

TABLE I

Compound	°C. B.P.,	Mm.	M.P., °C.	$d_{20}^{20}$	$n_D^{20}$	R	Calcd. Halide, %	% Found	Mol. Calcd.	wt. Found
$(n\text{-Pr}_3\text{Ge})_2\text{O}$	305	760	-55	1.068	1.4648	108.1	34.6 <sup>a</sup>	34.5 <sup>a</sup>	419.7	405
	175	14								
$n\text{-Pr}_3\text{GeF}$	203	760	-27.5	1.074	1.4340	53.6	8.60	9.0, 9.0	220.9	217
$n\text{-Pr}_3\text{GeCl}$	227	760	-70	1.100	1.4641	59.5	15.0	15.1, 15.2	237.2	235
	98-99	11								
$n\text{-Pr}_3\text{GeBr}$	242	760	-47	1.282	1.4832	62.7	28.4	28.4, 28.4	281.8	278
	112-113	12								
$n\text{-Pr}_3\text{GeI}$	259	760	-38	1.443	1.5144	68.7	38.5	38.6, 38.9	328.8	318
	122-123	10								
$n\text{-PrGe(NCO)}$	247	760	-19	1.055	1.4575	61.4	17.3	17.5, 17.6	234.9	230
	114	10								

<sup>a</sup> Per cent. germanium. All indices of refraction in white light. R for Ge, oxide to iodide, 8.4, 8.0 (if  $R_F$  is 1.0), 8.3, 9.0, 9.9 by  $n^2-1$  formula.

night with anhydrous sodium sulfate, the solvent was distilled, leaving 6.05 g. of tri-*n*-propylgermanium fluoride; after three distillations 0.40% free hydrogen fluoride still remained in the product, the properties of which are in Table I. Distillation from sodium fluoride would have been ideal.

**Chloride.**—Vigorous shaking of 12.8 g. of oxide and 25 ml. of 12 *M* hydrochloric acid gave a temperature rise of 17°; after standing overnight, there followed extraction with light petroleum ether, drying with calcium chloride and then distillation. A yield of 14.2 g. was essentially quantitative; the first center fraction contained 16.2% chlorine, but boiling for ten minutes with a half-gram of barium carbonate lowered the value to 15.14%. Table I lists the properties.

**Bromide and Iodide.**—Upon shaking 9.6 g. of oxide and 25 ml. of 48% hydrobromic acid the temperature rose 12°; after extraction and then drying with anhydrous sodium sulfate, the solvent was distilled, leaving 11.9 g. of tri-*n*-propylgermanium bromide or a yield of 93%. Before using 0.15 g. of sodium hydroxide the analysis was 29.1% bromine; afterwards, 28.4%. Nine grams of oxide and 29 ml. of 45% aqueous hydriodic acid when shaken rose 7.3°; after extraction, without drying, the solvent was distilled and then 11.1 g. of iodide remained—a yield of 85%, lowered by slight mechanical losses. Before using 0.10 g. of sodium hydroxide in seven pieces, the iodine content was 39.5%; afterwards, 38.3%. Table I lists the distillations at reduced pressure and the properties of center fractions.

**Isocyanate.**—Sixteen grams of silver isocyanate and 12 g. of tri-*n*-propylgermanium chloride in 30 ml. of pure benzene rose 13° in temperature; the usual one-hour reflux<sup>3</sup> also included presence of 3 ml. of nitromethane. After purification, the 12 g. of product contained no chlorine, but had 17.9% isocyanate; after boiling 5 g. with 0.10 g. of sodium hydroxide, the analysis was better. Table I lists the properties of the purer sample.

**Properties and Analysis.**—All six compounds are colorless, mobile liquids easily soluble in organic solvents; the melting points, good to a degree in all cases, indicate fairly pure compounds, sometimes bearing a few tenths of a per cent. of hydrogen halide. Because of low solubility in water, the compounds do not hydrolyze easily in pure water; overnight heating of 1.9 g. of tri-*n*-propylgermanium bromide with 0.22 g. of water at 100° gave an aqueous layer 0.70 *M* in hydrobromic acid—or 2.2% of the bromine was in the aqueous layer. Ethanolic sodium hydroxide and micro-pipets served in titrations of acidity, while the germanium content of the oxide relied upon fuming nitric acid and sulfuric acid in oxidation; the results are in Table I. All molecular weights are by freezing point of camphor.

Throughout the investigation all transfers were by pipet, not by pouring; all the distillation units bore interchangeable ground joints. Bis-(tri-*n*-propylgermanium) oxide had a weak aromatic odor, while the fluoride and chloride were penetrating and camphoraceous; the bromide and isocyanate were penetrating in odor, while the iodide had little odor.

