was then decanted. The oil was dissolved in ethyl acetate, and the extract was washed four times with water, treated with magnesium sulfate and activated carbon, filtered through diatomaceous earth, and evaporated to afford 5.0 g. of glass (III) which would not crystallize.

The above glass dissolved in 70 ml. of 50% aqueous acetic acid was heated on a steam bath for 1 hr., water was added and the mixture was cooled. Crude IV which separated was collected and recrystallized from acetone–petroleum ether to give 2.3 g. (55%) of IV, m.p. 147–150°, which exhibited a positive Blue Tetrazolium test. A 300-mg. portion was crystallized three times from acetone–petroleum ether to give pure IV, m.p. 152.5–153.5°; $[\alpha]_D^{25}$ +125° (*c*, 1.21, chloroform); $\lambda_{max}^{abs.\ alc.}$ 238–239 mμ (ε 8,050).

*Anal.* Calcd. for $C_{23}H_{30}O_4$ (370.47): C, 74.56; H, 8.16. Found: C, 74.44; H, 8.34.

*16α,21-Diacetoxy-17α-hydroxy-9(11)-pregnene-3,20-dione* (Vb). To a solution of 21-acetoxy-9(11),16-pregnadiene-3,20-dione (IV) (2.22 g.) in benzene (30 ml.) and pyridine (1.0 ml.) was added 1.75 g. of osmic acid, and the solution was allowed to stand at room temperature for 20 hr. To this was added 100 ml. of water, 50 ml. of methanol, and 10.5 g. each of sodium sulfite and potassium bicarbonate. After the mixture was stirred vigorously for 5 hr., 100 ml. of chloroform was added and the mixture was filtered. The inorganic filter cake was washed with 200 ml. of hot chloroform. The organic layer was washed with water to neutral, treated with anhydrous sodium sulfate and activated carbon, filtered, and evaporated to afford a light brown glass. Crystallization from acetone–petroleum ether gave 1.03 g. of a light brown solid (Va), m.p. 171–177° (dec.).

The above material (1.03 g.) was dissolved in 10 ml. pyridine and 1.0 ml. acetic anhydride and the mixture was allowed to stand at room temperature for 64 hr. Evaporation of the solvents under reduced pressure gave a green oil which was dissolved in ethyl acetate, washed with dilute sulfuric acid, saturated sodium bicarbonate, and with water to neutral. Treatment with sodium sulfate and activated carbon, filtration, and evaporation gave 900 mg. of green oil which resisted attempts to crystallize. Chromatography on 45 g. of silica gel gave 700 mg. of glass by elution with 40% ether in benzene. Three crystallizations from acetone–petroleum ether gave 275 mg. of Vb, m.p. 175–190°; $[\alpha]_D^{25}$ ±0° (*c*, 1.09, chloroform).

*Anal.* Calcd. for $C_{25}H_{34}O_7$ (446.52): C, 67.23; H, 7.68. Found: C, 67.24; H, 7.88.

In another run with 2.7 g. of IV there was obtained 1.7 g. (52%) of Vb, m.p. 176–192°.

*16α,21-Diacetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione* (VII). To a solution of 16α,21-diacetoxy-17α-hydroxy-9(11)-pregnene-3,20-dione (Vb, 600 mg., 1.34 millimoles) in 2 ml. of dimethylformamide and 11 mg. of *p*-toluenesulfonic acid monohydrate was added 4.0 ml. of a bromine solution (0.345*M* in dimethylformamide, 1.38 millimoles) dropwise over 5 hr. After this period, 50 ml. of water were added, the mixture was cooled, and 600 mg. of white glass (VI) was obtained.

The above glass was dissolved in 8 ml. of dimethylformamide containing 400 mg. of lithium chloride and was heated for 2.5 hr. at 100° under an atmosphere of nitrogen. Addition of water gave a yellow paste, which was dissolved in ethyl acetate, washed three times with water, treated with magnesium sulfate and activated carbon, filtered, and evaporated to give 540 mg. of glass which would not lend itself readily to purification.

Chromatography on 45 g. of silica gel gave 200 mg. of solid [eluted with ether-benzene (1:1)]. Two crystallizations from acetone–petroleum ether gave 55 mg. of VII, m.p. 187–189°; $\lambda_{max}^{abs.\ alc.}$ 239 mμ (ε 14,200). One further crystallization from the same solvents gave 20 mg., m.p. 193–194°; $[\alpha]_D^{25}$ +36° (*c*, 1.248). Infrared spectral analysis showed identity with an authentic sample of VII, and admixture melting point gave no depression.

