

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

The Mineral Acid-catalyzed Reaction of Cyclohexene with Formaldehyde<sup>1</sup>BY A. T. BLOMQUIST AND JOSEPH WOLINSKY<sup>2</sup>

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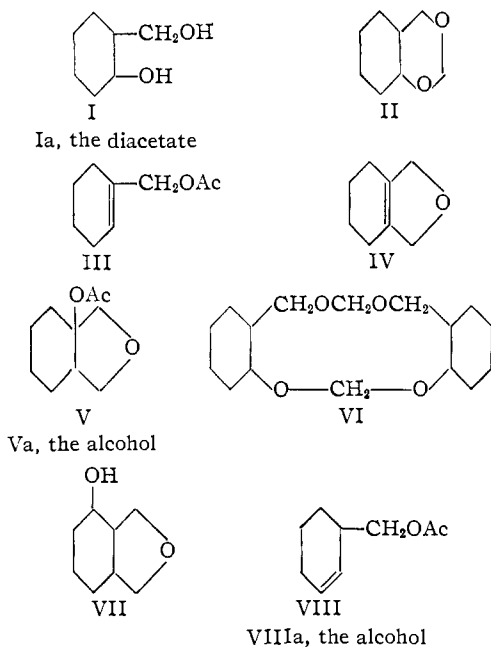
Condensation of cyclohexene with formaldehyde at 50–70° catalyzed by sulfuric acid in solvent acetic acid affords, depending upon the isolation procedure, (1) exclusively *trans*-2-hydroxymethyl-1-cyclohexanol or its acetate and (2) *trans*-4,5-tetramethylene-1,3-dioxane as major products. Minor products comprise (1) 2-cyclohexenemethanol, (2) 3-oxabicyclo[3.3.1]nonane-9-ol or its acetate and (3) *cis*-3-oxabicyclo[4.3.0]-6(7)-nonene. The structure and configuration of all of the products were established by conventional chemical and physical methods.

Complementary to our studies of olefin-formaldehyde condensations,<sup>3</sup> the mineral acid-catalyzed reaction (Prins reaction) of cyclohexene with formaldehyde in solvent acetic acid has been investigated. Literature covering the previous work on this reaction indicated that knowledge of the complex mixture of products formed was rather incomplete and perhaps, in certain instances, incorrect.<sup>4</sup> It seemed desirable, therefore, to examine the reaction in detail and to give particular attention to a complete elucidation of the structure and stereochemistry of the products.

In the most recent study of the Prins reaction of cyclohexene, Olsen<sup>4d</sup> indicated that five compounds result: the diacetate Ia of 2-hydroxymethyl-1-cyclohexanol (I), 4,5-tetramethylene-1,3-dioxane

(II), 1-cyclohexenemethanol acetate (III), 3,4-tetramethylene-2,5-dihydrofuran (IV) and 1-acetoxy-3-oxabicyclo[4.3.0]nonane (V). Hydrolysis of V afforded a compound having m.p. 205° which Matti<sup>4a</sup> had earlier represented as the cyclic formal VI. Olsen first considered it to be the alcohol Va derived from V but later advanced the structure 3-oxabicyclo[4.3.0]nonane-6-ol (VII) for it because of its ease of acetylation.<sup>4f,g</sup> At the same time<sup>4e</sup> Olsen suggested that the product represented as III might be 2-cyclohexenemethanol acetate (VIII). No chemical evidence was given to support these postulations.

In the present study two procedures were followed: A: adding cyclohexene to a slurry of paraformaldehyde in glacial acetic acid-sulfuric acid at 50–70° and isolating the products by direct fractional distillation of the reaction mixture; B: heating a solution of paraformaldehyde in glacial acetic acid-sulfuric acid with cyclohexene just above 50° and isolating the products, by distillation, after a prior methanolysis of the reaction mixture. The major products isolated following procedure A were the *trans* isomer of the diacetate Ia and the *trans* isomer of the dioxane II. The minor products isolated comprised the acetate VIII and 3-oxabicyclo[3.3.1]nonane-9-ol acetate (IX). Procedure B afforded the *trans* isomer of the glycol I as the principal product. The minor products comprised *cis*-3-oxabicyclo[4.3.0]-6(7)-nonene (X), 2-cyclohexenemethanol (VIIIa) and 3-oxabicyclo[3.3.1]nonane-9-ol (IXa).



The evidence most pertinent in establishing the structure and configuration of the various products is presented in the succeeding paragraphs.

***trans*-2-Hydroxymethyl-1-cyclohexanol and its Acetate (I and Ia).**—In order to establish the stereochemical nature of diol I pure samples of *cis*- and *trans*-I were desired. Catalytic hydrogenation of methyl salicylate gave a mixture comprising 80% *cis*- and 20% *trans*-methyl 2-hydroxyl-1-cyclohexanecarboxylate. The corresponding mixture of *cis*- and *trans*-I which resulted upon lithium aluminum hydride reduction of the mixture of esters slowly crystallized on standing. Pure *cis*-I, m.p. 47–49°, was then isolated by recrystallization from ether.

The *trans*-I chosen as a standard was that obtained in low yield by methanolysis of II isolated

(1) The work reported here was done as part of a general research program in organic chemistry at Cornell University sponsored by the B. F. Goodrich Co.

(2) Abstracted from part of the dissertation presented by Joseph Wolinsky in June, 1956, to the Graduate School of Cornell University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) See A. T. Blomquist, J. Verdol, C. L. Adami, J. Wolinsky and D. D. Phillips, THIS JOURNAL, **79**, 4976 (1957).

