phenol hydrochloride in 500 cc. of water, 99 g. (0.5 mole) of 4,7-dichloroquinoline[16] was added. The mixture was heated in a steam-bath for two hours. After standing for two days, the yellow product was collected on a filter, washed with water and dried at 110°; yield 145 g. (94%); m. p. over 320°. A small sample was recrystallized from methanol for analysis.[17]

Anal. Calcd. for $C_{15}H_{11}ClN_2O\cdot HCl$: C, 58.64; H, 3.94. Found: C, 59.17; H, 4.11.

6-Chloro-9-(4-hydroxyanilino)-2-methoxyacridine.—This compound was obtained as the orange monohydrochloride by the foregoing procedure in 98% yield; m. p. over 300°. Trituration of a small sample with excess ammonia gave the free base. Recrystallized from dioxane, it melted at 266° (dec.).

Anal. Calcd. for $C_{20}H_{15}ClN_2O_2\cdot H_2O$: C, 65.13; H, 4.65. Found: C, 65.54; H, 4.62.

4-(7-Chloro-4-quinolylamino)-α-monoethylamino-o-cresol Dihydrochloride (Table XII, Compound 3).—A mixture of 30.7 g. (0.1 mole) of 7-chloro-4-(4-hydroxyanilino)-quinoline monohydrochloride, 6.3 g. (0.2 mole) of 95% paraformaldehyde, 27.2 cc. (0.2 mole) of alcoholic ethylamine, and 125 cc. of alcohol was heated at refluxing temperature for sixteen hours. Upon cooling, 9 g. of starting material was recovered unchanged. The filtrate was evaporated to dryness and the residue triturated with acetone to yield a solid which was collected on a filter. Treatment of this solid with 100 cc. of warm water left a total of 23.2 g. of unchanged starting material. The aqueous filtrate was made basic with ammonia, and the precipitated free base was extracted with chloroform. After being washed with water, the extract was dried over potassium carbonate. The filtered solution was evaporated to dryness, and the residue taken up in acetone. The addition of excess alcoholic hydrogen chloride precipitated a crude yellow salt. Recrystallized first from alcohol and then from alcohol–methanol, only 1.5 g. (4% yield) of the desired product was obtained; m. p. 280° (dec.).

4-(6-Hydroxy-4-quinolylamino)-α-diethylamino-o-cresol Dihydrochloride (Table IX, Compound 2).—A mixture of 10 g. of 4-(6-methoxy-4-quinolylamino)-α-diethylamino-o-cresol dihydrochloride (Table IX, compound 3) and 100 cc. of 48% hydrobromic acid was heated at boiling temperature for two hours. The mixture was made basic with ammonia, precipitating a yellow solid base. This was collected on a filter, washed with water, converted to the dihydrochloride by treatment with alcoholic hydrogen chloride.

(16) Obtained through Dr. R. C. Elderfield from the University of Illinois.

(17) Microanalysis by Arlington Laboratories.

Summary

A group of 122 heterocyclic-amino α-amino-o-cresols and a related group of 12 heterocyclic-amino benzylamines have been synthesized with the object of finding the most effective antimalarial compounds in the general class. All these compounds are new. For the purpose of studying the relationship of chemical structure to antimalarial effectiveness, they have been classified in seven tables. Preparation of the intermediate acetamidophenols, acetamido-α-alkylamino-o-cresols, α-alkylamino-4-nitro-o-cresols, nitrobenzylamines, and 4-chloroquinolines is also described.

This general class includes the most active 4-aminoquinolines heretofore reported in trophozoite-induced *P. gallinaceum* infection in the chick. Recent clinical reports on one member of the series (Camoquin) are promising.