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## *O*-Alkyl Substituted Hydroxycarbamates

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Certain carbamates are used in human and veterinary medicine.[1] Ethyl carbamate has been used in the treatment of neoplastic diseases and as a mild hypnotic in man and animals. Meprobamate, $CH_3C(n\text{-}C_3H_7)(CH_2OCONH_2)_2$, is widely employed as a mild hypnotic and skeletal muscle relaxant.

There is evidence that some, but not all, *O*-alkyl substituted hydroxylamine derivatives possess pharmacological properties similar to those of the related amines.[2–5]

In the present work, ethyl hydroxycarbamate, $HONHCOOC_2H_5$, and a number of its *O*-alkyl derivatives have been prepared and examined pharmacologically. Ethyl hydroxycarbamate has been synthesized by the method of Jones,[6] except that it has been possible to obtain the hydroxycarbamate analytically pure by distillation *in vacuo*.

The related compound, ethyl methoxythionocarbamate, $CH_3ONHCSOC_2H_5$, has been prepared by the following series of reactions:[7]

$$C_2H_5OCSSNa + ClCH_2COONa \longrightarrow C_2H_5OCSSCH_2COONa \xrightarrow{CH_3ONH_2} C_2H_5OCSNHOCH_3$$

Various 2,2-dialkyl-1,3-propanediol bis(alkoxyalkylcarbamates), $R,R'C[CH_2OCON(R'')OR''']_2$, where R'' = H or alkyl, have been prepared by the following series of reactions:

(1) Osol-Farrar, *U. S. Dispensatory*, 25th ed., J. B. Lippincott Co., New York, N. Y., 1955, pp. 1477, 1861, 2038.

(2) L. W. Jones and R. T. Major, *J. Am. Chem. Soc.*, **49**, 1527 (1927).

(3) E. F. Rogers, D. Bovet, V. G. Longo, and G. B. Marini-Bettolo, *Experientia*, **9**, 260 (1953).

(4) G. Palazzo, E. F. Rogers, and G. B. Marini-Bettolo, *Gazz. Chim. Ital.*, **84**, 915 (1954).

(5) R. T. Major and L. G. Peterson, *J. Org. Chem.*, **22**, 579 (1957).

(6) L. W. Jones, *Am. Chem. J.*, **20**, 40 (1898).

TABLE I

2,2-DIALKYL-1,3-PROPANEDIOL BIS(CHLOROFORMATES)
$R,R'C(CH_2OCOCl)_2$

| R | R′ | B.P., °C. | Yield | Formula | Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|
| $CH_3$ | $CH_3$ | 122–125 (17 mm.) | 56% | $C_7H_{10}Cl_2O_4$ | 36.70 | 4.40 | 36.69 | 4.62 |
| $C_2H_5$ | $C_2H_5$ | 153–155 (24 mm.) | 64% | $C_9H_{14}Cl_2O_4$ | 42.04 | 5.49 | 41.73 | 5.54 |
| $C_2H_5$ | $n$-$C_4H_9$ | 165–168 (20 mm.) | 60% | $C_{11}H_{18}Cl_2O_4$ | 46.33 | 6.36 | 46.23 | 6.11 |