(4) (a) J. Matti, *Bull. soc. chim. France*, [4] **51**, 974 (1932); (b) Soc. des Usines Chim. Rhone-Poulenc, French Patent 717,912, *Chem. Zentr.*, **103**, II, 771 (1932); (c) C. D. Nenitzescu and V. Przemetsky, *Ber.*, **74**, 676 (1941); (d) S. Olsen and H. Padberg, *Z. Naturforsch.*, **1**, 448 (1946); (e) S. Olsen, *ibid.*, **1**, 671 (1946); (f) S. Olsen, *Angew. Chem.*, **59**, 32 (1947); (g) S. Olsen, *Z. Naturforsch.*, **3b**, 315 (1948); (h) L. A. Mikeska and E. Arundale, U. S. Patent 2,356,683; *C. A.*, **39**, 91 (1945).

from the Prins reaction. This diol cleanly gave bis-*p*-nitrobenzoate and bis-phenylurethan derivatives in essentially quantitative yields. The properties of these derivatives were in accord with those reported in the literature for *trans*-I. Impure samples of *trans*-I were also obtained from 2-hydroxymethyl-1-cyclohexanone by lithium aluminum hydride reduction<sup>5</sup> and catalytic hydrogenation using Adams catalyst in neutral methanol.

The infrared absorption spectrum of *cis*-I, as a melt, was very similar to that of *trans*-I, but there were sufficient differences in the region 8.5–12.0  $\mu$  to detect easily one isomer in the presence of the other. For example, it was easy to ascertain the presence of *cis*-I in the diol, predominantly *trans*-I, formed by lithium aluminum hydride reduction of 2-hydroxymethyl-1-cyclohexanone. Examination of infrared absorption spectra indicated that the diol I obtained from the Prins reaction either by methanolysis of Ia resulting from procedure A or directly by procedure B was exclusively the *trans* isomer.<sup>6</sup> No absorption characteristic of *cis*-I could be detected in any of the spectra. This assignment of the *trans* configuration of I was confirmed by the isolation of solid crystalline derivatives identical with those of known *trans*-I.

Because of the formation of exclusively *trans*-I in the Prins reaction of cyclohexene, it was of interest to ascertain the stability of *cis*-I under the conditions of the reaction. Treatment of pure *cis*-I with acetic acid-sulfuric acid at 50° gave an acetate which afforded pure *cis*-I, m.p. 47–49°, on hydrolysis. Thus *cis*-I is not an intermediate in the formation of the diol I during the Prins reaction.

***trans*-4,5-Tetramethylene-1,3-dioxane (II).**—The low-boiling fractions from procedure A consisted largely of the *trans*-*m*-dioxane II contaminated with appreciable amounts of the acetate VIII. The dioxane II was not found among the products obtained by procedure B. Methanolysis of crude II, using sulfuric acid as a catalyst, gave 15% of pure *trans*-I together with a mixture of the alcohol VIIIa and unchanged II in which VIIIa predominated. Through the use of dibutyltin oxide as a catalyst, the methanolysis of VIII was achieved selectively to give VIIIa. This, VIIIa, was removed by treatment with  $\alpha$ -naphthyl isocyanate, and pure II could then be isolated.

Authentic *cis*- and *trans*-II were synthesized from *cis*- and *trans*-I. A comparison of infrared absorption spectra showed that II from the Prins reaction was identical with synthetic *trans*-II.

**2-Cyclohexenemethanol and its Acetate (VIII and VIIIa).**—The acetate VIII was found in the fractions of II from procedure A and the alcohol VIIIa in the fractions of X from procedure B. Their presence was established by the isolation of solid crystalline derivatives identical with those reported for VIIIa.<sup>3</sup> Further confirmation resulted from observing strong absorption at 14.0  $\mu$ <sup>8</sup>

(5) For a recent study on hydride reductions of substituted cyclohexanones, see W. G. Dauben, G. J. Fonken and D. S. Noyce, *THIS JOURNAL*, **78**, 2579 (1956).

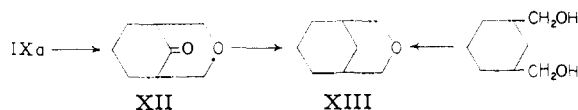
(6) A similar conclusion has been reached by E. Smismann and R. Mode, *ibid.*, **79**, 3447 (1957). We wish to thank Dr. Smismann for the opportunity of seeing his manuscript prior to its submission for publication.

in the infrared spectra of various fractions containing VIII or VIIIa. Absorption maxima around 12.5  $\mu$  were not observed. This indicated the absence of the isomeric alcohol 1-cyclohexenemethanol.<sup>7</sup>

**3-Oxabicyclo[3.3.1]nonane-9-ol and its Acetate (IX and IXa).**—The acetate IX was found in the forerun of diacetate Ia produced by procedure A and the alcohol IXa in the forerun of diol I from procedure B. Hydrolysis of IX afforded the alcohol IXa, m.p. 205°. This high melting alcohol was first described by Matti<sup>4a</sup> who considered it to be VI. Olsen<sup>4d</sup> later demonstrated the correct empirical formula, C<sub>8</sub>H<sub>14</sub>O<sub>2</sub>, and established the presence of one alcohol group. The alcohol could be dehydrated to a "tetrahydrophthalan" and readily formed an acetate derivative. On the basis of this evidence, structure Va was assigned to the alcohol. Windaus<sup>4f</sup> pointed out that the ease of acetylation was inconsistent with this formulation, causing Olsen<sup>4g</sup> to revise it to the secondary alcohol VII. Most of the accumulated data are in accord with VII, but this structure does not explain the high melting point of the alcohol. Furthermore, having demonstrated that 2-cyclohexenemethanol (VIIIa) is formed in the Prins reaction, it was reasonable to assume that it might react further with formaldehyde to give 3-oxabicyclo[3.3.1]nonane-9-ol (IXa). With structures V, VII and IX to consider, it was then necessary to demonstrate which was correct.