DETROIT 32, MICHIGAN RECEIVED OCTOBER 14, 1947

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

A New Synthesis of Cinnoline Derivatives: Heterocyclic Steroid Analogs

BY EDMUND C. KORNFELD

In connection with another synthetic problem in progress in these laboratories *m*-hydroxyphenylacetic acid (I) was coupled in alkaline solution with diazotized *p*-nitroaniline (II) to form the azo dye (III) in the normal fashion. It was planned to carry out reactions on the carboxyl group of this product, and in order to effect these changes it was necessary to protect the free hydroxyl function. The azo compound was, therefore, subjected to the action of acetic anhydride in the presence of a trace of sulfuric acid as catalyst, and from the resulting reaction mixture was isolated in good yield a non-acidic, yellow, crystalline product. The analyses indicated that one acetyl group had been introduced, but they showed also that one molecule of water had been eliminated under the acetylating conditions. From the properties and reactions of the product it was evident that cyclization to a cinnoline derivative (V) had taken place. The steps in the process involved first a cyclization of the azo compound in its tautomeric form (IIIa) to 2-*p*-nitrophenyl - 3,6 - diketo - 2,3,4,6 - tetrahydrocinnoline (IV) and then acetylation of the enol form of IV to yield 2-*p*-nitrophenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline (V).

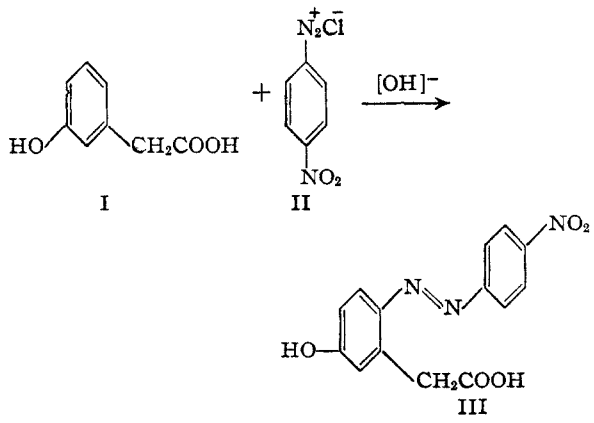
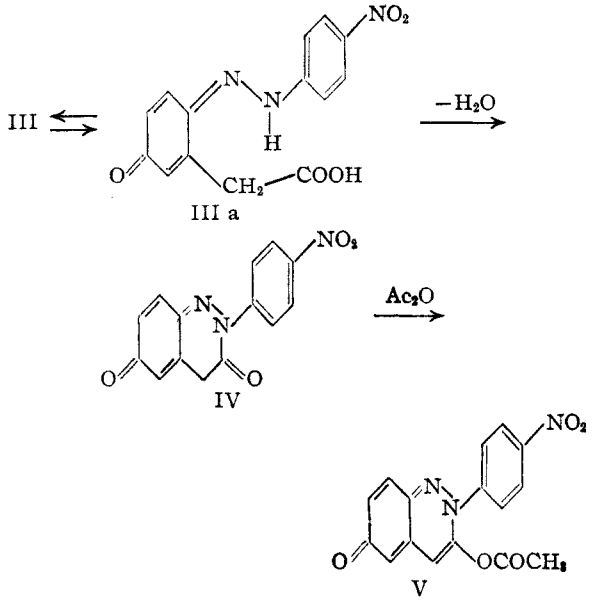


TABLE I

2-ARYL-3-ACETOXY-6-KETO-2,6-DIHYDROCINNOLINES

Aryl =	Yield, %[a]	M. p., °C.	Solvent[b]	Formula	% Composition Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
-phenyl	72	216–218	A	$C_{16}H_{12}N_2O_3$	68.56	68.30	4.32	4.40
-4-bromophenyl	71	226–228	B	$C_{16}H_{11}BrN_2O_3$[c]	53.50	53.41	3.09	2.98
-4-nitrophenyl	70	239–241	A	$C_{16}H_{11}N_3O_5$[d]	59.08	59.08	3.41	4.19
-4-carboxyphenyl	90	>290	C	$C_{17}H_{12}N_2O_5$	62.96	63.22	3.73	4.24
-4-acetaminophenyl	81	260–265 (dec.)	D	$C_{18}H_{15}N_3O_4$	64.09	64.00	4.48	4.79
-3-pyridyl	67	213–215	E	$C_{15}H_{11}N_3O_3$	64.05	64.20	3.94	4.01
-2-naphthyl	58	188–189	F	$C_{20}H_{14}N_2O_3$	72.72	72.55	4.27	4.51
-4-acetoxyphenyl	70	220–223 (dec.)	C	$C_{18}H_{14}N_2O_5$	63.90	63.56	4.17	3.89
-4-acetylphenyl	83	220–222	C	$C_{18}H_{14}N_2O_4$	67.07	67.03	4.38	4.38
-3-acetylphenyl	84	237–239 (dec.)	C	$C_{18}H_{14}N_2O_4$	67.07	66.22	4.38	4.36
-4-acetoxyacetylphenyl	68	237–238 (dec.)	C	$C_{20}H_{16}N_2O_6$	63.15	62.40	4.24	4.26

