[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY, ST. LOUIS, MO.]

Ring Enlargements. VII. The Reaction of Cycloalkanones with Bisdiazoalkanes[1]

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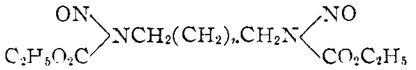
The products resulting from the interaction of cyclopentanone, cyclohexanone, cycloheptanone and acetone with one or more of the bis-diazoalkanes derived *in situ* from bis-nitrosourethans of the structure $[N(NO)(CO_2Et)]_2(CH_2)_n$ where *n* is 3, 4, 5 and 6 have been investigated. In several instances, bridged ring ketones are produced, leading to syntheses of 8-ketobicyclo[5,1,1]nonane, 9-ketobicyclo[4,2,1]nonane and 10-ketobicyclo[5,2,1]decane. In two instances fused ring ketones are formed and in every case a keto ether is a constituent of the reaction mixture. The structures of the bridged ring ketones, fused ring ketones and keto ethers were proved by a combination of chemical and spectral methods with particular attention to the nuclear magnetic resonance spectra. Certain of the properties of the bridged ring ketones were studied including their ability to exchange deuterium for hydrogen under base-catalyzed conditions (enolizability), their ability to undergo cleavage with sodium amide (non-enolizability) and their tendency to react with hydrogen cyanide (cyanohydrin equilibrium).

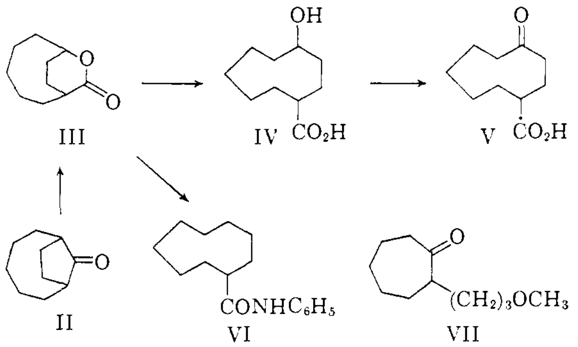
As the chemistry of a functional group reaches maturity an inevitable means by which the chemist sustains his interest is through attention to compounds containing two or more of the groups in question. Thus, recent studies of diazoalkanes, a slow maturer, have turned to bis-diazoalkanes.[3] The present communication[4] describes experiments with such compounds as ring-enlargement reagents, the logical outgrowth of investigations which have occupied our attention for a number of years.[5]

Preparation and Proof of Structure of Bridged Ring Ketones and Fused Ring Ketones from Ring Enlargement Reactions.—Our initial investigations concerned the interaction of 1,4-bisdiazobutane and cyclohexanone, a reaction which we later discovered had been explored as early as 1941 by Petersen.[6] Addition of N,N'-dicarbethoxy-N,N'-dinitroso-1,4-butanediamine (Ib) to a mixture of cyclohexanone, methanol and potassium carbonate (typical *in situ* ring enlargement conditions[7]) resulted in a smooth evolution of nitrogen and the formation of a mobile liquid with a camphor-like odor. By means of ordinary distillation, column chromatography or, preferably, vapor phase chromatography with a preparative-size column, this mixture could be separated into a solid ketone (50% yield) and a liquid ketone (16% yield). The solid ketone, responsible for the camphor-like odor of the original mixture, had an analysis compatible with a $C_{10}H_{16}O$ formula, formed carbonyl derivatives with analyses compatible with this formula, and showed a strong infrared absorption band at 1731 cm.$^{-1}$ characteristic of a cyclopentanone ring.[8] Treatment with peracids converted the solid ketone to a $C_{10}H_{16}O_2$ lactone (III) which could be hydrolyzed to a hydroxy acid (IV) and subsequently oxidized to a keto acid (V). Although attempts to degrade IV and V to known cyclononane compounds were unsuccessful, the lactone was converted to cyclononanecarboxanilide (VI) by treatment with thionyl chloride followed by ethanolysis, hydrogenation, saponification, and finally formation of the anilide *via* the acid chloride. The melting point of the anilide coincided with that reported for cyclononanecarboxanilide,[9] the mixed melting point with authentic material showed no depression, and the infrared spectra proved to be identical.[10] Thus, the demonstration of a five-membered ring and a nine-membered ring in the solid ketone, taken in conjunction with a reasonable interpretation of the course of the ring-enlargement reaction, leaves little doubt that 10-ketobicyclo[5,2,1]decane (II) correctly expresses the structure of this material.



$$\overset{ON}{\underset{C_2H_5O_2C}{}}\!\!>NCH_2(CH_2)_nCH_2N<\!\!\overset{NO}{\underset{CO_2C_2H_5}{}}$$

Ia, $n = 1$ b, $n = 2$ c, $n = 3$ d, $n = 4$



The liquid ketone had an analysis compatible with a $C_{11}H_{20}O_2$ formula, a methoxyl value indicating one methoxyl group per molecule, and infrared absorption bands at 1708 and 1118 cm.$^{-1}$ characteristic of a carbonyl group and an aliphatic ether group, respectively.[11] These data, taken in conjunction with a reasonable interpretation of the course of the reaction and the fact that nitrosoure-

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[2] Monsanto Chemical Co. Fellow 1958–1959.

[3] (a) H. Lettre and U. Brose, *Naturwiss.*, **36**, 57 (1949); (b) T. Lieser and G. Beck, *Ber.*, **83**, 137 (1950); (c) C. M. Samour and J. P. Mason, THIS JOURNAL, **76**, 441 (1954); (d) H. Reimlinger, *Ber.*, **92**, 970 (1959).

[4] For a previous communication describing part of the material in this paper *cf.* C. D. Gutsche, T. D. Smith, M. F. Sloan, J. J. Quarles van Ufford and D. E. Jordan, THIS JOURNAL, **80**, 4117 (1958).

[5] For the previous paper in this series *cf.* C. D. Gutsche, H. F. Strohmayer and J. M. Chang, *J. Org. Chem.*, **23**, 1 (1958).

[6] Petersen, U. S. Dept. of Commerce, Office of Technical Service Report PB 694 (1941).

[7] C. D. Gutsche, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 364.

[8] *Cf.*, for example, S. L. Friess and P. E. Frankenberg, THIS JOURNAL, **74**, 2679 (1952).

[9] V. Prelog and K. Schenker, *Helv. Chim. Acta*, **36**, 896 (1953).

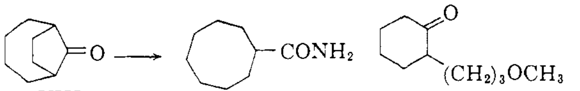
[10] We are indebted to Professor V. Prelog for the mixed melting point and infrared comparisons.

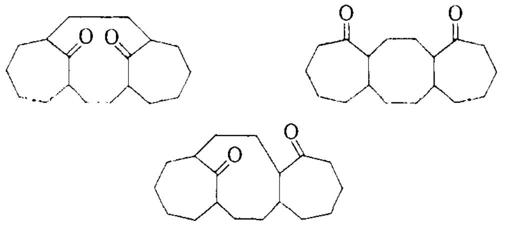
[11] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 116.

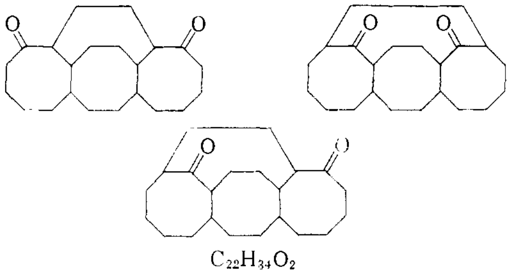
thans frequently yield ethers *via* solvolysis,[12] support structure VII as the most likely one for the liquid ketone.

