THE JOURNAL OF **Organic Chemistry**®

Volume 23, Number 1 © Copyright 1958 by the American Chemical Society January 27, 1958

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

Ring Enlargements VI. The Diazomethane-Carbonyl Reaction: Product Ratios from the Reactions of Diazomethane with Various Substituted 2-Phenylcyclohexanons[1]

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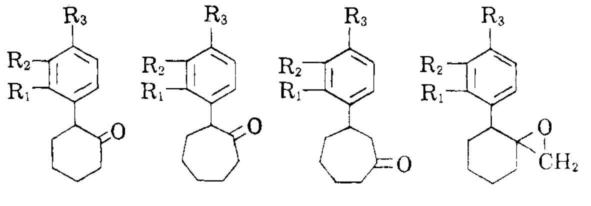
Received July 12, 1957

In a study of the possible electronic influences in the diazomethane-carbonyl reaction, 2-phenylcyclohexanone, 2-(*p*-methoxyphenyl)cyclohexanone, 2-(*p*-methylphenyl)cyclohexanone, 2-(*p*-chlorophenyl)cyclohexanone, and 2-(2',3',4'-trimethoxyphenyl)cyclohexanone were treated with diazomethane, and the resulting mixtures of products were quantitatively assayed. Only minor differences in product ratios were found, however, indicating a rather small effect of the ring substituents on the course of the reaction.

Paper IV of this series[2] was concerned with steric influences in the diazomethane-carbonyl reaction as ascertained from a pair of compounds in which electronic differences are negligible. The present study was intended as a counterpart to paper IV and involves a series of compounds in which steric differences are negligible and electronic differences are introduced. Compounds of the 2-(*p*-R-phenyl)-cyclohexanone type appeared to be suitable for this purpose; various R groups should be able to transmit their electrical influence to the region of the carbonyl group, but changes in R should not change the steric environment around the carbonyl group. Consequently, compounds of this class where R = H, CH_3O, CH_3, and Cl were prepared and subjected to ring enlargement.

The approach employed was similar to the one described in paper IV[2] and involved a quantitative analysis (infrared) of the reaction mixtures resulting from the action of diazomethane (from nitrosomethylurethane) on the various phenylcyclohexanones (I). The pure samples of α-phenylcycloheptanones (II), β-phenylcycloheptanones (III), and oxides (IV) required for the infrared analysis were obtained by isolation from the reaction mixtures in some instances and by independent syntheses in other instances.

Ring enlargement of 2-phenylcyclohexanone (Ia). Although this reaction and the quantitative assay of the product had been described previously,[3] the ring enlargement was repeated by the present authors to check the earlier results (close agreement was observed) and to serve as a reference point for the current investigation.



I II III IV

a, ($R_1 = R_2 = R_3 = H$)
b, ($R_1 = R_2 = H, R_3 = CH_3O$)
c, ($R_1 = R_2 = H, R_3 = CH_3$)
d, ($R_1 = R_2 = H, R_3 = Cl$)
e, ($R_1 = R_2 = R_3 = CH_3O$)

Ring enlargement of 2-(p-methoxyphenyl)cyclohexanone (Ib). From the diazomethane ring enlargement of Ib it was possible to separate, by distillation combined with chromatography, the oxide

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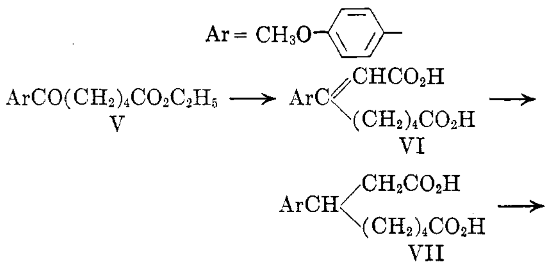
[1] This research was supported, in part, by (a) grant in aid No. G-1886 from the National Science Foundation, (b) grant in aid No. CH-11-A from the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council.

[2] C. D. Gutsche and H. H. Peter, *J. Am. Chem. Soc.*, **77**, 5971 (1955).

