0.0422 mole) and methyl iodide (11.5 g., 0.081 mole) in ether (40 cc.) was kept at room temperature for 12 hr. A white solid began to precipitate soon after the addition of methyl iodide. After 12 hr., additional methyl iodide (4.6 g., 0.032 mole) in ether (20 cc.) was added, and the mixture was kept at room temperature for 2 days more. The precipitate was then filtered off, being obtained as a white microcrystalline solid (16.4 g., 102%), m.p. 190–195°, lit.[5] m.p. 186–187°; ν_{OH} 3290 s cm.$^{-1}$ (Nujol).

2-(1-Dimethylaminocyclohexyl)-1-oxaspiro[2.5]octane (XXX).—Silver oxide, freshly prepared[16b] from silver nitrate (16.6 g., 0.098 mole) and sodium hydroxide (4.2 g., 0.105 mole), was added to a solution of XI (16.4 g., 0.0433 mole) in aqueous 43% methanol (280 cc.). The resulting mixture was stirred vigorously for 3 hr. and then filtered. The filtrate was concentrated by distilling off the solvents at aspirator pressure. In order to prevent foaming, the filtrate was added gradually to the distilling flask from a pressure equalized dropping funnel at a rate such that only a small volume of solution was present in the distilling flask at any time. When the concentrate became viscous, the aspirator was replaced by a vacuum pump. As the pyrolysis proceeded, a colorless, slightly viscous liquid distilled (7.30 g., 67%). Redistillation yielded a sample (6.70 g., 62%), b.p. 135–140° (0.5 mm.), $n^{25}\mathrm{D}$ 1.4939; ν_{OH} none, $\nu_{\mathrm{C=O}}$ none, on the liquid.

Anal. Calcd. for $C_{16}H_{29}NO$ (251.40): C, 76.44; H, 11.63; N, 5.57. Found: C, 76.47, 76.46; H, 11.61, 11.83; N, 6.53, 6.40, 5.54.

Picrate (XXXa) of XXX.—During an unsuccessful attempt to prepare the N-oxide of XXX, a solution of XXX (0.50 g., 0.00199 mole) and aqueous 30% hydrogen peroxide (2.0 cc.) in methanol (6 cc.) was kept at room temperature for 20 hr. Then platinum black was added to decompose the peroxide, and the mixture was kept for an additional 10 hr. A saturated solution (10 cc.) of picric acid in ethanol was added, causing formation of a yellow precipitate (0.80 g., 82%), m.p. 176–180°. Two recrystallizations from absolute ethanol yielded yellow plates, m.p. 178–180°.

Anal. Calcd. for $C_{22}H_{32}N_4O_8$ (480.51): C, 54.99; H, 6.71; N, 11.66. Found: C, 55.33; H, 6.44; N, 11.58.

Methiodide (XXXc) of XXX.—A solution of XXX (4.0 g., 0.0159 mole) and methyl iodide (4.6 g., 0.0324 mole) in ether (10 cc.) and light petroleum ether (b.p. 60–68°, 10 cc.) was stirred at room temperature overnight. More methyl iodide (4.6 g., 0.0324 mole) was added and the solution was refluxed for 24 hr. and kept at room temperature for an additional 24 hr. Filtration removed a white solid (4.82 g., 77%) in two crops, m.p. 161–165° and 163–165°. As attempted recrystallization from ethanol–ethyl acetate produced decomposition, the crude product was vacuum dried for analysis, yielding a white powder, m.p. 163–165°; ν_{OH} 3450 mw cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{17}H_{32}NOI$ (393.35): C, 51.91; H, 8.20. Found: C, 51.34; H, 8.09.

1-Dimethylaminomethylcyclohexanecarboxaldehyde (XXXI). (A) **From XXX by Periodic Acid Cleavage.**—Sodium periodate (5.35 g., 0.0250 mole) was added to a solution of XXX (5.00 g., 0.0199 mole) in water (100 cc.) containing concentrated sulfuric acid (2.5 cc.), causing separation of an oil. The mixture was

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[47] The variation in reported melting points, particularly of XIV, but also of other compounds in this series, including I, V, and XV, is attributed primarily to the extensive sublimation which occurs prior to the actual melting point.

[48] We are indebted to Prof. Dorothy V. Nightingale of the University of Missouri for sending us a sample of XIV, prepared as described in ref. 5.

[49] P. L. Julian, E. W. Meyer, and H. C. Printy, *J. Am. Chem. Soc.*, **70**, 887 (1948).

stirred at room temperature. At intervals, aliquots (2 cc. each) were removed and titrated for periodic acid with standard arsenite and iodine solutions.[50] The amount of sodium periodate consumed at the end of 2 hr. was 0.86 g. (0.00402 mole, 20% of theoretical), and at the end of 5 hr. a total of 1.23 g. (0.00575 mole, 29%) had been consumed. At this point 50 cc. of a solution prepared from sodium periodate (5.35 g., 0.0250 mole), concentrated sulfuric acid (2.5 cc.), and water (100 cc.) was added, and the mixture was stirred at room temperature for an additional 2 hr. The mixture was then made alkaline with sodium bicarbonate and extracted with ether. The ether layer was extracted with dilute hydrochloric acid. The ether layer was then concentrated and treated with 2,4-dinitrophenylhydrazine reagent, but the precipitate which formed melted over a wide range and could not be purified by recrystallization (see under XXXVIII).

The dilute hydrochloric acid layer was made alkaline with sodium hydroxide, and extracted with ether. The ether was distilled and the residue vacuum distilled. The first fraction of the distillate was **1-dimethylaminomethylcyclohexanecarboxaldehyde (XXXI)** (0.38 g., 12%), b.p. 75–80° (2 mm.), $n^{30}{}_D$ 1.4655, having an infrared spectrum on the oil identical, except for a band at 1687 m cm.$^{-1}$, with that of the sample prepared from cyclohexanecarboxaldehyde. The second fraction of the distillate consisted primarily of an **alcohol $C_{16}H_{29}NO$ (XXXII)** (1.57 g., 31%), b.p. 160° (2 mm.), $n^{25}{}_D$ 1.5119; ν_{OH} 3210 mw (very broad), $\nu_{C=O}$ 1722 mw cm.$^{-1}$ on the liquid. The infrared spectrum, including the carbonyl band at 1722 mw cm.$^{-1}$, indicates that the sample was contaminated with XXXI. See subsequent discussion for preparation of the methiodide (XXXIIa) from this sample of XXXII.

(B) **From Cyclohexanecarboxaldehyde.**—Essentially by the general procedure of Mannich, Lesser, and Silten,[17] a mixture of cyclohexanecarboxaldehyde (Columbia Organic Chemicals Co., Inc., Columbia, S. C.; 15.0 g., 0.134 mole), *sym*-trioxane (5.4 g., 0.18 mole as CH_2O), dimethylamine hydrochloride (10.0 g., 0.123 mole), and absolute ethanol (6 cc.) was refluxed for 1 hr. More *sym*-trioxane (5.4 g., 0.18 mole CH_2O) was added and the mixture was refluxed for an additional hour. The mixture was then diluted with ether, and the resulting two-phase system was extracted with dilute hydrochloric acid. The acid extract was made alkaline with sodium hydroxide and extracted with ether. The ether extract was dried, the ether was then distilled, and the residual liquid was distilled, yielding a colorless liquid (7.20 g., 34%), b.p. 90° (7 mm.), $n^{25}{}_D$ 1.4659; lit.[17] b.p. 102–104° (17 mm.); $\nu_{C=O}$ 1719 s cm.$^{-1}$ on the liquid.

Methiodide of XXXI: (1-Formylcyclohexyl)methyltrimethylammonium Iodide (XXXIa). (A) From XXXI Obtained from XXX by Periodic Acid Cleavage.—Methyl iodide (4.60 g., 0.0324 mole) was added to a solution of XXXI (0.29 g., 0.00182 mole) in ether (9 cc.). A white microcrystalline solid (0.338 g., 60%), m.p. 231–233°, was filtered off. This solid had an infrared spectrum (Nujol) identical with that of the sample prepared from XXXI obtained from cyclohexanecarboxaldehyde. Recrystallization from absolute ethanol–benzene yielded glistening white plates, m.p. 236–237°, having an infrared spectrum (Nujol) identical with that of the unrecrystallized product.