The vapor phase chromatogram of the crude reaction product indicated that in addition to the two major products described above, other materials were also present. Although none of these has been identified, it seems probable that one must be the diketone resulting from the reaction of two moles of cyclohexanone with one mole of bisdiazobutane. Petersen,[6] in fact, reported a product to which he assigned no structure but which he stated to have an analysis for $C_{16}H_{24}O_2$. From another reaction, described below, we have isolated such a product (*cf.* XIV).

In similar fashion to cyclohexanone, cyclopentanone reacted under *in situ* conditions with the bisnitrosourethan Ib to yield a liquid with a menthol-like odor which could be separated into two ketonic fractions. The solid, lower-boiling ketone, responsible for the odor, was obtained in 10% yield, had an analysis compatible with a $C_9H_{14}O$ formula, formed carbonyl derivatives with analyses compatible with this formula, and showed a strong infrared absorption band at 1737 cm.$^{-1}$ characteristic of a cyclopentanone ring.[8] Treatment of this ketone with sodium amide in a Haller–Bauer[13] reaction yielded cyclooöctanecarboxamide IX, the structure of which was verified by comparison with authentic material. Thus, the demonstration of a five-membered ring and an eight-membered ring is taken as adequate evidence in support of the 9-ketobicyclo[4,2,1]nonane structure (VIII). The higher-boiling ketone, obtained in 8% yield, had an analysis compatible with a $C_{10}H_{18}O_2$ formula, a methoxyl value indicating one such group per molecule, and infrared absorption bands at 1710 and 1118 cm.$^{-1}$ characteristic of a carbonyl group and an aliphatic ether group, respectively.[11] Accordingly, structure X is suggested for this compound. In addition to ketones VIII and X, column chromatography of the crude reaction mixture also yielded small amounts of two other materials. One of these was a high-melting solid with an analysis in accord with $C_{22}H_{34}O_2$ and an infrared band at 1708 cm.$^{-1}$ (carbonyl). The other was isolated as a 2,4-dinitrophenylhydrazone, the analysis of which indicated it to be the monoderivative of a $C_{18}H_{28}O_2$ diketone.[14]


VIII IX X


$C_{18}H_{28}O_2$


$C_{22}H_{34}O_2$

The lower homolog of Ib, *viz.*, N,N′-dicarbethoxy-N,N′-dinitroso-1,3-propane (Ia), also reacted smoothly with cyclohexanone to give a mixture, four components of which have been identified. The lowest-boiling fraction could be separated into two ketones, each possessing the empirical formula $C_9H_{14}O$. One of the C_9-compounds, obtained in 9% yield, formed carbonyl derivatives with analyses compatible with the assigned formula, possessed a terpene-like odor similar to that of II and VIII, and showed an infrared absorption band at 1769 cm.$^{-1}$ characteristic of a cyclobutanone.[8] Although treatment with sodium amide cleaved the compound but failed to yield cycloheptanecarboxamide, it is felt that the data cited above taken along with the precedent of the two previous examples provide fairly good substantiation for 8-ketobicyclo[5,1,1]nonane (XI) as the structure of this compound. This assignment is given further weight by the striking similarity between the nuclear magnetic resonance spectra of XI and cyclobutanone as discussed in a later section. The other C_9-compound, also obtained in 9% yield, formed a 2,4-dinitrophenylhydrazone with an analysis compatible with $C_9H_{14}O$, did not possess a terpene-like odor, and had infrared absorption bands, *inter alia*, at 3050, 1690, 1448, 1440 and 1420 cm.$^{-1}$, and an ultraviolet absorption band at 210 mμ (ϵ 2950). These data, particularly the spectral characteristics, are most easily accommodated by a 1-ketobicyclo[6,1,0]nonane structure (XII). Thus, the infrared band at 3050 cm.$^{-1}$ is characteristic of a C–H stretching vibration in a cyclopropane ring,[15] the infrared band at 1690 cm.$^{-1}$ and the ultraviolet band at 210 mμ are characteristic of a carbonyl group conjugated with a cyclopropane ring,[16,17] the infrared bands at 1448 and 1440 cm.$^{-1}$ may be associated with the C–H bending vibrations of ring methylene groups, and the infrared band at 1420 cm.$^{-1}$ falls in the region of a C–H bending vibration

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[12] *Cf.*, for example, C. D. Gutsche and H. E. Johnson, This Journal, **77**, 109 (1955).

[13] K. E. Hamlin and A. W. Weston, "Organic Reactions," Vol. IX, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 1.

[14] A $C_{18}H_{28}O_2$ diketone can be constructed from two moles of cyclopentanone and two moles of the residue (*i.e.*, CHCH$_2$CH$_2$CH) from 1,4-bisdiazobutane; a $C_{22}H_{34}O_2$ diketone can be constructed from two moles of cyclopentanone and three moles of this residue. A number of structures involving little if any bond strain (although possessing appreciable non-bonded interactions in several cases) can be postulated including the ones pictured.

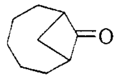
[15] A. R. H. Cole, *J. Chem. Soc.*, 3807, 3810 (1954).

[16] S. E. Wiberly and S. C. Bunce, *Anal. Chem.*, **24**, 623 (1952), report an infrared band at 1698 cm.$^{-1}$ for methyl cyclopropyl ketone. M.-L. Josien and N. Fuson, *Bull. soc. chim. France*, **19**, 389 (1952), report a band at 1685 cm.$^{-1}$ for carone.

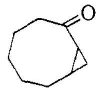
[17] A. E. Gillam and T. F. West [*J. Chem. Soc.*, 95 (1945)] report a band at <220 mμ (ϵ 2680) for carone; M. T. Rogers [This Journal, **69**, 2544 (1947)] report a band at <208 mμ (ϵ >422) for methyl cyclopropyl ketone.

of a methylene group adjacent to a carbonyl group.[18] Additional, although qualified, confirmation for structure XII was provided by the nuclear magnetic resonance spectrum which shows a group of bands at unusually high field, a characteristic of protons on cyclopropane rings (*cf.* discussion in later section).

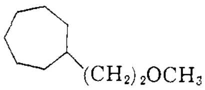
From a higher-boiling fraction of the reaction mixture from Ia and cyclohexanone a compound with an analysis in accord with $C_{10}H_{17}O_2$ was isolated which had infrared absorption bands at 1705 and 1118 cm.$^{-1}$. By analogy with similar compounds obtained from the previously-described reactions it is assigned the structure XIII. A fourth compound, isolated from the later eluates in a chromatographic separation as a mono-2,4-dinitrophenylhydrazone, had an analysis and an infrared spectrum in accord with the diketone XIV.



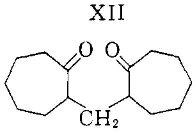
XI



XII

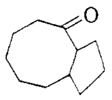


XIII

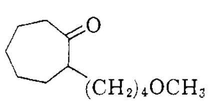


XIV

The higher homolog of Ib, *viz.*, N,N′-dicarbethoxy-N,N′-dinitroso-1,5-pentanediamine (Ic) similarly reacted smoothly with cyclohexanone to give a mixture from which two ketonic materials were isolated. The lower-boiling fraction obtained in 22% yield had an analysis compatible with $C_{11}H_{18}O$, possessed a terpene-like odor, and showed a vapor phase chromatographic behavior similar to that of the bridged ring ketones II, VIII and XI. The presence of a carbonyl absorption at 1700 cm.$^{-1}$ in the infrared, however, was more in accord with a cyclooöctanone than a cyclohexanone moiety, and a small band at 1410 cm.$^{-1}$ suggested the presence of a methylene group adjacent to a carbonyl. Also, the nuclear magnetic resonance spectrum of the C_{11}-ketone was in better agreement with that expected for 1-ketobicyclo[5,4,0]undecane than that for a bridged ring ketone. A definitive choice in favor of XV was provided by a deuterium exchange experiment which showed the incorporation of three atom-equivalents of deuterium. The higher-boiling fraction from Ic and cyclohexanone contained a $C_{12}H_{22}O_2$ ketone, the physical and chemical characteristics of which indicate it to have structure XVI.