[3] C. D. Gutsche, *J. Am. Chem. Soc.*, **71**, 3513 (1949).

(IVb) and the α-ketone (IIb). The β-ketone (IIIb) was prepared by an independent synthesis following the route previously described for the synthesis of IIa.[3] Ethyl δ-(p-methoxybenzoyl)valerate (V) was condensed with ethyl α-bromoacetate, and the resulting product was dehydrated and hydrolyzed to VI. Reduction of VI to VII followed by pyrolysis of the thorium salt of VII yielded the ketone IIIb.



Ring enlargement of 2-(p-methylphenyl)cyclohexanone (Ic). From the diazomethane ring enlargement of Ic it was possible to separate, by distillation and *via* semicarbazone formation, the oxide (IVc) and the β-ketone (IIIc). The α-ketone (IIc) had been prepared previously by the interaction of p-methylphenyldiazomethane with cyclohexanone.[4]

Ring Enlargement of 2-(p-Chlorophenyl)cyclohexanone (Id). From the diazomethane ring enlargement of Id it was possible to separate, by distillation and *via* semicarbazone formation, the oxide (IVd) and the β-ketone (IIId). The α-ketone (IId) was prepared[5] by the interaction of p-chlorophenyldiazomethane with cyclohexanone.

Ring enlargement of 2-(2′,3′,4′-trimethoxyphenyl)-cyclohexanone (Ie). From the diazomethane ring enlargement of Ie it was possible to isolate a pure sample of the β-ketone (IIIe) *via* the semicarbazone. The α-ketone (IIe) was available from previous work,[6] and a sample of the oxide (IVe) was unnecessary because in this instance it was removed prior to analysis.

The ring enlargements, in all cases, were carried out by adding nitrosomethylurethane to a solution of the ketone in 3% methanolic potassium carbonate at 0°. In addition, the ring enlargement of Ia and Ie was also carried out at 25°. The product ratios observed at 0° and 25° were identical, within experimental error, indicating that there is little, if any, temperature dependence. This is in contrast to the situation encountered in the α-decalone series.[2]

Quantitative analysis of ring enlargement mixtures. The crude products (*ca.* quantitative yield) from the reaction of nitrosomethylurethane in methanolic potassium carbonate with the various ketones (I) were subjected to quantitative infrared assay according to well known techniques. As a check on the accuracy of the method, known mixtures containing approximately the amounts of I, II, III, and IV actually formed were assayed in the case of the p-methyl series (c) and the p-chloro series (d). In the p-methyl series the maximum deviation was 2.6% and the average deviation was 1.75%; in the p-chloro series the maximum deviation was 1.5% and the average deviation was 0.8%. Calculations of the results using two different sets of absorption bands in the case of Ia, Ic, and Ie gave values with maximum deviations of 0.5%, 0.9%, and 1.4% respectively, and average deviations of 0.25%, 0.5%, and 1.0%, respectively. Chemical assay for oxide in the case of Ib yielded a value differing by 0.8% from that obtained by infrared assay. On the basis of these experiments it is assumed that the values reported in Table I are accurate to *ca.* ±2 to 3%

TABLE I

	2-Aryl-cyclo-hexanone (I)	2-Aryl-cyclo-heptanone (II)	3-Aryl-cyclo-heptanone (III)	Oxide (IV)	Ratio II/III[a]
Ia	7%	59%	14%	21%	3.6–5.1
Ib	8%	57%	21%	14%	2.4–3.1
Ic	4%	55%	20%	21%	2.4–3.2
Id	8%	45%	20%	26%	1.9–2.6
Ie	13%	40%	28%	18%	1.3–1.6

[a] The range of the values of the II/III ratio in the right hand column is based on a maximum deviation of ±2 in the values for II and III.