The alcohol IXa crystallized beautifully from ether as long needles. It is relatively volatile, subliming on a block at ca. 140°. IXa afforded phenylurethan and  $\alpha$ -naphthylurethan derivatives whose analytical values confirmed the empirical formula C<sub>8</sub>H<sub>14</sub>O<sub>2</sub> for the alcohol. Chromic anhydride in glacial acetic acid transformed IXa into a ketone (XII), m.p. 155°. This ketone was relatively unstable and was best characterized as its semicarbazone and 2,4-dinitrophenylhydrazone derivatives. Formation of a ketone narrowed the possible structures to VII and IXa.

Attempts to prepare the parent heterocycle by removing the alcohol group *via* lithium aluminum hydride reduction of the tosylate derivative or sulfite ester of IXa regenerated the parent alcohol. The sought-after conversion was accomplished by a modified Wolff-Kishner reduction of the ketone XII. There was obtained, in ca. 75% yield, an extremely volatile solid, m.p. 120° (sealed capillary), which was identical in all respects with an authentic sample of 3-oxabicyclo[3.3.1]nonane (XIII). Thus the original alcohol is IXa.

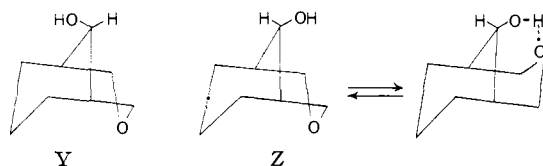


The two possible configurations Y and Z remained to be considered for IXa.

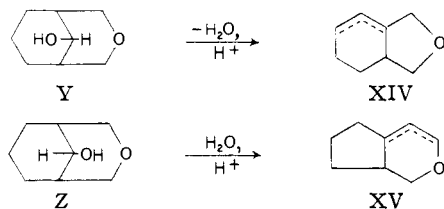
Both chemical and spectral data suggests that IXa possesses the configuration Y. The infrared absorption spectrum of IXa in carbon tetrachloride solution showed an increasingly sharper maximum

(7) We wish to thank Dr. A. S. Dreiding for furnishing the infrared absorption spectrum of authentic 1-cyclohexenemethanol.

at 2.75  $\mu$  as dilution increased. This maximum at 2.75  $\mu$  is characteristic of a free hydroxyl group.<sup>8</sup>



Further, Olsen<sup>4d</sup> demonstrated that IXa can be dehydrated to a "tetrahydrophtalan" which possesses a six-membered carbon ring.<sup>9</sup> Since Wagner-Meerwein shifts are known to be stereospecific with the migrating group *trans* to the departing group,<sup>10</sup> Z should lead to XV and only Y to XIV. For the above reasons IXa must have configuration Y.<sup>11</sup>



**3-Oxabicyclo[4.3.0]-6(7)-nonene (X).**—X was found only among the products obtained by procedure B. It was contaminated with alcohol VIIIa which was removed easily by treatment with  $\alpha$ -naphthyl isocyanate. Catalytic hydrogenation of X afforded *cis*-3-oxabicyclo[3.4.0]nonane (XVIII) whose identity was established by comparison of its infrared absorption spectrum with that of an authentic sample of XVIII. The position of the double bond in X has been tentatively assigned to the 6,7-position on the basis of the presence of a maximum at 14.00  $\mu$  and the absence of a band at *ca.* 12.5  $\mu$  in its infrared absorption spectrum.

### Discussion

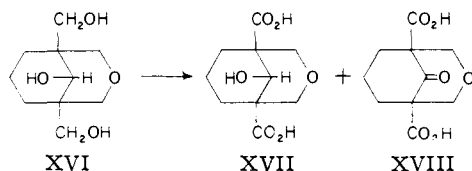
Several investigators have discussed the mechanism of the Prins reaction.<sup>14</sup> It is generally agreed that the first step involves the addition of a

(8) F. A. Smith and E. C. Creitz, *J. Research Natl. Bur. Standards*, **46**, 45 (1951).

(9) S. Olsen, *Ber.*, **81**, 131 (1948).

(10) D. J. Cram, *THIS JOURNAL*, **71**, 3863 (1949).

(11) Several syntheses of IXa were initiated but they were not pursued when the structure became clear. In one attempt XVI was oxidized following the procedure of Mannich.<sup>12</sup> The insoluble material which precipitated from the nitric acid solution was identified as XVII. All attempts to decarboxylate XVII or XVIII failed. XVIII distilled and/or sublimed unchanged at atmospheric pressure.<sup>13</sup>

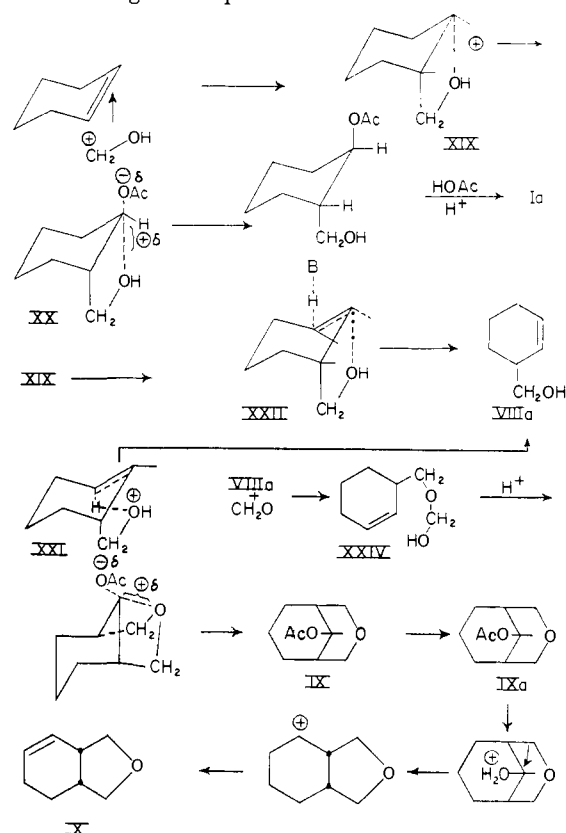


(12) C. Mannich and W. Brose, *Ber.*, **56**, 833 (1923).