XV



XVI

The Properties of the Bridged Ring Ketones (II, VIII, XI). (A) Bredt's Rule Considerations.—Bredt's rule[19] as modified in the light of recent experimental data is an empirically-derived statement regarding the ease with which a double bond can be accommodated at a bridge head position in a bridged ring structure. The present series of ketones provides an interesting example of compounds which fall into both categories of this rule, *i.e.*, some of which can and some of which cannot adjust to a bridge head double bond. The proof of structure of 9-ketobicyclo[4,2,1]nonane (VIII) included a Haller–Bauer degradation to cyclooctanecarboxamide, this cleavage reaction occurring only with non-enolizable ketones.[13] Thus, it would be inferred that VIII is non-enolizable, and this has been further substantiated by the demonstration that it does not undergo bromination and does not exchange deuterium for hydrogen when heated with an alkaline solution of deuterium oxide. On the other hand, an attempted Haller–Bauer degradation of 10-ketobicyclo[5,2,1]decane (II) failed to give anything but recovered starting material even under strenuous conditions, bromination of II proceeded very smoothly to give a dibromide, and treatment of II with hot, alkaline deuterium oxide resulted in the introduction of approximately two deuterium atoms. It is apparent that the lengthening of the α,α'-bridge from tetramethylene to pentamethylene in going from VIII to II has introduced sufficient flexibility in the molecule to allow the bridge head double bond required by an enol structure. Although experimental data are lacking, it would be anticipated that XI would be non-enolizable and "obey" Bredt's rule. In this series of bridged ring ketones, therefore, the cross-over point occurs when the sum of the bridging atoms (the S number[19]) is 7 and 8.

(B) **Cyanohydrin Formation.**—The equilibrium constants for the reaction of hydrogen cyanide with aldehydes and ketones to form cyanohydrins have been frequently used in studies which relate structure to chemical reactivity. Of particular interest in this regard have been the equilibrium constants for cycloalkanones of various ring sizes as determined by a number of workers.[20] Employing this reaction in the assessment of the effect of the polymethylene bridges in II, VIII and XI on the reactivity of the ketone function, the equilibrium data shown in Table I have been obtained.

In the bridged ring ketones the carbonyl group is present in rings of two sizes, and the factors governing the cyanohydrin equilibria for the simple ketones of these ring sizes might be expected to act coöperatively in the bridged ring compounds. This appears to be the case with the [4,2,1] and [5,2,1] compounds. Thus, the ratios of the dissociation constants of cycloheptanone and cyclooöctanone to that of cyclopentanone are 5 and 40, respectively; the ratios of the dissociation constants of the [4,2,1] and [5,2,1] ketones to that of cyclopentanone are 7 and 90, respectively. The explanations based on bond opposition forces and non-bonded interactions as applied to cyclopentane, cycloheptane, and

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[18] R. N. Jones and C. Sandorfy in "Technique of Organic Chemistry, Vol. IX. Chemical Applications of Spectroscopy," ed. by W. West, Interscience Publishers, Inc., New York, N. Y., 1956, p. 344.

[19] *Cf.* F. S. Fawcett, *Chem. Revs.*, **47**, 219 (1950), for an extensive discussion of Bredt's rule.

[20] (a) A. Lapworth and R. H. F. Manske, *J. Chem. Soc.*, 2533 (1928); (b) L. Ruzicka, P. A. Plattner and H. Wild, *Helv. Chim. Acta*, **28**, 613 (1945); (c) V. Prelog and M. Kobelt, *ibid.*, **32**, 1187 (1949); (d) A. M. El-Abbady, *J. Org. Chem.*, **21**, 828 (1956); (e) O. H. Wheeler and J. Z. Zabicky, *Can. J. Chem.*, **36**, 656 (1958).

TABLE I

DISSOCIATION CONSTANTS OF CYANOHYDRINS AT 20° IN 95% ETHANOL

Ketone corresponding to cyanohydrin	$K \times 10^2$	ΔF, kcal./mole
Cyclobutanone	0.87 ± 0.007	2.75
Cyclopentanone	1.91 ± .025	2.30
Cyclohexanone	0.176 ± .004	3.68
Cycloheptanone	9.53 ± .13	1.37
Cycloöctanone	75.6 ± 8.6	0.16
8-Ketobicyclo[5,1,1]nonane (XI)	2.12 ± 0.14	2.24
9-Ketobicyclo[4,2,1]nonane (VIII)	13.5 ± 0.5	1.16
10-Ketobicyclo[5,2,1]decane (II)	172 ± 23	−0.315

cycloöctane compounds[20c,21] provide an adequate interpretation for the cyanohydrin data of the [4,2,1] and [5,2,1] ketones.

The [5,1,1] bridged ring ketone containing a carbonyl in a cyclobutane and a cycloöctane ring behaves differently, however. Whereas the ratio of the dissociation constant of cycloöctanone to that of cyclobutanone is 90, the ratio of the dissociation constant of the [4,2,1] ketone to that of cyclobutanone is only 2.5. For cyclobutane rings the major source of strain is stated to be that arising from bond angle distortion,[21b,c] the relief of which in passing from cyclobutanone (three tetrahedral carbons and one trigonal carbon) to cyclobutanone cyanohydrin (four tetrahedral carbons) results in a relatively low dissociation constant for cyclobutanone cyanohydrin. In the [5,1,1] bridged ring ketone the additional bond angle strain imposed on the cyclobutane ring by the α,α'-pentamethylene bridge should result in a greater strain relief during cyanohydrin formation and a lower dissociation constant. Operating against cyanohydrin formation in the [5,1,1] ketone, however, are the steric forces (cf. above) associated with the cycloöctane ring. The competitive rather than coöperative action of steric forces in the [5,1,1] ketone, therefore, may explain its unexpectedly low dissociation constant.

In the expectation of arriving at a more detailed explanation for the cyanohydrin data, dissociation constants were measured at 0° and 35°, and entropy and enthalpy values were computed. Such striking variations in these values between the temperature intervals 0–20° and 20–35° were noted, however, as to raise the question of what "cyanohydrin equilibria" actually are. For this reason as well as the fact that published cyanohydrin equilibrium constants do not always show particularly close agreement,[22] there may be some question as to the quantitative validity of such data in assessing relative reactivities of cyclic ketones.

(C) Infrared Spectra.—The frequencies of the carbonyl absorptions for the eight ketones listed in Table I, determined in carbon tetrachloride solution, are: cyclobutanone (1781 cm.$^{-1}$), cyclopentanone (1741 cm.$^{-1}$), cyclohexanone (1714 cm.$^{-1}$), cycloheptanone (1705 cm.$^{-1}$), cycloöctanone (1702 cm.$^{-1}$), [5,1,1] ketone (1769 cm.$^{-1}$), [4,2,1] ketone (1737 cm.$^{-1}$), [5,2,1] ketone (1731 cm.$^{-1}$). In all three of the bridged ring ketones the introduction of the α,α'-polymethylene bridge lowers the frequency of the carbonyl absorption. At least a portion of this lowering may be ascribed to an alkyl group effect (*e.g.*, cyclopentanone and 2,5-dimethylcyclopentanone show carbonyl absorptions at 1741 cm.$^{-1}$ and 1736 cm.$^{-1}$, respectively). Thus, the shift of 4 cm.$^{-1}$ in the carbonyl absorption of the [4,2,1] ketone might be entirely the result of the additional alkyl groups. The greater shift of 10–12 cm.$^{-1}$ in the carbonyl absorptions of the [5,2,1] and [5,1,1] ketones might also be due solely to this effect[23] or might be the result of additional contributions from transannular hydrogen bonding, a phenomenon which has been suggested in explanation for certain of the characteristics of cyclooctanone and other medium ring ketones.[20c,21a] Dreiding models[24] do, in fact, show that the flexibility of the [5,1,1] ketone and [5,2,1] ketone is such as to allow hydrogen atoms on the other side of the ring to closely approach the carbonyl group but that in the [4,2,1] ketone this is less likely.