Discussion of results. The diazomethane-carbonyl reaction, according to the currently-accepted mechanism,[7] falls in the class of nucleophilic 1,2 rearrangements. In common with reactions of this type, the migrating center is thought to move with its electrons; thus, electron-releasing groups should favor migration and electron-withdrawing groups should hinder migration. A number of examples in the literature appear to support this proposition. Hydroxyacetone, for instance, gives 1-hydroxy-2-ketobutane as the main product,[8] the result of methyl migrating in preference to hydroxymethyl. 2-Chlorocyclohexanone gives 2-chlorocycloheptanone as the main carbonyl product,[9] the result of RCH_2 migrating in preference to RCHCl—. Isatin yields 2,3-dihydroxyquinoline as the main product,[10] the result of o-aminophenyl migrating in preference to —NHC=O. Exceptions are also to be

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(4) C. D. Gutsche and H. E. Johnson, *J. Am. Chem. Soc.*, **77**, 109 (1955).

(5) E. F. Jason, unpublished experiments.

(6) C. D. Gutsche and F. A. Fleming, *J. Am. Chem. Soc.*, **76**, 1771 (1954).

(7) *Cf.* C. D. Gutsche, *Organic Reactions*, Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 364 for a general discussion of the mechanism.

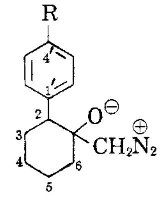
(8) H. Meerwein and G. Hinz, *Ann.*, **484**, 1 (1930).

(9) In paper I of this series[3] it was reported that the product from 2-chlorocyclohexanone and diazomethane consisted of a mixture containing 14% of oxide, 11% of 2-chlorocycloheptanone, and 40% of 3-chlorocycloheptanone. Later experiments have indicated, however, that there is probably little if any 3-chlorocycloheptanone in the products and that what was thought to be this compound is an oxide.

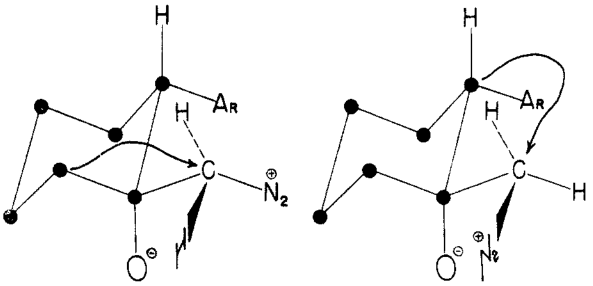
(10) F. Arndt, B. Eistert, and W. Ender, *Ber.*, **62**, 44 (1929); G. Heller, *Ber.*, **52**, 741 (1919); **59**, 704 (1926).

found, however. Camphorquinone, for instance, yields a β-diketone,[11] the result of RC=O migrating in preference to R_2CH—, instead of the expected α-diketone.

The present investigation was undertaken on the premise, based on the dissociation constants of various *p*-substituted benzoic and phenylacetic acids,[12] that the para substituent should be able to transmit its electrical requirements to the region of the carbonyl group and that the methyl and methoxyl groups should be electron-releasing and the chlorine atom electron-withdrawing in this respect. It was, therefore, anticipated that the II/III ratio would increase in the order Ib < Ic < Ia < Id. In actual fact, however, the II/III ratio was not particularly sensitive to changes in R and appeared to increase in the order Id < Ib < Ic < Ia. The following picture for the diazomethane-carbonyl reaction is postulated as a possible interpretation for these observations. The collision of a diazomethane molecule with a phenylcyclohexanone molecule results in the formation of a transient intermediate (written in the charge-separated form VIII) which, we postulate, breaks down to products by an intramolecular backside displacement of nitrogen (by C_2 to form III, by C_6 to form II, by oxygen to form IV). The preference for displacement by C_2, C_6, or oxygen will be determined by (a) the electron-releasing abilities of C_2, C_6, and oxygen, (b) the internal strain of the transition state, (c) the steric and electronic environment around the $CH_2N_2^+$ group. Thus, factors increasing the electron releasing ability of a particular center, factors minimizing the internal strain of a transition state, and factors favoring a particular conformation of the $CH_2N_2^+$ group appropriate to backside displacement of nitrogen should facilitate a given reaction path. In many cases, however, the several factors involved for any particular route operate in opposition rather than in communion. For instance, although the oxygen anion is a strongly electron-releasing center, the transition state (and the final product) involving attack by the oxygen has the high internal strain associated with a three-membered ring, and consequently the oxide is not the major product in many diazomethane-carbonyl reactions. In the case of the formation of ketones II and III factors *a* and *c* may operate in opposition in the following sense. A Stuart-Briegleb model of VIII with the cyclohexane ring in the chair conformation, the phenyl group in an equatorial position, the oxygen in an axial position and the diazomethyl group in an equatorial position shows that there is interference between the diazomethyl group and the phenyl ring in the conformation necessary for C_6 to effect a backside displacement of nitrogen.[13] This effect would operate to decrease the II/III ratio.



