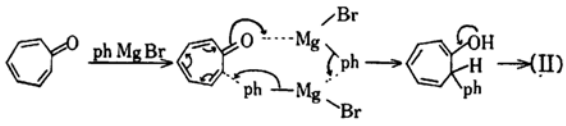
Reaction of Troponoids and Organometallic Compounds. VI. Reaction of Tropone with Grignard Reagents***

By Tetsuo NOZOE, Toshio MUKAI and Takahiro TEZUKA

(Received August 29, 1960)

It has been known that tropolone methyl ethers undergo reaction with Grignard reagents to give tropone derivatives substituted in the 2-position[1,2]. Considering that tropone, the parent compound of tropolone, possesses some degree of ketonic properties[3], its Grignard reaction is considered to be of interest, but no report has been published on this subject. The present paper describes the reaction of methyl-, isopropyl- and phenylmagnesium halide on tropone and the preparation of tropone derivatives via the products thereby formed.

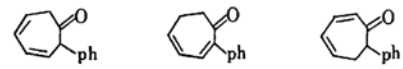
Applications of two molar equivalents of phenylmagnesium bromide on tropone (I) and subsequent decomposition of the magnesium complex with dilute hydrochloric acid gives an oil II, $C_{13}H_{12}O$; 2,4-dinitrophenylhydrazone, m. p. 135°C, maleic anhydride adduct, m. p. 147°C. Catalytic reduction of II results in absorption of 2 molar equivalents of hydrogen to form 2-phenylcycloheptanone. The NMR spectrum of II at 40 Mc. (Fig. 1)*** exhibits three sorts of signals due to phenyl (a), vinyl (b) and methylene (c) protons respectively. These observations indicate that II is one of the 2-phenylcycloheptadienone such as A, B or C, formed by ketonization of enolic intermediate III which was produced by 1,8-addition of the Grignard reagent to the conjugated system in I.



(I) (III)

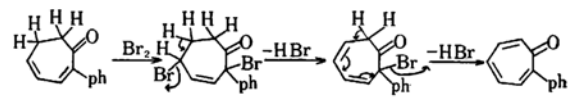
As in the reaction of Grignard reagents with tropolone methyl ethers, two molar equivalents of the reagent are also necessary in this reaction in order to obtain II in fair yield. This implies that the reaction proceeds through a complex formation between tropone and two molecules of the Grignard reagent, analogous to the cyclic intermediate suggested by Swain and others[4].

The infrared spectrum of II shows a carbonyl band at 1660 cm^{-1} characteristic of the conjugated dienone system[5], implying that II is represented by B or C. The maxima in the ultraviolet spectrum of II, 235 and 315 mμ (log ε : 3.98 and 3.85), also supports this view, and moreover, the bathochromic shift of 23 and 13 mμ compared with cyclohepta-2,4-dien-1-one[6], 292 mμ (log ε : 3.97) and eucarvone[7], 302 mμ (log ε : 3.82) respectively, indicates that II can be best represented by B rather than C.



(A) (B) (C)

II absorbs one molar equivalent of bromine in acetic acid to form an oily dibromide e. g. IV, which lacks the intensive maxima above 220 mμ in the ultraviolet spectrum. When IV is heated under reduced pressure, hydrogen bromide is liberated to form the hydrobromide of 2-phenyltropone, m. p. 145~147°C (30%), from which 2-phenyltropone (V)[1] is formed.



(II) (IV) (V)

Oxidation of II with selenium dioxide or chromium trioxide gives also 2-phenyltropone in 75 and 10% yield respectively.

In an earlier work[8] in this laboratory, it

* Part V: K. Kikuchi, This Bulletin 33, 628 (1960). This report is also Part VI of Tropones.