(D) Nuclear Magnetic Resonance Spectra.—The spectral characteristics of the simple ketones from cyclobutanone through cycloöctanone, of the bridged ring ketones (II, VIII, XI), and of the fused ring ketones (XII, XV and 1-keto-bicyclo[5,4,0]undecane) are pictured in Fig. 1 and listed in Table II. Of particular interest are the spectra of cyclobutanone, the [5,1,1]-ketone XI and the [6,1,0]-ketone XII. Cyclobutanone[25] shows a highly detailed spectrum with a triplet (J = 8 c.p.s.) centering at τ = 6.98 and a pentuplet (J = 8 c.p.s.) centering at τ = 8.02. The positions and relative areas of these envelopes are in accord with the assignment of the triplet to the four α-protons (splitting arising from two equivalent β-protons) and of the pentuplet to the two β-protons (splitting arising from four equivalent α-protons). The additional bands in each of the envelopes are assumed to arise from second-order splittings, the cyclobutanone molecule falling in the A_2B_4 (or A_2X_4) category for which a rather large number of bands would be expected.[26] The [5,1,1] ketone shows a trip-

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(21) (a) V. Prelog, *J. Chem. Soc.*, 420 (1950); (b) H. C. Brown, R. S. Fletcher and R. B. Johannesen, THIS JOURNAL, **73**, 5034 (1951); (c) H. C. Brown and M. Borkowski, *ibid.*, **74**, 1894 (1952); (d) H. C. Brown, J. H. Brewster and H. Schechter, *ibid.*, **76**, 467 (1954); (e) H. C. Brown and G. Ham, *ibid.*, **78**, 2735 (1956).

(22) Particularly notorious in this respect are the dissociation constants for cyclohexanone cyanohydrin, the reported values for which are (× 10^4): 5.9,[20e] 9.2,[20a] 10,[20c] 17.6 (present work), 26.5,[20b] 76.[20d] Also in poor agreement are the cyclobutanone cyanohydrin dissociation values: 4.55 × 10^{-2},[20b] 0.87 × 10^{-2} (present work).

(23) N. L. Allinger and S. Greenberg, THIS JOURNAL, **81**, 5733 (1959) have interpreted the changes in carbonyl absorptions in simple cyclic ketones in terms of changes in the C–C–C– angle at the carbonyl group. In a private communication Professor Allinger has expressed his belief that a similar interpretation is probably sufficient for the bridged ring ketones reported in this paper.

(24) A. S. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959). These models are commercially available from the G. M. Instrument Co., P.O. Box 167, Greenville, Illinois.

(25) The spectra of cyclobutanone, cyclopentanone and cyclohexanone at 25 Mc. have been reported by H. Primas, K. Frei and H. H. Gunthard, *Helv. Chim. Acta*, **41**, 35 (1958). The spectrum of cyclohexanone at 40 Mc. has been reported by W. D. Kumler, J. N. Shoolery and F. V. Brutcher, THIS JOURNAL, **80**, 2533 (1958).

(26) *Cf.* J. A. Pople, W. G. Schneider and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, Chapter 6, for a general discussion.

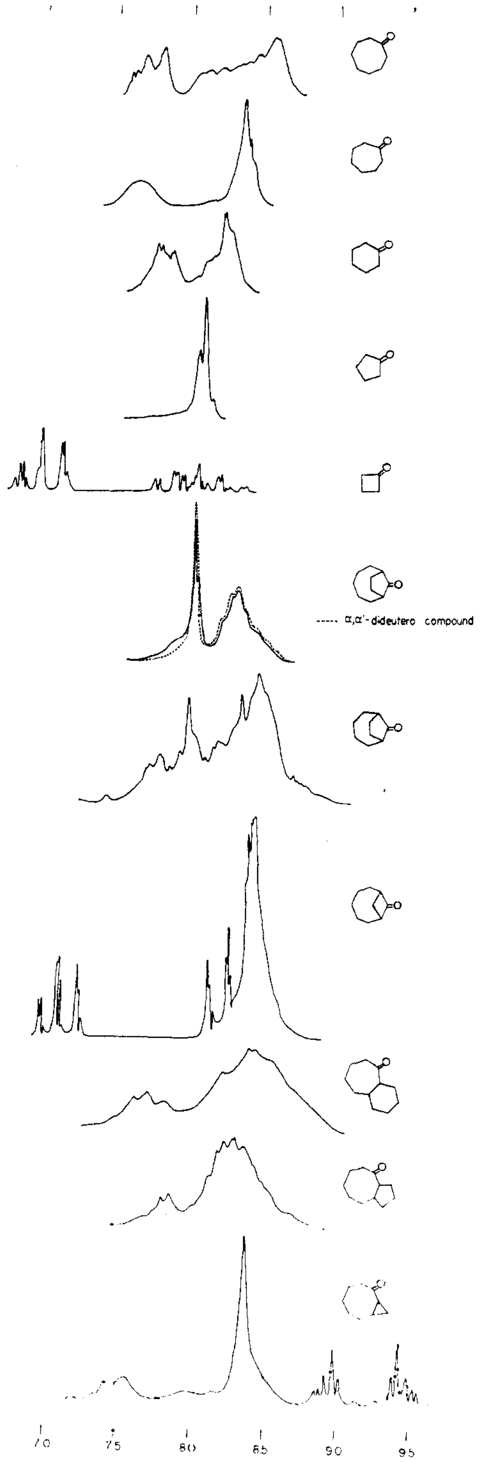

Fig. 1.—Nuclear magnetic resonance spectra.

let (J = 8 c.p.s.) centering at τ = 7.10 assigned to the two α-protons (splitting arising from two equivalent β-protons) and what is almost certainly a triplet (J = 8 c.p.s.) centering at τ = 8.22 assigned to the two β-protons (splitting arising from two equivalent α-protons) but with the high field member of the triplet buried under the band arising from the other proton resonances. Area calculations on the assumption that the resonance centering at τ = 8.22 is a triplet show a ratio of α-protons to β-protons of 0.96. As in cyclobutanone, the additional lines in these two triplets are ascribed to second-order splittings, although in the case of the α-protons additional splitting might also arise from coupling with the protons on the pentamethylene bridge.[27] The cyclobutane protons in the [5,1,1]-ketone comprise an A_2B_2 system[26] and, depending upon the various coupling constants, might show as many as 12 lines in each of the sets of triplets. That fewer lines appear is probably due to the fact that some of the coupling constants are equal (*e.g.*, $J_{\alpha\beta} = J_{\alpha\beta'}$) as is the case with β-propiolactone, the spectrum of which bears some similarity to this one.[28]

The [6,1,0]-ketone XII possesses an n.m.r. spectrum which clearly establishes the presence of protons attached to a cyclopropane ring but whose pattern is difficult to interpret. The set of bands between τ = 8.73 and τ = 9.45 (largest peaks at τ = 8.85 and 9.38) falls in the high field regioh characteristic of cyclopropane protons.[29] Area calculations on several spectra of XII measured at different rf levels show that the protons responsible for these resonances account for about 22% of the total protons, indicating that three (calcd. value 21.4%) rather than four (calcd. value 28.6%) protons give rise to these bands. The fourth proton on the cyclopropane ring, *viz.*, the one α to the carbonyl group, is thought to give rise to the broad band at τ = 7.87 with the two other α-methylene protons resonating at lower field in the region of τ = 7.29 and 7.43. Although the position and the area of the set of bands at τ = 8.73–9.45 is in complete accord with the [6,1,0]-structure, the pattern of these bands closely resembles that expected for an A_2B_2 system.[26] We feel that the present evidence favors the [6,1,0]-structure over alternate structures,[30] but a definitive decision in this regard must await further work.