(13) A. C. Cope and M. E. Synerholm, *THIS JOURNAL*, **72**, 5228 (1950).

(14) (a) H. J. Prins, *Rec. trav. chim.*, **51**, 469 (1932); (b) C. C. Price "Reactions at Carbon-Carbon Double Bonds," Interscience Publishers, Inc., New York, N. Y., 1946, p. 44; (c) J. W. Baker, *Nature*, **161**, 171 (1948); (d) C. C. Price, *Ind. Eng. Chem.*, **40**, 257 (1948); (e) H. E. Zimmerman and J. English, *THIS JOURNAL*, **76**, 2367 (1953).

proton to a neutral formaldehyde molecule. The polarizable electrons of the carbon-carbon double bond can then interact with this electron-deficient species to give an intermediate which has been variably described as a free carbonium ion<sup>14b-d</sup> or a solvated trimethylene oxide.<sup>14e</sup> The stereospecific *trans* addition of the elements of methylene glycol to cyclohexene argues against a free carbonium ion intermediate but can be accommodated by a solvated carbonium ion in the following manner. A protonated formaldehyde molecule approaches the carbon-carbon double bond promoting the initial energetically favored axial attachment and thus giving rise to the intermediate XIX. The incoming acetate group must then arrive from the backside affording transition state XX which leads exclusively to *trans*-I and Ia. *trans*-II is probably formed in an analogous fashion, except that the oxygen atom of a formaldehyde molecule acts as the incoming nucleophile.



By analogy to a mechanism proposed by Price<sup>14</sup> the formation of VIIIa may proceed *via* intramolecular removal of a proton (intermediate XXI). This mechanism must be very rapid and essentially concerted; otherwise a carbonium ion would have to exist for some finite time. Possibly a more plausible path to VIIIa involves removal of a *quasi-axial* hydrogen in XIX by an anion or solvent molecule *via* the transition state XXII.

IX undoubtedly stems from the interaction of VIIIa with another formaldehyde molecule. A likely intermediate is the hemiformal XXIV which after protonation may arrive at IX through steps similar to those described for the formation of Ia. Finally, X is formed *via* a Wagner-Meerwein de-

hydration of IX. The stereospecificity of this latter reaction would require the formation of *cis*-X.

### Experimental Part<sup>15</sup>

**Acid-catalyzed Reaction of Cyclohexene with Formaldehyde. Procedure A.**—To a stirred mixture of 300 g. (10 moles) of paraformaldehyde, 1150 ml. of glacial acetic acid and 10 ml. of concentrated sulfuric acid at 50° there was added slowly 600 g. (7.32 moles) of cyclohexene. After completion of the addition, the mixture was heated at 70° with stirring for another 2 hr. At the end of this time all the paraformaldehyde had dissolved. The mixture was then dissolved in ether and the resulting solution was washed thoroughly with water and dilute aqueous sodium carbonate solution. Distillation of this solution, after removal of ether and unreacted cyclohexene, gave the following fractions: A-1, 9 g., b.p. 31–72° (24 mm.),  $n_D^{25}$  1.4412; A-2, 17 g., b.p. 73–83° (24 mm.),  $n_D^{25}$  1.4470; A-3, 93 g., b.p. 84–93° (24 mm.),  $n_D^{25}$  1.4650; A-4, 128 g., b.p. 93–94° (24 mm.),  $n_D^{25}$  1.4631; A-5, 13 g., b.p. 75–78° (4–6 mm.),  $n_D^{25}$  1.4631; A-6, 31 g., b.p. 79–98° (3.3–3.5 mm.),  $n_D^{25}$  1.4643; A-7, 32 g., b.p. 98–115° (4.0–4.2 mm.),  $n_D^{25}$  1.4700; A-8, 238 g., b.p. 115–124° (3.8 mm.),  $n_D^{25}$  1.4645.

**Procedure B.**—To a solution of 400 g. (13.3 moles) of paraformaldehyde in 1,800 g. of glacial acetic acid and 25 ml. of concentrated sulfuric acid, 1,000 g. (12.2 moles) of cyclohexene was added at a rate which maintained the reaction temperature above 50°. The mixture was stirred for 2 hr. after completion of the addition. Unreacted starting materials were then removed by direct distillation. This gave 378 g. of cyclohexene, b.p. 75–102°,  $n_D^{25}$  1.410 (after separating a lower layer of  $n_D^{25}$  1.3800) and 876 g. of acetic acid, b.p. 100–107°, having a strong odor of formic acid. Methanol (500 ml.) was added to the residue, and the resulting solution was refluxed under an esterification head which permitted removal of volatile materials and addition of fresh methanol. The refluxing was continued until the distillate comprised pure methanol as indicated by its refractive index. Benzene was added to the mixture which was then distilled to remove all methanol. Distillation of the residue, after washing with aqueous sodium carbonate solution, afforded the following fractions: B-1, b.p. 45–70° (30 mm.); B-2, 115 g., b.p. 89–106° (30 mm.); B-3, 370 g., b.p. 120–130° (1.4–9 mm.). There was ca. 200 g. of a black resinous residue.

**2-Hydroxymethyl-1-cyclohexanol (I). A. The *cis*-Isomer.**—Hydrogenation of 453 g. (3.18 moles) of methyl salicylate in a high pressure apparatus at 140–170° and 2,000 p.s.i. using Raney nickel catalyst afforded 317 g. (68%) of methyl 2-hydroxy-1-cyclohexane-carboxylate, b.p. 103–113° (5–8.5 mm.),  $n_D^{25}$  1.4658, which appeared to be identical with that reported by Connor and Adkins.<sup>16</sup> Reaction of 1 g. of this ester with 1 ml. of hydrazine hydrate gave, after fractional crystallization, 0.18 g. of the *trans*-hydrazide derivative having m.p. 209–211° and 0.83 g. of the *cis*-hydrazide derivative having m.p. 116–117°. The m.p.'s reported in the literature for these are *trans*-hydrazide, m.p. 208°, and *cis*-hydrazide, m.p. 119–120°.<sup>17</sup> The ratio of hydrazides obtained indicates that the saturated hydroxy-ester comprised ca. 80% of the *cis* isomer and 20% of the *trans* isomer.

