

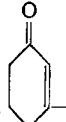
[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

Syntheses with Dihydroresorcinol Mono Ethyl Ether: 3-Alkyl- $\Delta^2$ -cyclohexenones

BY G. FORREST WOODS, PAUL H. GRISWOLD, JR., BERNARD H. ARMBRECHT, DAVID I. BLUMENTHAL AND ROBERT PLAPINGER

We have reported in earlier communications<sup>1</sup> constitutes an excellent procedure for the synthesis on the reaction of dihydroresorcinol and the synthesis of this type of substance.

TABLE I

PHYSICAL AND ANALYTICAL VALUES FOR -R AND ITS DERIVATIVES<sup>2,3,4</sup>

| R  | B. p., °C. (mm.)<br>Yield, % | C/H<br>Calcd. | C/H<br>Found | $n_D$                | 2,4-Dinitro-<br>phenylhydrazones<br>Color, m. p., °C. | C/H<br>Calcd. | C/H<br>Found | Semicarbazone,<br>color, m. p., °C. | C/H<br>Calcd. | C/H<br>Found |
|--|------------------------------|---------------|--------------|----------------------|---|---------------|--------------|-------------------------------------|---------------|--------------|
| CH <sub>3</sub> <sup>2,3</sup>                       | 40 (0.8)                     | 76.32         | 75.93        |                      | Red   | 53.79         | 54.01        | White                               | 57.46         | 57.65        |
|  | 34                           | 9.15          | 9.37         | 1.4945 <sup>20</sup> | 177-178   | 4.86          | 4.92         | 198.5-199.5                         | 7.84          | 7.81         |
| C <sub>2</sub> H <sub>5</sub> <sup>2,4</sup>         | 56-57 (0.8)                  | 77.36         | 77.29        |                      | Red   | 55.26         | 55.22        | White                               | 59.66         | 59.60        |
|  | 75                           | 9.68          | 10.11        | 1.4913 <sup>20</sup> | 159-160   | 5.26          | 5.53         | 185-186                             | 8.28          | 8.71         |
| <i>n</i> -C <sub>3</sub> H <sub>7</sub> <sup>2</sup> | 59-60 (0.4)                  | 78.22         | 78.24        |                      | Red   | 56.57         | 56.64        | White                               | 61.50         | 61.10        |
|  | 75                           | 10.21         | 10.27        | 1.4876 <sup>25</sup> | 156   | 5.70          | 5.94         | 174-175                             | 8.77          | 8.68         |
| <i>i</i> -C <sub>3</sub> H <sub>7</sub> <sup>2</sup> | 59-60 (0.3)                  | 78.22         | 77.84        |                      | Red   | 56.57         | 56.75        | White                               | 61.5          | 61.14        |
|  | 12                           | 10.21         | 10.45        | 1.4842               | 154.4-155.5   | 5.70          | 5.69         | 179-179.5                           | 8.78          | 9.03         |
| <i>n</i> -C <sub>4</sub> H <sub>9</sub> <sup>2</sup> | 82-89 (0.3)                  | 78.89         | 78.45        |                      | Red   | 57.82         | 57.91        | White                               | 63.12         | 63.02        |
|  | 85                           | 10.59         | 10.93        | 1.4865 <sup>25</sup> | 105-106   | 6.07          | 6.02         | 175-176                             | 9.15          | 9.34         |
| <i>i</i> -C <sub>4</sub> H <sub>9</sub>              | 83-84 (1-1.5)                | 78.89         | 78.10        |                      | Red   | 57.82         | 57.81        | White                               | 63.12         | 62.91        |
|  | 43                           | 10.59         | 10.67        | 1.4840 <sup>25</sup> | 123-124   | 6.07          | 6.22         | 179-181                             | 9.15          | 9.38         |
| <i>s</i> -C <sub>4</sub> H <sub>9</sub>              | 57-58 (0.3)                  | 78.89         | 78.50        |                      | Red   | 57.82         | 57.58        | White                               | 63.12         | 63.33        |
|  | 15                           | 10.59         | 10.67        | 1.4948 <sup>25</sup> | 115-116   | 6.07          | 6.24         | 148-149                             | 9.15          | 9.25         |
| <i>t</i> -C <sub>4</sub> H <sub>9</sub>              | 70 (0.3)                     | 78.89         | 78.63        |                      | Red   | 57.82         | 57.53        | White                               | 63.12         | 62.99        |
|  | 13                           | 10.59         | 10.75        | 1.4875 <sup>25</sup> | 167-168   | 6.07          | 6.35         | 214-215                             | 9.15          | 9.30         |