Rationalization of Ring-enlargement Reactions.—It is an interesting and not easily interpreted fact that cyclohexanone reacts with 1,4-bisdiazobutane to give mainly bridged ring ketone, with 1,5-bisdiazopentane to give mainly fused ring ketone, and with 1,3-bisdiazopropane to give approximately equal amounts of both types of ketones. The product-determining step with respect to these two alternatives occurs in the decomposition of the intermediate (A), migration of CH_2 leading to bridged ring ketone (path a) and migration of

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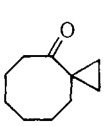
[27] However, bridge-head protons have been observed in other bridged ring systems not to couple strongly with neighboring protons [*cf.* ref. 25 and E. J. Corey, M. Ohmo, S. V. Chow and R. A. Scherrer, THIS JOURNAL, **81**, 6305 (1959)]. Consideration of probable conformations for the [5,1,1]-ketone suggests that the angle between the bridgehead proton and adjacent protons would be in the low coupling constant region [*cf.* M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959)].

[28] W. A. Anderson, *Phys. Rev.*, **102**, 151 (1956).

[29] *Cf.* ref. 26, p. 236.



A

[30] An isomer of XII possessing an A_2B_2 system is compound A. To arrive at such a structure *via* the reactions employed, however, would require novel rearrangements.

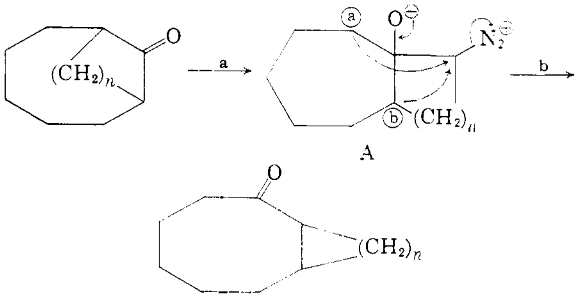
TABLE II

NUCLEAR MAGNETIC RESONANCE DATA[a]

Compound	α-Protons (τ-Values)	Other protons (τ-Values)	Proton ratios		
			Proton types	Calcd.	Obsd.
Cyclobutanone	6.98 (triplet)	8.02 (triplet)	α-H to β-H	2.0	2.02
Cyclopentanone		8.00, 8.05			
Cyclohexanone	7.75 (multiplet)	8.05, 8.18	Other H to α-H	1.5	1.4
Cycloheptanone	7.59	8.34	Other H to α-H	2.0	1.96
Cycloöctanone	7.64 (multiplet)	8.06–8.53	Other H to α-H	2.5	2.2
[5,1,1]-Ketone	7.10 (triplet)	8.22 (triplet),[b] 8.46	Other H to α-H	5.0	5.1
			Cyclobutane α-H to β-H	1.0	0.96[b]
[4,2,1]-Ketone	7.75	8.03, 8.31, 8.43	Other H to α-H	6.0	5.1
[5,2,1]-Ketone	7.86	7.92, 8.22	Other H to α-H	1.67	1.37
[6,1,0]-Ketone	7.29, 7.43, 7.87	8.28, (8.85, 9.38)[c]	Other H to α-H	6.0	6.2
			Other H to α′-H	13.0	10.5
			Other H to β-H of cyclopropane	3.67	3.57
[6,3,0]-Ketone	7.78 (multiplet)	8.22–8.76	Other H to α-H	5.0	4.8
[5,4,0]-Ketone	7.70 (multiplet)	8.14–8.67	Other H to α-H	5.0	3.6

[a] The chemical shifts are expressed in τ-values as defined by G. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958). [b] The right hand member of what is presumed to be a triplet probably lies under the larger band at $\tau = 8.37$. [c] These are the strongest bands in a set extending from $\tau = 8.73$ to $\tau = 9.45$.

bridge head CH leading to fused ring ketone (path b). When $n = 3$ (reaction with 1,5-bisdiazopentane), the intermediate A can easily exist in a *cis-cis*[31] form (two conformations possible), *cis-trans* form (two conformations possible), *trans-cis* form and *trans-trans* form. Of these six structures only one, *viz.*, one of the conformations of the *cis-cis* form, is geometrically suited to backside displacement of N_2 by the CH_2 group (path a), while the remaining forms are geometrically suited to backside displacement of N_2 by the CH group (path b).[5] The *trans-cis* form may, in fact, be the preferred one for steric and electrostatic (attraction between O^- and N_2^+) reasons; it is particularly well constituted for the path b displacement. When $n = 2$ (reaction with 1,4-bisdiazobutane) the intermediate A can exist in a *cis-cis*, *cis-trans*, *trans-cis* and *trans-trans* form, the *trans-cis* form possibly being the preferred one for stereochemical[32] and electrostatic reasons. In this structure the CH_2 and CH groups are equally well situated for backside displacement. The reason for path a being favored is not obvious but may be related to the greater flexibility of a cycloheptane ring as compared with a cyclopentane ring, thus allowing the CH_2 group to be brought into better position for the displacement step. When $n = 1$ (reaction with 1,3-bisdiazopropane) the intermediate A has the same structures available as in the previous case, with the *cis-cis* form possibly the preferred one. In this intermediate, unlike that in the previous case the CH carbon is *ca.* 0.3 Å. closer than the CH_2 carbon to the center of displacement,[21] and this may account for the obtention of fused ring ketone (path b) in addition to bridged ring ketone (path a).



Other Reactions with Bis-diazoalkanes.—The *in situ* reactions of 1,4-bisdiazobutane (from Ib) with cycloheptanone and of 1,6-bisdiazohexane (from Id) with cyclohexanone resulted in the evolution of nitrogen and at least partial consumption of the starting ketone. The resulting mixtures, however, proved to be particularly complex (up to twelve components), and no pure materials have been isolated in either instance. From a study of the vapor phase chromatographic behavior of these mixtures it has been inferred that the bridged ring ketones can be no more than minor constituents. Thus, it appears that for the synthesis of bridged ring ketones the cycloalkanone component cannot be larger than a cyclohexanone, and the bis-diazoalkane component must have a chain length no greater than four atoms. Within this area there are, of course, numerous variations possible, and the more subtle nature of the scope and limitations of this aspect of the reaction provides the basis for further study.

One acyclic ketone, acetone, was subjected to reaction with 1,4-bisdiazobutane (from Ib) and found to yield a mixture which could be separated into 20% of a $C_7H_{12}O$ ketone and 20% of a $C_8H_{16}O_2$ ketone. The C_7-material was identified as 2,5-dimethylcyclopentanone, and the C_8-material has been assigned the structure XVII on the basis of infrared data. A diketone of structure XVIII was not isolated, although it must be presumed to be present at least as a minor component in view of the isolation in 63% yield[3c] of its homolog from the reaction of 1,6-bisdiazohexane and acetone. It is interesting to note that the reaction of 1,4-bisdiazobutane with benzaldehyde is reported to yield 85% of diketone and no phenylcyclopentanone,[3c] a good demonstration of the ability of an aldehyde function to out-compete a ketone function even when the latter has the advantage of intramolecularity.

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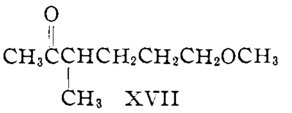
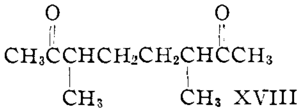
(31) The stereochemical designation refers first to the configuration between the rings and second to the configuration between O^- and N_2^+.

(32) D. C. Ayres and R. A. Raphael, *J. Chem. Soc.*, 1779 (1958).


$CH_3\overset{O}{\overset{\|}{C}}\underset{CH_3}{\underset{|}{C}H}CH_2CH_2CH_2OCH_3$

XVII


$CH_3\overset{O}{\overset{\|}{C}}\underset{CH_3}{\underset{|}{C}H}CH_2CH_2\underset{CH_3}{\underset{|}{C}H}\overset{O}{\overset{\|}{C}}CH_3$

XVIII

Acknowledgment.—In addition to the support acknowledged in footnotes 1 and 2 we also want to express our indebtedness to the National Institutes of Health for a grant (A-2674) to the Department of Chemistry of Washington University which made possible the purchase and maintenance of the nuclear magnetic resonance spectrometer.