Reduction of 316 g. (2.13 moles) of the saturated hydroxyester with lithium aluminum hydride (76 g., 2 moles) in ether gave, after the usual work-up, 183 g. (66%) of a viscous liquid having b.p. 110–112° (1.5 mm.),  $n_D^{25}$  1.4878–1.4882. This liquid slowly solidified after standing in the refrigerator for one month. Recrystallization of a portion of this solidified glycol from ether gave pure *cis*-I of m.p. 47–49° (reported<sup>18</sup> m.p. 49–50°).

Using the crude *cis*-I, prior to its solidification, the bis-*p*-nitrobenzoate derivative was prepared. The derivative having m.p. 131–133° was obtained in 70% yield. After re-

crystallization from ethanol-acetic acid, it showed m.p. 133–134° (reported<sup>19</sup> m.p. 134°).

The bis-phenylurethan derivative of *cis*-I was obtained using pure crystalline *cis*-I and had m.p. 147.8–148.2° after several recrystallizations from benzene (reported<sup>20</sup> m.p. 147°).

*Anal.* Calcd. for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>: C, 68.46; H, 6.57. Found: C, 68.31; H, 6.28.

Acetylation of pure *cis*-I with acetic anhydride-pyridine gave *cis*-Ia as a colorless liquid, b.p. 85° (0.4 mm.),  $n_D^{25}$  1.4487,  $d_4^{25}$  1.0645.

*Anal.* Calcd. for C<sub>11</sub>H<sub>16</sub>O<sub>2</sub>: C, 61.66; H, 8.47. Found: C, 61.59, 61.51; H, 8.56, 8.42.

**B. The *trans* Isomer. (1) From the Dioxane V.**—Fractions A-3 and A-4, described earlier under procedure A, were combined, and 136 g. of this was refluxed with 60 ml. of methanol containing 1.5 ml. of concentrated sulfuric acid for several days. Through use of an esterification head, portions of distillate were removed occasionally and fresh methanol added. During the course of methanolysis the reaction mixture changed in color from black to light tan. After washing an ether solution of the reaction mixture with aqueous sodium carbonate solution, it was distilled to give the following fractions: (1) 25.5 g., b.p. 89–93° (28 mm.),  $n_D^{25}$  1.4730; (2) 51.2 g., b.p. 94–101° (30 mm.),  $n_D^{25}$  1.4745; (3) 4 g., b.p. 94–110° (6.8–28 mm.); (4) 20 g., b.p. 115° (3.7–6.8 mm.),  $n_D^{25}$  1.4852. Redistillation of fraction 4 gave *trans*-I showing b.p. 104–105° (0.7 mm.) and  $n_D^{25}$  1.4845.

*Anal.* Calcd. for C<sub>7</sub>H<sub>14</sub>O<sub>2</sub>: C, 64.57; H, 10.84. Found: C, 64.67, 64.58; H, 10.73, 10.70.

The bis-phenylurethan derivative of this *trans*-I as initially obtained from benzene had m.p. 156–159°. After recrystallization from ethanol, it had m.p. 157–159° and when heated to 170°, allowed to cool and resolidify, it showed m.p. 153–154°.

*Anal.* Calcd. for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>: C, 68.46; H, 6.57. Found: C, 68.64, 68.52; H, 6.59, 6.66.

The crude bis-*p*-nitrobenzoate derivative of this *trans*-I had m.p. 96–100° which was raised to 103–104° by recrystallization from ethanol-acetic acid.<sup>19</sup>

*Anal.* Calcd. for C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>: C, 58.88; H, 4.71. Found: C, 58.90, 58.76; H, 4.73, 4.75.

(2) From 2-Hydroxymethyl-1-cyclohexanone.—Reduction of 2.3 g. of 2-hydroxymethyl-1-cyclohexanone with lithium aluminum hydride afforded 2.0 g. of I, b.p. 113–116° (1.4 mm.),  $n_D^{25}$  1.4868. Treatment of 1 g. of this I with *p*-nitrobenzoyl chloride afforded 2.46 g. of a crude bis-*p*-nitrobenzoate, m.p. 97–103° (trace higher). The infrared absorption spectrum of this diol indicated it was largely *trans* but contaminated with some *cis*-I.

Similar results were observed on hydrogenation of 2-hydroxymethyl-1-cyclohexanone with Adams catalyst in methanol. The I obtained gave a quantitative yield of a bis-*p*-nitrobenzoate which on fractional crystallization gave a 20% yield of solid having m.p. 130.5–131.5° (the derivative of *cis*-I). The remainder of the derivative consisted largely of the *trans*-bis-*p*-nitrobenzoate contaminated to a slight extent with the *cis* isomer.

(3) From Procedure A.—Fraction A-8 described under procedure A (238 g.) was redistilled and the diacetate of *trans*-I was obtained which showed b.p. 90–91° (0.8 mm.) and  $n_D^{25}$  1.4600. Transesterification of 39 g. of this diacetate with methanol using dibutyltin oxide as a catalyst gave 18.6 g. of *trans*-I having b.p. 103–107° (1.9 mm.) and  $n_D^{25}$  1.4868. The infrared absorption spectrum of this *trans*-I was identical with that of *trans*-I obtained from the dioxane V. The crude bis-*p*-nitrobenzoate derivative of this *trans*-I had m.p. 99–102°.