** Presented before the Local Meeting of the Chemical Society of Japan, Sendai, December, 1958.

1) (a) T. Nozoe, T. Mukai and J. Minegishi, *Proc. Japan Acad.*, 27, 419 (1951); (b) T. Nozoe, T. Mukai and I. Murata, ibid., 28, 142 (1952); (c) T. Nozoe, T. Mukai, J. Minegishi and T. Fujisawa, *Sci. Repts. Tohoku Univ., I*, 37, 388 (1953).

2) (a) K. Kikuchi, *J. Chem. Soc. Japan, Pure Chem. Sec. (Nippon Kagaku Zasshi)*, 77, 1439 (1956); (b) K. Kikuchi, ibid., 81, 505 (1960); (c) K. Kikuchi, This Bulletin, 33, 628 (1960).

3) T. Nozoe, T. Mukai and K. Takase, *Sci. Repts. Tohoku Univ., I*, 39, 164 (1956).

*** All NMR spectra were measured with a Varian V-4300B spectrometer.

4) C. G. Swain and H. B. Boyles, *J. Am. Chem. Soc.*, 73, 871 (1951).

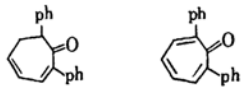
5) Eucarvon shows carbonyl band at 1661 cm^{-1}.

6) E. E. van Tamelen and G. T. H. Hildahl, *J. Am. Chem. Soc.*, 75, 5451 (1953).

7) E. J. Corey and H. J. Burke, ibid., 76, 5257 (1954).

8) (a) T. Nozoe, T. Mukai, M. Ishii and Y. Ikegami, unpublished work; (b) T. Mukai, This Bulletin, 31, 852 (1958).

had been shown that the reaction of phenylmagnesium bromide on 2-phenyltropone afforded colorless plates (VII) $C_{19}H_{16}O$, m. p. 87°C, accompanied by 2,7-diphenyltropone (VIII), both of which gave 2,7-diphenylcycloheptanone on catalytic hydrogenation, but the structure of compound VII remained unestablished. It is likely now that VII has the structure as shown below.



(VII) (VIII)

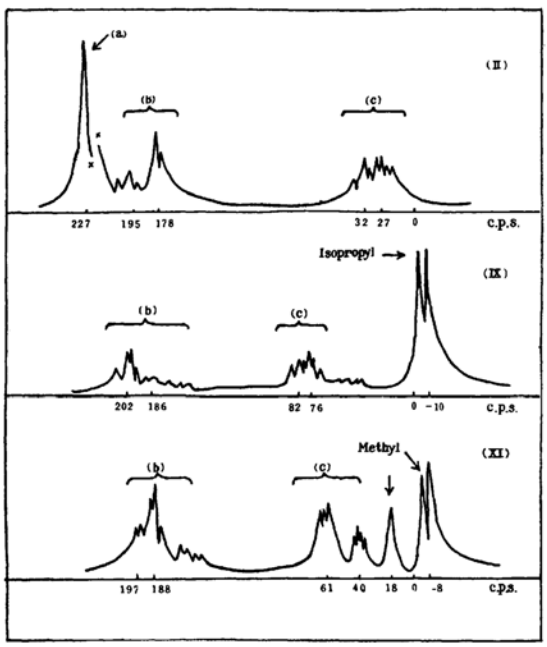
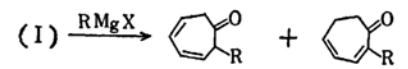


Fig. 1. NMR spectra of 2-phenyl-(II), 2-isopropyl-(IX) and 2-methylcycloheptadienone-(XI) at 40 Mc., relative to cyclohexane as inner reference.

The reaction of tropone with isopropylmagnesium bromide affords a liquid (IX), $C_{10}H_{14}O$, λ_{max} 302 mμ ($\log\varepsilon$: 3.31), which absorbs 2 molar equivalents of hydrogen on catalytic hydrogenation to give 2-isopropylcycloheptanone. The NMR spectrum of IX (Fig. 1) also suggests the cycloheptadienone type. Since the infrared spectrum indicates two carbonyl absorption bands at 1705 and 1658 cm^{-1}, it is assumed that IX is a mixture of IXa and IXb (R=*i*-C_3H_7). From the comparison of the absorption intensity in the ultraviolet spectrum of IX at 302 mμ with that of eucarvon (mentioned above), the proportion of IXa to IXb is assumed to be about 2 to 1.