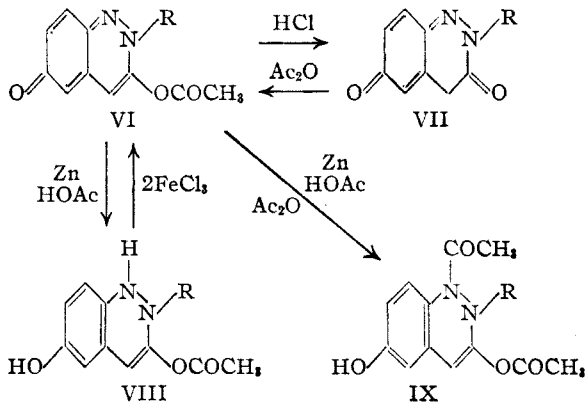
[a] Based on azo compound. [b] Solvent used in recrystallization, A = dioxane–ether, B = dioxane, C = acetic acid, D = dilute acetic acid, E = pyridine–ethanol, F = dilute dioxane. [c] Calcd.: N, 7.80. Found: N, 7.76. [d] Calcd.: N, 12.92. Found: N, 12.36.



Tautomerism of the type III ⇄ IIIa is well known and has been thoroughly studied by previous investigators.[1]

Further investigation proved the above reaction to be quite a general one. A number of diazotized aromatic amines were coupled with *m*-hydroxyphenylacetic acid, and the resulting azo compounds were cyclized with great facility to cinnoline derivatives similar to V. Table I lists the properties of these products. In most cases the azo compounds were used for the cyclization reaction without purification.

Evidence supporting the above proposed formulations was obtained from several of the reactions of the cinnoline derivatives. Hydrolysis of the monoacetyl compound (VI) (R = 3-acetylphenyl) with concentrated hydrochloric acid produced the 2-*m*-acetylphenyl-3,6-diketo-2,3,4,6-tetrahydrocinnoline (VII). Reacetylation of VII regenerated the starting material (VI). Reduction of VI (R = 3-acetylphenyl, 2-naphthyl, or 4-acetoxyphenyl) with zinc dust and acetic acid



gave the corresponding colorless, phenolic, dihydro derivatives (VIII), which could be oxidized by means of ferric chloride at room temperature to the original quinonoid compound (VI). When the reduction was conducted in the presence of acetic anhydride, two hydrogen atoms and one acetyl group were introduced. The structure of the product is probably IX (R = 2-naphthyl in this case) since amines are more readily acetylated than phenols under these conditions.[2]

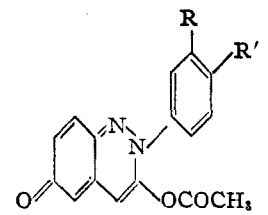
The ultraviolet absorption spectra of the first three cinnoline derivatives in Table I were determined in ethanol, and that of 2-phenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline is shown in Fig. 1. This compound shows maxima at 235, 330 and 413 mμ, while the 4-bromophenyl derivative has peaks at 235, 338 and 415 mμ. The corresponding maxima for the 4-nitrophenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline lie at 239, 311 and 415 mμ. For clarity and because of the close similarity of these spectra only one is shown in Fig. 1.

The gross structural resemblance of these 2-phenyl-cinnoline derivatives to the basic ring system of the steroid hormones prompted the prepa-

(1) Fierz-David, *et al.*, *Helv. Chim. Acta*, **29**, 1718, 1765 (1946).