(4) From Procedure B.—Fractional distillation of fraction B-3 (370 g.) obtained in procedure B gave the following fractions: C-1, 4 g., b.p. 43–86° (1.0–1.2 mm.); C-2, 25 g., b.p. 85–91° (0.8–1.5 mm.); C-3, 131 g., b.p. 92–105° (1.4–1.7 mm.),  $n_D^{25}$  1.4902; C-4, 202 g., b.p. 105–110° (1.7 mm.),  $n_D^{25}$  1.4850. Redistillation of fraction C-4 gave *trans*-I having b.p. 106° (1.6 mm.) and  $n_D^{25}$  1.4876. This *trans*-I gave a bis-*p*-nitrobenzoate derivative having m.p.

(15) All melting points and boiling points are uncorrected. Infrared absorption spectra were determined using a Perkin-Elmer double beam infrared spectrophotometer, model 21.

(16) R. Connor and H. Adkins, *THIS JOURNAL*, **54**, 4678 (1932).

(17) M. Mousseron and R. Jaquier, *Bull. soc. chim. France*, [5] **17**, 238 (1950); M. Mousseron and M. Canet, *ibid.*, [5] **19**, 190 (1952).

(18) S. Siegel, *THIS JOURNAL*, **75**, 1317 (1953).

(19) M. Mousseron, J. Julien and F. Winternitz, *Bull. soc. chim. France*, [5] **15**, 883 (1948).

(20) H. Gault and E. Streckel, *Compt. rend.*, **207**, 475 (1938).

98–102°. Acetylation of this *trans*-I (10 g.) with acetic anhydride and pyridine gave 14 g. of pure *trans*-diacetate Ia, b.p. 90–91° (0.25 mm.) and  $n_D^{25}$  1.4546.

**4,5-Tetramethylene-1,3-dioxane (II).** A. The *cis* Isomer.—A solution of 23 g. (0.177 mole) of *cis*-I, 45 ml. of 30% formalin and 20 drops of concentrated sulfuric acid was kept at room temperature for three days (two layers after one day). The mixture was extracted with ether, and the ether solution was washed with aqueous sodium carbonate. Distillation, after drying, gave 13.3 g. of crude *cis*-II, b.p. 121–130° (65 mm.), and 10 g. of an extremely viscous liquid, b.p. 174–184° (0.55 mm.).<sup>21</sup>

The *cis*-II showed b.p. 186–188°,  $n_D^{25}$  1.4648 and  $d_4^{25}$  1.0371 after redistillation.

*Anal.* Calcd. for C<sub>8</sub>H<sub>14</sub>O<sub>2</sub>: C, 67.57; H, 9.92. Found: C, 67.87, 67.68; H, 10.11, 9.98.

B. The *trans* Isomer.—(1) Using the method described above 28 g. of *trans*-I was converted into 10.2 g. of crude *trans*-II, b.p. 93–100° (35 mm.). A redistilled sample showed b.p. 102–104° (45 mm.),  $n_D^{25}$  1.4632.

(2) Transesterification of 41 g. of fraction A-3 with methanol and dibutyltin oxide gave a liquid with a camphor-like odor; b.p. 91–97° (30 mm.),  $n_D^{25}$  1.4700–1.4679. Treatment of 25 g. of this product with 15 g. of  $\alpha$ -naphthyl isocyanate at 120° for 15 minutes followed by rapid distillation gave 14.3 g. of a liquid, b.p. 69–84° (10–20 mm.). Redistillation to remove traces of the isocyanate gave a product showing b.p. 90–93° (30 mm.),  $n_D^{25}$  1.4651,  $d_4^{25}$  1.0301.

**Derivatives of 2-Cyclohexenemethanol (VIIIa).**—From the residue obtained by treatment of II with  $\alpha$ -naphthyl isocyanate there was obtained a solid showing m.p. 86–87°. This material did not depress the melting point of an authentic sample of the  $\alpha$ -naphthylurethan derivative of VIIIa.<sup>3</sup>

In a similar manner, a phenylurethan derivative, m.p. 62–63°, was obtained by treatment of crude II with phenyl isocyanate. This derivative was identical with the phenylurethan derivative of authentic VIIIa.<sup>3</sup>

**3-Oxabicyclo[3.3.1]nonane-9-ol (IXa).** A. From Procedure A.—Hydrolysis of a portion of fraction A-7 with methanolic potassium hydroxide gave an oil which deposited a white crystalline solid when its ether solution was cooled in a Dry Ice-bath. Recrystallization from ether afforded beautiful needles, m.p. ca. 205°.

B. From Procedure B.—Fraction B-2 was acetylated and distilled. The intermediate fraction thus obtained, 43 g., b.p. 83–88° (1.4 mm.),  $n_D^{25}$  1.4734, was hydrolyzed with methanolic sodium hydroxide to give 15 g. of IXa.

The phenylurethan derivative of IXa showed m.p. 148.5–151°. After several recrystallizations from hexane the  $\alpha$ -naphthylurethan derivative of IXa melted at 143–144°.

*Anal.* Calcd. for C<sub>10</sub>H<sub>21</sub>NO<sub>2</sub>: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.12; H, 6.88; N, 4.54.

The tosylate derivative of IXa, m.p. 105–106° from benzene-pentane, was obtained in 72% yield by a standard procedure.

*Anal.* Calcd. for C<sub>15</sub>H<sub>20</sub>O<sub>4</sub>S: C, 60.78; H, 6.80. Found: C, 60.34; H, 6.95.

Either adding thionyl chloride to a pyridine solution of IXa or adding IXa to excess of thionyl chloride in pyridine gave the sulfite ester of IXa, m.p. 107.5–108.5° from ether. On standing, this derivative slowly evolved sulfur dioxide.

Lithium aluminum hydride reduction of the tosyl derivative or sulfite ester of IXa gave only the alcohol IXa.