(IXa) R=*i*-C_3H_7 (IXb) R=*i*-C_3H_7
(XIa) R=CH_3 (XIb) R=CH_3

IX adds one molar equivalent of bromine, but the dibromide thereby formed easily loses hydrogen bromide during removal of the solvent to afford an oily product (X) which gives the known 2-amino-7-isopyropyltropone[9] on being treated with hydrazine hydrate, indicating that X is 2-isopropyltropone.

Although the ultraviolet spectrum and the infrared diagram of X are analogous to those of known 2-methyl- and 2-ethyltropone[10], X does not form a picrate, an oxime or a 2,4-dinitrophenylhydrazone by the usual process and this may be due to the steric hindrance of the isopropyl group.

Similarly, the reaction of tropone with methylmagnesium iodide gives an oil (XI), λ_{max} 235 and 298 mμ ($\log\varepsilon$: 3.54 and 3.53), whose catalytic hydrogenation produces 2-methylcycloheptanone. Treatment of XI with bromine easily effects bromination-dehydrobromination to give the known 2-methyltropone.

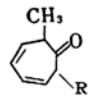
The infrared spectrum of XI exhibits carbonyl bands at 1710 and 1665 cm^{-1} as in the case of IX, and XI is considered to be a mixture of XIa and XIb (R=CH_3). This is also supported by its NMR spectrum (Fig. 1) in which two kinds of signals due to the methyl group appear at +18 c. p. s. (singlet) and −8 c. p. s. (doublet). The former is assumed to come from the methyl group in XIb, whereas the latter is due to the methyl group in XIa. Moreover, the calculation of the areas of two signals due to methyl groups in NMR spectrum and the intensity in the ultraviolet spectrum of XI shows that XIa is more prominent than XIb in that mixture.

Both IX and XI are easily dehydrogenated by the treatment with selenium dioxide to give 2-isopropyl- or 2-methyltropone in 55 and 60% yields, respectively.

It follows, therefore, that the Grignard reaction of tropone is also useful as a general method for the preparation of tropone derivatives.

After the present work had been completed, it was learned very recently that Closs and Closs[11] had obtained a compound XII (R=H or CH_3) from the reaction of methyllithium on tropone or 2-methyltropone. They also

9) T. Nozoe et al., unpublished work.
10) T. Mukai, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **79**, 1547 (1958).
11) G. L. Closs and L. E. Closs, Abstracts of Papers, National Meeting of the American Chemical Society, Cleveland, April, 1960.



(XII)

obtained similar compounds by the application of methylene chloride and methyllithium on phenol or cresol, but details are not available. Our results in which the conjugated dienones with the double bond in position different from that in XII (R=H) has been obtained, would be due to a migration of the double bond during the decomposition of the magnesium complex with dilute hydrochloric acid.

Experimental[12]

2-Phenylcycloheptadienone (II).—A solution of 3.0 g. of tropone in 40 ml. of absolute ether was added dropwise at 0°C with stirring to 2.2 mol. equiv. of Grignard reagent prepared from 10.3 g. of bromobenzene and 1.5 g. of magnesium in 40 ml. of absolute ether. After additional stirring for half an hour, the reaction mixture was decomposed with 1 N hydrochloric acid, extracted with ether, washed with water and dried over anhydrous sodium sulfate. Removal of the solvent afforded 7.5 g. of crude oil, whose distillation in vacuo gave 4.35 g. (84%) of pale yellow oil (II), b. p. 139～145°C (3 mmHg), n_D^{16} 1.4890, λ_{max}^{MeOH} 235 mμ (log ε: 3.98), 315 mμ (log ε: 3.85). For analysis, this oil was redistilled to give b. p. 143～145°C (3 mmHg).