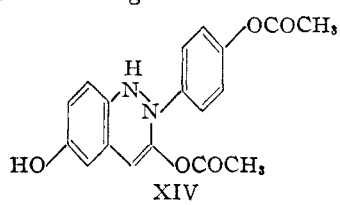
(2) Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., New York, N. Y., 1941, p. 398.

ration of several new heterocyclic steroid analogs by the method outlined above. 2-*p*-Acetoxyphenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline (X)



X R = H, R′ = $OCOCH_3$
XI R = H, R′ = $COCH_3$
XII R = $COCH_3$, R′ = H
XIII R = H, R′ = $COCH_2OCOCH_3$

resembles the testosterone esters, while 2-*p*-acetylphenyl - 3 - acetoxy - 2,6 - dihydrocinnoline (XI), and its isomer (XII) are related to progesterone. Finally, 2-*p*-acetoxyacetylphenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline (XIII) was prepared as an analog of desoxycorticosterone acetate. In the partially reduced series 2-*p*-acetoxyphenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline (X) on reduction with zinc and acetic acid gives the corresponding phenolic derivative (XIV) which is a model for the estrogenic hormones.



XIV

The aromatic amine intermediates requisite for the preparation of these analogs were available by published procedures.

Pharmacology.—The various steroid analogs were tested for hormone activity by Drs. K. K. Chen, R. C. Anderson and E. D. Campbell of these laboratories. Compounds X, XIV, and XII showed one mouse unit of estrogenic activity at levels of 1800, 500 and 100γ, respectively. Analogs X and XII, however, had no testosterone or progesterone activity. Compound XIII, the analog of desoxycorticosterone, was found to be ineffective in maintaining adrenalectomized rats.

Acknowledgment.—The author is indebted to Dr. R. G. Jones for helpful suggestions throughout the course of this work.

Experimental[3]

***m*-Hydroxyphenylacetic Acid.**—*m*-Methoxyphenylacetothiomorpholide was prepared by the method of Schwenk and Bloch[4] from *m*-methoxyacetophenone, morpholine and sulfur. The thioamide (600 g.) was dissolved in a mixture of 1.5 l. of glacial acetic acid and 2.5 l. of concentrated hydrochloric acid, and the solution was refluxed for seventeen hours. The solvents were removed *in vacuo*, and water was added to the residue. The crude *m*-methoxyphenylacetic acid was filtered and washed with water and then dissolved in dilute sodium hydroxide. The solution was filtered, and the product was reprecipitated with hydrochloric acid. It was filtered, washed with water, and dried; yield, 60%. The methoxy compound (1.4 moles) was then dissolved in 750 ml. of hydriodic acid (sp. gr., 1.7), and the solution was refluxed for one and one-half hours while continuously separating the methyl iodide which was formed. The solvent was removed by distillation *in vacuo*, and the *m*-hydroxyphenylacetic acid was filtered and washed with a small portion of cold water. The crude, dry product weighed 153 g. (72%), and was easily purified by recrystallization from ethyl acetate–petroleum ether, m. p. 133–134°.

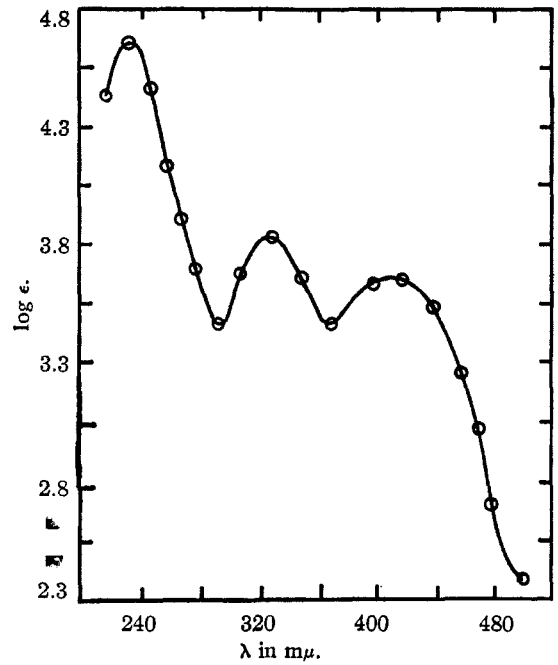


Fig. 1.—Ultraviolet absorption spectrum of 2-phenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline.