VIII



Displacement by $C_6 \longrightarrow$ II Displacement by $C_2 \longrightarrow$ III

In addition to this steric influence on the conformation of the diazomethyl group (an effect which is essentially constant for Ia, Ib, Ic, and Id), there may also be an electrostatic influence. Depending upon the electron-withdrawing or releasing character of the substituent in the 4′ position, the 1′ position of the phenyl ring will become the positive or negative end of a dipole. In the case where it is the negative end (*p*-methyl and *p*-methoxyl), there will be an electrostatic attraction between the 1′-position and the $CH_2N_2^+$ group. In the case where it is the positive end (*p*-chloro) there will be an electrostatic repulsion between the 1′-position and the $CH_2N_2^+$ group. The former situation favors C_6 migration (formation of III). Thus 2-(*p*-chlorophenyl)cyclohexanone according to factor *a* should show a high II/III ratio but according to factor *c*

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[11] H. Rupe and F. Haflinger, *Helv. Chim. Acta*, **23**, 139 (1940); H. Rupe and C. Frey, *Helv. Chim. Acta*, **27**, 627 (1944); T. Isshiki, *J. Pharm. Soc. Japan*, **65**, No. 2A, 10 (1945).

[12] J. F. J. Dippy, *Chem. Revs.*, **25**, 151 (1939) gives the following values ($K_A \times 10^5$) for the dissociation constants: benzoic acid, 4.88; *p*-methoxybenzoic acid, 4.36; *p*-methylbenzoic acid, 4.25; *p*-chlorobenzoic acid, 6.45; phenylacetic acid, 6.27; *p*-methoxyphenylacetic acid, 3.38; *p*-methylphenylacetic acid, 4.26; *p*-chlorophenylacetic acid, 10.52.

[13] D. Y. Curtin and coworkers [*Cf.* D. J. Cram in *Steric Effects in Organic Chemistry*, (ed. by M. S. Newman), John Wiley and Sons, Inc., New York, N. Y., 1956, p. 273 for references] have shown that in various nucleophilic 1,2 rearrangements the conformation of the transition state, not the ground state, is critical in determining the course of the reaction. In the present instance it is assumed that the transition states involved in the conversion of IX to products sufficiently resemble the ground states (*e.g.* IXa and the transition state leading to II) as to allow predictions based on steric conditions in the ground states. Furthermore, it seems reasonable, assuming the reaction to involve the backside displacement of nitrogen, that the transition state leading to II arises from IXa and that the transition state leading to III arises from IXb. Since it is supposed that any equilibrium between these transition states would involve IX as a common intermediate, the relative populations in the transition states would be determined, at least in part, by the relative populations of IX in *a* and *b*.

should show a low II/III ratio; 2-(*p*-methoxyphenyl)cyclohexanone according to factor *a* should show a low II/III ratio but according to factor *c* a high II/III ratio. The failure to observe a significant dependence of the II/III ratio on the *p*-substituent along with the unexpected trend of the II/III ratio may be due to the counterbalancing of these various factors. Efforts are now being directed to a system in which factors *b* and *c* should be relatively insensitive to changes in the *p*-substituent and where the electron-withdrawing or releasing character of the *p*-substituent should have a considerably greater influence on factor *a* than in the present case.