Found: C, 84.31; H, 6.38. Calcd. for $C_{13}H_{12}O$: C, 84.75; H, 6.57%.

Application of 1.0 and 1.5 molar equivalents of the Grignard reagent on tropone afforded II in 30% and 75% yields with the recovery of tropone (35 and 3% respectively).

2,4-Dinitrophenylhydrazone, m. p. 134～135°C, λ_{max}^{MeOH} 375 mμ (log ε: 4.15).

Found: C, 62.54; H, 4.31; N, 15.08. Calcd. for $C_{19}H_{16}O_2N_4$: C, 62.63; H, 4.43; N, 15.38%.

Catalytic Reduction of 2-Phenylcycloheptadienone (II).—A solution of 300 mg. of II in 4.5 ml. of ethanol was hydrogenated at 1 atm. and 18°C with prereduced palladium-carbon catalyst. After 125 min., 87 ml. (2.4 mol. equiv.) of hydrogen was absorbed. Removal of the catalyst and evaporation of the solvent afforded 300 mg. of an oil, which gave semicarbazone m. p. 150～151.5°C, undepressed on admixture with an authentic sample of 2-phenylcycloheptanone semicarbazone[13a].

Bromination of 2-Phenylcycloheptadienone (II).—A solution of bromine in acetic acid (88 mg./0.5 ml.) was added dropwise at 0°C to a solution of 100 mg. of II in 5 ml. of acetic acid, by which 1.2 mol. equiv. of bromine was absorbed. After stirring for one hour, the reaction mixture was diluted with water, extracted with benzene, washed with water and dried over anhydrous sodium sulfate. Removal of the solvent at room temperature under reduced pressure gave 200 mg. of brown oil, a chromatographic purification of which on alumina afforded dibromide IV as a viscous oil.

Found: C, 44.76; H, 3.34. Calcd. for $C_{13}H_{12}OBr_2$: C, 45.36; H, 3.51%.

2-Phenyltropone.—a) The dibromide (200 mg.) obtained above was heated at 80°C under reduced pressure (20 mmHg) overnight. The resultant residue was extracted with benzene, washed with water and dried. Evaporation of the solvent and chromatographic purification on alumina yielded 2-phenyltropone (70 mg.) as a reddish oil. On treatment of this oil (70 mg.) with hydrazine hydrate, crystals (20 mg.), m. p. 200～202°C were obtained. Recrystallization from benzene gave yellow needles, m. p. 203～204°C, identical with authentic 2-amino-7-phenyltropone[1].

b) II (1 g.) was brominated in acetic acid and the reaction mixture was treated as described above. On removal of the solvent at 80°C, 400 mg. of 2-phenyl tropone as colorless needles, m. p. 145～147°C*, which showed almost identical ultraviolet absorption maximum with that of 2-phenyltropone. This hydrobromide (200 mg.) was heated at 100°C under reduced pressure (20 mmHg) for 2 hr. and subsequently sublimed to afford 90 mg. of yellow needles, m. p. 82～83°C, undepressed on admixture with authentic 2-phenyltropone.

Dehydrogenation of II with Selenium Dioxide.—A solution of 200 mg. of II in 2 ml. of dioxane was heated under reflux with selenium dioxide (140 mg.) for 7 hr. The deposited selenium (30 mg.) was filtered off and the filtrate was concentrated. The resultant residue was dissolved in benzene, washed successively with saturated sodium bicarbonate solution and water, and dried. On removal of the solvent, 150 mg. (75%) of crystals, m. p. 70～75°C was obtained. Recrystallization from benzene and chromatographic purification on alumina gave yellow prisms, m. p. 83～84°C, identical with 2-phenyltropone.