Experimental[33-36]

Preparation of Bis-nitrosourethans (I).—Commercial samples of the appropriate diamine[37] were converted to the corresponding urethans by standard procedures.[38]

The di-urethan from 1,3-propanediamine was a solid with m.p. 41.5–43° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_9H_{18}N_2O_4$: C, 49.53; H, 8.31. Found: C, 49.47; H, 8.30.

The di-urethan from 1,5-pentanediamine was a solid with m.p. 66–68° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{11}H_{22}N_2O_4$: C, 53.64; H, 9.00. Found: C, 53.31; H, 8.60.

Nitrosation by standard methods[39] yielded the corresponding bis-nitrosourethans (I) as orange oils in the case of the 1,3-, the 1,5- and the 1,6-compounds and as an orange solid in the case of the 1,4- compound in yields of 88–94% with assay values (*via* nitrogen evolution) of 86–96%. The crude products were used without further purification.

Ring Enlargement Procedure.—Following previously-described procedures for the *in situ* mode of reaction,[7] a three-necked flask equipped with a magnetic stirring device, a dropping funnel, a thermometer reaching nearly to the bottom of the flask, and a gas outlet tube was placed in an ice-bath. The flask was charged with the cycloalkanone, methanol and finely ground potassium carbonate and then cooled to *ca.* 5–10°. The gas outlet tube was connected through a sulfuric acid scrubber to a wet-test meter, and to the cooled and stirred mixture the bis-nitrosourethan, dissolved in chloroform, was added at such a rate as to maintain the temperature below 10° (3–5 hr.). After the reaction was complete, the mixture was stirred an additional 30 min., and the solids were separated by filtration. The filtrate was worked up in the usual way to give a crude product which was placed on an alumina column (Woelm, neutral, activity grade III) and the column then eluted with benzene. The residue from the evaporated eluate was distilled through a 60-cm. Vigreux column, and fractions were collected as noted in the specific examples.

N,N′-Dicarbethoxy-N,N′-dinitroso-1,4-butanediamine (Ib) and Cyclohexanone.—The product from 49 g. (0.5 mole) of cyclohexanone and 145 g. (0.5 mole) of Ib yielded 22.0 g. with b.p. 35–50° (0.1 mm.), 20.0 g. with b.p. 50–53° (0.05 mm.), and 10.5 g. of higher-boiling fraction. The second fraction, which partially solidified, was steam distilled, and 15.2 g. (20%) of **10-ketobicyclo[5,2,1]decane** (II) was obtained from the distillate as a solid with m.p. 90–105°. Further recrystallizations from petroleum ether (b.p. 33–37°) cooled in a Dry Ice–acetone-bath yielded colorless needles, m.p. 113–115° (clear at 120°), $\bar{\nu}_{CCl_4}$ 1731 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.63; H, 10.37.

The 2,4-dinitrophenylhydrazone of II was obtained as red plates after recrystallization from ethanol; m.p. 176–177.5°.

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07. Found: C, 57.53; H, 6.00.

The oxime of II was obtained as colorless needles after recrystallization from ethanol; m.p. 144–144.5°.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25. Found: C, 71.80; H, 10.06.

10-Keto-1,7-dibromobicyclo[5,2,1]decane was obtained as white plates crystallizing from methanol and from ether through the action of a 5% solution of bromine in carbon tetrachloride (10 min. at room temp.); m.p. 134–135°.

Anal. Calcd. for $C_{10}H_{14}Br_2O$: C, 38.71; H, 4.52. Found: C, 39.05; H, 4.77.

Redistillation of the higher-boiling fraction (see above) yielded 2.0 g. (2%) of **2-(γ-methoxypropyl)-cycloheptanone** (VII) as a colorless oil, b.p. 68–69° (0.1 mm.); $\bar{\nu}$ 1708, 1118 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94; OCH_3, 16.85. Found: C, 71.12; H, 10.88; OCH_3, 17.19.

By means of vapor phase chromatography the composition of the crude reaction mixture could be fairly accurately ascertained and by using a preparative size column improved yields of II could be obtained, albeit on a 2–3-g. scale. In a study of the effect of variations in reaction conditions on the yield of II it was found that (a) temperature changes from −15 to 10° had little effect on the yield of II, (b) as the ratio of cyclohexanone to bis-nitrosourethan was changed from 1:1 to 2:1 to 5:1 the yield of II dropped from 52 to 42 to 34%, and (c) as the ratio of methanol to cyclohexanone was changed from 10:1 to 3:1 the yield of II dropped from 52 to 44%. Thus, the optimum conditions for II appear to be a 1:1 ratio of ketone and urethan, a 10:1 ratio of methanol to ketone, and a reaction temperature of 5–10°. The amount of keto ether VII remained relatively constant in all of the experiments cited and was 16 ± 4%. The isolable yield of II that could be achieved by preparative vapor phase chromatography was *ca.* 50%.

Conversion Products from 10-Ketobicyclo[5,2,1]decane. (A) Lactone of 1-Carboxy-4-hydroxycyclononane (III).[40]—Following a published procedure[41] a 6.1-g. sample of II was oxidized with 7.3 g. of trifluoroacetic anhydride and 1.80 ml. of 90% hydrogen peroxide in methylene dichloride solution. Distillation of the crude product (6.45 g.) yielded 4.2 g. (63%) of material with b.p. 98–100° (0.1 mm.) which slowly crystallized; m.p. 85–94°. Recrystallization from petroleum ether (b.p. 63–69°) at Dry Ice temperature gave colorless needles, m.p. 96–98°, $\bar{\nu}_{CCl_4}$ 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; sapon. equiv., 168.0. Found: C, 70.89; H, 9.38; sapon. equiv., 167.9.

(B) 1-Carboxy-4-hydroxycyclononane (IV).[40,42]—A 4.0-g. sample of the lactone III was hydrolyzed with 20 ml. of 1.2 *N* alcoholic sodium hydroxide solution to yield 3.3 g. (76%) of an ivory-colored, waxy solid, m.p. 80–84°. Recrystallization from ethanol yielded pure material as colorless granules, m.p. 86–87.5°.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.68; H, 9.58.

(C) 1-Carboxy-4-ketocyclononane (V).[42]—A 1.0-g. sample of II dissolved in 5 ml. of glacial acetic acid was oxidized for

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[33] All melting points are corrected; all boiling points are uncorrected.

[34] The ultraviolet spectra were obtained on a Beckman model DU spectrophotometer; the infrared spectra were obtained on a Perkin–Elmer model 21 spectrophotometer; the nuclear magnetic resonance spectra were obtained on a Varian Associates spectrometer operating at 56.4 Mc. We are indebted to Mr. T. R. Hughes for the n.m.r. determinations.

[35] Analytical gas chromatographic determinations were carried out in a Perkin–Elmer model 154B instrument containing a 1/4″ × 6′ column packed with fire brick and silicone oil (Dow-Corning no. 710) as the adsorbed phase. Preparative gas chromatographic separations were carried out in a home-made apparatus containing a 1/2″ × 16′ column with the same packing as used in the analytical column. We are deeply indebted to Dr. Robert Barker for his invaluable aid in the construction of the preparative instrument.

[36] Microanalyses were carried out by Micro-tech Laboratories of Skokie, Ill., and by Manser Laboratories of Zürich, Switzerland. Deuterium analyses were carried out by Josef Nemeth of Urbana, Ill.

[37] We are indebted to the American Cyanamid Co. for generous gifts of 1,3-propanediamine and 1,4-butanediamine. 1,5-Pentanediamine was obtained from Columbia Organic Chemicals Co. and 1,6-hexanediamine from Matheson Co.