EXPERIMENTAL[14]

Ring enlargement of 2-phenylcyclohexanone (Ia). A 7.0-g. sample (0.04 mole) of 2-phenylcyclohexanone[15] (m.p. 56–58°) was dissolved in 130 ml. of a 3% solution of potassium carbonate in methanol. The solution was cooled to 0°, stirred and treated, over a period of 0.5 hr., with 10.0 g. (0.08 mole) of nitrosomethylurethane. The reaction mixture was kept at 0° and stirred until the nitrogen evolution ceased (*ca.* 1 hr.) after which the volatile components of the mixture were removed under vacuum. The residue was taken up in ether, the ether solution was washed with water and dried, and the ether was evaporated leaving 7.45 g. (99%) of a yellow oil. One portion of the product was assayed for oxide by the method of Swern,[16] and another portion was assayed by quantitative infrared analysis. Still another portion was treated with acetic anhydride and pyridine and refluxed for 1 hr. to convert the oxide to the diacetate. Distillation of the residue gave material which was also assayed by the infrared method.

Ring enlargement of 2-(p-methoxyphenyl)cyclohexanone (Ib): (A) *reaction mixture for quantitative assay.* A 1.5-g. sample of 2-(*p*-methoxyphenyl)-cyclohexanone[17] (m.p. 88–89°) was ring-enlarged as described above to give 1.57 g. (98%) of a yellow oil. (B) *Reaction mixture for isolation of products.* A 19.9-g. sample (0.102 mole) of I-B was dissolved in 120 ml. of methanol containing 1 g. of suspended potassium carbonate, and the mixture was treated with 15.8 g. (0.120 mole) of nitrosomethylurethane, added at 25° over a period of 1 hr. The reaction mixture was then allowed to stand at room temperature for 2 days and worked up to give 21.2 g. (100%) of crude product. Distillation of this material through a 12 inch glass helix packed column yielded, *inter alia*, 1.21 g. with b.p. 137–141° (2 mm.), 2.37 g. with b.p. 150–157° (2 mm.), and 10.46 g. with b.p. 157–163° (2 mm.).

4-(p-Methoxyphenyl)-1-oxaspiro[2,5]octane (IVb). The lowest boiling fraction from the above distillation solidified (m.p. 57–60°) and was recrystallized from aqueous methanol to yield 0.89 g. of the oxide (IVb) as a colorless solid; m.p. 65–66°.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.75; H, 8.13.

A *piperidine hydrochloride derivative of* IVb was prepared by refluxing 0.75 g. of IVb with 1 ml. of piperidine for 3 hr. When a benzene extract of the reaction mixture was shaken with dilute hydrochloric acid, 0.95 g. of a light yellow solid with m.p. 225–231° precipitated. Two recrystallizations from benzene-methanol gave colorless, short needles; m.p. 247–248°.

Anal. Calcd. for $C_{19}H_{30}ClNO_2$: C, 67.13; H, 8.81. Found: C, 67.40; H, 8.88.

2-(p-Methoxyphenyl)cycloheptanone (IIb). A 5-g. sample of the highest-boiling fraction from the above distillation was dissolved in 60 ml. of petroleum ether (b.p. 63–69°) and was passed through a 1.8 × 30 cm. column of activated alumina (Merck chromatographic grade). Elution with petroleum ether (63–69°) yielded the oxide (IVb) in the first fractions and the ketone (IIb) in the last fractions. The ketone was recrystallized from aqueous ethanol and was obtained as colorless prisms; m.p. 59–60° reported 60°,[18] 57–58°.[19] A mixed m.p. with the ketone prepared by an alternate route showed no depression.

2-(p-Methoxyphenyl)-1,6-dicarboxyhexene-1 (VI). A mixture of 79 g. (0.30 mole) of ethyl δ-(*p*-methoxybenzoyl)-valerate (V), 54 g. (0.106 mole) of ethyl α-bromoacetate, 200 ml. of dry, thiophene-free benzene, and 50 ml. of anhydrous ether was added, over a period of 2 hr., to a stirred mixture of 21 g. (0.30 mole) of activated[20] zinc and 0.3 g. of iodine heated on a steam bath.