mono ethyl ether of dihydroresorcinol with aryl-metallic reagents. The former reaction was shown to be very complex while the latter proceeded normally. This paper is a report of the behavior of these two substances in their reaction with alkylmagnesium halides.

The mono ethyl ether of dihydroresorcinol reacts with alkylmagnesium halides as shown by the equations

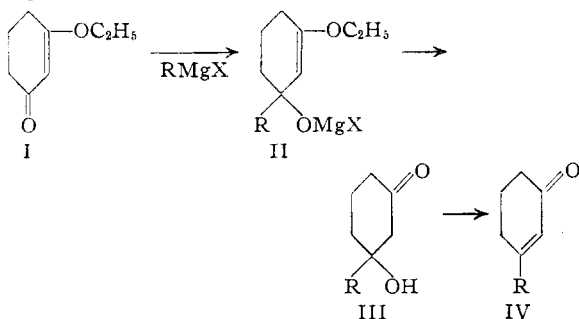


Table I contains the list of 3-alkyl- $\Delta^2$ -cyclohexenones and data related to them which have been obtained where R has been varied from methyl to the *t*-butyl group. This method of preparation thus

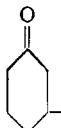
(1) (a) Woods and Tucker, *THIS JOURNAL*, **70**, 2174 (1948); (b) Woods and Tucker, *ibid.*, **70**, 3340 (1948); (c) Woods and Reed, *ibid.*, **71**, 1348 (1949).

(2) Mousseron and Winternitz, (*Bull. Soc. Chim.*, **12**, 71 (1945)) have reported a general method of synthesis of this type of compound. 2-Alkyl-cyclohexadiene-1,3 is prepared by the addition of bromine to the appropriate 1-alkylcyclohexene-1 followed by dehydrohalogenation with sodium ethoxide. Addition of hydrogen chloride reportedly yields predominately 1-chloro-3-alkylcyclohexene-2. 3-Alkyl- $\Delta^2$ -cyclohexenones were obtained by the simultaneous hydrolysis and oxidation of the chloro compound. No data are reported for the ketones which apparently were not isolated as such but of which the semicarbazones were prepared. The melting points of these were: methyl 199-201°; ethyl 240°; *n*-propyl 162-163°; *i*-propyl 177-178°; *n*-butyl, 166-167°.

(3) 3-Methyl- $\Delta^2$ -cyclohexenone has been prepared among various procedures by (a) pyrolysis of the polymer of methyl vinyl ketone [b. p. 68-71° (3 mm.)  $n_D^{20}$  1.4940; m. p. of 2,4-dinitrophenylhydrazones 172.5-173°; m. p. of semicarbazone 201-201.2°], Marvel and Levesque, *THIS JOURNAL*, **60**, 280 (1938); (b) treating ethyl  $\alpha$ -(3-chloro-crotyl) acetoacetate with concentrated sulfuric acid [b. p. 74-75° (7 mm.),  $n_D^{20}$  1.4946; m. p. of semicarbazone 191-192°], Wichterle, Prochazka and Hofman, *C. A.*, **42**, 8162 (1948); (c) treating 2-chloro-2-heptene-6-one with 85% sulfuric acid [b. p. 61-64° (8 mm.),  $n_D^{20}$  1.4935; m. p. of semicarbazone 193-196°], Tatevosyan, Melikyan and Tuteryan, *C. A.*, **40**, 2802 (1946); (d) alkaline condensation of heptandione-2,6 [( $n_D^{20}$ ) 1.4930; m. p. of semicarbazone 199-200°]. Harries, *Ber.*, **71**, 748 (1914).

