[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Addition of α-Naphthylmethylmagnesium and α-Naphthylmethylcadmium Chlorides to Alkylidenemalonic Esters

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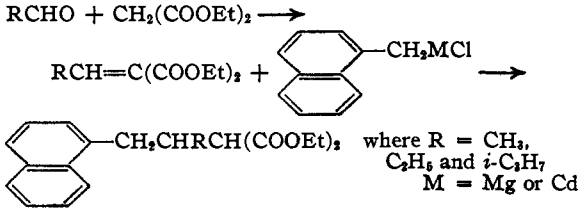
An investigation of the tumor producing activity of polycyclic hydrocarbons structurally related to the steroids[3] motivated this study. The intermediates required for the preparation of 3-alkyl-3′-keto-1,2-cyclopentenophenanthrenes by by the Stobbe synthesis, as recently developed by Johnson and co-workers,[4] are β-alkyl-γ-(1-naphthyl)-butyric acids. These substituted butyric acids can be readily prepared from the corresponding ethyl α-carbethoxy-β-alkyl-γ-(1-naphthyl)-butyrates. The synthesis of these malonic esters, by the usual method of alkylating diethyl malonate, is not suitable because the preparation of the necessary secondary alkyl halides is generally tedious and the yields from the alkylation[5] are unsatisfactory. The low yields from the latter reaction can be attributed to the tendency for this type of halide, 1-(1-naphthyl)-2-bromoalkane, to undergo the elimination of hydrogen bromide in the presence of bases[6] and to the slowness of the reaction leading to the alkylation of malonic esters with secondary halides.

A modification of the method, discovered by Kohler,[7] for the synthesis of malonic esters was particularly suited to the present problem. Kohler found that phenyl- or methylmagnesium bromide reacted exclusively by 1,4-addition to benzalmalonic ester. In order to obtain the esters desired in the present work, it was convenient to add the Grignard reagent obtained from α-chloromethylnaphthalene to alkylidenemalonic esters. The reactants did not yield exclusively the primary 1,4-addition product and certain more complex products were also obtained. Since the interest of this work was centered upon the synthetic aspect of the problem, these latter substances were not investigated.



The alkylidenemalonic esters are very readily prepared from the corresponding aldehydes and malonic ester. The yield of the 1,4-addition product from these esters was substantially increased by the use of α-naphthylmethylcadmium chloride instead of the usual Grignard reagent[8] as shown in Table I. The cadmium compound can be prepared so easily from the Grignard reagent that this conversion does not materially increase the complexity of the synthesis. Piperidinium acetate seems to catalyze the 1,4-addition of the organo-cadmium reagent. For the reasons just stated, this effect was not thoroughly investigated but certainly merits further work.

TABLE I

ADDITION PRODUCT FROM REACTION OF α-NAPHTHYLMETHYLMAGNESIUM OR CADMIUM CHLORIDES WITH DIETHYL ALKYLIDENEMALONATE

Alkylidene ester	Yield, % Magnesium	Yield, % Cadmium
Ethylidene	45	60
Propylidene	55	65
Isobutylidene	68	77

The 1,4-addition product had the normal[9] α-naphthylmethyl group. The identity of the product obtained from diethyl ethylidenemalonate and α-naphthylmethylmagnesium chloride with that obtained from the alkylation of diethyl malonate with 1-(1-naphthyl)-2-bromopropane was established. The dicarboxylic and monocarboxylic acids derived from the above esters by hydrolysis and decarboxylation were shown to be identical by melting points and mixture melting points. By analogy to these results, the course of the reaction with the other alkylidenemalonic esters studied has been assumed to be normal with respect to the α-naphthylmethyl group. The ethyl α-carbethoxy-β-alkyl-γ-(1-naphthyl)-butyrates and their corresponding dicarboxylic and monocarboxylic acids have been characterized.

The synthesis of substituted butyric acids described in this paper leads directly to a convenient preparation of 3-alkyl and aryl phenanthrenes by the excellent methods reported by Bachmann[5] for the preparation of 3-methylphenanthrene. The tetracyclic hydrocarbons prepared from these intermediates will be described in a subsequent publication.

Experimental[10]

Addition of 1-Naphthylmethylmagnesium Chloride to Diethyl Ethylidenemalonate.—A solution of 1-naphthylmethylmagnesium chloride was prepared in the manner described by Grummitt and Buck[11] from 1-chloromethyl-

(1) Anna Fuller Fund Research Associate, 1942–1943.

(2) Anna Fuller Fund Research Associate, 1943–1944.

(3) B. Riegel, M. H. Gold and M. A. Kubico, THIS JOURNAL, **64**, 2221 (1942); **65**, 1772 (1943).

(4) W. S. Johnson and J. W. Petersen, *ibid.*, **67**, 1366 (1945).

(5) W. E. Bachmann and G. D. Cortes, *ibid.*, **65**, 1329 (1943).

(6) E. D. Hughes, C. K. Ingold, S. Masterman and B. J. McNulty, *J. Chem. Soc.*, 899 (1940).

(7) E. P. Kohler, *Am. Chem. J.*, **34**, 132 (1905).

(8) H. Gilman and R. H. Kirby, THIS JOURNAL, **63**, 2046 (1941).

(9) H. Gilman and J. E. Kirby, *ibid.*, **51**, 3475 (1929).

(10) All melting points are corrected. Microanalyses by Dr. T. S. Ma, University of Chicago.

(11) O. Grummitt and A. C. Buck, THIS JOURNAL, **65**, 295 (1943).