(B) **From XXXI Obtained from Cyclohexanecarboxaldehyde.**—According to the procedure described in part A, XXXI (1.00 g., 0.00628 mole), obtained from cyclohexanecarboxaldehyde, gave a white microcrystalline solid (1.01 g., 52%), m.p. 227–232°. Two recrystallizations from absolute ethanol–benzene yielded glistening white plates, m.p. 239–240°, lit.[17] m.p. 223°; $\nu_{C=O}$ 1725 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{11}H_{22}NOI$ (311.21): C, 42.45; H, 7.13; N, 4.50. Found: C, 42.67; H, 7.06; N, 4.57.

Alcohol $C_{16}H_{29}NO$ (XXXII) and Its Methiodide (XXXIIa). (A) From Attempted Deoxygenation[51] of XXX with Acetic Acid in the Presence of Sodium Iodide and Zinc Dust.—A solution of sodium iodide (2.1 g., 0.0140 mole), sodium acetate (0.7 g.), and water (0.4 cc.) in acetic acid (5 cc.) was cooled in an ice bath and zinc dust (2.1 g., 0.032 g.-atom) was added. Compound XXX (1.00 g., 0.00398 mole) was added dropwise, with stirring, over a period of about 10 min., and then the mixture was allowed to warm to room temperature over a period of 2 hr. The mixture was filtered, diluted with water, and extracted with ether. The ether layer was washed with aqueous sodium carbonate solution and then extracted with dilute hydrochloric acid. The hydrochloric acid extract was made alkaline with sodium hydroxide and extracted with ether. The ether extract was dried and evaporated, giving a white solid (0.537 g., 54%), m.p. 62–85°. Two recrystallizations from light petroleum ether (b.p. 30–60°) in a Dry Ice–acetone bath yielded the **alcohol $C_{16}H_{29}NO$ (XXXII)**, m.p. 85.5–87°, having an infrared spectrum (Nujol) identical with that of the unrecrystallized sample; ν_{OH} 3150 m, $\nu_{C=O}$ none cm.$^{-1}$ (Nujol). The n.m.r. spectrum of a 12% solution in carbon tetrachloride contains (in τ ± 0.01 average deviation, with areas relative to 29 protons given in parentheses; 1 τ = 56.44 c.p.s.) a major peak at 8.55 (10.1 protons, attributed to an intact cyclohexane ring) and an associated peak at 8.39 (3.9), a peak at 7.99 (4.0), a sharp peak at 7.68 (6.7, the 6 protons of the two N-methyl groups), two sharp peaks (possibly the lower half of an AB pattern due to the N-methylene protons) at 7.36 (0.9) and 7.14 (0.4), a sharp peak at 6.22 (1.1 proton, the CH proton of a secondary alcohol), and the two broader singlets at 4.47 (1.0 vinyl proton) and 3.90 (1.0 vinyl proton).

Anal. Calcd. for $C_{16}H_{29}NO$ (251.40): C, 76.44; H, 11.63; N, 5.57. Found: C, 76.68; H, 11.63; N, 5.89.

Attempted hydrogenation of XXXII in methanol at 2 atm. over palladium on calcium carbonate or Raney nickel gave unchanged XXXII in recoveries of 31%, m.p. 83–87°, and 46%, respectively.[52]

Reaction of this sample of XXXII (0.10 g., 0.00040 mole) with excess methyl iodide in ether gave a white solid precipitate (0.048 g., 31%), m.p. 190–221°. Recrystallization from absolute ethanol–benzene yielded the **methiodide (XXXIIa) of XXXII** (0.018 g., 11%), m.p. 216–219°, having an infrared spectrum (Nujol) identical with that of the sample of XXXIIa prepared by methylation of XXXII obtained from attempted deoxygenation of XXX with triphenylphosphine (part B).

(B) **From Attempted Deoxygenation[53] of XXX with Triphenylphosphine.**—Compound XXX (1.00 g., 0.00398 mole) and triphenylphosphine (1.05 g., 0.00400 mole) were heated together at 200° for 40 min. Distillation of the product at 155–158° (1 mm.) gave an oil, which was dissolved in ether and extracted with dilute hydrochloric acid. The hydrochloric acid layer was made alkaline with sodium hydroxide and extracted with ether. The ether extract was dried and evaporated, giving the **alcohol $C_{16}H_{29}NO$ (XXXII)** as an impure oil, identified by comparison of its infrared spectrum (Nujol) with that of pure XXXII obtained from XXX as described in part A. Reaction of the oil with excess methyl iodide in ether gave a white microcrystalline solid precipitate (0.60 g., 38%), m.p. 218–223°. Two recrystallizations from absolute ethanol–benzene yielded the **methiodide (XXXIIa) of XXXII** as fluffy white needles, m.p. 220–222°; ν_{OH} 3330 m cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{17}H_{32}NOI$ (393.35): C, 51.91; H, 8.20; N, 3.56. Found: C, 52.17; H, 8.36; N, 3.59.

(C) **Methiodide (XXXIIa) of XXXII Obtained from XXX by Attempted Periodic Acid Cleavage.**—Reaction of XXXII (1.57 g., 0.00625 mole), obtained in the form of an oil as the major product from the attempted periodic acid cleavage of XXX, with excess methyl iodide in ether soon caused precipitation of a small amount of XXXIa, having an infrared spectrum (Nujol) identical with that of the sample of XXXIa prepared from XXXI obtained from cyclohexanecarboxaldehyde. After filtration of the XXXIa, the filtrate was kept at room temperature for one day, and then the precipitated XXXIIa (1.02 g., 41%), m.p. 218–220°, was filtered off. Recrystallization from absolute ethanol–benzene yielded the **methiodide (XXXIIa) of XXXII** as white needles, m.p. 221–223°, having an infrared spectrum (Nujol) identical with that of the sample prepared from XXXII obtained from attempted deoxygenation of XXX with triphenylphosphine (part B).

Alcohol $C_{16}H_{29}NO_2$ (XXXVIII) from XXX by Periodic Acid Cleavage and Oxidation.—Sodium periodate (3.9 g., 0.0182 mole) was added to a solution of XXX (4.0 g., 0.0159 mole) in water (25 cc.) containing concentrated sulfuric acid (1.8 cc.), causing separation of an oil. The mixture was stirred at room

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[50] E. L. Jackson, *Org. Reactions*, **2**, 361 (1944).

[51] J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959).

[52] This failure of XXXII to hydrogenate and the apparent absence of olefinic unsaturation in the infrared spectrum led to the description of XXXII in our Communication[9] as a "saturated alcohol." The n.m.r. spectrum, as noted, shows the presence of two vinyl protons.

[53] G. Wittig and W. Haag, *Ber.*, **88**, 1654 (1955).

temperature for 9 hr. Aqueous 25% sulfuric acid (20 cc.) was then added, causing the oil to dissolve and the brown color of iodine to develop. The brown solution was then extracted rapidly with ether, and the dark ether extract was treated with aqueous sodium thiosulfate, causing partial decolorization. The acidic aqueous layer was made alkaline with sodium hydroxide, and the brown oil which separated was extracted with ether. Evaporation of the ether extract left a brown oil, which, after being kept and scratched, partially crystallized. The remaining oil was decanted from the crystals and distilled, giving **1-dimethylaminomethylcyclohexanecarboxaldehyde (XXXI)**, b.p. 70° (0.7 mm.), $n^{29}\text{D}$ 1.4732, having an infrared spectrum on the liquid identical with that of the sample prepared from cyclohexanecarboxaldehyde. The infrared spectrum (Nujol) of the **methiodide (XXXIa)**, m.p. 224–227°, was also identical with that of the methiodide of XXXI prepared from cyclohexanecarboxaldehyde.

The crystallized fraction of the oil was dissolved in methylene chloride, treated with charcoal, and then recrystallized from ethanol–water, giving a sample (0.86 g., 20%), m.p. 120–126°. Two recrystallizations from ethanol–water yielded the **alcohol $C_{16}H_{29}NO_2$ (XXXVIII)** as glistening white platelets, m.p. 126.5–127.5°; ν_{OH} 3280 s, 2660 m (broad) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{16}H_{29}NO_2$ (267.40): C, 71.86; H, 10.93; N, 5.24. Found: C, 71.99; H, 10.86; N, 5.22.