(4) 3-Ethyl- $\Delta^2$ -cyclohexenone has been prepared by (a) condensation of ethyl  $\alpha$ -(pentanone-3)-acetoacetate with dry hydrogen chloride followed by decarboxylation of the ethyl-4-ethyl- $\Delta^2$ -cyclohexenone-2-carboxylate-1 with 25% sulfuric acid [b. p. 83° (8 mm.) m. p. of semicarbazone 240° (dec.)], Blaise and Maire, *C. A.*, **2**, 1825 (1908) (b) condensation of 3-chloro- $\Delta^2$ -cyclohexenone-1 with ethyl sodiomethylmalonate followed by decarboxylation with acid [b. p. 73-75° (1-2 mm.) m. p. of semicarbazone 191-192°; m. p. of 2,4-dinitrophenylhydrazones 133-134°], Clemons, Cocker and Hornsby, *J. Chem. Soc.*, 616 (1946).

TABLE II


 PHYSICAL AND ANALYTICAL VALUES FOR  $\text{---R}$  AND ITS DERIVATIVES<sup>5,6,7,8</sup>

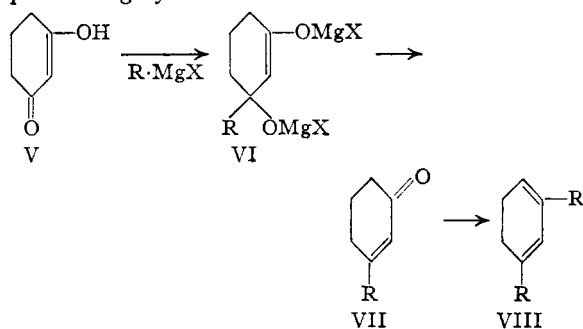
| R  | B. p., °C.<br>(mm.) | C/H    |       | n <sub>D</sub>       | 2,4-Dinitro-<br>phenylhydrazone,<br>color, m. p., °C. | C/H    |       | Semicarbazone,<br>color, m. p., °C. | C/H    |       |
|--|---------------------|--------|-------|----------------------|---|--------|-------|-------------------------------------|--------|-------|
|  |                     | Calcd. | Found |                      |   | Calcd. | Found |                                     | Calcd. | Found |
| CH <sub>3</sub> <sup>5</sup>                 | 93 (15)             | 74.95  | 74.82 |                      | Yellow  | 53.42  | 53.67 | White                               | 56.78  | 56.85 |
|  |                     | 10.78  | 10.87 | 1.4446               | 146-147   | 5.52   | 5.50  | 184-185                             | 8.94   | 9.03  |
| C <sub>2</sub> H <sub>5</sub> <sup>6</sup>   | 38-41 (0.8)         | 76.13  | 75.70 |                      | Yellow  | 55.00  | 55.27 | White                               | 59.02  | 59.21 |
|  |                     | 11.18  | 10.90 | 1.4537 <sup>20</sup> | 139   | 5.88   | 5.96  | 173.5-174.5                         | 9.30   | 9.29  |
| n-C <sub>3</sub> H <sub>7</sub>              | 41-42 (0.7)         | 77.11  | 76.76 |                      | Yellow  | 56.24  | 56.07 | White                               | 60.87  | 60.50 |
|  |                     | 11.50  | 11.50 | 1.4530 <sup>20</sup> | 143-144   | 6.29   | 6.38  | 168-169                             | 9.71   | 9.66  |
| i-C <sub>3</sub> H <sub>7</sub> <sup>7</sup> | 50-51 (1)           | 77.11  | 77.56 |                      | Yellow  | 56.24  | 56.18 | White                               | 60.87  | 60.58 |
|  |                     | 11.50  | 11.87 | 1.4540 <sup>20</sup> | 139-140   | 6.29   | 6.39  | 194.5-195                           | 9.71   | 9.38  |
| n-C <sub>4</sub> H <sub>9</sub>              | 64-66 (0.4)         | 77.86  | 76.33 |                      | Yellow  | 57.47  | 57.41 | White                               | 62.52  | 62.04 |
|  |                     | 11.76  | 11.58 | 1.4535 <sup>25</sup> | 121-121.5   | 6.63   | 6.72  | 163-163.5                           | 10.02  | 10.12 |
| i-C <sub>4</sub> H <sub>9</sub>              | 50-55 (0.2)         | 77.86  | 77.95 |                      | Yellow  | 57.47  | 57.51 | White                               | 62.52  | 62.21 |
|  |                     | 11.76  | 12.02 | 1.4525 <sup>25</sup> | 125-126.5   | 6.63   | 6.85  | 176-177                             | 10.02  | 9.86  |
| t-C <sub>4</sub> H <sub>9</sub> <sup>8</sup> | 56 (0.3)            | 77.86  | 78.06 |                      | Yellow-orange   | 57.47  | 57.21 | White                               | 62.52  | 62.52 |
|  |                     | 11.76  | 11.94 |                      | 127-128   | 6.63   | 6.77  | 195-196                             | 10.02  | 10.12 |

