[From the Department of Chemistry, University of California]

THE SYNTHESIS OF 20-METHYLCHOLANTHRENE LABELED IN THE 11-POSITION WITH CARBON FOURTEEN[1]

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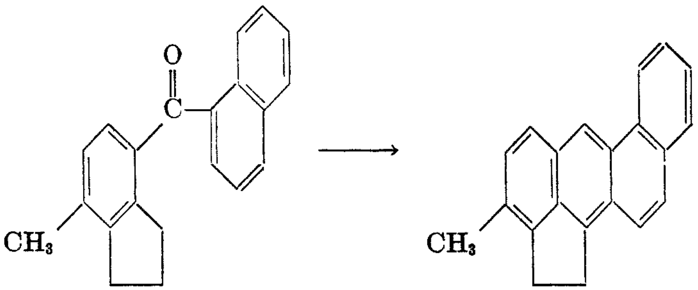
In connection with investigations (1) under way in this university concerning the distribution and the metabolism of carcinogenic hydrocarbons, it was desired to prepare 20-methylcholanthrene labeled with C^{14}. All of the reported syntheses (2, 3, 4) of this carcinogen (II) make use of the Elbs reaction (5) on 4-(1-naphthoyl)-7-methylhydrindene (I).



I II

Three routes to this desired ketone have been described. The method of Fieser and Seligman (2), using 4-cyano-7-methylhydrindene and 1-naphthylmagnesium bromide, gives the ketone in 89% yield. Bachmann (4) has reported that this same ketone is obtained in only 49% yield when the Grignard reagent of 4-bromo-7-methylhydrindene is condensed with 1-naphthonitrile. From the viewpoint of a synthesis using C^{14}, neither of these two methods is highly desirable, since the cyano compound must be prepared from sodium cyanide. The preparation of inorganic cyanide from barium carbonate, the form in which radioactive carbon is received at present, is known to be troublesome and erratic.[2]

Fieser and Seligman (3) also have prepared the ketone in 45% yield by allowing 1-naphthoyl chloride to react with the Grignard reagent of 4-bromo-7-methylhydrindene. This method would be desirable since 1-naphthoic acid could easily be prepared by the carbonation of 1-naphthylmagnesium bromide with radioactive carbon dioxide. However, in view of low yield obtained in the above condensation, other methods of preparation of the desired ketone, employing the acid chloride, were investigated.

It was found that when 1-naphthoyl chloride was allowed to react with the cadmium derivative of 4-bromo-7-methylhydrindene, 4-(1-naphthoyl)-7-methyl-

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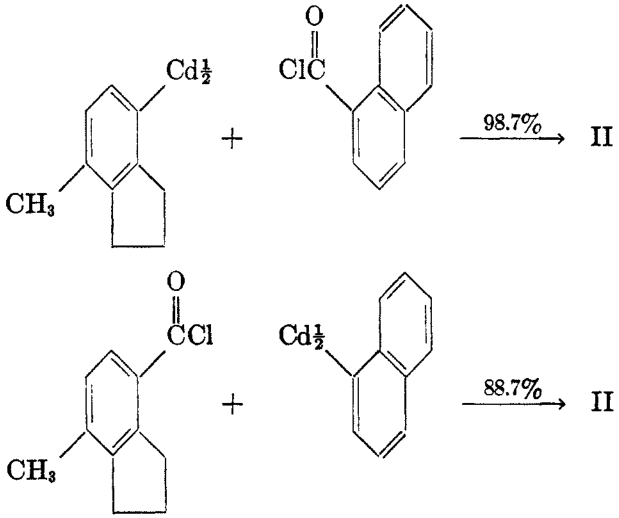
[2] Since this work was completed, Loftfield (6) has reported that sodium cyanide can readily be prepared from barium carbonate in a yield of 96%.

hydrindene was isolated in 98.7% yield. When the acid chloride of 4-carboxy-7-methylhydrindene was allowed to react with *bis*-(1-naphthyl)cadmium, the ketone was obtained in 88.7% yield.



It is interesting to note that when the nitrile method is employed the yield varies from 48% to 89% depending on whether 4-cyano-7-methylhydrindene or 1-naphthonitrile is used. However, when the above cadmium method is employed, little difference in yield is found.

In order to evaluate more fully each of the above schemes, the two acids were prepared in the manner usually employed for carbonation with radioactive carbon (7). It was found that when 1-naphthylmagnesium bromide was carbonated, 1-naphthoic acid was formed in 82% yield. When the Grignard of 4-bromo-7-methylhydrindene was treated in similar manner, 4-carboxy-7-methylhydrindene was isolated in a yield of only 64%.

20-Methylcholanthrene-11-C^{14} (3-methylcholanthrene-6-C^{14}) was prepared by the route employing 1-naphthoic acid. The over-all yield based on radioactive barium carbonate was 30.6%.

It is found that if the volatile by-products of the Elbs pyrolysis are burned, the carbon dioxide received is highly radioactive. A similar result was obtained in the preparation of radioactive 1,2,5,6-dibenzanthracene (1). Fieser has postulated (5) that in this reaction, the ketone suffers some cleavage by the water evolved, and perhaps the acid formed is subsequently decarboxylated. This might explain the presence of the radioactive carbon in the volatile gases. It was not determined, however, if the carbon dioxide was evolved from the reaction directly.

EXPERIMENTAL[3]

Carboxyl-labeled 1-naphthoic acid. 1-Naphthylmagnesium bromide was prepared in an all-glass apparatus in a nitrogen atmosphere from 0.75 g. (0.031 mole) of magnesium and

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[3] All melting points are uncorrected.