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### The Reaction of Methylmagnesium Iodide with $\beta$ -(1-Hydroxy-3,4-dihydro-2-naphthyl)-butyric Acid Lactone<sup>1</sup>

By B. BELLEAU<sup>2</sup>

In another communication,<sup>3</sup> we reported the synthesis of 1-methyl-3-keto-1,2,3,9,10,10a-hexahydrophenanthrene (XI) as an intermediate in a projected synthesis of doisyonic acid analogs. This paper deals with an improved synthesis of this phenanthroid ketone together with an original synthesis of 1,3-dimethylphenanthrene.

Attempted applications of the technique of Wilds and Johnson<sup>4</sup> to the synthesis of the diketone II from the ketoacid I<sup>3</sup> were fruitless because of the spontaneous lactonization to III that the acid chloride of I underwent. In view of this result, a method for the preparation of the diketone II from the enol lactone III was desirable, and in this respect, the reaction of an equimolar amount of methylmagnesium iodide with the latter was attempted. This led to an oily reaction mixture which was hydrolyzed with hydrochloric acid to give a 15% yield of the ketone XI identified by means of mixed melting point determination with an authentic sample<sup>3</sup> and a 30% yield of a hydrocarbon of empirical formula  $C_{18}H_{18}$ . Dehydrogenation of the latter produced 1,3-dimethylphenanthrene identical with a sample prepared from the ketone XI.<sup>3</sup>

The hydrocarbon exhibited absorption bands at 274, 280, 290, 307, 314 and 322  $m\mu$  with respective molar extinction coefficients ( $\log \epsilon$ ) of 3.73, 3.76, 3.64, 2.98, 2.80 and 2.88; these values are characteristic of a naphthalenoid conjugated system and the spectrum is superimposable to that reported for 1,2,3,4-tetrahydrophenanthrene.<sup>5</sup> Since the hydrocarbon  $C_{18}H_{18}$  also formed a picrate, the presence in it of a naphthalenoid ring system is unquestionable and provisionally, the compound can best be formulated as 1,3-dimethyl-1,2,3,4-tetrahydrophenanthrene (X). The latter has previously been prepared by Haworth, Mavin and Sheldrick,<sup>6</sup>

(1) Abstracted from the Ph.D. thesis of B. Belleau presented to the Department of Biochemistry, McGill University, 1950.

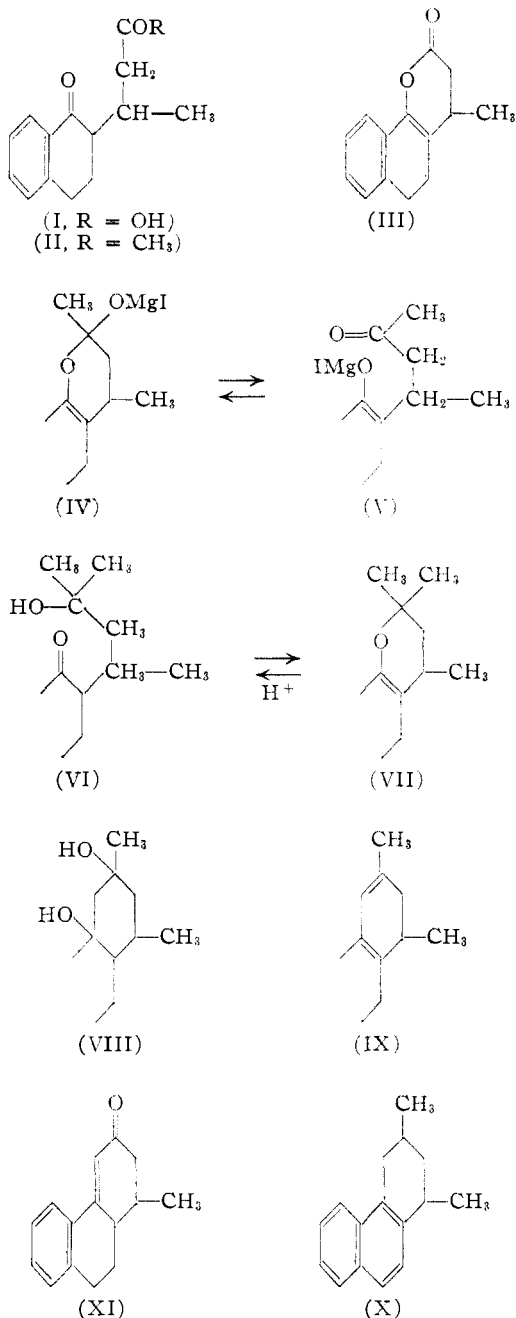
(2) The Sloan-Kettering Institute for Cancer Research, New York, N. Y.