The original ether extract, which had been treated with sodium thiosulfate, was evaporated. The residue was treated with 2,4-dinitrophenylhydrazine reagent, giving a reddish solid. Two recrystallizations from ethanol yielded a red powder, m.p. 213.5–216.5°; ν_{NH} 3320 mw, 3120 mw, $\nu_{C=N}$ 1629 s, $\nu_{C=C}$ 1600 s cm.$^{-1}$ (Nujol). This compound is not cyclohexanone 2,4-dinitrophenylhydrazone (lit.[54] m.p. 160.5–161.5°).

Anal. Found: C, 39.35; H, 3.09.

When cyclohexanone was treated under the conditions of the periodic acid cleavage, followed by treatment with 2,4-dinitrophenylhydrazine reagent, cyclohexanone 2,4-dinitrophenylhydrazone was still not isolated. Instead, a red compound was isolated, having an infrared spectrum (Nujol) almost identical with that of the 2,4-dinitrophenylhydrazone isolated from the periodic acid cleavage of XXX. Thus, it was not possible to establish that cyclohexanone is a product of the periodic acid cleavage of XXX.

1-Aminocyclohexanecarbonitrile (XXXIV).—This compound, previously prepared by other methods,[55-57] was prepared[19] by passing ammonia through cyclohexanone cyanohydrin[58] ($n^{23}\text{D}$ 1.4635, m.p. 30–33°; 100 g., 0.798 mole) for 6 hr., with cooling in an ice bath during the initial exothermic stage of the reaction. At the end of the 6 hr., the reaction flask was stoppered and kept at room temperature for 15 hr., after which ammonia was passed through the solution for 5 hr. more. Then nitrogen was passed through the solution for 3 hr. to remove excess ammonia. The residual oil was dissolved in benzene (in later runs, ether was used to facilitate subsequent isolation of solvent free XXXV) and the solution extracted with water. The benzene layer was dried and the benzene evaporated, leaving a yellowish orange oil (61 g., 61%); ν_{NH} 3560 m infl., 3370 ms, 3320 ms, 2660 w, 1614 ms, $\nu_{C\equiv N}$ 2230 w, $\nu_{C=O}$ 1706 m cm.$^{-1}$ on the liquid. As the compound is reported to be unstable towards heat and distillation,[57] further purification was not attempted.

1-(2-Ethoxycarbonylacetamido)cyclohexanecarbonitrile (XXXV).—Ethyl chloroformylacetate[59,60] (29.8 g., 0.198 mole) was added dropwise, with stirring, over a period of 1 hr. to a solution of 1-aminocyclohexanecarbonitrile (prepared as described previously from 45.0 g., 0.359 mole, of cyclohexanone cyanohydrin) in anhydrous pyridine (100 cc.) and benzene (200 cc.). The resulting mixture of orange solution and white precipitate was stirred at room temperature for 24 hr. and then washed successively with 10% hydrochloric acid and aqueous sodium bicarbonate solution. The benzene layer was dried and evaporated, leaving an orange oil (21.7 g., 42% from 1-aminocyclohexanecarbonitrile). The oil was chromatographed on alumina and eluted with benzene, yielding a yellow oil, $n^{24}\text{D}$ 1.4839; ν_{NH} 3320 ms, $\nu_{C\equiv N}$ 2230 w, $\nu_{C=O}$ 1736 s, 1667 s cm.$^{-1}$ on the liquid.

Anal. Calcd. for $C_{12}H_{18}N_2O_3$ (238.28): C, 60.48; H, 7.61; N, 11.76. Found: C, 59.87; H, 7.69; N, 11.01.

4-Amino-3-ethoxycarbonyl-1-azaspiro[4.5]dec-3-en-2-one (XXXVI).—A solution of sodium ethoxide prepared from sodium (0.37 g., 0.0161 g.-atom) in absolute ethanol (5 cc.) was added to a solution of XXXV (2.75 g., 0.0116 mole) in absolute ethanol (5 cc.). The resulting solution was refluxed for 3 hr., and then a solution of concentrated hydrochloric acid (1.6 cc.) in hot water (10 cc.) was added. Dimorph A (1.88 g., 68%) crystallized in two crops, m.p. 263–265° dec. and 267–269° dec. Recrystallization from ethanol yielded **dimorph B** as a granular white solid, m.p. 269–273° dec., having an infrared spectrum (Nujol) different from that of dimorph A; λ_{max} mμ (log ϵ) in 95% ethanol: 220 (4.27), 269 (4.12); ν_{NH} 3400 mw, 3330 m, 3040 m, 1580 ms, $\nu_{C=O}$ 1702 s, 1660 s, $\nu_{C=C}$ 1628 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{12}H_{18}N_2O_3$ (238.28): C, 60.48; H, 7.61; N, 11.76. Found: C, 60.68; H, 7.65; N, 11.84.

Dimorph B was reconverted to Dimorph A by dissolving Dimorph B in chloroform and allowing the solution to evaporate slowly to dryness. The residue had an infrared spectrum (Nujol) identical, except for a band at 1724 mw cm.$^{-1}$ in the former, with that of Dimorph A obtained by recrystallizing the sample from chloroform. By recrystallization from chloroform **dimorph A** was obtained as a white powder, m.p. 267–270° dec.; λ_{max} mμ (log ϵ) in 95% ethanol: 220 (4.25), 269 (4.11); ν_{NH} 3370 m, 3170 ms, 1552 ms, $\nu_{C=O}$ 1675 s, 1659 s, $\nu_{C=C}$ 1623 cm.$^{-1}$ (Nujol).

Anal. Found: C, 60.40; H, 7.28.

4-Hydroxy-1-azaspiro[4.5]dec-3-en-2-one (XXXVII).—Compound XXXVI (8.3 g., 0.0348 mole) was dissolved in a solution of potassium hydroxide (8.0 g., 0.143 mole) in water, and the resulting solution was refluxed for 1 hr. Concentrated hydrochloric acid was added until the solution became just acidic. Cooling caused precipitation of a white powder (3.9 g., 67%), m.p. 220–222°. Recrystallization from hot water yielded a white powder, m.p. 219–220°; λ_{max} mμ (log ϵ) in 95% ethanol: 261 (3.78); ν_{NH} 3180 m, ν_{OH} 3500–2160 mw (very broad), $\nu_{C=O}$ 1764 w, 1677 m (infl.), 1655 s, $\nu_{C=C}$ 1595 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_9H_{13}NO_2$ (167.20): C, 64.65; H, 7.84; N, 8.38. Found: C, 64.72; H, 8.01; N, 8.35.

Dibromo Derivative of XXXVII: 3,3-Dibromo-1-azaspiro[4.5]decane-2,4-dione (XXXVIIa).—A solution of XXXVII (0.040 g., 0.000239 mole) in ethanol (2 cc.) was diluted with hot water (20 cc.), and bromine (1 drop) was added to the warm solution, causing a white precipitate to form almost instantaneously. Filtration gave a white powder (0.056 g., 72%), m.p. 243–248° dec. (sublimes). Three recrystallizations from methanol yielded small white prisms, m.p. 246–250° dec. (sublimes); ν_{NH} 3160 m, 3060 m, $\nu_{C=O}$ 1778 m, 1707 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_9H_{11}NO_2Br_2$ (325.02): C, 33.26; H, 3.41; N, 4.31. Found: C, 33.07; H, 3.54; N, 4.26.

Synthesis of 14-Azadispiro[5.1.5.2]pentadecane-7,15-dione (XV).—A solution of XXXVII (2.55 g., 0.0152 mole) in freshly distilled N,N-dimethylformamide (100 cc.) was added dropwise to a suspension of solid sodium hydride (0.74 g., 0.0308 mole) in N,N-dimethylformamide[25] (100 cc.). Then the resulting solution was stirred until hydrogen evolution became very slow (about 1 hr.). The solution was then transferred to a dropping funnel. This solution and a solution of 1,5-dibromopentane (3.90 g., 0.0170 mole) in N,N-dimethylformamide (50 cc.) were then dropped into a flask maintained at 110° at rates such that the two reagents were always present in nearly equivalent amounts. The addition was complete in 10 hr., and the solution was then refluxed for 12 hr. The solvent was removed under reduced pressure, leaving a semisolid orange residue. The residue was partitioned between dilute aqueous potassium hydroxide solution and chloroform. The orange chloroform solution was then washed with dilute hydrochloric acid, dried, and the chloroform evaporated, leaving an oil. The oil was redissolved in chloroform (30 cc.) and hot light petroleum ether (b.p. 60–68°) was added. A brown oil separated rapidly. The supernatant liquid was decanted from the oil after about 15 min., and was allowed to evaporate. The residual orange-white solid, m.p.