[38] W. W. Hartman and M. R. Brethen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 278.

[39] W. W. Hartman and R. Phillips, *ibid.*, p. 464.

[40] We are indebted to Mr. J. J. Quarles van Ufford for the investigation of the details of this reaction.

[41] W. D. Emmons and G. B. Lucas, THIS JOURNAL, **77**, 2287 (1955).

[42] We are indebted to Mr. Martin F. Sloan for the investigation of the details of this reaction.

2 hr. at 20° with 0.72 g. of chromium trioxide in 2 ml. of water and 7 ml. of acetic acid. The product was a pasty solid which upon recrystallization from ether–petroleum ether (b.p. 63–69°) gave 0.23 g. of a colorless solid, m.p. 33–35° $\bar{\gamma}$ 1715, 1705 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.81; H, 8.55.

(D) **Cyclononanecarboxanilide** (VI).—Following the general procedure of Cason, *et al.*,[43] a 0.96-g. sample of II was treated with 15 ml. of dry benzene and 1.0 ml. of purified thionyl chloride and was refluxed for 5 hr. The reaction mixture was cooled to 0°, treated with 15 ml. of absolute ethyl alcohol, and refluxed for 1 hr. The distilled product from this reaction ($\bar{\nu}$ 3400 cm.$^{-1}$ for OH and 1725 cm.$^{-1}$ for CO_2Et) was dissolved in 20 ml. of benzene and refluxed for 3 hr. with 1.0 g. of phosphorus pentoxide. Short-path distillation of the product from this treatment yielded 0.42 g. of material ($\bar{\nu}$ 1725 cm.$^{-1}$) which was indicated to be a single entity by vapor phase chromatography. A 0.306-g. sample in the presence of hydrogen and 10% palladium-on-charcoal catalyst absorbed 98% of the theoretical amount of hydrogen for one double bond to yield 0.300 g. of what is presumed to be ethyl cyclononanecarboxylate. This material was hydrolyzed with 15 ml. of 1.2 *N* alcoholic sodium hydroxide, the resulting acid was converted to the acid chloride with thionyl chloride, and the acid chloride was treated with aniline. The material so obtained was taken up in methanol, the solution was decolorized with charcoal, and upon concentration of the solution silvery white plates of cyclononanecarboxanilide deposited. Further recrystallization from methanol yielded pure material, m.p. 140–141° (reported[9] 140–141°).

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45. Found: C, 78.36; H, 9.39.

A mixed m.p. with an authentic sample of cyclononanecarboxanilide showed no depression in m.p., and a comparison of the infrared spectra of the two samples showed them to be identical.[10]

N,N′-Dicarbethoxy-N,N-dinitroso-1,4-butanediamine (Ib) and Cyclopentanone.—The crude product from 16.8 g. (0.2 mole) of cyclopentanone and 58 g. (0.2 mole) of Ib was distilled and 5.5 g. of material boiling up to 65° (0.5 mm.) was collected. Passage through a preparative vapor phase fractometer yielded 2.8 g. (10%) of **9-ketobicyclo[4,2,1]nonane (VIII)** as a colorless solid, m.p. 97–105°. Recrystallization from petroleum ether (b.p. 63–69°) at *ca.* −75° yielded colorless needles, m.p. 109–111°, $\bar{\nu}_{CCl_4}$ 1737 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.48; H, 10.34.

The 2,4-dinitrophenylhydrazone of VIII was obtained as yellow needles after recrystallization from ethanol; m.p. 159–160°.

Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.59; H, 5.70. Found: C, 56.62; H, 5.70.

A second material from the separation in the vapor fractometer was obtained as a colorless oil and is thought to be **2-(γ-methoxypropyl)-cyclohexanone (X)**; $\bar{\nu}$ 1710, 1118 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66; OCH_3, 18.23. Found: C, 70.91; H, 10.49; OCH_3, 17.90.

A careful chromatographic separation of 1.90 g. of crude material on a 32 × 340 mm. column of alumina (Woelm, neutral, activity grade III) yielded 0.40 g. of VIII, 0.32 g. of X and 0.12 g. of a solid which, after several recrystallizations from petroleum ether (b.p. 63–69°), had m.p. 245–260°; $\bar{\nu}$ 1708, 1250, 1105, 1090, 934 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.45; H, 10.15.

Treatment of the last eluates from the column with 2,4-dinitrophenylhydrazine yielded a product which appears to be the mono-2,4-dinitrophenylhydrazone of a $C_{18}H_{28}O_2$ diketone (possibly XII), m.p. 168.5–170°, $\bar{\nu}$ 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{32}N_4O_5$: C, 63.14; H, 7.07. Found: C, 63.32; H, 7.20.

Cycloöctanecarboxamide (IX): (A) From 9-Ketobicyclo-[4,2,1]nonane (VIII).—A 0.5-g. sample of VIII in 10 ml. of dry benzene was added to a suspension of 1 g. of powdered sodium amide in 20 ml. of dry benzene. The mixture was stirred and refluxed for 6 hr. and then worked up in the usual way to yield a crude product from which a solid material was obtained upon trituration with carbon tetrachloride. Recrystallization from aqueous ethanol yielded glistening plates, m.p. 193–196°. A mixed m.p. with authentic cycloöctanecarboxamide showed no depression in m.p.

(B) **From Cycloöctanone**—Following standard procedures[44] cycloöctanone was reduced with lithium aluminum hydride to cycloöctanol, the alcohol was converted to cyclooctyl bromide,[45] and the bromide was transformed to cyclooctanecarboxylic acid *via* carbonation of the Grignard reagent. The amide prepared from this acid had m.p. 192–194° (reported[46] 192–194°).

N,N′-Dicarbethoxy-N,N′-dinitroso-1,3-propanediamine (Ia) and Cyclohexanone:—The crude product from 24.7 g. (0.25 mole) of cyclohexanone and 73.5 g. (0.25 mole) of Ia was distilled, and 8.9 g. of material boiling up to 65° (0.1 mm.) was collected. Passage through a preparative vapor phase fractometer yielded three materials as described below. The first fraction, amounting to 3.1 g. (9%), was an oil and is identified as 8-ketobicyclo[5,1,1]nonane (XI), n^{20}D 1.4733, d^{20} 0.9581, $\bar{\nu}_{CCl_4}$ 1769 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.38. Found: C, 77.89; H, 10.40.

The 2,4-dinitrophenylhydrazone of XI was obtained as fine yellow needles after recrystallization from ethyl acetate–petroleum ether (b.p. 63–69°); m.p. 136–137°.

Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.59; H, 5.70. Found: C, 56.63; H, 5.76.

The semicarbazone of XI was obtained as colorless plates after recrystallization from ethanol; m.p. 215.5–217°.

Anal. Calcd. for $C_{19}H_{17}N_3O$: C, 61.51; H, 8.78. Found: C, 62.03; H, 8.89.

The second fraction, amounting to 3.1 g. (9%), was an oil and is identified as **1-ketobicyclo[6,1,0]nonane (XII)**, n^{20}D 1.4819, d^{20} 0.9834; $\bar{\nu}$ 3050, 2890, 2830, 1690, 1448, 1440, 1420, 1361, 1195, 1150, 1108, 1095, 1070, 1025, 908, 828; λ_{max}^{EtOH} 210 mμ (ϵ 2950).

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.68; H, 10.18.

A 2,4-dinitrophenylhydrazone of XII was obtained as blood-red needles from petroleum ether (b.p. 63–69°); m.p. 113–114°.

Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.59; H, 5.70. Found: C, 56.71; H, 5.79.

The third fraction, amounting to 1.0 g. (2.4%), was an oil which is identified as **2-(β-methoxyethyl)-cycloheptanone (XIII)**, n^{23}D 1.4612; $\bar{\nu}$ 1703, 1118 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66; OCH_3, 18.25. Found: C, 70.19; H, 10.52; OCH_3, 17.44.