Coupling of Diazotized Aromatic Amines with *m*-Hydroxyphenylacetic Acid.—The amines used in this study were commercial products except for *p*-acetoxyaniline[5] and *p*-acetoxyacetylaniline.[6] The procedure employed in the preparation of the azo compounds was as follows: The amine was dissolved or suspended in ice and water containing 2.2 equivalents of hydrochloric acid, and the solution was diazotized with a slight excess of sodium nitrite below 0°. The diazo solution was then poured with stirring into a prepared solution of one equivalent of *m*-hydroxyphenylacetic acid and 4.2 equivalents of sodium hydroxide in ice water. Excess ice kept the temperature below 0° throughout. The bright orange solution was then filtered and acidified with acetic acid or hydrochloric acid. The azo compound was filtered, washed with water and dried. The yields averaged 84%. Analytic data for several of these coupling products are given in Table II. The other azo compounds

TABLE II

2-ARYLAZO-5-HYDROXYPHENYLACETIC ACIDS

Aryl =	Solvent	Formula	Percentage N Calcd.	Found
-C_6H_5	[a]	$C_{14}H_{12}N_2O_3$	10.93	10.50
-4-C_6H_4Br	Dil. acetone	$C_{14}H_{11}BrN_2O_3$	50.17[b]	50.10
-4-$C_6H_4NO_2$	Dil. ethanol	$C_{14}H_{11}N_3O_5$	13.95	14.29
-4-C_6H_4COOH	Dil. acetone	$C_{15}H_{12}N_2O_5$	9.33	9.21

[a] Purified by reprecipitation from ammonium hydroxide solution with acetic acid. [b] % C; % H: calcd. 3.31, found 3.06.

(3) All melting points are corrected.

(4) Schwenk and Bloch, THIS JOURNAL, **64**, 3051 (1942).

(5) Ruggli and Courtin, *Helv. Chim. Acta*, **15**, 75 (1932).

(6) Robinson and Robinson, *J. Chem. Soc.*, 1939 (1932).

were not purified but were used directly for the cyclization reaction.

Cyclization of Azo Compounds to Cinnoline Derivatives.—For the cyclization reaction the azo compounds were dissolved in about 10 parts of acetic anhydride containing 0.02 part of concentrated sulfuric acid, and the solutions were refluxed for thirty to sixty minutes. (The sulfuric acid was omitted in the case of the pyridine derivative derived from 3-aminopyridine.) The solutions were then concentrated *in vacuo* to a small volume, and ether was added. The products were filtered and washed thoroughly with ether. The other pertinent details are given in Table I.

Hydrolysis of 2-*m*-Acetylphenyl-3-acetoxy-6-keto-2,6-dihydrocinnoline (VI).—This acetyl compound (0.5 g.) was dissolved in 50 ml. of concentrated hydrochloric acid, and the solution was refluxed for fifteen minutes. The yellow product began to separate from the reaction mixture toward the end of the reflux period. The solvent was then distilled *in vacuo*, and water was added to the residue. The product was filtered and washed with water and dried. The yield was practically quantitative. Pure 2-*m*-acetylphenyl-3,6-diketo-2,3,4,6-tetrahydrocinnoline (VII) was obtained by precipitation from pyridine solution with ether, m. p. 290–300°, dec.

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32. Found: C, 68.53; H, 4.45.

Acetylation of 2-*m*-Acetylphenyl-3,6-diketo-2,3,4,6-tetrahydrocinnoline (VII).—The diketo compound (VII), when treated with acetic anhydride in the manner described above for the azo compounds, gave a 70% yield of VI.

Reduction of 2-β-Naphthyl-3-acetoxy-6-keto-2,6-dihydrocinnoline.—The quinonoid compound (1.8 g.) was dissolved in 100 ml. of boiling glacial acetic acid, and 3.6 g. of zinc dust was added gradually. After a few minutes the mixture was filtered through sintered glass and the filtrate was concentrated *in vacuo* to a small volume. Addition of water precipitated the product, which was obtained in the theoretical yield. The 2-β-naphthyl-3-acetoxy-6-hydroxy-1,2-dihydrocinnoline was purified by recrystallization from dilute methanol, and was obtained as colorless plates, m. p. 131–133°.

Anal. Calcd. for $C_{20}H_{16}N_2O_3$: C, 72.27; H, 4.85. Found: C, 72.60; H, 4.98.