Following this, three additional 19-g. portions of zinc along with an iodine crystal were added at 0.75 hr. intervals, and three additional 17 g.-portions of ethyl α-bromoacetate were added at 1 hr. intervals. After a final hour of refluxing, the reaction mixture was treated with dilute hydrochloric acid and worked up in the usual manner to yield 106 g. (100%) of a neutral, red oil. This was dehydrated with phosphorus oxychloride according to the method of Lipkin and Stewart[21] to yield 96 g. (96%) of an oily product. Saponification with aqueous-alcoholic sodium hydroxide yielded 67.5 g. (83%) of a solid, m.p. 95–113°, from which there was obtained, after 3 recrystallizations (first from water and then from benzene), 15.6 g. (20%) of colorless needles; m.p. 136–137.5°.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.49; H, 6.33.

2-(p-Methoxyphenyl)-1,6-dicarboxyhexane (VII). A 13.0-g. sample of VI was dissolved in aqueous sodium bicarbonate solution, treated with Raney nickel catalyst, and hydrogenated for 12 hr. at 2–3 atmospheres of pressure. The product consisted of 12.5 g. (95%) of a white solid, m.p. 121–122°, from which colorless needles were obtained after recrystallization from aqueous ethanol; m.p. 121–122°.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.05; H, 7.39.

3-(p-Methoxyphenyl)cycloheptanone (IIIb). Following the method of Ruzicka and Brugger[22] a 12.5-g. sample of VII was converted to the thorium salt and pyrolyzed at 385–395° (1 mm.) for 6 hr. to yield 3.32 g. (34%) of product as a yellow solid; m.p. 38–40°. Crystallization from petroleum ether (b.p. 37–39°) gave 2.5 g. (25.5%) of colorless, broad needles, m.p. 45–46°, which showed no increase in m.p. upon further recrystallization.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.93; H, 8.24.

The semicarbazone of IIIb was obtained as colorless needles after recrystallization from ethanol; m.p. 193–194°.

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(14) All melting points are corrected; all boiling points are uncorrected. The microanalyses were performed by Mr. William Parr and Miss Charlotte Peterson, Washington University.

(15) M. S. Newman and M. D. Farbman, *J. Am. Chem. Soc.*, **66**, 1550 (1944).

(16) D. Swern, T. W. Findley, G. N. Billen, and J. T. Scanlan, *Anal. Chem.*, **19**, 414 (1947). Instead of ether, however, 95% ethanol was used as the solvent.

(17) W. E. Bachmann, G. I. Fujimoto, and L. B. Wick, *J. Am. Chem. Soc.*, **72**, 1995 (1950).

(18) P. Weill, J. Gutmann, and B. Tschoubar, *Compt. rend.*, **201**, 277 (1935).

(19) C. D. Gutsche and H. E. Johnson, *J. Am. Chem. Soc.*, **77**, 109 (1955).

(20) L. F. Fieser and W. S. Johnson, *J. Am. Chem. Soc.*, **62**, 575 (1940).

(21) D. Lipkin and T. D. Stewart, *J. Am. Chem. Soc.*, **61**, 3295 (1939).

(22) L. Ruzicka and W. Brugger, *Helv. Chim. Acta*, **9**, 339 (1926).

Anal. Calcd. for $C_{15}H_{22}N_3O_2$: C, 65.17; H, 8.06. Found: C, 65.34; H, 7.70.

Ring enlargement of 2-(p-methylphenyl)-cyclohexanone (Ic). (A) *Preparation of 2-(p-methylphenyl)cyclohexanone.* Following the general procedure described by Buchmann, Fujimoto, and Wick,[17] the Grignard reagent from *p*-bromotoluene was treated with 2-chlorocyclohexanone. After a reflux period of 2 hr., the reaction mixture was worked up to give a 64% yield of semi-solid material with b.p. 110–120° (0.5 mm.). Two recrystallizations from petroleum ether (b.p. 33–37°) gave 2-(*p*-methylphenyl)cyclohexanone as colorless crystals; m.p. 50–51°.

