

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

## Polycyclic Compounds Containing Nitrogen. II. Hydroindoles

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Octahydro-5,6-dimethylindole was prepared by reduction of 4-(2-ethoxyethyl)-1,2-dimethyl-5-nitrocyclohexene to 2-(2-ethoxyethyl)-4,5-dimethylcyclohexylamine followed by cyclization. A product which probably contains 2,3,3a,4,7,7a- or 2,3,3a,6,7,7a-hexahydroindole was prepared by a similar method from 4-(2-ethoxyethyl)-2-methoxy-5-nitrocyclohexene. Attempts to prepare the usual derivatives from the products of this latter cyclization were unsuccessful.

A general method for the preparation of substituted cyclohexylamines, by the Diels-Alder reaction of nitroalkenes with dienes, and reduction of the nitrocyclohexenes, has been reported.<sup>3</sup> A study of the conversion of certain of the resulting cyclohexylamines to heterocyclic substances is described in this paper. Similar cyclizations have yielded *cis* and *trans* octahydroindole and 8-azabicyclo[5.3.0]decane.<sup>4,5</sup> The availability of cyclohexylamines such as 2-(2-ethoxyethyl)-4,5-dimethylcyclohexylamine, I, makes possible the preparation of a variety of hydroindoles; substituted 2-(3-ethoxypropyl)cyclohexylamines could also be prepared by the same method and converted into hydroquinolines.<sup>6</sup>

Treatment of 2-(2-ethoxyethyl)-4,5-dimethylcyclohexylamine with hydrobromic acid, followed by cyclization of 2-(2-bromoethyl)-5,6-dimethylcyclohexylamine hydrobromide with dilute sodium hydroxide, gave octahydro-5,6-dimethylindole. The nitrocyclohexene, prepared from a *trans*-1-nitro-1-alkene,<sup>7</sup> would give a hydroindole with a *trans* ring fusion. In a compound derived from 2,3-dimethyl-1,3-butadiene, two additional carbon atoms become asymmetric during catalytic hydrogenation to the cyclohexylamine by the use of a palladium or platinum catalyst in acetic acid. The expected *cis* arrangement of the methyl groups would limit the possible configurations to two racemates. Confirmation of the stereochemical nature of our product has not yet been obtained.

Use of 2-methoxybutadiene in the Diels-Alder process under discussion leads to some interesting compounds. Chart I shows the reactions carried out.

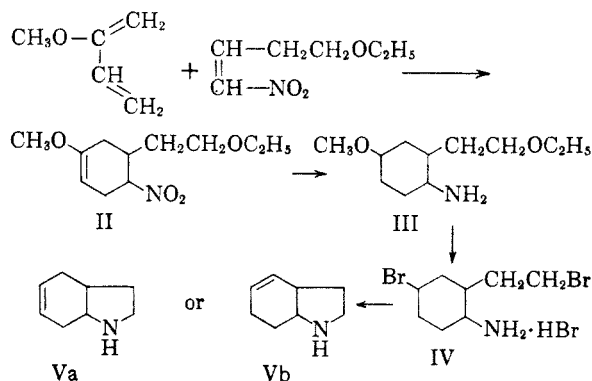


CHART I

The adduct of 2-methoxybutadiene and 4-ethoxy-1-nitrobutene is an enol ether. It was readily converted to 3-(2-ethoxyethyl)-4-nitrocyclohexanone. The carbonyl frequency of the latter was at 1722  $\text{cm}^{-1}$ , while the infrared spectrum of the adduct, II, had strong maxima at 1658  $\text{cm}^{-1}$  ( $\text{C}=\text{C}$ ), and 1178, 1166  $\text{cm}^{-1}$  ( $\text{C}=\text{C}-\text{OR}$ ).<sup>8</sup>

The directive influence of the alkoxy group of the diene<sup>9,10</sup> would cause formation of the adduct shown, II, rather than 4-(2-ethoxyethyl)-1-methoxy-5-nitrocyclohexene. Catalytic hydrogenation of II by the use of palladium in 95% ethanol gave 2-(2-ethoxyethyl)-4-methoxycyclohexylamine, III. Cyclization to a hexahydroindole was carried out by the same reactions used for the ring closure which produced octahydro-5,6-dimethylindole described above.

