Anal. Calcd. for $C_4H_9NO_2S$: C, 35.53; H, 6.72. Found: C, 35.27; H, 6.87.

2,2-Dialkyl-1,3-propanediol bis(chloroformates).[8] *See Table* I. *2,2-Dimethyl-1,3-propanediol bis(chloroformate).* To a stirred solution of 16.0 g. (1.17 mole) freshly distilled phosgene in 400 ml. of dry toluene was slowly added a solution of 220 g. (1.17 mole) of antipyrine and 70 g. (0.53 mole) of 2,2-dimethyl-1,3-propanediol in 500 ml. of chloroform. The temperature was kept between −10° and 0° with an ice salt mixture. After the addition was completed, the mixture was warmed to room temperature and was stirred overnight. The antipyrine hydrochloride was filtered (yield nearly theoretical), washed with ether, and the combined filtrates evaporated *in vacuo*. Distillation of the yellow oily residue furnished 86 g. (56%) of pure 2,2-dimethyl-1,3-propanediol bis(chloroformate), b.p. 122–125° (17 mm.).

2,2-Dialkyl-1,3-propanediol bis(alkoxyalkylcarbamates). *See Table* II. Method I. *2,2-Dimethyl-1,3-propanediol bis(methoxymethylcarbamate).* To a stirred mixture of 3.0 g. (0.05 mole) *N*-methoxymethylamine[9] in 30 ml. of absolute ether and 5.0 g. (0.04 mole) of powdered anhydrous potassium carbonate was added with ice cooling 5.0 g. (0.025 mole) of 2,2-dimethyl-1,3-propanediol bis(chloroformate). Carbon dioxide was evolved slowly. The mixture was stirred at room temperature for 24 hr., following which the ether was evaporated and the residue was dissolved in 25 ml. of water. An oil separated and was extracted with ether. Upon evaporation of the dried extract, the crude biscarbamate remained as an oil. It was purified by distillation, yield 5.0 g. (86%), b.p. 183–184° (20 mm.). The microanalytical data are recorded in Table II.

Method II.[8a] *2,2-Diethyl-1,3-propanediol bis(methoxymethylcarbamate).* To 25.7 g. (0.1 mole) of 2,2-diethyl-1,3-propanediol bis(chloroformate) in 150 ml. of absolute ether was added dropwise 30.5 g. (0.5 mole) of *N*-methoxymethylamine with shaking and cooling. The hydrochloride of *N*-methoxymethylamine separated immediately and was filtered after the mixture had stood overnight at room temperature. The filtrate was washed with 25 ml. of water, dried over sodium sulfate, and the solvents evaporated. The oily residue furnished upon distillation 18.0 g. (60%) of biscarbamate, b.p. 163–165° (0.3 mm.). The microanalytical data are recorded in Table II.

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Synthesis of Coprostane-3α,7α,12α-triol-27-C^{14}, Coprostane-3α,7α,12α-triol-24-one-27-C^{14}, and Coprostane-3α,7α,12α,24ξ-tetrol-27-C^{14}

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A synthesis of coprostane-3α,7α,12α-triol (I), coprostane-3α,7α,12α-triol-24-one (II), and coprostane-3α,7α,12α,24-ξ tetrol (III) labeled at C_{27} with carbon-14 was required for studies of their metabolism and possible role as intermediates in the enzymatic conversion of cholesterol to cholic acid. Two methods of synthesizing I have been reported[2–4] These procedures were found to be unsuitable for the purpose intended because a large excess of relatively inaccessible carbon-14 intermediate was required or yields proved to be very poor in our hands. Cole and Julian[5] have reported an elegant method for the synthesis of steroid compounds with a ketonic group in the side chain. We have applied this procedure to prepare II using triformylcholyl chloride and diisopropylcadmium as the starting materials.

A preliminary report on the synthesis has already been given.[6]

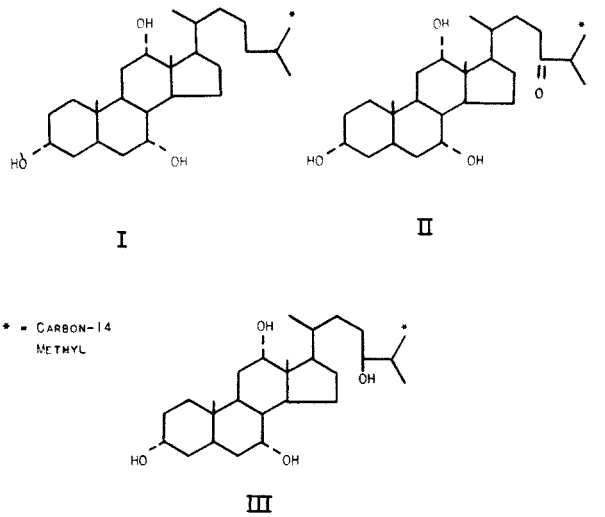

Figure 1.

EXPERIMENTAL

Materials. Triformylcholyl chloride was prepared from cholic acid by the method of Cortese and Bauman.[7] By modifying their crystallization procedure using benzene–petroleum ether (b.p. 60–80°) as solvent, triformylcholic acid was obtained as crystalline solid with m.p. 209–211°. This was converted to the acid chloride by treatment with oxalyl chloride. 2-Propanol-1,3-C^{14}[8] (specific activity 1.0 millicurie per millimole) was diluted twenty-fold with unlabeled 2-propanol and then converted to 2-bromopropane-1,3-C^{14} by reaction with phosphorus tribromide on a semimicro scale.