TABLE II

	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$C_{10}H_7CH_2CH(C_2H_5)CH(COOEt)_2$	Oil[a]	73.66	73.65	7.66	7.72
$C_{10}H_7CH_2CH(i\text{-}C_3H_7)CH(COOEt)_2$	Oil[b]	74.12	74.17	7.92	7.44
$C_{10}H_7CH_2CH(C_2H_5)CH(COOH)_2$	169–171 d.	71.31	71.35	6.34	6.70
$C_{10}H_7CH_2CH(i\text{-}C_3H_7)CH(COOH)_2$	183–185 d.	72.00	72.48	6.71	7.18
$C_{10}H_7CH_2CH(C_2H_5)CH_2COOH$	Oil[c]				
$C_{10}H_7CH_2CH(i\text{-}C_3H_7)CH_2COOH$	124–125 d.	80.41	80.15	7.57	7.72

[a] B. p. 176–180° at 0.3 mm. and $n^{20}D$ 1.5434. [b] B. p. 182–183° at 0.3 mm. and $n^{20}D$ 1.5418. [c] *p*-Bromophenacyl ester: m. p. 106–107°. *Anal.* Calcd. for $C_{24}H_{23}O_3Br$: C, 65.61; H, 5.28. Found: C, 66.06; H, 5.27. Mixture melting point with *p*-bromophenacyl bromide, 80–100°.

naphthalene (35 g., 0.21 mole), magnesium (15 g., 0.62 g. atom), and 500 ml. of anhydrous ether. The solution was separated from the excess magnesium, transferred to a clean flask and cooled in ice. A solution of diethylethylidenemalonate[12] (30 g., 0.16 mole) in 75 ml. of ether was added slowly to the rapidly stirred reagent. After the addition was completed, the temperature of the mixture was allowed to approach that of the room, the stirring being continued for two hours. The mixture was then poured over ice and hydrochloric acid (a 10% excess over the calculated amount) and the product separated. It was washed successively with dilute acid, aqueous sodium bicarbonate, and water, then dried over anhydrous magnesium sulfate. **Ethyl α-carbethoxy-β-methyl-γ-(1-naphthyl)-butyrate** (22 g., 42%), distilled at 170–175° at 0.3 mm.; $n^{20}D$ 1.5470.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.35; H, 7.44.

α-Carboxy-β-methyl-γ-(1-naphthyl)-butyric Acid.—The above ester (2.3 g., 0.007 mole) was heated for four hours with a solution of 2.5 g. potassium hydroxide in 30 ml. of methanol and 5 ml. of water. The alcohol was removed in a stream of air, the residue dissolved in water, and the solution separated from solid impurities by filtration through a shallow bed of charcoal. The filtrate was acidified with 6 *N* hydrochloric acid, whereupon an oil separated which solidified slowly upon standing at ice temperature. The crude acid was collected on a filter and dried (1.7 g., m. p. 150–152° dec.). After repeated recrystallizations from dilute alcohol, the acid was obtained in the form of shining platelets, m. p. 159–160° dec.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.17; H, 5.62.

A mixture melting point with a sample prepared by the method described by Bachmann and Cortes[5] was identical to the above.

β-Methyl-γ-(1-naphthyl)-butyric Acid.—The acid from the preceding preparation was decarboxylated by heating at 190° for thirty minutes. It was recrystallized from dilute alcohol. The melting point of this acid and a mixture melting point with a sample prepared in another way[5] were identical, 91–92° (dec.).

Addition of 1-Naphthylmethylmagnesium Chloride to Diethyl Propylidenemalonate and Diethyl Isobutylidenemalonate.[13]—These preparations were carried out in the manner described for diethyl ethylidenemalonate. The products were distilled, hydrolyzed to the corresponding malonic acids and these in turn were decarboxylated as above. The properties of these materials are given in Table II.

Addition of 1-Naphthylmethylcadmium Chloride to Diethyl Alkylidenemalonates.—To a well-cooled solution of 1-naphthylmethylmagnesium chloride prepared from 35 g. of chloromethylnaphthalene was added anhydrous cadmium chloride (36 g., 0.20 mole) in several portions. When the addition had been completed, 200 ml. of dry benzene was added and the mixture stirred at room temperature for one-half hour. A solution of the appropriate ester (0.16 mole) in 100 ml. of ether was added slowly to the cooled reagent. After the addition was completed, the mixture was stirred for thirty minutes longer and allowed to stand overnight. The product was separated in the usual manner. The yields were uniformly better than those obtained by use of the Grignard reagent with the corresponding ester (Table I).

For the propylidenemalonic ester it was definitely established that a small amount of piperidine and acetic acid catalyze the 1,4-addition of the organo-cadmium reagent. After this discovery, piperidinium acetate was added to the other two addition reactions.

Summary

1. α-Naphthylmethylmagnesium chloride adds readily to alkylidenemalonic esters to give ethyl α-carbethoxy-β-alkyl-γ-(1-naphthyl)-butyrates.

2. The organo-cadmium reagent gave better yields than the Grignard reagent in this reaction.

3. Piperidinium salts apparently catalyze this addition.

4. From the now readily available α-naphthyl substituted butyric acids, 3-alkyl and aryl phenanthrenes and 1,2-cyclopentenophenanthrenes can be prepared.

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(12) The method of E. Knoevenagel, *Ber.*, **31**, 730 (1898), was used for its preparation; however, its physical constants are recorded by K. v. Auwers and F. Eisenlohr, *J. prakt. Chem.*, [2] **84**, 101 (1911).

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