The product, V, was an intractable oil; derivatives could not be crystallized. Maxima in the infrared spectrum of the amine indicated the presence of a *cis* double bond (677, 1655, and 3030  $\text{cm}^{-1}$ ); the maximum at 3390  $\text{cm}^{-1}$  was assigned to the NH group.<sup>8</sup>

The intermediate 4-bromo-2-(2-bromoethyl)cyclohexylamine hydrobromide, IV, was not identified or purified. Cyclization of the 2-bromoethyl side chain by 0.2N sodium hydroxide would be accompanied by reactions at the 4-bromo group

(1) From the thesis submitted by A. B. Ross in partial fulfillment of the requirements for the Ph.D. degree, University of Maryland, 1957.

(2) Monsanto Chemical Co. Fellow, 1956-57.

(3) N. L. Drake and A. B. Ross, *J. Org. Chem.*, **23**, 717 (1958).

(4) F. E. King, D. M. Bovey, K. G. Mason, and R. L. St. D. Whitehead, *J. Chem. Soc.*, 250 (1953).

(5) V. Prelog and U. Geyer, *Helv. Chim. Acta*, **28**, 576 (1945).

(6) F. E. King, T. Henshall, and R. L. St. D. Whitehead, *J. Chem. Soc.*, 1373 (1948).

(7) E. E. van Tamelen and R. J. Thiede, *J. Am. Chem. Soc.*, **74**, 2615 (1952).

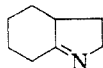
(8) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1954.

(9) H. L. Holmes and K. M. Mann, *J. Am. Chem. Soc.*, **69**, 2000 (1947).

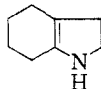
(10) W. C. Wildman, R. B. Wildman, W. T. Norton, and J. B. Fine, *J. Am. Chem. Soc.*, **75**, 1912 (1953).

such as elimination to give the cyclohexene, displacement to give the cyclohexanol, or reaction with an amino group. Elimination was favored<sup>11,12</sup> and the product was formulated as 2,3,3a,4,7,7a-hexahydroindole, Va, or 2,3,3a,6,7,7a-hexahydroindole, Vb; it has proved impossible, thus far, to prepare any of the usual derivatives of this cyclization product with the exception of the chloroplatinate. Benzoyl chloride and *p*-nitrobenzoyl chloride both yielded resinous products which did not crystallize. Both resinous derivatives decolorized bromine in carbon tetrachloride but the addition products, like the starting materials, showed no tendency to crystallize. The picrate also formed a dark red oil which failed to crystallize. A chloroplatinate prepared in ethanol melted with decomposition at 180–181° but could not be successfully recrystallized.

The hexahydroindoles which have been reported have the pyrroline structure, VI<sup>4,12</sup> or VII.<sup>13</sup> Other polycyclic nitrogen compounds, containing



VI



VII

one double bond, could be prepared from adducts of 2-alkoxybutadienes by the method described here.

#### EXPERIMENTAL

Melting points are corrected and were determined with the Hershberg apparatus. Boiling points are uncorrected. We are indebted to Miss M. Kathryn Gerdeman, Dr. Mary Aldridge, and Miss Jane Swan for the microanalyses. The infrared spectra were determined on a Perkin-Elmer infrared spectrophotometer, Model 12-C, and a Beckmann IR-4 double beam infrared spectrophotometer.

*2-(2-Bromoethyl)-4,5-dimethylcyclohexylamine hydrobromide.* Into a 100-ml. flask fitted with a capillary inlet for nitrogen was put 4.83 g. of 2-(2-ethoxyethyl)-4,5-dimethylcyclohexylamine, I;<sup>3</sup> 40 ml. of 68% hydrobromic acid was added. There was a vigorous reaction and the flask became warm. Nitrogen was bubbled through the solution while it was heated in an oil bath at 150° for 3 hr. and then cooled. The reaction mixture was almost solid; filtration gave 6.62 g. (87%) of grey-pink needles. The hydrobromide could not be recrystallized; the crude product melted at 196–197.5°.

The picrate, yellow needles from 50% methanol, melted at 139.5–140°.