Several of the 3-alkyl- $\Delta^2$ -cyclohexenones were reduced to the corresponding 3-alkylcyclohexanones by catalytic hydrogenation generally with palladinized charcoal, at atmospheric pressure and room temperature. The yields of these reductions were essentially quantitative. Table II contains the data pertinent to these substances.

The yields of the 3-alkyl- $\Delta^2$ -cyclohexenones as observed in Table I are rather normal in the sense that increasing complexity of the Grignard reagents leads to lower yields of normal products. The notable exception to the preceding is the surprisingly low yield of 3-methyl- $\Delta^2$ -cyclohexenone which we were unable to increase by varying any and all the conditions of the reaction of the Grig-

nard reagent (CH<sub>3</sub>MgBr and CH<sub>3</sub>MgCl) with ketone and the mode of isolation of the product. The solution of the Grignard reaction medium always developed marked color and after isolation a large amount of presumably polymeric substance was observed. Substances of similar nature were also encountered in those reactions where low yields of 3-alkyl- $\Delta^2$ -cyclohexenone were obtained.

In order to learn whether better yields of these substances could be obtained we turned to the reaction of dihydroresorcinol with methyl (as well as ethyl) magnesium bromide. The reaction of dihydroresorcinol with phenylmagnesium bromide had been shown to yield hydrocarbons possibly proceeding by the mechanism



The reaction in which the alkyl residue of the Grignard reagent was methyl or ethyl was also found to be very complex for only traces of 3-methyl- $\Delta^2$ -cyclohexenone and very small yields of 3-ethyl- $\Delta^2$ -cyclohexenone were obtained. The main product from both of these reactions was polymeric, and no product corresponding to substances of the formula VIII were obtained. Therefore, the Grignard reaction with dihydroresorcinol does not appear promising for synthetic purposes with alkylmagnesium halides. This was also the situation with arylmetallic reagents.