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.78; H, 8.63.

The *semicarbazone of 2-(p-methylphenyl)cyclohexanone* was obtained, after 3 recrystallizations from ethyl acetate, as colorless crystals; m.p. 163–164°.

Anal. Calcd. for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81. Found: C, 68.72; H, 7.60.

(B) *Ring enlargement of* Ic. A 12.0 g. (0.064 mole) sample of 2-(*p*-methylphenyl)cyclohexanone (m.p. 50–51°) was dissolved in 300 ml. of a 3% solution of potassium carbonate in methanol. The solution was cooled to 0°, treated with 17.0 g. (0.128 mole) of nitrosomethylurethane, and then worked up in the usual way. A small portion of the product was taken for infrared analysis, while an 11-g. portion was distilled through a Piros-Glover spinning band column. The fraction boiling at 88–89° (0.5 mm.) amounted to 1.20 g. and consisted of pure *4-(p-methylphenyl)-1-oxaspiro[2,5]-octane* (IVc); n_D^{25} 1.5353.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.96; H, 9.05.

The *piperidino hydrochloride derivative of* IVc was prepared as described above and was obtained as colorless, fine needles after 2 recrystallizations from benzene containing a few drops of methanol; m.p. 258–259° (dec.).

Anal. Calcd. for $C_{19}H_{30}ClNO$: C, 70.45; H, 9.34. Found: C, 70.21; H, 9.18.

From the crude reaction mixture, *3-(p-methylphenyl)-cycloheptanone* (IIIc) could be isolated *via* its semicarbazone. Cleavage of the semicarbazone with aqueous oxalic acid followed by distillation of the crude product yielded IIIc as a colorless oil; b.p. 110–111° (0.5 mm.), n_D^{30} 1.5336.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.76; H, 9.28.

The *semicarbazone of* IIIc was obtained, after 3 recrystallizations from ethanol, as colorless plates; m.p. 202–203° (dec.).

Anal. Calcd. for $C_{15}H_{21}N_3O$: C, 69.46; H, 8.16. Found: C, 69.34; H, 8.16.

Ring enlargement of 2-(p-chlorophenyl)cyclohexanone (Id). (A) *Preparation of 2-(p-chlorophenyl)-cyclohexanone. p*-Chlorophenylmagnesium iodide, prepared from 66 g. of *p*-iodochlorobenzene, was treated with 34 g. of chlorocyclohexanone in 200 ml. of ether according to the directions of Bachmann *et al.*[17] After removing the ether and adding benzene (*ca.* 500 ml.), the reaction mixture was refluxed overnight. It was then worked up to yield 32.6 g. (61%) of crude product; b.p. 110–120° (0.1 mm.), m.p. 65–70°. Pure *2-(p-chlorophenyl)cyclohexanone* (Id) was obtained after several recrystallizations from petroleum ether (b.p. 63–69°) in the form of colorless plates; m.p. 77–78°.

Anal. Calcd. for $C_{12}H_{13}ClO$: C, 69.06; H, 6.28. Found: C, 68.66; H, 6.14.

The *semicarbazone of* Id was obtained, after 2 recrystallizations from aqueous ethanol, as colorless needles.

Anal. Calcd. for $C_{13}H_{16}ClN_3O$: C, 58.76; H, 6.07. Found: C, 58.98; H, 5.95.

The *2,4-dinitrophenylhydrazone of* Id was obtained, after 3 recrystallizations from ethyl acetate, as yellow-orange needles; m.p. 163–164°.

Anal. Calcd. for $C_{18}H_{17}ClN_4O$: C, 55.60; H, 4.41. Found: C, 55.63; H, 4.31.