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(55) (a) A. P. Snyesarev, *J. Russ. Phys. Chem. Soc.*, **46**, 206 (1914); *Chem. Abstr.*, **8**, 2550 (1914); (b) A. P. Snessarew, *J. prakt. Chem.*, [2] **89**, 361 (1914).

(56) W. Cocker, A. Lapworth, and A. T. Peters, *J. Chem. Soc.*, 1382 (1931).

(57) R. M. Herbst and T. B. Johnson, *J. Am. Chem. Soc.*, **54**, 2463 (1932).

(58) S. M. McElvain and R. E. Starn, Jr., *ibid.*, **77**, 4571 (1955).

(59) R. E. Strube, *Org. Syn.*, **37**, 34 (1957).

(60) D. S. Breslow, E. Baumgarten, and C. R. Hauser, *J. Am. Chem. Soc.*, **66**, 1286 (1944).

150–200°, was dissolved in ethanol (7 cc.), hot water (7 cc.) was added, and the solution was filtered quickly. Upon cooling of the solution, fine white needles (0.123 g., 3%), m.p. 233–241°, separated. The infrared spectrum (Nujol) of the white needles was identical with that of a sample of XV prepared by hydrogenation of IV. In another similar experiment, XV, m.p. 236–239°, was isolated in 2% yield. The infrared spectrum (Nujol) of this sample was also identical with that of the sample of XV, m.p. 236–238°, prepared by hydrogenation of IV, and there was no depression in m.m.p., 236–239°.[47]

In contrast to the successful reactions catalyzed by sodium hydride, an attempt to synthesize XV by catalyzing the condensation of XXXVII with 1,5-dibromopentane with potassium *t*-butoxide in refluxing solutions of benzene and N,N-dimethylformamide was unsuccessful. The only crystalline solid isolated was unchanged XXXVII, in 42% recovery, having an infrared spectrum (Nujol) identical with that of the starting material.

Cyclohexanecarboxylic Acid from Acid Cleavage of IV. (A) Under Wolff–Kishner Conditions.—A solution of IV (8.00 g., 0.0321 mole), potassium hydroxide (8.4 g., 0.150 mole), and hydrazine (95%, 25 cc.) in diethylene glycol (150 cc.) was refluxed for 8 hr. The condenser was then removed and the vapors allowed to escape until the temperature of the boiling solution reached 195°. Refluxing was then resumed for an additional 10 hr. The hot solution was poured into hot water (500 cc.) and acidified. After being kept at room temperature for several hours, the acidic solution was extracted with chloroform. The chloroform extract was dried and evaporated, leaving an oil. The oil was distilled, giving a colorless liquid (0.38 g., 9%), b.p. 81–83° (0.9 mm.), m.p. 28°; lit.[61,62] m.p. 27–29°, lit.[63,64] 29–30°. The infrared spectrum was identical with that of authentic cyclohexanecarboxylic acid.

(B) **With Potassium Hydroxide in Diethylene Glycol.**—A solution of IV (10.0 g., 0.0401 mole) and potassium hydroxide (10.0 g., 0.178 mole) in water (10 cc.) and diethylene glycol (120 cc.) was refluxed for 2 hr. The condenser was then removed and the vapors allowed to escape until the temperature of the boiling solution reached 200°. Refluxing was then resumed for an additional 16 hr. The dark solution was poured into hot water, kept at room temperature for 24 hr., washed with chloroform, and acidified. The acidic solution was extracted with chloroform, and the chloroform extract dried and evaporated, leaving a dark oil. The oil was distilled, giving a colorless liquid (2.42 g.), b.p. 83–88° (0.7 mm.), estimated from the infrared spectrum to contain about 70% cyclohexanecarboxylic acid (32% yield). A portion of the liquid (2.2 g.) was refluxed with thionyl chloride (10 cc., 0.14 mole) for 30 min. The resulting brown solution was poured into ammonia, giving a precipitate (0.91 g.), m.p. 130–170° sublimes. Recrystallization from chloroform–light petroleum ether (b.p. 60–68°) yielded **cyclohexanecarboxamide** (0.34 g., 7% based on IV), m.p. 188–190° sublimes; lit.[62,63] m.p. 184°, lit.[61] 185–186°. The infrared spectrum (Nujol) was identical with that of an authentic sample.

14-Hydroxy-3,11-dimethyl-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione, 7-Oxime (M-I).[12,31]—Compound M-I was obtained in 5% yield, essentially according to the procedure of Nightingale, Reich, and Erickson,[5] as a white solid, m.p. 276–279°. Recrystallization from 95% ethanol yielded a white powder, m.p. 277–279°; reported 5%,[32] 9%,[5] 15–40%[7]; m.p. 257–258° dec.,[7,32] 272–274° [7]; ν_{OH} 3180 ms, 3060 ms, $\nu_{\text{C=N}}$ 1695 ms, $\nu_{\text{C=O}}$ 1653 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{24}N_2O_3$ (292.37): C, 65.72; H, 8.27; N, 9.58. Found: C, 65.72; H, 8.30; N, 9.56.

Methyl Derivative of M-I: 14-Methoxy-3,11-dimethyl-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione, 7-Oxime (M-Id).—Methyl iodide (11.4 g., 0.080 mole) was added to a solution of M-I (5.0 g., 0.0171 mole) and potassium hydroxide (0.95 g., 0.0169 mole) in methanol (50 cc.) and the resulting solution refluxed for 4 hr. About half of the methanol was then boiled off, and the concentrated solution was diluted to the point of cloudiness with hot water. Fluffy yellow crystals (4.82 g., 92%, m.p. 180–190°) separated. Two recrystallizations from methanol–water yielded fluffy white needles, m.p. 192–194°; ν_{OH} 3210 m, 3050 vw, $\nu_{\text{C=O}}$ 1692 s, $\nu_{\text{C=C}}$ 1645 m cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{17}H_{26}N_2O_3$ (306.39): C, 66.64; H, 8.55; N, 9.14. Found: C, 66.90; H, 8.69; N, 9.22.

14-Methoxy-3,11-dimethyl-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (M-IVa).—A suspension of M-Id (2.0 g., 0.065 mole) in a solution of concentrated hydrochloric acid (10 cc.) in methanol (10 cc.) and water (20 cc.) was refluxed for 2 hr., but the mixture did not become homogeneous. Additional concentrated hydrochloric acid (10 cc.) in methanol (20 cc.) and water (10 cc.) was added and refluxing was continued for 12 more hr., during which time the mixture became homogeneous. Some of the methanol was then boiled off, and the concentrated solution was diluted with hot water and allowed to cool. Colorless needles (1.07 g., 57%), m.p. 121–124°, crystallized. Two recrystallizations from methanol–water yielded white needles, m.p. 128–129°; $\nu_{\text{C=O}}$ 1764 m, 1701 s, $\nu_{\text{C=C}}$ 1639 mw cm.$^{-1}$ (Nujol). The n.m.r. spectrum of a 10% solution in carbon tetrachloride contains (in $\tau \pm 0.01$ average deviation; 1 τ = 56.44 c.p.s.) a strong peak at 8.97 and a lesser peak at 8.86 (3- and 11-methyl group protons), a very strong peak at 8.39 with lesser declining peaks at 8.26, 8.05, and 7.86 (ring protons on saturated carbon atoms), and a sharp peak at 6.16 (14-methoxyl group protons). The two vinyl protons appear as a doublet (J = 10.2 c.p.s.) at 4.84 and 4.66 (stronger); and another doublet (J = 10.7 c.p.s.) at 4.10 (stronger) and 3.91, each member of which is itself a finely split doublet (J = 3.1 c.p.s.).

Anal. Calcd. for $C_{17}H_{25}NO_3$ (291.38): C, 70.07; H, 8.65; N, 4.81. Found: C, 70.11; H, 8.80; N, 4.88.