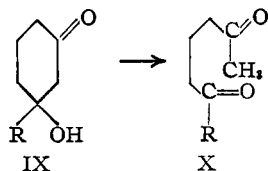
(5) Among other references for the synthesis of 3-methylcyclohexanone see: Neves, *Helv. Chim. Acta*, **26**, 162 (1943), who reports for the ketone b. p. 52-52.5° (2 mm.),  $n_D^{20}$  1.4439, and m. p. of the semicarbazone 178-178.5°; Whitmore and Pedlow, *THIS JOURNAL*, **63**, 758 (1941), report m. p. of the 2,4-dinitrophenylhydrazone 157-158°, m. p. of semicarbazone 181-182°; Signaigo and Cramer, *ibid.*, **55**, 3326 (1926), report for the ketone  $n_D^{20}$  1.4463 and m. p. of the semicarbazone 182°; Skita, *Ber.*, **56**, 1014 (1923), report for the ketone b. p. 168°,  $n_D^{20}$  1.4430, and m. p. of the semicarbazone 180°.

(6) For the synthesis of 3-ethylcyclohexanone see: Ungnade and McLaren, *J. Org. Chem.*, **10**, 29 (1945), who report for the ketone b. p. 189-191°,  $n_D^{20}$  1.4511 and m. p. for the semicarbazone 181-182°; Whitmore and Pedlow, *loc. cit.*, report for the ketone  $n = 1.4518$  and m. p. for the 2,4-dinitrophenylhydrazone 146-147°, m. p. for the semicarbazone 182-183°; Adams, Loewe, Theobald and Smith, *THIS JOURNAL*, **64**, 2653 (1942), report for the ketone b. p. 81° (12 mm.),  $n_D^{20}$  1.4499 and m. p. for the semicarbazone 166-167°; Braun, Mannes and Reuter, *Ber.*, **66**, 1499 (1933) report for the ketone  $n_D^{20}$  1.4543 and m. p. for the semicarbazone 184°.

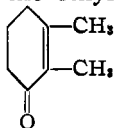
(7) 3-Isopropylcyclohexanone: Mousseron and Winternitz, *Bull. soc. chim.*, 604 (1946), report m. p. for the semicarbazone 187°; Crossley and Pratt, *J. Chem. Soc.*, **107**, 171 (1915), report for the ketone b. p. 208° and m. p. for the semicarbazone 186-187°; Whitmore and Pedlow, *loc. cit.*, report for the ketone  $n = 1.4562$  and m. p. for 2,4-dinitrophenylhydrazone 139-140°, m. p. for the semicarbazone 189-190°.

(8) 3-*t*-Butylcyclohexanone: Whitmore and Pedlow, *loc. cit.*, report for the ketone b. p. 96-98° (20 mm.),  $n_D^{20}$  1.4615 and m. p. for the 2,4-dinitrophenylhydrazone 158-159° and m. p. for the semicarbazone 207-208° (dec.).

It should be noted that if the first product of the Grignard reaction with dihydroresorcinol or its ether, formula VI or formula II, were stable, decomposition of the Grignard addition complex would lead to an aldol structure (IX) which could undergo reverse aldolization to yield X.



In the instance that R is  $C_2H_5$  the diketone could again aldolize this time utilizing the  $CH_2$  group of the ethyl residue. This final product would be



If R is methyl, opening and closing of the aldol obviously leads to the same product regardless of mode.

The discrepancies observed between the physical properties of our substances (Tables I and II) with those few available in the literature, what with the complexity of these Grignard reactions made a more desirable proof of structure necessary. Therefore, our sample of 3-ethyl- $\Delta^2$ -cyclohexenone was treated with phenylmagnesium bromide, the product aromatized and converted by oxidation to 3-xenylcarboxylic acid; while 3-phenyl- $\Delta^2$ -cyclohexenone was treated with methylmagnesium bromide, the product aromatized and oxidized to the same acid. The acids were identical with each other and with the known 3-xenylcarboxylic acid.

This work was supported in part by a grant from the National Institute of Health.