From the later eluates of a chromatographic separation of the crude material on alumina a derivative was obtained which is identified as the **mono-2,4-dinitrophenylhydrazone of di-(α-cycloheptanoyl)-methane (XIV)**. It existed as bright yellow needles after recrystallization from ethyl acetate–petroleum ether (b.p. 63–69°), m.p. 173–174.5°, $\bar{\nu}$ 1708 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}N_4O_5$: C, 60.56; H, 6.78. Found: C, 60.55; H, 6.75.

N,N′-Dicarbethoxy-N,N′-dinitroso-1,5-pentanediamine (Ic) and Cyclohexanone.—The crude product from 10.7 g. (0.1 mole) of cyclohexanone and 32.6 g. (0.1 mole) of Ic was distilled, and 6.0 g. of material boiling up to 83° (0.5 mm.) was collected. Passage through a preparative vapor phase fractometer yielded two materials as described below. The first fraction, amounting to 3.7 g. (22%), was an oil and is identified as 1-ketobicyclo[6,3,0]undecane (XV), n^{24}D 1.4933; $\bar{\nu}$ 1700, 1455, 1410 (weak) cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.11; H, 10.88.

The 2,4-dinitrophenylhydrazone of XV was obtained as bright orange plates after recrystallization from ethanol; m.p. 168.5–169.5°.

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Anal. Calcd. for $C_{17}H_{11}N_4O_4$: C, 58.94; H, 6.40. Found: C, 58.88; H, 6.70.

The second fraction, amounting to 0.2 g., was an oil and is identified as **2-(δ-methoxybutyl)-cycloheptanone** (**XVI**); $\bar{\nu}$ 1710, 1118 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.98; H, 11.09.

N,N'-Dicarbethoxy-N,N'-dinitroso-1,4-butanediamine (Ib) and Acetone.—The crude reaction product from 25 ml. (0.34 mole) of acetone and 43.5 g. (0.15 mole) of Ib was distilled to give 5.05 g. of a colorless oil with b.p. up to 58° (30 mm.) and 3.40 g. of a slightly yellow oil boiling up to 56° (0.3 mm.). Vapor phase chromatography of the lower-boiling fraction yielded two components, the first of which amounted to 2.4 g. (14.5%) of a colorless oil which is identified as **2,5-dimethylcyclopentanone**, b.p. 146° (reported[47] 143–144°), $n^{23}D$ 1.4305 (reported[47] 1.4322), $\bar{\nu}$ 1736 cm.$^{-1}$. It formed a 2,4-dinitrophenylhydrazone with m.p. 174–175° (reported[47] 172–172.5°).

Anal. Calcd. for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52. Found: C, 53.26; H, 5.55.

The second component from the lower-boiling fraction amounted to 1.0 g. of a colorless oil identified as **3-methyl-6-methoxyhexanone-2** (**XVII**); $n^{23}D$ 1.4264; $\bar{\nu}$ 1710, 1118 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.87; H, 11.05.

Deuterium Exchange Experiments. (A) **10-Ketobicyclo[5,2,1]decane(II).**—A solution from 1.0 g. of sodium metal in anhydrous methanol was evaporated to dryness. The sodium methoxide residue was added to 1 g. of the ketone mixed with 10 ml. of deuterium oxide (99.8% D_2O). The mixture was refluxed for 12.5 hr. and then worked up to give ketone of m.p. 100–112°. Deuterium analysis indicated this material to have 1.75 atom-equivalents of deuterium.

(B) **9-Ketobicyclo[4,2,1]nonane (VIII).**—A 0.5-g. sample of VIII after treatment with sodium methoxide and deuterium oxide as described above incorporated 0.14 atom-equivalent of deuterium. This small but apparently real deuterium uptake is ascribed to impurities rather than to the [4,2,1]-ketone.

(C) **1-Ketobicyclo[6,3,0]undecane (XV).**—A 0.5-g. sample of XV after treatment with sodium methoxide and deuterium oxide as described above incorporated 2.80 atom-equivalents of deuterium.

Cyanohydrin Equilibrium Constants.—The method of Prelog and Kobelt[20c] was employed for the determination of the hydrogen cyanide present at equilibrium. The ketones were carefully purified by passage through the preparative vapor phase fractometer. The temperature for the establishment of equilibrium was held constant at ±0.1°, and the titrations were carried out at the same temperature. The mixtures were allowed to stand for 24 hr. in the constant temperature bath before titrations were carried out. Several determinations were made with each ketone, and the data reported in Table I are the averaged values with an indication of the extreme values.

Nuclear magnetic resonance spectra were measured with a Varian high resolution spectrometer equipped with a Varian model V4311 fixed frequency rf unit operating at 56.4 Mc. The "side-band" technique employing an audio oscillator equipped with a frequency counter was used to determine the positions of the resonance lines relative to the reference compound. Area measurements were made by graphical means on spectra obtained at sufficiently low rf values to minimize saturation errors. In all cases the measurements were made on solutions containing 10% of the ketone, 89% carbon tetrachloride and 1% tetramethylsilane, the latter serving as the reference material. All of the solutions were thoroughly de-gassed before the spectra were obtained.

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Transannular Interaction between Sulfide and Ketone Groups[1]

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This study has demonstrated the possibility of S–C_{CO} transannular interaction in medium-ring thiaketones by the examination of the properties of a representative compound, 1-thiacycloöctan-5-one (I). The existence of interacted as well as non-interacted conformations of the ring in solution was demonstrated by a study of its infrared spectrum in the 6μ region, while the conformational equilibrium was studied as a function of solvent polarity in a qualitative manner. The charge separation implied in this interaction was emphasized by excitation of the molecules with ultraviolet light, the energy required for the transition (at 226–242 mμ, ε 2400–2800) also being a (linear) function of solvent polarity as measured by the **Z**-parameter. Chemical evidence for the abnormal electron distribution was furnished by the isolation of several bicyclic sulfonium salts (IX, X, XI) formed by transannular reaction. These salts were reversibly dissociated in aqueous solution, and the dissociation constant of one of them (5-hydroxybicyclo[3.3.0]octane-1-thianium perchlorate) was measured (pK_a' 0.2) spectroscopically. The dissociation was also detected by nuclear magnetic resonance spectroscopy. By contrast, the oxygen analog, 1-oxacycloöctan-5-one (II), exhibited no such transannular effects in the infrared spectrum, even though its dipole moment indicated the preponderance of the requisite folded conformation of the ring. It would not form stable transannular salts, but was cleaved easily with hydrochloric acid to 1,7-dichloro-4-heptanone in a reaction which may proceed through such a salt as an intermediate.

A systematic study of transannular interaction between tertiary amino nitrogen and ketone carbonyl in mesocyclic[4] aminoketones and aminoacyloins has led to an understanding of the modification in the properties of these donor–acceptor functional groups and the limitation of N–C_{CO} interaction by steric, electronic and structural factors.[5,6] The prediction was made, in 1954, that transannular S–C_{CO} and O–C_{CO} interaction might be detected in heterocyclic ketones of appropriate size.[7] Preliminary announcements of

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[2] Sinclair Refining Co. Fellow in Organic Chemistry, 1957–1958. Work done under the sponsorship of the Sinclair Research Laboratories, Inc.

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[4] "Mesocycle" is here suggested as a concise descriptive term to serve as a possible alternative to designate a "medium sized ring" (8–11 members).

[5] For the most recent article on transannular N–C_{CO} interaction, see N. J. Leonard, J. A. Adamcik, C. Djerassi and O. Halpern, THIS JOURNAL, **80**, 4858 (1958).

[6] For a review of the subject, see N. J. Leonard, *Rec. Chem. Progress*, **17**, 243 (1956).

[7] N. J. Leonard, R. C. Fox and M. Ōki, THIS JOURNAL, **76**, 5708 (1954).