Coprostane-3α,7α,12α-triol-24-one-27-C^{14}. A Grignard re-

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agent was prepared from 2.40 g. 2-bromopropane-1,3-C^{14} (specific activity, 0.050 millicurie per millimole) and 0.600 g. magnesium turnings in 25 ml. anhydrous ethyl ether. The solution was cooled in an ice bath and stirred while 7.5 g. powdered anhydrous cadmium bromide (dried for 3 hr. at 120°) were added. After stirring for 30 min., the ice bath was removed and a solution of 1.50 g. triformylcholyl chloride, dissolved in 8 ml. anhydrous benzene, was added dropwise. Stirring was continued for 30 min. after the addition and the reaction mixture was heated to reflux for 1 hr. The mixture was then allowed to stand overnight. Ice water followed by sufficient 3*N* HCl solution to dissolve the precipitate was added to the reaction mixture. The benzene-ether layer was separated and washed with water until the washings were neutral. The washed solvent layer was then evaporated to dryness and the residual gum was dried *in vacuo*. This residue was saponified by heating for 1 hr. with 10 ml. 5% KOH in methanol solution. The saponification mixture was diluted with 100 ml. water and this solution was extracted with ethyl ether. The ether extract was evaporated to dryness. The residual crude ketone was subjected to chromatography on a silicic acid column. The column was washed through with benzene first and the ketone was eluted with ethyl ether–benzene (1:2). After evaporation of this eluate, 0.698 g. coprostane-3α,7α,12α-triol-24-one-27-C^{14} were obtained. Upon crystallizing twice from acetone solution, colorless crystals melting at 151–152° were obtained. This product had a specific activity of 0.051 millicurie per millimole. The infrared spectrum of this ketone exhibited a characteristic carbonyl absorption peak at 5.82 μ.

Anal. Calcd. for $C_{27}H_{46}O_4$: C, 74.60; H, 10.67. Found: C, 74.26; H, 10.63.

Coprostane-3α,7α,12α-triol-27-C^{14}. To 0.500 g. coprostane-3α,7α,12α-triol-24-one-27-C^{14} dissolved in 1 ml. ethanol, 1 ml. hydrazine hydrate (99%) was added. The mixture was swirled for a few minutes until a homogeneous solution resulted. To this solution was added 10 ml. triethylene glycol and 1 g. KOH. The mixture was heated and allowed to reflux for 30 min. The reflux condenser was then removed and the mixture heated at 180–200° for 2 hr. At the end of this period the reaction mixture was allowed to cool in a stream of nitrogen gas and it was then poured into 50 ml. of water. The precipitated compound was filtered, washed with water, and dried. The crude product was crystallized from acetone, 0.269 g. coprostane-3α,7α-12α-triol-27-C^{14} melting at 184–185° were obtained. Upon mixing with coprostane-3α,7α,12α-triol prepared by the previously cited procedure,[2] no depression in melting point was observed. The infrared spectra of the two samples were identical. Major absorption peaks were observed at 2.94 μ, 3.42 μ, 6.80 μ, 7.26 μ, 7.95 μ, 9.28 μ, 9.60 μ, 10.21 μ, 10.55 μ, 10.96 μ, and 11.70 μ.

Anal. Calcd. for $C_{27}H_{48}O_3$: C, 77.08; H, 11.50. Found: C, 77.04; H, 11.49.

Coprostane-3α,7α,12α,24ξ-tetrol-27-C^{14}. A solution containing 0.150 g. lithium aluminum hydride in 25 ml. anhydrous ethyl ether was prepared. To this solution in a flask provided with a magnetic stirrer and reflux condenser was slowly added a solution of 0.300 g. coprostane-3α,7α,12α-triol-24-one-27-C^{14} in 25 ml. anhydrous ethyl ether. Stirring was continued for 1.5 hr. at room temperature. The reaction mixture was cooled in ice and 20 ml. 2*N* H_2SO_4 solution was added slowly. The acidified reaction mixture was stirred for a few minutes and the ether layer separated and washed with water until the washings were neutral. The ether extract was then dried and evaporated to dryness. The residue was crystallized from acetone or benzene-petroleum ether to yield 0.102 g. coprostane-3α,7α,12α,24-ξ-tetrol-27-C^{14} melting at 169–170°. The infrared spectrum of this compound was qualitatively similar to that of compound I but showed an enhanced C—OH absorption peak at 2.94 μ.

Anal. Calcd. for $C_{27}H_{48}O_4$: C, 74.25; H, 11.08. Found: C, 74.14; H, 10.95.

Radiochemical purity of Compounds I, II, and III above was determined as follows: (1) A mixture of each radioactive compound and a large excess of corresponding unlabeled compound was recrystallized three times. No substantial changes (±5%) in specific activity were observed. (2) Samples of the radioactive compounds were chromatographed on paper together with samples of corresponding unlabeled compounds using the phenoxyethanol and heptane system of Neher and Wettstein[9] and the acetic acid and isopropyl ether–heptane system of Sjövall.[10] In each case practically all (90% or more) of the radioactivity was recovered from the spot corresponding to the unlabeled substance. (3) Compounds I and II were subjected to the reversed-phase partition column chromatographic procedure of Danielsson[11] modified by the use of 1:1 2-propanol–water mixture as the mobile phase. The weight and radioactivity curves of the eluted substances coincided in each case and the elution volumes corresponded to those obtained with unlabeled samples of each compound.

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Synthesis of Potential Anticancer Agents. XVIII. Analogs of Carbamoyl Phosphate[1]

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In an effort to uncover new classes of anticancer agents we have directed our attention to the synthesis of carbamoyl phosphate analogs, since carbamoyl phosphate has been shown to be involved in the *de novo* biosynthesis of pyrimidines, where it acts as the cofactor in the formation of *N*-carbamoylaspartic aicd.[2,3] The identity of this natural carbamoyl donor has been further corroborated by Hall,[4] who, in addition, has compiled a comprehensive bibliography on the subject.

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