### Experimental

**Preparation of 3-Alkyl- $\Delta^2$ -cyclohexenone.**—A typical procedure will serve for the preparation of any of the substances given in Table I. An ethereal solution of alkylmagnesium halide in approximately 50% excess was prepared from the appropriate alkyl halide and magnesium turnings. To this solution was added 0.25 mole of dihydroresorcinol monoethyl ether<sup>18</sup> dissolved in 150 ml. of ether. The Grignard addition complex was decomposed with dilute sulfuric acid and the whole solution subjected to steam distillation. The steam distillate was extracted several times with ether (in practice the ether of the Grignard reaction was separated in the process of steam distillation and used for the subsequent extractions). After drying, the ether was removed under reduced pressure and the residue distilled. The yields, physical properties, and analytical values are given in Table I.

In the instance of the preparation of 3-methyl- $\Delta^2$ -cyclohexenone, methyl bromide and also methyl chloride was used in preparing the Grignard reagent to which was then added under (a) reflux temperature or (b) at approximately  $-40^\circ$  the solution of the enol ether. Certain Grignard addition complexes were decomposed with (a) sulfuric acid, (b) ammonium chloride, or (c) with ice. The best results were obtained by using  $-40^\circ$  for addition of the enol ether and decomposing the Grignard addition complex with ice.

**Preparation of the Carbonyl Derivatives.**—The 2,4-dinitrophenylhydrazones were prepared in the usual manner by adding the carbonyl compounds to an ethyl alcoholic solution of 2,4-dinitrophenylhydrazine which had been acidified with concentrated hydrochloric acid. For the m. p. and analytical data see Tables I and II.

The semicarbazones were prepared in the usual manner from aqueous solution of semicarbazide hydrochloride, potassium acetate and appropriate amount of ethyl alcohol. The m. p. and analytical data are given in Tables I and II.

**Reduction of the Unsaturated 3-Alkyl- $\Delta^2$ -cyclohexenones.**—3-Alkyl- $\Delta^2$ -cyclohexenone was dissolved in about ten times its volume of 95% ethyl alcohol and reduced with hydrogen at atmospheric pressure and room temperature with palladinized charcoal (3-methylcyclohexenone was reduced with platinum). The solution was filtered and after removal of the ethyl alcohol under reduced pressure, the residue distilled. Where the constants of the cyclohexanone are not reported, the alcoholic solution was divided into two parts from which the semicarbazone and the 2,4-dinitrophenylhydrazone were prepared. The b. p. and analytical data is given in Table II.

**The Reaction of Dihydroresorcinol with Methyl- and Ethyl-magnesium Bromide.**—The complete details of the continuous extraction of dihydroresorcinol using Soxhlet extraction technique are given in ref. 1a. In this procedure the Grignard reagent solution was of course either methyl- or ethylmagnesium bromide. The isolation of the product was carried out as described in the earlier section. Only traces of methyl- $\Delta^2$ -cyclohexenone were obtained, while the yield of ethyl- $\Delta^2$ -cyclohexenone was 7–10%. It was observed that if dihydroresorcinol (54 g.) was dissolved in pyridine (100 ml.) to which ether (50 ml.) was added the Soxhlet extraction could be avoided. In this procedure the yield of 3-methyl- $\Delta^2$ -cyclohexenone was increased to 8%. This however is still considerably below that yield observed with the enol ether.