The Two Diastereoisomers (IXa and IXb) of 7-Hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene (IX) and the Nitrone, 7-Hydroxy-14-azadispiro[5.1.5.2]pentadeca-9,14-diene 14-Oxide (IXc).—A solution of IV (18.00 g., 0.0723 mole) in anhydrous tetrahydrofuran (120 cc.) was added dropwise to a stirred suspension of lithium aluminum hydride (7.5 g., 0.198 mole) in anhydrous ether (600 cc.). The resulting mixture was refluxed for 71 hr. Then the excess lithium aluminum hydride was destroyed by adding moist ether and absolute ethanol. Cold water (90 cc.) was then added to the vigorously stirred suspension. After 15 min. of stirring, the ether layer was decanted from the coagulated white precipitate, and the residual solid was washed with ether. The combined ether decantate and washings were extracted with dilute hydrochloric acid, and the acidic extract was made alkaline with sodium hydroxide. The alkaline solution was extracted with chloroform and the extract dried and evaporated, leaving an oil. The oil was dissolved in hot light petroleum ether (b.p. 60–68°) and, upon cooling, it crystallized as a white solid (14.2 g., 89%), m.p. 115–132°. The solid was dissolved in 1:1 benzene–chloroform and chromatographed on a column of alumina (4 × 30 cm.). Elution with solutions of 0–20% chloroform in benzene removed a white solid, in fractions melting from 128–135°. Crystallization from light petroleum ether gave **diastereoisomer IXa** (2.34 g., 15%), m.p. 129.5–131°. Three recrystallizations from light petroleum ether yielded glistening white plates, m.p. 129–131°; $\nu_{\text{OH,NH}}$ 3500–2300 s (very broad), 3100 m, $\nu_{\text{C=C}}$ 1639 vw cm.$^{-1}$ (Nujol). The n.m.r. spectrum of a 7% solution in deuteriochloroform contains (in $\tau \pm 0.02$ average deviation; 1 τ = 56.44 c.p.s.) a complex in the aliphatic methylene proton region, with the major peak at 8.57, a medium strong peak at 8.25, a sharp strong peak at 8.19, and a medium weak peak at 8.00; a 4 peak AB pattern at 7.38 w, 7.18 m, 7.11 m, and 6.91 w, centered at 7.15 (J = 11.3 c.p.s.); and a sharp medium peak at 6.66. The two vinyl protons appear as a doublet (J = 10.7 c.p.s.) at 4.46 and 4.27 (stronger), and a more complex doublet (J = 10.2 c.p.s.) at 4.09 (stronger) and 3.91.

Anal. Calcd. for $C_{14}H_{23}NO$ (221.33): C, 75.97; H, 10.47; N, 6.33. Found: C, 76.04; H, 10.31; N, 6.56.

In another run, crystallization of IXa from light petroleum ether (b.p. 60–68°) produced what is assumed to be a dimorphic form, m.p. 133–134°, having an infrared spectrum (Nujol) different from that of a previous sample; $\nu_{\text{OH,NH}}$ 3450–2370 s (very broad), 3110 s, $\nu_{\text{C=C}}$ 1639 vw cm.$^{-1}$ (Nujol). Attempts to prepare an analytical sample of the second form by recrystallization from light petroleum ether only reconverted it to the first form.

Elution with solutions of 25–33% chloroform in benzene removed fractions melting from 144–152°. Crystallization from light petroleum ether (b.p. 60–68°) gave **diastereoisomer IXb** (3.12 g., 20%), m.p. 150–152°. Three recrystallizations from light petroleum ether yielded colorless needles, m.p. 150–152°; $\nu_{\text{OH,NH}}$ 3400–2400 s (very broad), 3060 m, $\nu_{\text{C=C}}$ 1639 vw cm.$^{-1}$

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(61) M. Markownikoff, *Ber.*, **25**, 3355 (1892).

(62) O. Aschan, *Ann.*, **271**, 231 (1892).

(63) J. S. Lumsden, *J. Chem. Soc.*, **87**, 90 (1905).

(64) G. S. Hiers with R. Adams, *J. Am. Chem. Soc.*, **48**, 2385 (1926).

(Nujol). The n.m.r. spectrum of a 9% solution in deuteriochloroform contains (in $\tau \pm 0.01$ average deviation; $1\ \tau = 56.44$ c.p.s.) a complex with the major peak at 8.58, a medium peak at 8.30, a medium weak peak at 8.10, and a medium strong peak at 7.80; a sharp medium peak at 7.15; and a sharp weaker medium peak at 6.59. The two vinyl protons appear as a doublet ($J = 9.6$ c.p.s.) at 4.64 and 4.47 (strongest), and a more complex doublet ($J = 11.9$ c.p.s.) at 4.27 (stronger) and 4.06.

Anal. Found: C, 75.96; H, 10.37; N, 6.55.

Elution with chloroform removed a third product, which was crystallized from benzene, giving the **nitrone IXc** (3.60 g., 21%), m.p. 182–184°. Three recrystallizations from benzene yielded colorless prisms, m.p. 182.5–184.5°; $\lambda_{\max}$ mμ (log ϵ) in 95% ethanol: 241 (3.93); $\nu_{OH,NH}$ 3090 s, $\nu_{C=C}$ 1647 w, $\nu_{C=N^+}$ 1577 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{21}NO_2$ (235.32): C, 71.45; H, 9.00; N, 5.95. Found: C, 71.57; H, 8.99; N, 6.06.

In another run under slightly more severe conditions, in which 70% more lithium aluminum hydride, 275% more tetrahydrofuran, and only half as much ether were used, and the reflux time was extended by 21 hr., the yields were 13% of IXa, 33% of IXb, and 4% of the nitrone IXc.

Methyl Derivatives of IX: Mixture of the Two Diastereoisomers of 7-Hydroxy-14-methyl-14-azadispiro[5.1.5.2]pentadecane (IXg).—For the purpose of methylation,[15] a solution of the crude mixture of diastereoisomers of IX (15.0 g., 0.0679 mole) in aqueous 35% formaldehyde solution (50 cc., 0.58 mole) and aqueous 88% formic acid (50 cc., 1.16 mole) was refluxed for 20 hr. Dilute aqueous hydrochloric acid was added, and the solution was washed with chloroform and made alkaline with sodium hydroxide. The alkaline solution was extracted with light petroleum ether (b.p. 60–68°), and the extract dried and evaporated, leaving a brown oil. Distillation of the oil at 135–140° (0.3 mm.) gave a very viscous yellow oil, which soon solidified to a hard white solid (4.92 g., 31%), m.p. 70–73°. Three crystallizations from light petroleum ether (b.p. 60–68°) yielded white plates, m.p. 75–88°; ν_{OH} 3110 m, $\nu_{C=C}$ 1639 vw cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{15}H_{25}NO$ (235.36): C, 76.54; H, 10.71; N, 5.95. Found: C, 76.66; H, 10.68; N, 6.04.

Methiodide (IXe) of IXa.—Potassium hydroxide (1.0 g., 0.018 mole) was added to a solution of IXa (1.80 g., 0.00814 mole) and methyl iodide (9.1 g., 0.0642 mole) in absolute ethanol (50 cc.), and the solution was kept at room temperature for 48 hr. The precipitated potassium iodide was filtered off, and the filtrate was concentrated and diluted with hot benzene, causing precipitation of white needles (1.32 g., 43%), m.p. 214–216°. Two recrystallizations from absolute ethanol–benzene yielded white needles, m.p. 216–217°; ν_{OH} 3330 m, $\nu_{C=C}$ 1642 vw cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{28}NOI$ (377.31): C, 50.93; H, 7.48; N, 3.71. Found: C, 51.12; H, 7.47; N, 3.69.

Partial evaporation of the benzene mother liquor gave a **benzene complex** as plates (0.80 g., 24%), m.p. 195–197°. Two recrystallizations from ethanol–benzene yielded plates, m.p. 189–193°; ν_{OH} 3250 s, $\nu_{C=C}$ 1642 vw cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{28}NOI \cdot {}^1/_2C_6H_6$ (416.37): C, 54.80; H, 7.51; N, 3.36. Found: C, 54.82; H, 7.62; N, 3.31.

Heating the benzene complex (0.41 g., 0.0098 mole) to 190° expelled benzene and left a white powder (0.37 g., 100%), m.p 215–217°, having an infrared spectrum (Nujol) identical with that of the uncomplexed sample.