*Anal.* Calcd. for C<sub>16</sub>H<sub>26</sub>BrN<sub>4</sub>O<sub>7</sub>: C, 41.48; H, 5.01; N, 12.09. Found: C, 41.85, 41.97; H, 4.85, 4.82; N, 12.73.

*Octahydro-5,6-dimethylindole, IV.* Two liters of 0.1*N* sodium hydroxide was heated to about 50°. A solution of 4.82 g. of 2-(2-bromoethyl)-4,5-dimethylcyclohexylamine hydrobromide in 2 l. of water was added dropwise with stirring over a period of 6.5 hr., while the temperature was maintained at 50°. The solution was then extracted with 500

(11) H. C. Brown, R. S. Fletcher, and R. F. Johannesen, *J. Am. Chem. Soc.*, **73**, 212 (1951).

(12) J. v. Braun and K. Schwarz, *Ann.*, **481**, 56 (1930). W. E. Bachmann and E. J. Fornefeld, *J. Am. Chem. Soc.*, **73**, 51 (1951).

(13) M. Hadano and T. Matsuno, *J. Pharm. Soc. Japan*, **48**, 904 (1924); *Chem. Abstr.*, **23**, 1635 (1929).

ml. of ether in a continuous extractor for 2 days. About 50 ml. of benzene was added to the ether and the solvents were removed at reduced pressure. The residue was an amber oil, 1.50 g. (64%), *n*<sub>D</sub><sup>25</sup> 1.4804.

The picrate, yellow needles from 50% ethanol, melted at 178–179°.

*Anal.* Calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>4</sub>O<sub>7</sub>: C, 50.25; H, 5.80; N, 14.65. Found: C, 50.20, 50.48; H, 5.62, 5.41; N, 14.90, 14.95.

The 3,5-dinitrobenzoyl derivative (prepared by the Schotten-Baumann procedure) crystallized as colorless microneedles from absolute ethanol, m.p. 175.6–176.6°.

*Anal.* Calcd. for C<sub>17</sub>H<sub>21</sub>N<sub>5</sub>O<sub>5</sub>: C, 58.78; H, 6.09. Found: C, 58.85, 58.75; H, 5.66, 5.84. Mol. wt., Calcd.: 347; Found: 346 (Rast).

*4-(2-Ethoxyethyl)-2-methoxy-5-nitrocyclohexene.* The procedure which was used has been described for the preparation of Diels-Alder adducts of nitroalkenes.<sup>3</sup> A solution of 7.0 g. (0.048 mole) of 4-ethoxy-1-nitro-1-butene, 19.8 g. (0.24 mole) of 2-methoxybutadiene, a few mg. of hydroquinone, and 20 ml. of acetonitrile was heated, in a glass liner in a steel bomb, at 100° for 6 hr. Distillation gave 5.7 g. (52%) of adduct, b.p. 124–126° (0.5–1.0 mm.), *n*<sub>D</sub><sup>25</sup> 1.4788. The dark brown residue weighed 4.4 g. The results were similar when the acetonitrile was omitted; a 56% yield of adduct, b.p. 126–128° (0.8 mm.), *n*<sub>D</sub><sup>25</sup> 1.4758, was obtained.

Redistillation gave a pale yellow-green oil, b.p. 137–138° (2 mm.), 82% recovery, *n*<sub>D</sub><sup>20</sup> 1.4782, *d*<sub>4</sub><sup>20</sup> 1.102, *M*<sub>D</sub><sup>20</sup> Calcd.:<sup>14</sup> 59.76. Found: 58.88. The infrared spectrum of a 2.5% solution of the product in carbon tetrachloride showed the following strong maxima (cm.<sup>-1</sup>): 2844 (C—H); 1658 (C=C); 1377 (NO<sub>2</sub>); 1178, 1166 (—C=C—OR); 1117 (C—O—C).

*3-(2-Ethoxyethyl)-4-nitrocyclohexanone.* To a solution of 8.9 g. of II in 20 ml. of 95% ethanol was added 3 ml. of concentrated hydrochloric acid and 4 ml. of water with thorough mixing. After storage in a refrigerator for 3 hr., the mixture was diluted to 100 ml., neutralized with sodium carbonate solution, and extracted with ether. The dried ether extract was evaporated and the product, 8.2 g. (97.5%), was a red-brown oil, *n*<sub>D</sub><sup>25</sup> 1.4728.