**Preparation of 3-Xenylcarboxylic Acid from 3-Ethyl- $\Delta^2$ -cyclohexenone and 3-Phenyl- $\Delta^2$ -cyclohexenone.**—An ethereal solution (75 ml.) of 3-ethyl- $\Delta^2$ -cyclohexenone (25 g.) was added to an ethereal solution (150 ml.) of phenylmagnesium bromide prepared from 62 g. of bromobenzene and 8.4 g. of magnesium. The Grignard solution was decomposed with dilute sulfuric acid and the product extracted with ether. The ether solution was washed with water and with sodium bicarbonate solution and dried with sodium sulfate. After removal of the ether under reduced pressure the product distilled at  $89-90^\circ$  (0.1 mm.). This material (16.1 g.) was dehydrogenated by refluxing with 5% palladinized charcoal (1 g.) for four hours. Distillation from this mixture at atmospheric pressure yielded 3-ethylbiphenyl (13.0 g.) boiling at  $278-280^\circ$ ,  $n_D^{25}$  1.5671, which was not further purified.<sup>9</sup> Two grams of this last product was refluxed in a stirred mixture of 275 ml. of an aqueous 2% potassium permanganate solution until the oxidant had been consumed. Acidification of the filtrate after removal of manganese dioxide yielded 3-xenylcarboxylic acid which after recrystallization from water melted at  $167-168^\circ$ . *Anal.* Calcd. for  $C_{13}H_{10}O_2$ : C, 78.77; H, 5.09. Found: C, 78.86; H, 5.12.

In a similar manner 3-phenyl- $\Delta^2$ -cyclohexenone was reacted with methylmagnesium bromide and the product aromatized. 3-Methylbiphenyl<sup>10</sup> was obtained which boiled at  $264-266^\circ$  (760 mm.),  $n_D^{25}$  1.5992. *Anal.* Calcd. for  $C_{13}H_{12}$ : C, 92.81; H, 7.19. Found: C, 92.97; H, 7.10. Oxidation of this substance yielded 3-xenylcarboxylic acid which melted at  $165-166^\circ$  and gave no depression in a mixed melting point determination with the sample described above.

(9) A. b. p. of  $143^\circ$  (11 mm.) and  $n_D^{25}$  of 1.5859 is reported for this substance by Huber, *et al.*, *THIS JOURNAL*, **68**, 1109 (1946).

(10) The boiling point of  $272-277^\circ$  and  $n_D^{25}$  of 1.5916 is reported for this substance by Sherwood, Short and Stansfield, *J. Chem. Soc.*, 1884 (1932).

## Summary

1. A method of preparation of 3-alkyl- $\Delta^2$ -cyclohexenones is reported.

2. The semicarbazones and 2,4-dinitrophenylhydrazones of the 3-alkyl- $\Delta^2$ -cyclohexenones have been obtained and characterized.

3. Some 3-alkylcyclohexanones have been prepared by hydrogenation of 3-alkyl- $\Delta^2$ -cyclohexenones and their derivatives, the semicarbazones and 2,4-dinitrophenylhydrazones characterized.

COLLEGE PARK, MD.

RECEIVED JANUARY 24, 1949

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

## Antitubercular Compounds. bis-(Aminoaryl)-cyclopropane Derivatives. II.

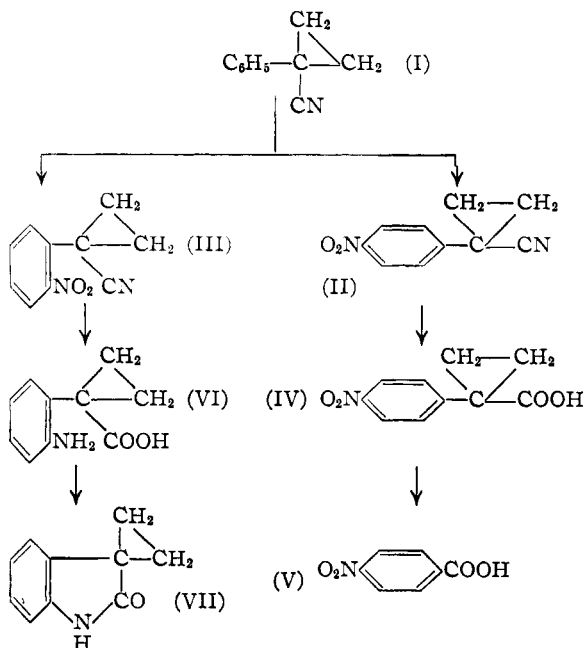
BY DIETER G. MARKEES<sup>1</sup> AND ALFRED BURGER