(B) *Ring enlargement of* Id. An 18.7 g. (0.09 mole) sample of 2-(*p*-chlorophenyl)cyclohexanone (m.p. 77–78°) in 450 ml. of 3% solution of potassium carbonate in methanol was cooled to 0° and treated with 24 g. (0.18 mole) of nitrosomethylurethane. The product consisted of 19.5 g. (98%) of a yellow oil, part of which was set aside for infrared analysis and part of which was distilled through a Piros-Glover spinning band column. The fraction with b.p. 100–102° (0.5 mm.) solidified and yielded, after 2 recrystallizations from petroleum ether (b.p. 33–37°), colorless blades of *4-(p-chlorophenyl)-1-oxaspiro[2,5]octane* (IVd); m.p. 56–57°.

Anal. Calcd. for $C_{13}H_{15}ClO$: C, 70.11; H, 6.79. Found: C, 70.21; H, 6.94.

The *piperidino hydrochloride derivative of* IVd was prepared as described above and was obtained as colorless needles after 2 recrystallizations from benzene containing a few drops of methanol; m.p. 256–257° (dec.).

Anal. Calcd. for $C_{18}H_{27}Cl_2NO$: C, 62.79; H, 7.96. Found: C, 62.59; H, 7.72.

From the fraction boiling at 119–124° (0.5 mm.) a semicarbazone could be obtained which upon treatment with aqueous oxalic acid followed by distillation of the resulting product yielded *3-(p-chlorophenyl)-cycloheptanone* (IIId). Recrystallization from petroleum ether (b.p. 33–37°) gave IIId as colorless needles; m.p. 47–48°.

Anal. Calcd. for $C_{13}H_{15}ClO$: C, 70.11; H, 6.79. Found: C, 70.01; H, 7.03.

The semicarbazone of IIId was obtained, after 3 recrystallizations from ethanol, as colorless needles; m.p. 202–203° (dec.).

Anal. Calcd. for $C_{14}H_{18}ClN_3O$: C, 60.09; H, 6.49. Found: C, 60.06; H, 6.55.

Ring enlargement of 2-(2′,3′,4′-trimethoxyphenyl)-cyclohexanone (Ie): (A) *Reaction mixture for quantitative assay.* A 2.9-g. sample of 2-(2′,3′,4′-trimethoxyphenyl)cyclohexanone[6] (b.p. 180–190°/0.5 mm.) was ring-enlarged as described above to give 3.0 g. (98%) of a yellow oil.

(B) *Reaction mixture for isolation of products.* A 26.4-g. sample (0.1 mole) of Ie in 260 ml. of 3% methanolic potassium carbonate was treated with 20 g. (0.16 mole) of nitrosomethylurethane. The product, consisting of 26.7 g. (96%) of a yellow oil, was treated with semicarbazide hydrochloride, and 10.7 g. of a sticky semicarbazone was isolated. After several recrystallizations from aqueous ethanol 5.4 g. of colorless product with m.p. 182–183° was obtained.

3-(2′,3′,4′-Trimethoxyphenyl)cycloheptanone (IIIe). Hydrolysis of the semicarbazone described above by means of oxalic acid yielded, after evaporative distillation of the initial oil, 4.15 g. of material with m.p. 43–44°.

Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.85; H, 7.87.

The *semicarbazone of* IIIe (described above) consisted of colorless plates; m.p. 182–183°.

Anal. Calcd. for $C_{17}H_{25}N_3O_4$: C, 60.88; H, 7.51. Found: C, 60.71; H, 7.49.

The *2,4-dinitrophenylhydrazone of* IIIe was obtained as orange prisms after several recrystallizations from ethanol; m.p. 161–162°. A low-melting form, m.p. 146–147°, was also obtained which did not depress the m.p. of the higher-melting form upon admixture.

Anal. Calcd. for $C_{22}H_{26}N_4O_7$: C, 57.63; H, 5.72. Found: C, 57.79; H, 5.57.

Infrared analysis. The quantitative infrared analyses were carried out in carbon disulfide solution in 0.5 mm. thick cells. A Perkin-Elmer Model 21 double beam instrument was used with compensation for the solvent. The methods employed followed well established procedures.[23]

ST. LOUIS, MO.

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(23) *Cf.*, for example, M. G. Mellon, *Analytical Absorption Spectroscopy*, John Wiley and Sons, Inc., New York, N. Y., 1950.