**3-Oxabicyclo[3.3.1]nonane-9-one (XII).**—To 5 g. (0.034 mole) of IXa in 100 ml. of ether was added slowly 5.6 g. (0.056 mole) of chromium trioxide in 75 ml. of glacial acetic acid and 5 ml. of water. After standing overnight water was

added and the resulting mixture was extracted with five 200-ml. portions of ether. The ether solution was dried and the ether removed to give 3.3 g. (67%) of crude ketone. Sublimation gave a waxy solid, m.p. 154–157°. This solid was transformed into a viscous yellow oil on standing for several months.

*Anal.* Calcd. for C<sub>8</sub>H<sub>12</sub>O<sub>2</sub>: C, 68.54; H, 8.63. Found: C, 67.70; H, 8.90.

The yellow-orange 2,4-dinitrophenylhydrazone derivative of the ketone melted at 220–221° after several recrystallizations from ethanol.

*Anal.* Calcd. for C<sub>14</sub>H<sub>16</sub>N<sub>4</sub>O<sub>6</sub>: C, 52.48; H, 5.04; N, 17.51. Found: C, 52.48, 52.49; H, 5.25, 5.17; N, 17.39.

The semicarbazone derivative of XII after recrystallization from aqueous ethanol seemed to begin to decompose at ca. 200° and finally melted at 222°.

*Anal.* Calcd. for C<sub>9</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>: C, 54.80; H, 7.67. Found: C, 54.88, 54.77; H, 7.58, 7.72.

**Modified Wolff-Kishner Reduction of XII.**—A solution of 1 g. (0.0071 mole) of XII and 2.0 g. of hydrazine hydrate in 10 ml. of triethylene glycol was heated at 120–130° for 5 hr. Two grams of potassium hydroxide was added and the temperature was then raised to 180°. A white solid sublimed into the condenser. This substance was dissolved in ether and separated from the small amount of aqueous codistillate. Removal of the ether and sublimation *in vacuo* at room temperature afforded 0.7 g. of a white solid, m.p. ca. 120°. The infrared spectrum of this compound was identical with that of an authentic sample of 3-oxabicyclo[3.3.1]nonane.

**3-Oxabicyclo[3.3.1]nonane.**<sup>23</sup>—A mixture of 2.6 g. of *cis*- and *trans*-1,3-cyclohexanedimethanol and 0.4 ml. of concentrated sulfuric acid was placed in a Woods metal-bath at ca. 200°. A distillate consisting of two layers was obtained. The organic material was extracted with ether. The ether was evaporated and the resulting oil was sublimed *in vacuo* at room temperature to give a waxy solid. This material was resublimed at 100° (atm.) to give a product softening at 100° and melting at 118–120° (sealed capillary) (reported<sup>24</sup> m.p. 113–115°).

**XVII and XVIII.**—2,2,6,6-Tetrakis-(hydroxymethyl)-1-cyclohexanol, 10 g. (0.0455 mole), was cyclized with dry gaseous hydrochloric acid at 150–160° as described by Mannich.<sup>12</sup> The resulting product was not isolated but was oxidized directly with 40 ml. of concentrated nitric acid. On concentration a white solid, m.p. 315°, was deposited. After this material was removed, the filtrate was evaporated to dryness and the residue dissolved in acetone. Addition of benzene gave 2.3 g. of insoluble material. On recrystallization from 1:1 hydrochloric acid, 0.23 g. of solid, m.p. 315–320°, separated at room temperature. Concentration of the mother liquor and cooling afforded 1.8 g. of 3-oxabicyclo[3.3.1]nonane-9-oxo-1,5-dicarboxylic acid, m.p. 219.5–221° (reported<sup>12</sup> m.p. 218°).

The insoluble product obtained above showed m.p. ca. 320° from water. Its infrared spectrum showed a maximum at 3.05  $\mu$ , indicative of a hydroxyl group and a band at 5.95  $\mu$ , characteristic of a carboxyl group.

*Anal.* Calcd. for C<sub>10</sub>H<sub>14</sub>O<sub>6</sub>: C, 52.17; H, 6.13; neut. equiv., 107.5. Found: C, 52.33, 52.29; H, 6.30, 6.30; neut. equiv., 109.

On treatment with acetic anhydride and pyridine the high melting solid gave a compound, m.p. 273–279°, whose infrared spectrum no longer contained an alcohol band at 3.0  $\mu$  but which showed characteristic acetate absorption at 5.79  $\mu$  and carboxyl absorption at 5.95  $\mu$ .

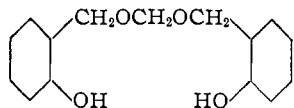
***cis*-3-Oxabicyclo[4.3.0]-6(7)-nonene (X).**—Treatment of 25 g. of fraction B-1 from procedure B with 16 g. of  $\alpha$ -naphthyl isocyanate gave, after removal of  $\alpha$ -naphthylurea, addition of pentane and cooling in the refrigerator, 6.8 g. of a white solid, m.p. 82–83°. This solid was identical with the  $\alpha$ -naphthylurethan derivative of VIIIa. The pentane filtrate was then distilled to give 13.6 g. of a colorless liquid, b.p. 91–96° (45 mm.),  $n_D^{25}$  1.4880. Redistillation gave a pure sample of X, b.p. 83–84° (35 mm.),  $n_D^{25}$  1.4876,  $d_4^{25}$  1.0038.

*Anal.* Calcd. for C<sub>8</sub>H<sub>12</sub>O: C, 77.37; H, 9.74. Found: C, 77.16, 77.44; H, 9.71, 9.93.

(23) This preparation was carried out by Mr. Vincent du Vigneaud, Jr.

(24) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 390 (1953).

(21) The high boiling point of this compound and the presence of hydroxyl group absorption at 3.0  $\mu$  in its infrared spectrum indicate it is probably the dimeric formal.