In the study of the effect of replacing the sulfone group in certain predominantly tuberculostatic sulfones by the aromatic type electron-attracting<sup>2</sup> cyclopropane group, we recently reported<sup>3</sup> that 1-(2-amino-4-thiazolyl)-2-(4-aminophenyl)-cyclopropane exhibits a low *in vitro* tuberculostatic activity. Since bacteriostasis was still produced by 1,1,1-trichloro-2,2-bis-(4-aminophenyl)-ethane<sup>4</sup> at a dilution of  $1 \times 10^{-6}$ , it appeared desirable to prepare an isomer of the first cyclopropane derivative carrying both basically substituted nuclei on the same carbon atom (X).

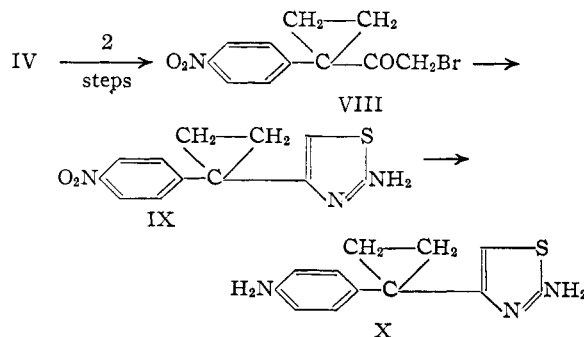
The synthesis of 1-(2-amino-4-thiazolyl)-1-(4-aminophenyl)-cyclopropane was patterned on that of the 1,2-isomer. 1-Phenyl-1-cyanocyclopropane (I)<sup>5</sup> was nitrated and yielded a mixture which consisted largely of 1-(*p*-nitrophenyl)-1-cyanocyclopropane (II) contaminated by small amounts of the *o*-isomer (III); the latter could be separated readily by crystallization. The position of the nitro group in the main reaction product was elucidated by hydrolyzing the nitrile group to carboxyl (IV), opening the cyclopropane ring with a boiling solution of hydrogen bromide in acetic acid, and oxidizing the side chain with potassium permanganate. This series of reactions furnished *p*-nitrobenzoic acid (V).

Evidence for the presence of the *o*-isomer (III) was obtained by hydrolyzing the crude nitration products from the mother liquors of the *p*-nitro nitrile (II) in acid solution, and reducing the mixture of 1-(nitrophenyl)-cyclopropane-1-carboxylic acids thus obtained to a mixture of 1-(aminophenyl)-cyclopropane-1-carboxylic acids. The *o*-amino isomer (VI) presumably contained in this mixture furnished, on treatment with hydrochloric acid, a neutral product, which showed the properties of the expected 3-(1,1-cyclopropano)-oxindole (VII).

1-(*p*-Nitrophenyl)-cyclopropane-1-carboxylic acid (IV) was converted to the bromo ketone VIII by way of its chloride and diazo ketone, and the



bromo ketone VIII was condensed with thiourea to the thiazole derivative IX in a yield of 80%. Catalytic reduction of this nitro compound led to the desired diamine X.



In the course of this work an analogous synthesis of the unsubstituted 1-phenyl-1-(4-thiazolyl)-cyclopropane (XI) was carried out, starting from 1-phenylcyclopropane-1-carboxylic acid, and using thioformamide in the thiazole ring closure.

(1) Merck Post-Doctorate Fellow, 1948.

(2) Cloke, Knowles and Anderson, *THIS JOURNAL*, **58**, 2547 (1936).

(3) Markees and Burger, *ibid.*, **70**, 3329 (1948).

(4) Kirkwood, Phillips and McCoy, *ibid.*, **68**, 2405 (1946).

(5) Knowles and Cloke, *ibid.*, **54**, 2028 (1932); Case, *ibid.*, **56**, 715 (1934); Weston, *ibid.*, **68**, 2345 (1946).