(3) B. Belleau, *THIS JOURNAL*, **73**, 5149 (1951).

(4) A. L. Wilds and T. L. Johnson, *ibid.*, **70**, 1166 (1948).

(5) F. A. Askew, *J. Chem. Soc.*, 512 (1935).

(6) R. D. Haworth, C. R. Mavin and G. Sheldrick, *ibid.*, 454 (1934).



but not characterized so that comparison is impossible. The yield in ketone XI was increased to 30% by reversing the order of addition of the reactants and by operating at low temperature.<sup>7</sup>

The course of the reaction follows undoubtedly a pattern similar to that reported in the case of the addition of Grignard reagents to dihydrocoumarins and coumarins<sup>8</sup>; thus, the hemiketal salt IV would be first formed followed by equilibration with its opened form V which would then react further with the Grignard reagent to yield after hydrolysis with

(7) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948), developed this technique for the synthesis of ketoacids from acid anhydrides and Grignard reagents.

(8) R. L. Shriner and A. G. Sharp, *ibid.*, **4**, 575 (1939); L. I. Smith and P. M. Ruoff, *This Journal*, **62**, 145 (1940); T. A. Geissman and L. Morris, *ibid.*, **63**, 1111 (1941).

water a mixture of the diketone II and the ketol VI or its naphthopyran form VII. Attempts to isolate the latter compounds failed thus far. Unquestionably, acid hydrolysis of the mixture caused ring closure of II to XI; provisionally, however, we have assumed that under these conditions, the ketol VI would undergo cyclization to VIII although there appears to be insufficient activation of the methyl groups for such an aldol condensation to take place. Subsequent dehydration of VIII would yield an unstable hydrocarbon IX followed by isomerization to X. The latter isomerization step is not unique since it has previously been observed that partial reduction of 9,10-dihydrophenanthrene leads to 1,2,3,4-tetrahydrophenanthrene instead of the tetrahydride analogous to IX.<sup>9</sup>

Although the formation of hydrocarbon C<sub>16</sub>H<sub>18</sub> is difficult to explain, the fact remains that it leads to 1,3-dimethylphenanthrene and this represents therefore an independent synthesis of the latter which was previously available through the Friedel and Crafts<sup>6</sup> and Pschorr<sup>10</sup> syntheses of polynuclear hydrocarbons. Moreover, the reaction of the enol lactone III with methylmagnesium iodide constitutes a new method for the synthesis of cyclic  $\alpha,\beta$ -unsaturated ketones from ketoacids of the type of I.<sup>11</sup>

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#### Experimental<sup>12</sup>

**$\beta$ -(1-Hydroxy-3,4-dihydro-2-naphthyl)-butyric Acid Lactone (III).**—A suspension of the dry powdered sodium salt from 4 g. of  $\beta$ -(1-tetralone-2)-butyric acid (I)<sup>8</sup> in benzene was treated at 0° with 2 ml. of oxalyl chloride and stirred for 5 min. The benzene was evaporated *in vacuo* at room temperature and the residue redissolved in benzene which was again removed *in vacuo*. The oil was dissolved in ether and the solution washed three times with 5% aqueous bicarbonate. The ether was dried and evaporated to yield a yellowish oil solidifying upon cooling. Recrystallization from hexane afforded 3.58 g. (97% yield) of colorless plates of  $\beta$ -(1-hydroxy-3,4-dihydro-2-naphthyl)-butyric acid lactone (III), m.p. 90–92°. Three additional recrystallizations from the same solvent produced crystals m.p. 91–92.5°.

*Anal.* Calcd. for C<sub>14</sub>H<sub>14</sub>O<sub>2</sub>: C, 78.50; H, 6.54. Found: C, 78.56; H, 6.74.

The lactone III could also be obtained in comparable yield by treating the free  $\beta$ -(1-tetralone-2)-butyric acid (I) for 30 min. with an excess of thionyl chloride in benzene containing a trace of pyridine by treatment for 3 hours with five times its weight of a mixture of equal volumes of acetic anhydride and acetyl chloride at the boiling point of the mixture.

**Reaction of  $\beta$ -(1-Hydroxy-3,4-dihydro-2-naphthyl)-butyric Acid Lactone (III) with Methylmagnesium Iodide. Procedure (a).**—To a stirred and ice-cold solution of methyl-

(9) G. Schroeter, H. Müller and S. Y. S. Huang, *Ber.*, **62**, 645 (1929).