Two other dihydro derivatives were similarly prepared: 2-*m*-acetylphenyl-3-acetoxy-6-hydroxy-1,2-dihydrocinnoline, m. p. 164–166°, 70%.

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.65; H, 4.97. Found: C, 66.15; H, 4.86. 2-*p*-Acetoxyphenyl-3-acetoxy-6-hydroxy-1,2-dihydrocinnoline (XIV), m. p. 164–165°, 83%. *Anal.* Calcd. for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74. Found: C, 63.32; H, 4.87.

Reductive Acetylation of 2-β-Naphthyl-3-acetoxy-6-keto-2,6-dihydrocinnoline.—This compound (2.0 g.) was dissolved in a mixture of 40 ml. of acetic anhydride and 20 ml. of glacial acetic acid, and 3 g. of zinc dust was added. The mixture was then refluxed for one-half hour, after which it was filtered and the filtrate concentrated *in vacuo* to a straw-colored oil. The oil was taken up in ether, washed with water, and the ether solution was dried over calcium chloride (acetone was added to prevent precipitation of the product at this point). Concentration of the ether solution *in vacuo* gave the product; yield, 32%. The 1-acetyl-2-β-naphthyl-3-acetoxy-6-hydroxy-1,2-dihydrocinnoline (IX) was recrystallized several times from benzene–petroleum ether for analysis, m. p. 141–143°.

Anal. Calcd. for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.57; H, 5.01; N, 7.66, 7.37.

Oxidation of 2-*m*-Acetylphenyl-3-acetoxy-6-hydroxy-1,2-dihydrocinnoline.—This colorless dihydro derivative (2.3 g.) was dissolved in 50 ml. of acetic acid at room temperature, and to it was added a solution of 4.0 g. of ferric chloride crystals in 5 ml. of water and 1.0 ml. of concentrated hydrochloric acid. Upon dilution of the solution with two volumes of water the yellow 2-*m*-acetylphenyl-3-acetoxy-6-keto-2-6-dihydrocinnoline separated. It was filtered and washed with water; yield, 84%; m. p. 236–238°, dec.

Summary

1. Azo dyes formed by coupling diazotized aromatic amines with *m*-hydroxyphenylacetic acid have been found to cyclize to 2-aryl-substituted cinnolines under acetylating conditions.

2. This new synthesis of cinnoline derivatives has been used to prepare heterocyclic analogs of the steroid hormones.

3. Several of the compounds show a slight estrogenic activity.

INDIANAPOLIS, INDIANA RECEIVED OCTOBER 20, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA, BERKELEY]

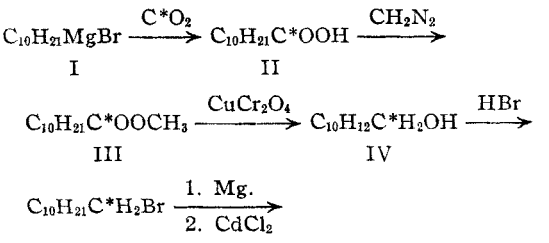
The Synthesis of Palmitic Acid and Tripalmitin Labeled with Carbon Fourteen

BY WILLIAM G. DAUBEN

Isotopic high molecular weight fatty acids, such as palmitic and stearic, have been prepared containing deuterium and radioactive bromine. In order to study the fate of the carbon chain itself, palmitic acid containing radioactive carbon was prepared.

The synthesis of palmitic acid labeled in the carboxyl group with C^{14} was readily accomplished, in a yield of 72%, by the carbonation of *n*-pentadecylmagnesium bromide with radioactive carbon dioxide.[1] Carboxyl-labeled tripalmitin was prepared from this acid in a yield of 75% by employing the acid chloride method of Stephenson.[2] The tripalmitin has a specific activity of 760 cts./min./mg. ester.

The preparation of *n*-hexadecanoic acid (palmitic acid) labeled at carbon atom six with C^{14} was carried out as shown in the scheme.



(1) Dauben, Reid and Yankwich, *Anal. Chem.*, **19**, 828 (1947).

(2) Stephenson, *Biochem. J.*, **7**, 429 (1913).