Methiodide (IXd) of IXb.—Methylation of IXb (2.50 g., 0.0113 mole) with methyl iodide and potassium carbonate in methanol, and work-up in a manner similar to that described previously for the preparation of IXe, gave a **benzene complex** as lustrous plates (4.20 g., 89%), m.p. 120–150°, resolidifying and then remelting at 228–230°. Two recrystallizations from absolute ethanol–benzene yielded lustrous plates, m.p. 144–147°, resolidifying and remelting at 225–227°; ν_{OH} 3220 ms, $\nu_{C=C}$ 1634 vw cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{28}NOI \cdot {}^1/_2C_6H_6$ (416.37): C, 54.80; H, 7.51; N, 3.36. Found: C, 54.47; H, 7.48; N, 3.55.

Heating the benzene complex (0.20 g., 0.00048 mole) to 200° caused it to melt and resolidify to a hard, granular white solid (0.17 g., 94%), m.p. 225–227°; ν_{OH} 3230 s, $\nu_{C=C}$ 1645 vw cm.$^{-1}$ (Nujol). The infrared spectrum (Nujol) is different from that of the diastereoisomer IXe.

Anal. Calcd. for $C_{16}H_{28}NOI$ (377.31): C, 50.93; H, 7.48; N, 3.71. Found: C, 51.00; H, 7.47; N, 3.99.

Recrystallization of the uncomplexed sample from ethanol–benzene regenerated the benzene complex, as shown by its infrared spectrum (Nujol).

Mixture of 2-(1-Dimethylaminomethylcyclohexyl)-1-oxaspiro[2.5]oct-4-ene (XLV) and 1-(Cyclohexa-1,3-dienyl)-1-(1-dimethylaminomethylcyclohexyl)methanol (XLVII).—Silver oxide, freshly prepared[16b] from silver nitrate (8.4 g., 0.0494 mole) and sodium hydroxide (3.0 g., 0.075 mole), was added to a solution of IXd benzene complex (9.73 g., 0.0233 mole) in water (60 cc.). The mixture was filtered, and the filtrate concentrated at 30 mm. and then pyrolyzed by distillation at 1 mm., giving an oil (4.17 g., 72%), b.p. 142–145° (1 mm.). Redistillation gave a sample, b.p. 137–140° (0.6 mm.), $n^{25}D$ 1.5098; $\lambda_{\max}$ mμ (log ϵ) in 95% ethanol: 267 (2.97); ν_{OH} 3130 mw (broad), $\nu_{C=C}$ 1639 vw cm.$^{-1}$ on the liquid. The n.m.r. spectrum of a 7.5% solution in carbon tetrachloride contains (in $\tau \pm 0.01$ average deviations; $1\ \tau = 56.44$ c.p.s.) complex aliphatic proton absorption, with the strongest peak at 8.59; and major peaks at 8.12 m, 7.78 s, 7.69 ms, 7.59 m, and 7.40 w; a very weak peak at 6.09 (CH proton of the secondary alcohol group in XLVII); olefinic peaks consisting of a sharp doublet (proton at the 4-position of the double bond in XLV; $J = 11.3$ c.p.s.) at 5.08 and 4.88 (stronger); and a larger more complex multiplet (proton at the 5-position of the double bond in XLV, plus the olefinic protons in XLVII) containing a pair of stronger peaks at 4.22 and 4.14 and a lesser peak at 3.94.

Anal. Calcd. for $C_{16}H_{27}NO$ (249.38): C, 77.06; H, 10.91; N, 5.62. Found: C, 77.10; H, 10.89; N, 5.64.

Picrate (XLVa) from the Mixture of XLV and XLVII.—A saturated solution of picric acid in 95% ethanol (5 cc.) was added to a solution of the mixture of XLV and XLVII (0.25 g., 0.00100 mole) in 95% ethanol (5 cc.), causing crystallization of glistening yellow plates (0.32 g., 67%), m.p. 214–215°. Recrystallization from 95% ethanol yielded yellow plates, m.p. 214–217°; ν_{OH} 3320 ms cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{22}H_{30}N_4O_8$ (478.49): C, 55.22; H, 6.32; N, 11.70. Found: C, 55.19; H, 6.34; N, 11.68.

1-Benzyl-1-dimethylaminomethylcyclohexane (XLVI). (A) From IXd.—Silver oxide, freshly prepared[16b] from silver nitrate (4.2 g., 0.0247 mole) and sodium hydroxide (1.5 g., 0.037 mole), was added to a slurry of IXd benzene complex (4.30 g., 0.0103 mole) in water (30 cc.), and the mixture was stirred for 3 hr. The mixture was filtered, and the filtrate concentrated at 30 mm. and then pyrolyzed by distillation at 1 mm. Redistillation of the colorless distillate gave a colorless oil (1.10 g., 46%), b.p. 129–135° (2 mm.), $n^{28}D$ 1.5161; $\lambda_{\max}$ mμ (log ϵ) in 95% ethanol: 255 infl. (2.97), 262 (3.01), 265 (3.01), 269 infl. (2.99); ν_{OH} 3340 m, $\nu_{C=O}$ 1715 m, $\nu_{C=C}$ 1592 w cm.$^{-1}$ on the liquid.

Anal. Calcd. for $C_{16}H_{25}N$ (231.27): C, 83.05; H, 10.89; N, 6.05. Found: C, 80.28; H, 10.89; N, 6.74.

As the sample was obviously impure, it was purified through the picrate XLVIa, described subsequently. The picrate XLVIa (0.77 g., 0.00167 mole) was shaken with aqueous 5% sodium hydroxide solution until it dissolved. The resulting yellow orange solution was extracted with light petroleum ether (b.p. 60–68°) and with ether, and the combined extracts dried and evaporated, leaving a colorless oil. Distillation at a bath temperature of 180° (0.5 mm.) yielded a colorless oil (0.33 g., 86%), $n^{28}D$ 1.5235; $\lambda_{\max}$ mμ (log ϵ) in 95% ethanol: 248 infl. (2.29), 255 (2.30), 260 (2.33), 265 (2.23), 269 (2.13); $\nu_{C=C}$ 1590 m cm.$^{-1}$ on the liquid.

Anal. Found: C, 82.61; H, 10.94; N, 6.32.

(B) **From IXe.**—Silver oxide, freshly prepared[16b] from silver nitrate (2.1 g., 0.0123 mole) and sodium hydroxide (0.8 g., 0.020 mole), was added to a slurry of IXe (1.70 g., 0.00451 mole) in water (20 cc.), and the mixture was stirred for 1.5 hr. The mixture was filtered, and the filtrate concentrated and pyrolyzed as described in part A, giving as the distillate an oil (0.15 g., 14%), having an infrared spectrum identical with that of the crude sample isolated from IXd, as described in part A. The residual oil which did not distill from the reaction flask was treated with a saturated solution of picric acid in 95% ethanol, giving a picrate (0.40 g., 19%), m.p. 169–171°, having an infrared spectrum (Nujol) identical with that of the picrate (XLVIa) of XLVI from IXd, described subsequently.

Picrate (XLVIa) of XLVI.—A crude sample of XLVI (0.56 g., 0.00242 mole), prepared from IXd, gave a picrate (1.02 g., 91%), m.p. 168–170°. Two recrystallizations from 95% ethanol yielded yellow prisms, m.p. 170–172°; ν_{OH} none (Nujol).

Anal. Calcd. for $C_{22}H_{28}N_4O_7$ (460.48): C, 57.38; H, 6.13; N, 12.17. Found: C, 57.37; H, 6.00; N, 12.16.

1-(1-Dimethylaminomethylcyclohexyl)-1-phenylmethanol (LVI).—Phenyllithium (0.0159 mole) was prepared by adding a solution of bromobenzene (2.5 g., 0.0159 mole) in anhydrous ether (5 cc.) to lithium metal (0.25 g., 0.036 g.-atom) in ether (15 cc.). The resulting mixture was refluxed until the lithium had completely dissolved (4 hr.) and then a solution of 1-dimethylaminomethylcyclohexanecarboxaldehyde (XXXI, 2.50 g., 0.0157 mole) in ether (10 cc.) was added dropwise. The solution was stirred at room temperature for 16 hr. and then hydrolyzed with dilute hydrochloric acid. The ether layer was separated, extracted with dilute hydrochloric acid, and the acid extract combined with the acidic aqueous layer. The acidic layer was then made alkaline with sodium hydroxide and extracted with methylene chloride. The extract was dried, evaporated, and distilled, yielding a colorless, very viscous oil (2.66 g., 69%), b.p. 152–157° (1–2 mm.), $n^{25}\text{D}$ 1.5348; λ_{max} mμ (log ϵ) in 95% ethanol: 247 infl. (2.38), 253 (2.36), 259 (2.36), 265 (2.23), 268 infl. (1.98); ν_{OH} 3150 w, 3570–2370 m (very broad), $\nu_{\text{C=C}}$ 1600 w cm.$^{-1}$ on the liquid.