Oxidation of II with Chromium Trioxide.—A solution of 1.9 g. of II in 6 ml. of pyridine was added to pyridine-chromic acid complex (1 g. CrO_3/10 ml. pyridine) at 15～20°C. After stirring for 10 hr. and standing for another 12 hr. at room temperature, the reaction mixture was treated with methanol to decompose excess of chromium trioxide, neutralized with concentrated hydrochloric acid, extracted with chloroform, washed with water and dried. Removal of the solvent and subsequent purification on alumina gave 70 mg. of an oil. Treatment of this oil (70 mg.) with hydrazine hydrate by usual way afforded 20 mg. of crystals, m. p. 198～202°C. Recrystallization from benzene gave yellow prisms, m. p. 206～207°C, identical with 2-amino-7-phenyltropone[1].

Diels-Alder Reaction of II.—A mixture of 200 mg. of II and 130 mg. (1.2 mol. equiv.) of maleic anhydride in 2 ml. of dry benzene was heated under reflux for 11 hr. On removal of the solvent 200 mg. of an oil was obtained which on standing for 10 days, gave 70 mg. of crystals, m. p. 145～170°C. Recrystallization from benzene gave white needles, m. p. 186～187°C.

Found: C, 71.88; H, 4.53. Calcd. for $C_{17}H_{14}O_4$: C, 70.33; H, 4.86%. λ_{max}^{MeOH} 295 mμ (log ε: 2.43).

12) All the melting points are not crroected.

* On exposure in the air it decomposed to an oil.

2-Isopropylcycloheptadienone (IX).—A solution of 5 g. of tropone in 50 ml. of absolute ether was added at 0°C to a 2.2 mol. equiv. of Grignard reagent prepared from 13.36 g. of isopropyl bromide and 2.50 g. of magnesium in 40 ml. of absolute ether. The reaction mixture was treated as in the case of II. The resultant residue was distilled in vacuo to give three fractions: i) b. p. below 70°C (4 mmHg) n_D^{15} 1.4870, 0.5 g.; ii) b. p. 70~75°C (4 mmHg), n_D^{15} 1.4850, 4.4 g. (62%); iii) b. p. above 75°C (4 mmHg), small amount.

Found [for fraction (ii)]: C, 79.51; H, 9.05. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39%.

Hydrogenation of IX.—2-Isopropylcycloheptadienone (IX) (300 mg.) was hydrogenated in 5 ml. of acetic acid at 1 atm. and 18°C with 10 mg. of prereduced platinum oxide catalyst. Ninty-five milliliters of hydrogen (2.0 mol. equv.) was taken up within 80 min. After removal of the catalyst, the mother liquor was diluted with water, extracted with petroleum ether, washed and dried. On evaporation of the solvent, 250 mg. of an oil was remained, which afforded semicarbazone, m. p. 170.5 ~171.5°C, undepressed on admixture with that of 2-isopropylcycloheptanone[13].

Formation of 2-Isopropyltropone (X) by Bromination of IX.—Bromine in carbon tetrachloride was added to a solution of 650 mg. of IX in 6.5 ml. of carbon tetrachloride by which 1.0 mol. equiv. bromine was absorbed. The reaction mixture was treated as in the case of II. Residual oil thus obtained was purified through its hydrochloride and then chromatographed on alumina, by which 160 mg. of brown oil was obtained. An ethanolic solution of this oil (160 mg.) was heated under reflux with 0.23 ml. of 80% hydrazine hydrate for 1 hr. Removal of the solvent followed by chromatography on alumina gave 100 mg. of crystals m. p. 40~50°C, λ_{max}^{MeOH} 242, 336, 399 mμ, identical with that of 2-amino-7-isopropyltropone[9]. Hydrolysis of this crystals (100 mg.) with potassium hydroxide in aqueous ethanol afforded 60 mg. of an oil, having identical R_f value with that of α-thujaplicin.