The ketone was distilled (b.p. about 116° at 0.8 mm.), with about 80% recovery. A second distillation gave a golden yellow oil, *n*<sub>D</sub><sup>20</sup> 1.4742, *d*<sub>4</sub><sup>20</sup> 1.128, *M*<sub>D</sub><sup>20</sup> Calcd.:<sup>14</sup> 53.75. Found: 53.65.

The infrared spectrum of a 2.5% solution of the product in carbon tetrachloride showed the following strong maxima (cm.<sup>-1</sup>): 2844 (C—H); 1722 (C=O); 1373, 1350 (NO<sub>2</sub>); 1117 (C—O—C).

The thiosemicarbazone was prepared<sup>15</sup>; it crystallized as cream colored needles from 50% ethanol, m.p. 113.5–114°.

*Anal.* Calcd. for C<sub>11</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>S: C, 45.82; H, 6.99; N, 19.43. Found: C, 45.85, 45.84; H, 6.64, 6.75; N, 19.23, 19.38.

*2-(2-Ethoxyethyl)-4-methoxycyclohexylamine.* A solution of 5.35 g. of II in 50 ml. of 95% ethanol was shaken with 2.0 g. of 10% palladium-on-charcoal with hydrogen at atmospheric pressure (25°). Four molar equivalents of hydrogen were absorbed in 2 hr.; the solution was filtered and the solvent removed by distillation at reduced pressure under nitrogen. The product was 4.20 g. of colorless oil, *n*<sub>D</sub><sup>25</sup> 1.4630.

The benzoyl derivative, fine colorless needles from 50% ethanol, melted at 163–163.5°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>27</sub>NO<sub>3</sub>: C, 70.79; H, 8.91; —OR (as OC<sub>2</sub>H<sub>5</sub> + OCH<sub>3</sub>), 24.92. Found: C, 71.13, 71.06; H, 8.89, 9.33; —OR (as OC<sub>2</sub>H<sub>5</sub> + OCH<sub>3</sub>), 24.99, 25.20.

*4-Bromo-2-(2-bromoethyl)cyclohexylamine hydrobromide.* Treatment of 3.65 g. of 2-(2-ethoxyethyl)-4-methoxycyclohexylamine, III, with 50 ml. of 48% hydrobromic acid (b.p. 125–126°), caused warming to about 40°. The mixture was heated in an oil bath at 150° for 1.5 hr. in a nitrogen

(14) A. I. Vogel, W. T. Cresswell, G. F. Jeffrey, and J. Leicester, *Chem. & Ind. (London)*, 358 (1950).

(15) P. P. T. Sah and T. C. Daniels, *Rec. trav. chim.*, **69**, 1545 (1950).

atmosphere and at 100° for 1.5 hr. Crystallization did not occur after cooling; evaporation at reduced pressure under nitrogen left a sticky amber residue which was not purified.

*Attempted cyclization of IV.* A solution of IV in 2 l. of water was added, over a period of 9 hr., to 2.5 l. of 0.2*N* sodium hydroxide at about 50°, with stirring. Continuous extraction of the mixture for 2 days with ether, and evaporation of the ether gave 1.52 g. (68%) of light amber oil,  $n_D^{25}$  1.5059, with a strong amine-like odor.

The product did not react with sodium iodide in acetone or with 2,4-dinitrophenylhydrazine reagent.

The infrared spectrum of a 20% solution of the product in carbon tetrachloride showed the following maxima (cm.<sup>-1</sup>): 3390 (m) NH; 3030 (shoulder) CH=CH; 2960 (s) CH<sub>2</sub> and CH; 1759 (m) CO; 1655 (m) C=C; 1460 (m) CH<sub>2</sub>; 1268 (m), 1163 (m), 1098 (m), 1038 (m), 677 (s), *cis* C=C.

Treatment of the product with benzoyl chloride or *p*-nitrobenzoyl chloride, by the Schotten-Baumann method, gave brown gums which could not be crystallized. Both derivatives decolorized bromine in carbon tetrachloride; the dibromides were also noncrystalline. The picrate was a dark red oil which would not crystallize.