Anal. Calcd. for $C_{16}H_{25}NO$ (247.37): C, 77.68; H, 10.19; N, 5.66. Found: C, 77.43; H, 9.99; N, 5.93.

Attempted Hydrogenolysis of LVI to XLVI. (A) By Reduction of the Corresponding Chloride.—A solution of LVI (0.50 g., 0.00202 mole) and thionyl chloride (4 cc., 0.055 mole) in benzene (2 cc.) was kept at room temperature for 1 hr. and then refluxed for 1.5 hr. Benzene (10 cc.) was added and then boiled off to remove excess thionyl cloride. Addition of light petroleum ether (b.p. 60–68°) caused precipitation of an oil, which was separated and washed with ether. Then anhydrous ether (10 cc.) and lithium aluminum hydride (0.20 g., 0.0053 mole) were added and the mixture was kept at room temperature for 24 hr. The excess hydride was destroyed by addition of ethanol and the product, assumed to be an oil, isolated as a picrate (0.26 g.). Recrystallization from 95% ethanol yielded yellow prisms, m.p. 156–157°; ν_{OH} none, ν_{NH} 2700 w cm.$^{-1}$ (Nujol). The elemental analyses show that the desired product was not obtained.

Anal. Calcd. for $C_{22}H_{28}N_4O_7$ (460.48): C, 57.38; H, 6.13; N, 12.17. Found: C, 54.22; H, 5.73; N, 8.03.

(B) By Catalytic Hydrogenolysis. (1) With Palladium on Charcoal in Concentrated Hydrochloric Acid.—A solution of LVI (0.30 g.) in concentrated hydrochloric acid (7 cc.) was hydrogenated at 2 atm. over palladium-on-charcoal (0.1 g.) at room temperature for 17 hr. The solution was diluted with water, filtered, and washed with chloroform. The aqueous acidic layer was made alkaline with sodium hydroxide and extracted with chloroform. Drying and evaporation of the chloroform layer left unchanged LVI, as shown by its infrared spectrum.

(2) With Raney Nickel.—A solution of LVI (1.00 g.) in absolute ethanol (150 cc.) was refluxed with Raney nickel (8.0 g.) for 4 hr. Removal of the catalyst and evaporation of the ethanol left unchanged LVI (0.80 g., 80%), having an infrared spectrum identical with that of the starting material.

Oxidation of IV with Peracids. (A) 9,10,14-Trihydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione (Isomer 1, IVc) and 10(?)-Acetoxy-9(?),14-dihydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione (IVd) by Oxidation of IV with Peracetic Acid.—A solution of IV (3.90 g., 0.0157 mole) and aqueous 30% hydrogen peroxide (10 cc., 0.10 mole) in glacial acetic acid (50 cc.) was kept at 90° for 5 hr. Platinum black was then added to destroy excess peroxides, and the solvents were removed under reduced pressure, leaving a brown oil, which soon solidified to a glass. The glass was dissolved in ethyl acetate–chloroform, and the solution was concentrated and more chloroform added to the warm concentrate. Upon cooling of the solution, crystals formed (0.52 g., 12%), m.p. 220–223°. Two recrystallizations from ethyl acetate-chloroform, followed by two recrystallizations from methanol–ethyl acetate, yielded **IVc** as fine white needles, m.p. 220–221°; ν_{OH} 3390 ms, 3060 w, 3220–2450 m (very broad), $\nu_{\text{C=O}}$ 1767 m, 1675 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{21}NO_5$ (283.32): C, 59.35; H, 7.47; N, 4.94. Found: C, 59.39; H, 7.53; N, 4.90.

The mother liquor from the isolation of IVc was concentrated, producing crystals (0.32 g., 6%), m.p. 244–250°. Recrystallization from methanol–ethyl acetate yielded **IVd** as small white plates, m.p. 242–246° dec.; ν_{OH} 3060 ms, $\nu_{\text{C=O}}$ 1736 s, 1692 s, 1629 m cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{23}NO_6$ (325.35): C, 59.06; H, 7.13; N, 4.31. Found: C, 58.49; H, 6.99; N, 4.91.

(B) Sodium 9,10-Dihydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione-14-hydroxylate (IVf) and 9,10,14-Trihydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione (Isomer 2, IVg). (1) By Oxidation of IV with Peracetic Acid.—A mixture of IV (20.0 g., 0.0804 mole) in aqueous 30% hydrogen peroxide (45 cc., 0.44 mole) and glacial acetic acid (150 cc.) was kept at 90° for 4 hr. and at room temperature for 10 hr. The resulting solution was stirred with platinum black for several hours to destroy excess peroxides, and the solvents were evaporated. The residual glass was then dissolved in methanol (200 cc.) and treated with hydrogen at 2 atm. over Raney nickel[65] at room temperature for 12 hr. The catalyst was then filtered off and the filtrate concentrated to a volume of about 50 cc. Sodium hydroxide (20 g., 0.50 mole) and water (10 cc.) were added and the alkaline solution was refluxed for 2 hr. Dilute hydrochloric acid (3 *N*, 15 cc.) was then added cautiously to the hot solution. Upon cooling of the solution needles formed (4.92 g., 19%), which decomposed above 220° without melting. Three recrystallizations from 95% ethanol yielded **IVf** as fine white needles, which decomposed above 215° without melting; ν_{OH} 3370 s, 2620 m (very broad), $\nu_{\text{C=O}}$ 1748 m, 1639 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{20}NO_5Na \cdot H_2O$ (323.32): C (after allowing for 0.5 C atom in the residue as Na_2CO_3), 50.14; H, 6.86; N, 4.33. Found: C, 50.48; H, 6.83; N, 4.24.

The mother liquor from the isolation of IVf was acidified with hydrochloric acid and extracted with chloroform. The extract was dried, concentrated, and diluted with light petroleum ether (b.p. 60–68°), causing precipitation of a solid (3.02 g., 13%), m.p. 215–220°. Extraction of the solid with hot 1:2 chloroform–light petroleum ether (b.p. 60–68°) left undissolved a white solid (2.10 g., 9%), m.p. 230–235°. Two recrystallizations from methanol–ethyl acetate yielded **IVg** as a granular white solid, m.p. 235–237°; ν_{OH} 3280 ms, 3130 w, $\nu_{\text{C=O}}$ 1757 m, 1672 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{21}NO_5$ (283.32): C, 59.35; H, 7.47; N, 4.94. Found: C, 59.19; H, 7.23; N, 4.76.

(2) By Oxidation of IV with Performic Acid.—A mixture of IV (8.30 g., 0.0333 mole) in aqueous 30% hydrogen peroxide (20 cc., 0.20 mole) and aqueous 90% formic acid (80 cc.) was stirred at room temperatre for 2 hr. Then more 30% hydrogen peroxide (20 cc., 0.20 mole) and 90% formic acid (80 cc.) were added, and stirring at room temperature was continued for 6 hr. more, during which time the mixture became homogeneous. A catalytic amount of platinum black was then added and the mixture was stirred at room temperature for 12 hr. to destroy excess peroxides. The mixture was filtered, and the filtrate was concentrated under reduced pressure in a rotary evaporator, giving a brown oil. Aqueous 10% sodium hydroxide solution was added to the oil, and the resulting mixture of brown solution and solid precipitate was kept at 90° for 1.5 hr. The mixture was then filtered, and the tan solid was washed with a small amount of cold water. The solid (3.27 g., 0.0101 mole, 30%) was shown to be **IVf** by comparison of its infrared spectrum (Nujol) with that of IVf from the oxidation of IV with peracetic acid, described in part 1.

Acidification of the combined alkaline filtrate and water wash with concentrated hydrochloric acid gave **IVg** (2.17 g., 23%), m.p. 227–239°, identified by comparison of its infrared spectrum (Nujol) with that of IVg from the oxidation of IV with peracetic acid, described in part 1. Recrystallization from methanol–ethyl acetate gave a sample, m.p. 241–244°.