Formation of 2-Isopropyltropone (X) by Dehydrogenation of IX with Selenium Dioxide.—A solution of 1 g. of IX in 10 ml. of dioxane was heated under reflux with 440 mg. (1.2 mol. equiv.) of selenium dioxide for 1 hr. The reaction mixture was filtered to remove deposited selenium (150 mg.) which contains tarry matter and the mother liquor was concentrated. The resultant residue was dissolved in ether, washed with dilute silver nitrate solution and water, and dried. Removal of the solvent and subsequent distillation gave 550 mg. of an oil, b. p. ca. 80°C (2 mmHg), λ_{max}^{MeOH} 233 mμ (log ε: 4.37), 312 mμ (log ε: 3.90). Heating of this oil (100 mg.) with 80% hydrazine hydrate (0.25 ml.) for 2 hr. under reflux afforded 90 mg. of yellow crystals, m. p. 40~60°C. Recrystallization from a mixture of benzene and petroleum ether gave yellow prisms, m. p. 88°C, undepressed on admixture with 2-amino-7-isopropyltropone[9].

2-Methylcycloheptadienone (XI).—A solution of 2.4 g. of tropone in 30 ml. of absolute ether was added to 2.2 mol. equiv. of Grignard reagent prepared from 7.5 g. of methyl iodide and 1.2 g. of magnesium, at 0°C and the reaction mixture was treated as in the case of II. On evaporation of the solvent, 1.7 g. of pale yellow oil was obtained. Distillation in vacuo gave three fractions: i) b. p. below 60°C (2 mmHg), trace; ii) b. p. 60~65°C (2 mmHg), 1.0 g. (38%), n_D^{14} 1.480; iii) b. p. above 65°C (2 mmHg), trace.

Found [for fraction (ii)]: C, 77.42; H, 8.04. Calcd. for $C_8H_{10}O$: C, 78.65; H, 8.25%.

Hydrogenation of XI.—XI (500 mg.) in 10 ml. of acetic acid was hydrogenated at 1 atm. and 18°C with prereduced platinum oxide. After 100 min., 122 ml. (2.2 mol. equiv.) of hydrogen was absorbed. The catalyst was removed by filtration and the filtrate was diluted with water, extracted with petroleum ether, washed and dried. Removal of the solvent gave a volatile oil, which gave semicarbazone, m. p. 118°C on allowing to stand with semicarbazide for 20 days at room temperature, undepressed 2-methylcycloheptanone[14].

2-Methyltropone by Bromination of XI.—To a solution of 500 mg. of XI in 10 ml. of carbon tetrachloride was added with stirring a solution of bromine into carbon tetrachloride, by which 1.4 mol. equiv. of bromine was easily absorbed. Treatment of the reaction mixture as in the case of IX afforded 500 mg. (60%) of crystals, decomp. 135°C, λ_{max}^{MeOH} 232, 315 mμ, similar with that of 2-methyltropone hydrochloride. Neutralization of these crystals (100 mg.) with saturated sodium bicarbonate solution gave an oil, which afforded picrate, m. p. 126~127°C (60 mg.). Recrystallization from ethanol gave yellow crystals, m. p. 127~128°C, undepressed on admixture with those of 2-methyltropone[10].

Formation of 2-Methyltropone by Dehydrogenation of XI with Selenium Dioxide.—A solution of 300 mg. of XI in 3 ml. of dioxane was refluxed with 163 mg. (1.2 mol. equiv.) of selenium dioxide for half an hour. Deposited selenium contaminated with tar (80 mg.) was filtered off and similar treatment of the mother liquor as in the case of X afforded 180 mg. of an oil (60%) which gave picrate m. p. 127~128°C, identical with that of 2-methyltropone[10].

The authors thank to Professor T. Isobe for NMR spectra measurement and his kind discussions thereof. Expenses for the present series of experiments were defrayed by a Grant in Aid for Scientific Research from the Ministry of Education.

Department of Chemistry
Faculty of Science
Tohoku University
Katahira-cho, Sendai

13) S. Seto, *Sci. Repts. Tohoku Univ.*, I, 37, 292 (1953).

14) D. N. Adamson and J. Kenner, *J. Chem. Soc.*, 1939, 181.