(10) M. T. Bogert and G. S. Stamatoff, *Rec. trav. chim.*, **52**, 584 (1933).

(11) Note added in proof: after this manuscript was submitted for publication, reports by G. I. Fujimoto, *This Journal*, **73**, 1856 (1951) and R. B. Woodward and co-workers, *ibid.*, **73**, 2403 (1951), on the reaction of methylmagnesium iodide with  $\delta$ -enol lactones were published. See also R. D. H. Heard and P. Ziegler, *ibid.*, **73**, 4036 (1951).

(12) Melting points are uncorrected and ultraviolet absorption spectra were determined with a standard Beckmann quartz spectrophotometer. Microanalyses were kindly performed by Mr. Y. Perron of University of Montreal.

magnesium iodide prepared from 0.50 g. of magnesium and 1.5 ml. of methyl iodide in 25 ml. of ether was added dropwise over a period of 5 min. a solution of 4.30 g. of the lactone III in 25 ml. of ether. The mixture was heated under reflux for 15 min. and then hydrolyzed with dilute hydrochloric acid. The ether layer was washed with water and bisulfite solution and finally dried and evaporated to yield a colorless oil which resisted crystallization. It was dissolved in a mixture of 60 ml. of glacial acetic acid, 30 ml. of concentrated hydrochloric acid and 5 ml. of water and the solution heated under reflux for 2 hours. The reddish solution was diluted with 200 ml. of water and extracted with ether. The ether extract was washed with water and extracted twice with dilute aqueous sodium hydroxide. Acidification of the alkaline extract liberated 2.28 g. (49% recovery) of the crystalline  $\beta$ -(1-tetralone-2)-butyric acid (I) melting at 101–102° after recrystallization from heptane.<sup>3</sup> The ether layer was dried and evaporated to yield a yellow oil which when triturated under a little hexane deposited 640 mg. (15% yield) of white crystals, m.p. 119–125°. Two additional recrystallizations from methanol afforded large prisms of 1-methyl-3-keto-1,2,3,9,10,10a-hexahydrophenanthrene (XI) melting at 124–125° when alone or admixed with an authentic sample.<sup>3</sup>

The hexane filtrate from the preceding crystals was diluted to 200 ml. with more hexane and the solution passed through a column of 15 g. of activated alumina. The filtrate upon evaporation yielded 1.26 g. (30% yield) of a colorless oil solidifying when chilled and melting at 55–61°. Four recrystallizations from methanol produced colorless rods of 1,3-dimethyl-1,2,3,4-tetrahydrophenanthrene (X), m.p. 64–65°.

*Anal.* Calcd. for  $C_{18}H_{18}$ : C, 91.43; H, 8.54. Found: C, 91.20; H, 8.26.

The picrate crystallized from methanol in the form of orange-colored needles, m.p. 133–135°.

*Anal.* Calcd. for  $C_{22}H_{21}O_7N_3$ : C, 60.13; H, 4.78. Found: C, 59.96; H, 5.06.

The ultraviolet absorption spectrum of the hydrocarbon was determined in methanol at a concentration of 1 mg. %. It showed absorption bands at 280  $m\mu$  ( $\log e$  3.75), 307  $m\mu$  ( $\log e$  2.98) and 322  $m\mu$  ( $\log e$  2.88) (see text). The spectrum coincides with that reported<sup>6</sup> for 1,2,3,4-tetrahydrophenanthrene.

Dehydrogenation of the hydrocarbon was carried out on 500 mg of product in the presence of 100 mg. of 10% palladium-on-charcoal. The mixture was heated to 300–320° for 45 min. then cooled and dissolved in 100 ml. of hexane. The solution was filtered through 10 g. of activated alumina and the filtrate evaporated to yield a colorless oil (420 mg. or 84% yield) which solidified on cooling. Recrystallization from methanol afforded colorless needles of 1,3-dimethylphenanthrene melting at 74.5–75.5° when alone or admixed with a sample prepared from the ketone XI.<sup>3</sup> The picrate crystallized from methanol in the form of orange-colored needles, m.p. 155–156° (reported<sup>6</sup>: hydrocarbon, 75–76°; picrate, 154–155°).