(22) The infrared spectrum of this *trans*-II had several extraneous peaks which probably were due to the presence of trace amounts (ca. 1%) of X. X had  $n_D^{25}$  1.4876, hence the slightly higher value observed for  $n_D$  here.

Hydrogenation of 3.5 g. of pure X in ethyl acetate using a Parr apparatus and Adams catalyst resulted in the uptake of one equivalent of hydrogen. Distillation afforded 3.0 g. of a liquid, b.p. 172–174°,  $n_D^{25}$  1.4682. The infrared spectrum of this compound was identical with that of an authentic sample of *cis*-3-oxabicyclo[4.3.0]nonane prepared as described below.

To 3 g. of *cis*-1,2-cyclohexenedimethanol, m.p. 40–42°, in 25 ml. of boiling water was added slowly 1.0 ml. of con-

centrated sulfuric acid. The resulting distillate was collected and the organic layer separated. The aqueous layer was extracted with ether. The ether layer was combined with the organic material and this in turn was washed with water and sodium carbonate solution. Distillation afforded 1.0 g. of a liquid, of characteristic camphor-like odor, b.p. 168–170°,  $n_D^{25}$  1.4680.

ITHACA, NEW YORK

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

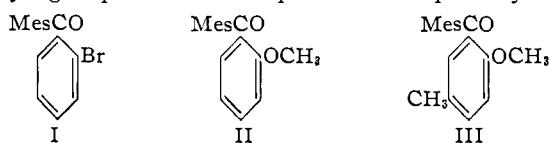
## Duryl 2,6-Disubstituted Phenyl Ketones<sup>1</sup>

BY REYNOLD C. FUSON AND BRUNO VITTIMBERGA

RECEIVED MARCH 30, 1957

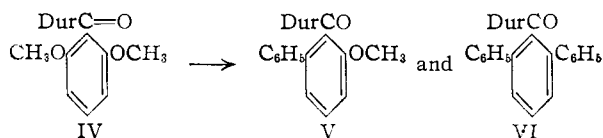
Duryl 2,6-dimethoxyphenyl ketone (IV) has been found to suffer displacement of both methoxyl groups by the action of phenylmagnesium bromide. The resulting duryl 2,6-diphenylphenyl ketone (VI) reacted with the *t*-butyl Grignard reagent to give duryl 4-*t*-butyl-2,6-diphenylphenyl ketone (XI). This same ketone was prepared from the dimethoxy ketone by an alternative route; *t*-butylation at the 4-position was followed by displacement of the methoxyl groups by use of the phenyl reagent.

Diphenylated products have been obtained by the action of phenylmagnesium bromide on mesityl 2-bromophenyl (I), mesityl 2-methoxyphenyl (II) and mesityl 2-methoxy-5-methylphenyl (III) ketones.<sup>2</sup> It seems safe to conclude that a radical that replaces the bromine atom or one of the methoxyl groups enters the position occupied by the



substituent which is replaced. That the second radical occupies the remaining *o*-position might be questioned. If the products are indeed 2,6-diphenylated ketones, the further question arises as to whether the crowding at these positions might deactivate the ring to such a degree that attack by the *t*-butyl reagent at the 4-position would become difficult or impossible. From this point of view, it would be even more interesting to see what effect *t*-butyl groups would exert if they could be introduced into the 2- and 6-positions. The present study was undertaken with the hope of finding answers to these questions.

A logical starting point seemed to be duryl 2,6-dimethoxyphenyl ketone (IV), a compound readily obtainable from duryl chloride and the lithium derivative of the dimethyl ether of resorcinol. It was found to react with the phenyl reagent to give a mixture of the mono-(V) and diphenylated (VI) ketones.



The diphenyl compound was formed also from duryl 2-methoxyphenyl ketone (VII) along with

(1) This investigation was supported in part by a grant from the Office of Ordnance Research, U. S. Army (Contract No. DA-11-022-ORD-874).

(2) R. C. Fuson and S. B. Speck, *THIS JOURNAL*, **64**, 2446 (1942).

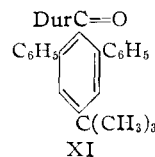
duryl 2-biphenyl ketone (VIII), which was identified by comparison with an authentic sample.<sup>3</sup>

From these results it is apparent that the phenyl radicals in all cases occupy positions *ortho* to the ketone function. Moreover, no example is known of phenylation of a ketone in the *p*-position by the action of a Grignard reagent.

The possibility of introducing a *t*-butyl group into an *o*-position in a similar manner was explored with duryl 2-methoxyphenyl ketone (VII), which was found to undergo *t*-butylation in the *p*-position. The structure of the product (IX) was established by cleavage to the known duryl 4-*t*-butyl-2-hydroxyphenyl ketone. Duryl 2,6-dimethoxyphenyl ketone (IV) likewise was attacked only at the *p*-position; the product was duryl 4-*t*-butyl-2,6-dimethoxyphenyl ketone (X).

The effect of the phenyl groups in the 2- and 6-positions on the reactivity of duryl phenyl ketone was studied by the use of *t*-butylmagnesium chloride, which had shown itself to be especially effective in substitution at the *p*-position. Alkylation occurred at that position to give duryl 4-*t*-butyl-2,6-diphenylphenyl ketone (XI).

An examination of the molecular model of the diphenylated ketone VI reveals that the phenyl groups can lie in positions perpendicular to the plane of the middle ring of the terphenyl system (Fig. 1).



In this perpendicular position, the *o*-substituents offer little if any resistance to the coplanarity of the carbonyl group with the central benzene ring. Indeed, the electronegativity of the phenyl rings in the 2,6-positions might even render the middle ring more sensitive to attack by nucleophilic agents.

It is interesting to consider the possibility that large *o*-substituents such as *t*-butyl groups might

(3) R. C. Fuson and W. S. Friedlander, *ibid.*, **76**, 5782 (1954).