6.2 g. (0.03 mole) of 1-bromonaphthalene in a mixture of 50 cc. of anhydrous ether and 10 cc. of dry benzene. An aliquot of the solution was titrated and the concentration was found to be 0.0005 mole of Grignard reagent per cc. of solution.

A volume of 42 cc. (0.021 mole) of the Grignard solution was carbonated with carbon dioxide generated from 3.640 g. (0.0184 mole) of radioactive barium carbonate, following the procedure described in previous publications (1, 7). The barium carbonate contained approximately 4.4 millicuries of carbon fourteen. The reaction was conducted at 0°, and was processed in the usual manner. The acid was isolated by extraction with 100 cc. of 1 *N* sodium hydroxide and was recrystallized from 25 cc. of dry toluene (Norit). The acid melts from 162.5–163.5° and the yield was 2.596 g. (82.4%).

Carboxyl-labeled 1-naphthoyl chloride. The carboxyl-labeled 1-naphthoic acid, 2.480 g. (0.014 mole), was heated on a steam-bath for 2 hours with 10 cc. of purified thionyl chloride. The excess reagent was removed at reduced pressure and the residual acid chloride was dissolved in dry benzene and the benzene distilled. This process was repeated two times, and the acid chloride was finally dissolved in 10 cc. of benzene.

Carbonyl-labeled 4-(1-naphthoyl)-7-methylhydrindene. A mixture of 12.3 g. (0.058 mole) of 4-bromo-7-methylhydrindene, 1.46 g. (0.06 mole) of magnesium, and a few drops of ethyl iodide in 50 cc. of ether and 20 cc. of benzene was refluxed in a nitrogen atmosphere for 24 hours. The resulting Grignard reagent was converted into the dialkylcadmium compound with 6.4 g. (0.035 mole) of anhydrous cadmium chloride (8). After refluxing the mixture for 1 hour, the solvents were distilled and 25 cc. of benzene was added. A solution of the carboxyl-labeled 1-naphthoyl chloride prepared above was added to the refluxing suspension of the cadmium compound, and the resulting mixture was heated for 1 hour. The reaction mixture was decomposed with dilute hydrochloric acid and the mixture distilled with steam to remove the volatile neutral products and the benzene. The remaining aqueous suspension of the sirup was extracted with ether and the ethereal solution washed with water, 1 *N* sodium hydroxide, water, and dried. The product distils at 223–225° at 2 mm. and the yield was 4.063 g. (98.7% based on the acid).

20-Methylcholanthrene-11-C^{14}. The Elbs reaction was run in a small distillation flask with a sealed-on receiver, and was heated in a salt-bath at 405–410°. Four and six-hundredths grams (0.0145 mole) of 4-(1-naphthoyl)-7-methylhydrindene was pyrolyzed for 40 minutes, the evolved gases were passed directly into a combustion furnace, and the entire system swept with nitrogen. A precipitate of 265 mg. of highly radioactive barium carbonate was collected from the combustion.

When the reaction was complete, glass wool was added, the top of the flask sealed, and the methylcholanthrene was distilled at 1 mm., bath temperature 350–400°. The yellow distillate was dissolved in 70 cc. of *n*-propanol and the solution was concentrated to a volume of 45 cc. The yellow precipitate was recrystallized from 50 cc. of *n*-propanol, m.p. 176.5–177.5°, yield 1.436 g. (37.8%). Thus the over-all yield of methylcholanthrene, based on barium carbonate, is 30.6%.

4-Carboxy-7-methylhydrindene. The Grignard reagent of 4-bromo-7-methylhydrindene (0.006 mole) was carbonated with 1.06 g. (0.005 mole) of non-radioactive barium carbonate following the procedure used above. The acid was isolated by extraction with 1 *N* sodium hydroxide and was recrystallized from 12 cc. of ethanol. The yield was 0.60 g. (64%), and the acid melts at 223–225°. Fieser and Seligman (3) report the m.p. 227–229° (corr.).

4-(1-Naphthoyl)-7-methylhydrindene. 1-Naphthylmagnesium bromide was prepared from 3.1 g. (0.015 mole) of 1-bromonaphthalene as described above. The Grignard reagent was converted to *bis*-(1-naphthyl)cadmium by heating for 2 hours in benzene with 1.47 g. (0.008 mole) of anhydrous cadmium chloride. The resulting dialkylcadmium compound was allowed to react with 0.6 g. (0.003 mole) of the acid chloride of 4-carboxy-7-methylhydrindene and the reaction mixture was processed as described above. The resulting ketone boils at 223–225° at 2 mm., and the yield was 0.780 g. (88.7%).

Radioactivity measurements. The measurement of radioactivity was carried out with a thin-mica-window Geiger-Mueller tube on a scale of 64 circuit with a geometry of 17.6 ± 2.5 disintegrations per count. The activity was determined with thin, uniform layers of barium carbonate, according to the procedure described in earlier publications (7). The 20-methylcholanthrene-11-C^{14} has a specific activity of 150,000 cts/min/mg. barium carbonate, or 110,000 cts/min/mg. methylcholanthrene, or 0.88 microcurie/mg. methylcholanthrene.

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SUMMARY

1. 20-Methylcholanthrene-11-C^{14} has been synthesized in 30.6% over-all yield based on barium carbonate.

2. It has been shown that the yield of 4-(1-naphthoyl)-7-methylhydrindene is approximately the same whether the cadmium derivative of 4-bromo-7-methylhydrindene is allowed to react with 1-naphthoyl chloride, or *bis*-(1-naphthyl)cadmium is allowed to react with the acid chloride of 4-carboxy-7-methylhydrindene.

3. It has been found that the volatile by-products of the Elbs reaction result largely from the carbonyl carbon of the pyrolyzed ketone.

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