The chloroplatinate, prepared by addition of an excess of chloroplatinic acid in 95% ethanol to the amine, melted at 180–181° with decomposition (preliminary darkening at 170°). Recrystallization could not be effected.

*Anal.* Calcd. for (C<sub>8</sub>H<sub>13</sub>N)<sub>2</sub>H<sub>2</sub>PtCl<sub>6</sub>: C, 29.28; H, 4.30; N, 4.27; Pt, 29.74. Found: C, 30.55; H, 4.59; N, 4.20; Pt, 28.45.

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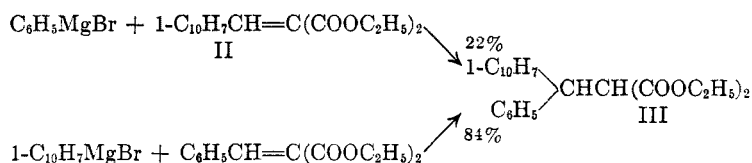
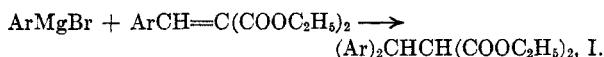
[CONTRIBUTION FROM THE McPHERSON CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

## Some Factors Influencing the 1,4-Addition of Grignard Reagents to Arylidenemalonic Esters

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The 1,4-addition of Grignard reagents to  $\alpha$ ,  $\beta$ -unsaturated esters has long been known.<sup>2</sup> In this laboratory this type of reaction has often been used to build up compounds needed for the synthesis of polycyclic aromatic hydrocarbons.<sup>3</sup> In each case the product was a compound of the symmetrical benzhydryl type, I.



We became interested in the question of whether the yield of type I compound would vary significantly depending on the order of introduction of two different aryl groups. We have found that when phenylmagnesium bromide is added to diethyl 1-naphthylidenemalonate, II, the yield of diethyl phenyl-1-naphthylmalonate, III, is 22%, whereas the addition of 1-naphthylmagnesium bromide to diethyl benzylidenemalonate affords III in 84%

yield.<sup>4</sup> Thus, the yield is significantly better when the Grignard reagent with the larger steric requirement is added to the unsaturated ester with the lesser steric requirement, than in the reverse case. The greater tendency of 1-naphthylmagnesium bromide to add to  $\alpha$ ,  $\beta$ -unsaturated malonic ester is also apparent in the 45–53% yields obtained in the addition to II<sup>5</sup>, whereas the addition of phenylmagnesium bromide to II afforded at most a 22% yield.

In an attempt to account for the erratic yields previously obtained<sup>3c</sup> in the addition of 1-naphthylmagnesium bromide to II, we have found that the addition of excess magnesium bromide solution to the Grignard reagent prior to reaction with II had little effect on the yield. However, when di-1-naphthylmagnesium was used, no addition reaction occurred and II was recovered in 97% yield.

When 1-naphthylmagnesium bromide was added to ethyl 1-naphthylideneacyanoacetate, IV, a 94% yield of ethyl di-1-naphthylmethylcyanoacetate,

(1) The work reported herein was part of a thesis presented by H. R. Flanagan to the Ohio State University, 1956, for the M.S. degree.

(2) The first example was provided by E. P. Kohler, *Am. Chem. J.*, **34**, 132 (1905) who added phenylmagnesium iodide to diethyl benzylidenemalonate.

(3) (a) M. S. Newman and M. Wolf, *J. Am. Chem. Soc.*, **74**, 3225 (1952). (b) M. S. Newman and R. M. Wise, *J. Am. Chem. Soc.*, **78**, 450 (1956). (c) M. S. Newman and D. Lednicer, **78**, 4765 (1956).

(4) Inverse addition, *i.e.* addition of ester to Grignard reagent, was used in all cases since previous work had indicated no difference when direct addition was made. However, the results reported herein were not checked by direct addition experiments.

(5) The yields of diethyl di-1-naphthylmethylmalonate were more consistently in the 45–53% range in the present work than in that reported previously.<sup>3e</sup>