**Procedure b.**—A solution of methylmagnesium iodide in ether was prepared in a dropping funnel from 0.72 g. of magnesium and 2 ml. of methyl iodide. This was added dropwise over a period of 45 min. to a stirred solution of 6.4 g. of the enol lactone III in 250 ml. of pure toluene cooled to –70° in a Dry Ice-acetone-bath. The reaction mixture was allowed to warm to room temperature and the reaction products isolated as described in the preceding experiment. The oily material was dissolved in a mixture of 80 ml. of glacial acetic acid, 40 ml. of concentrated hydrochloric acid and 8 ml. of water and the solution heated under reflux for 2 hours and worked up for  $\beta$ -(1-tetralone-2)-butyric acid, the ketone XI and the hydrocarbon X as described in the preceding experiment.

In this manner, there were obtained, respectively, 2.83 g. (41% recovery) of  $\beta$ -(1-tetralone-2)-butyric acid, m.p. 101–102°, 1.90 g. (30% yield) of 1-methyl-3-keto-1,2,3,9,10,10a-hexahydrophenanthrene (XI), m.p. 124–125°, and 0.82 g. (13% yield) of 1,3-dimethyl-1,2,3,4-tetrahydrophenanthrene (X). Identifications were made by means of mixed melting point determinations.

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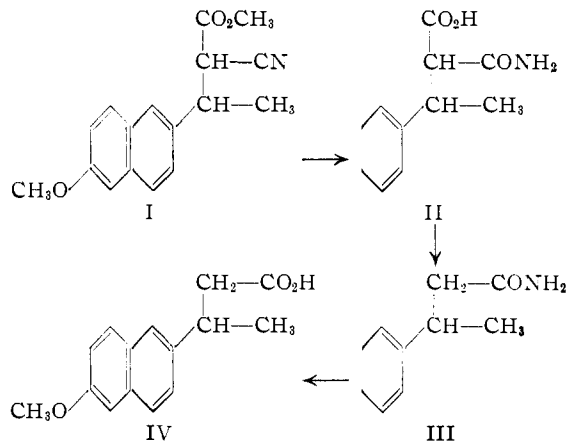
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## A New Route to the Allenolic Acid Type of Compound<sup>1</sup>

By B. BELLEAU<sup>2</sup>

With the discovery by Courrier, Horeau and Jacques<sup>3</sup> of the high estrogenic activity exhibited by  $\alpha,\alpha$ -dimethyl- $\beta$ -ethylallenolic acid ( $\alpha,\alpha$ -dimethyl- $\beta$ -ethyl-6-hydroxy-2-naphthalene-propionic acid), interest in analogs of the latter was stimulated with the purpose of extending correlative studies between molecular structure and estrogenic activity. A sequence described by Horeau and Jacques<sup>4</sup> for the synthesis of this interesting estrogen, involves Blaise condensation of 2-cyano-6-methoxynaphthalene with methyl  $\alpha$ -bromoisobutyrate followed by addition of ethyl Grignard reagent to the resulting  $\beta$ -ketoester; the carbinol so obtained is then dehydrated and hydrogenation of the double bond constitutes the final step.

This paper deals with a new and simplified approach to Horeau's type of acid. We exemplified our method by preparing  $\beta$ -methylallenolic acid methyl ether (IV). By analogy with the observation of Kohler and Reimer,<sup>5</sup> that ethyl  $\alpha$ -cyanocinnamate reacts with phenylmagnesium bromide to yield exclusively ethyl  $\alpha$ -cyano- $\beta,\beta$ -diphenylpropionate through a 1,4-addition mechanism, we attempted the reaction of methyl  $\alpha$ -cyanocrotonate with 6-methoxy-2-naphthylmagnesium bromide. This led to an oily reaction product (I) which upon heating with alkali produced a crystalline acid formulated as II. When



heated above the melting point, the latter lost carbon dioxide to give the amide III which was then saponified to  $\beta$ -methylallenolic acid methyl ether (IV). The resistance of the amide group of II toward strong alkali is only apparent and finds an explanation in the very low solubility of the sodium salt of II in alcohol. Since a 1,2-addition of the Grignard reagent to methyl  $\alpha$ -

(1) Abstracted from the Ph.D. thesis of B. Belleau, presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy, McGill University, 1950.

(2) The Sloan-Kettering Institute for Cancer Research, New York, N. Y.

(3) R. Courrier, A. Horeau and J. Jacques, *Compt. rend. soc. biol.*, **141**, 747 (1947).

(4) A. Horeau and J. Jacques, *Bull. soc. chim. France*, **58** (1947); J. Jacques and A. Horeau, *ibid.*, 707 (1948).

(5) E. P. Kohler and M. Reimer, *Am. Chem. J.*, **33**, 333 (1905).