(C) 9,10,14-Trihydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione (Isomer 3, IVh), from Acidification of IVf.—Compound IVf (0.20 g., 0.00062 mole) was stirred with hydrochloric acid (2.4 *N*, 5 cc.) for 5 min. The mixture was filtered, giving a white powder (0.14 g., 80%), m.p. 235–238° sublimes. Two crystallizations from methanol–ethyl acetate yielded **IVh** as glistening white needles, m.p. 240–243° sublimes; ν_{OH} 3230 ms, 3110 ms, $\nu_{\text{C=O}}$ 1760 m, 1672 s cm.$^{-1}$ (Nujol). The infrared spectrum (Nujol) was different from those of IVc and IVg.

Anal. Calcd. for $C_{14}H_{21}NO_5$ (283.32): C, 59.35; H, 7.47; N, 4.94. Found: C, 59.40; H, 7.41; N, 4.89.

10(?)-Acetoxy-9(?)-hydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione (IVe).—Compound IVd (0.90 g., 0.00277 mole) dissolved in 95% ethanol (100 cc.) was hydrogenated over Raney nickel at 2 atm. and room temperature for 8 hr. The mixture

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(65) Apparently in this case the catalyst was deactivated by reaction products; see the preparation of IVj and IVi for the successful hydrogenolysis of IVf and IVg.

was then heated, the catalyst filtered off, and the filtrate concentrated and diluted with hot water. Upon cooling, glistening white needles separated (0.60 g., 70%), m.p. 261–264°. Recrystallization from ethanol–water yielded white needles (0.25 g., 29%), m.p. 268–270°; ν_{OH} 3440 ms, ν_{NH} 3150 m, 3060 m, $\nu_{C=O}$ 1751 ms, 1689 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{23}NO_5$ (309.35): C, 62.12; H, 7.49; N, 4.53. Found: C, 62.36; H, 7.69; N, 4.54.

9,10-Dihydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione (Isomer 2, IVi).—Compound IVg (1.38 g., 0.00487 mole) dissolved in 95% ethanol (120 cc.) was hydrogenated over Raney nickel at 2 atm. and room temperature for 24 hr. The catalyst was filtered off and the filtrate evaporated to dryness. Crystallization of the residue from methanol–ethyl acetate gave crystals (0.95 g., 73%), m.p. 289–292°. Recrystallization from methanol–ethyl acetate yielded fine white needles, m.p. 290–292°; ν_{OH} 3340 m, ν_{NH} 3130 m, 3040 w, $\nu_{C=O}$ 1751 m, 1650 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{21}NO_4$ (267.32): C, 62.90; H, 7.92; N, 5.24. Found: C, 62.64; H, 8.00; N, 5.25.

9,10-Dihydroxy-14-azadispiro[5.1.5.2]pentadecane-7,15-dione (Isomer 3, IVj).—Compound IVf (2.0 g., 0.0062 mole) was converted to IVh by stirring with aqueous 10% hydrochloric acid (50 cc.) for 10 min. The white solid (IVh) was then filtered off, dissolved in ethanol (50 cc.), and hydrogenated over Raney nickel at 2 atm. and room temperature for 24 hr. The catalyst was filtered off and the filtrate evaporated to dryness. Crystallization from ethanol–ethyl acetate–light petroleum ether (b.p. 60–68°) gave a white solid (1.13 g. 68%), m.p. 178–180°. Two recrystallizations from ethyl acetate–light petroleum ether yielded a granular white solid, m.p. 178–180°; ν_{OH} 3310 m, $\nu_{C=O}$ 1748 mw, 1681 s cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{14}H_{21}NO_4$ (267.32): C, 62.90; H, 7.92; N, 5.24. Found: C, 63.19; H, 8.18; N, 4.83.

Cyclohexanehydroxamic Acid (LXXIX).—The product, prepared in 38% yield from cyclohexanecarbonyl chloride[66] according to a procedure for benzohydroxamic acid,[67] was crystallized twice from chloroform, giving matted white needles, m.p. 136–137°; lit.[68] 65%, lit.[68] m.p. 132°, lit.[69] 132–133°; $\nu_{NH,OH}$ 3160 s, 3010 m, $\nu_{C=O}$ 1658 s, $\nu_?$ 1538 m cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_7H_{13}NO_2$ (143.18): C, 58.72; H, 9.15; N, 9.78. Found: C, 58.53; H, 9.06; N, 9.92.

Methylation of LXXIX: Preparation of N-Methoxycyclohexanecarboxamide (LXXX).—A solution of cyclohexanehydroxamic acid (1.4 g., 0.0098 mole), potassium hydroxide (0.6 g., 0.011 mole), and methyl iodide (2.0 g., 0.0141 mole) in methanol (10 cc.) was refluxed for 2 hr. The solution was then evaporated to dryness in a rotary evaporator. The residue was extracted with light petroleum ether (b.p. 60–68°), and the extract filtered, concentrated, and cooled, causing precipitation of feathery needles (0.23 g., 15%), m.p. 73–75°. Two recrystallizations from light petroleum ether yielded feathery white needles, m.p. 77–79°; ν_{NH} 3170 s, $\nu_{C=O}$ 1650 s, $\nu_?$ 1513 m cm.$^{-1}$ (Nujol)

Anal. Calcd. for $C_8H_{15}NO_2$ (157.21): C, 61.12; H, 9.62; N, 8.91. Found: C, 60.87; H, 9.53; N, 9.07.

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The Preparation and Stereospecific Rearrangement of Spiro[bicyclo[2.2.1]hept-2-en-*anti*-7,2'-oxacyclopropane]. The Effect of a Nonclassical Intermediate[1]

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The addition of dimethylsulfoxonium methylide in dimethyl sulfoxide to bicyclo[2.2.1]hept-2-en-7-one occurs in a stereospecific manner to yield spiro[bicyclo[2.2.1]hept-2-en-*anti*-7,2'-oxacyclopropane]. This epoxide is rearranged stereospecifically with retention of configuration at the migration terminus by the action of heat and/or Lewis acids to yield bicyclo[2.2.1]hept-2-ene-*syn*-7-carboxaldehyde. The structures of the epoxide and aldehyde are established by chemical and physical means. A mechanism for the rearrangement is suggested which incorporates a nonclassical intermediate.

Norton[2] reports that bicyclo[2.2.1]hept-2-en-7-one (2) reacts with the nitrogen-containing nucleophiles, hydroxylamine, semicarbazide, and 2,4-dinitrophenylhydrazine with exceptional ease. Therefore, when searching for a suitable starting material for the preparation of some 7-functionally substituted bicyclo[2.2.1]hept-2-enes, we decided to examine the reactions of this ketone with some nucleophiles in which the attacking atom would be carbon rather than nitrogen. One of the more interesting nucleophiles, whose reactivity toward ketones has recently been demonstrated, is dimethylsulfoxonium methylide.[3] We report here the results of our investigation into the reaction of dimethylsulfoxonium methylide in dimethyl sulfoxide with bicyclo[2.2.1]hept-2-en-7-one (2).

Results

Bicyclo[2.2.1]hept-2-en-7-one (2) was first prepared and characterized by Norton.[2] The final step in his synthetic scheme involved the oxidation of bicyclo-[2.2.1]hept-2-en-7-ol (of unspecified configuration but probably *anti*) with chromic acid in acetone.[4] The ketone, obtained in 38% yield, was identified by its infrared and ultraviolet spectra, its facile reaction with hydroxylamine, 2,4-dinitrophenylhydrazine, and semicarbazide, and by its reduction with lithium aluminum hydride back to bicyclo[2.2.1]hept-2-en-7-ol. As the starting point for our synthesis we used bicyclo[2.2.1]hept-2-en-*anti*-7-ol (1), prepared in 21% over-all yield from bicyclo[2.2.1]heptadiene by the procedure

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[1] (a) Portions of this work have been presented at the 14th Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., November, 1962, and at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963 (Abstracts of meeting, p. 25M); (b) Since there are presently no accepted conventions for designating the stereochemistry of 7-substituted bicycloheptenes we will arbitrarily refer to those in which the functional group of the 7-substituent and the bicycloheptene double bond are on the same side of the plane defined by the 1, 4, and 7 carbons as *syn*, those in which they are on opposite sides as *anti*.

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