TABLE II

$R,R'C[CH_2OCON(R'')OR''']_2$

| R | R′ | R″ | R‴ | Method Used | B.P., °C. | Formula | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | I | 183–184 (20 mm.) | $C_{11}H_{22}N_2O_4$ | 47.47 | 7.97 | 10.07 | 47.05 | 7.97 | 9.84 |
| $CH_3$ | $CH_3$ | H | $CH_3$ | I | 194–195 (1 mm.) | $C_9H_{18}N_2O_4$ | 43.19 | 7.25 | 11.20 | 42.87 | 6.93 | — |
| $CH_3$ | $CH_3$ | $C_2H_5$ | $C_2H_5$ | II | 136–138 (0.15 mm.) | $C_{15}H_{30}N_2O_4$ | 53.87 | 9.04 | 8.38 | 54.43 | 9.06 | 8.07 |
| $CH_3$ | $CH_3$ | H | $C_2H_5$ | II | 175–180 (0.5 mm.) | $C_{11}H_{22}N_2O_4$ | 47.47 | 7.97 | 10.07 | 47.47 | 7.95 | 10.04 |
| $C_2H_5$ | $C_2H_5$ | $CH_3$ | $CH_3$ | II | 163–165 (0.3 mm.) | $C_{13}H_{26}N_2O_4$ | 51.00 | 8.55 | 9.14 | 51.05 | 8.22 | 8.56 |
| $C_2H_5$ | $C_2H_5$ | $C_2H_5$ | $C_2H_5$ | II | 133–138 (0.1 mm.) | $C_{17}H_{34}N_2O_4$ | 56.33 | 9.45 | 7.73 | 56.32 | 9.25 | 7.89 |
| $C_2H_5$ | $n$-$C_4H_9$ | $CH_3$ | $CH_3$ | II | 166–169 (0.3 mm.) | $C_{15}H_{30}N_2O_4$ | 53.87 | 9.04 | 8.38 | 53.83 | 8.89 | 8.52 |
| $C_2H_5$ | $n$-$C_4H_9$ | $C_2H_5$ | $C_2H_5$ | II | 142–148 (0.2 mm.) | $C_{19}H_{38}N_2O_4$ | 58.43 | 9.81 | — | 58.62 | 9.63 | — |

$$R,R'C(CH_2OH)_2 \xrightarrow[\text{toluene}]{COCl_2} R,R'C(CH_2OCOCl)_2 \xrightarrow[K_2CO_3]{2R''NHOR'''} R,R'C[CH_2OCON(R'')OR''']_2$$

The chloroformates needed in this synthesis were prepared by the method of Ludwig and Piech[8]; the biscarbamates were produced from these intermediates in 60–86% yield.

Dr. Donald A. Clarke of the Sloan-Kettering Institute for Cancer Research, New York, N. Y., has tested the following compounds *in vivo* for Sarcoma 180 inhibition: ethyl hydroxycarbamate[6]; ethyl methoxycarbamate[9]; ethyl ethoxycarbamate[9]; ethyl methoxythionocarbamate; 2,2-dimethyl-1,3-propanediol bis(methoxycarbamate) and bis(ethoxycarbamate); and 2-ethyl-2-*n*-butyl-1,3-propanediol bis(methoxymethylcarbamate). None of these compounds inhibited Sarcoma 180 at nontoxic doses.

Dr. C. A. Stone of the Merck Institute for Therapeutic Research, West Point, Pa., has examined the pharmacological properties of many of the compounds described in this paper. He has reported that ethyl ethoxycarbamate[9] showed little effect in mice when administered intraperitoneally in Mazola oil in doses below the toxic level of 441 mg. per kg. Ethyl ethoxyethylcarbamate[9] produced depression in mice in doses at or near the lethal level of 1069 mg. per kg. administered intraperitoneally. However, a 1% suspension of this compound in tragacanth abolished the corneal reflex for 18 min. when instilled into the rabbit eye. The biscarbamates with the structure $R,R'C[CH_2OCON(R'')OR''']_2$, where $R,R',R'',R''' = CH_3$; $R,R' = CH_3$, $R'' = H$ and $R''' = C_2H_5$; $R,R' = CH_3$ and $R''$, $R''' = C_2H_5$; $R,R' = C_2H_5$ and $R''$, $R''' = CH_3$; and $R = C_2H_5$, $R' = n$-$C_4H_9$ and $R'',R''' = CH_3$, were inactive in tests designed to evaluate their meprobamate-like activity in mice.

## EXPERIMENTAL

All melting points and boiling points are uncorrected.

*Ethyl hydroxycarbamate.* To a stirred mixture of 195 g. (2.80 mole) of hydroxylamine hydrochloride and 380 g. (2.75 mole) of anhydrous potassium carbonate, both finely powdered, with 1500 ml. of ether was added 20 ml. of water. Subsequently, with ice cooling 300 g. (2.77 mole) of ethyl chloroformate was added to the stirred mixture within about 1 hr. Carbon dioxide was evolved immediately. After the addition was completed the mixture was stirred overnight at room temperature, the potassium chloride was removed by filtration, and the filtrate was evaporated under a slight vacuum. The remaining colorless oil had an ester-like odor. Distillation through a 15-cm. Vigreaux column afforded 193 g. (66%) of ethyl hydroxycarbamate, b.p. 113–116°( 3 mm.), as a slightly hygroscopic odorless oil, which gave a deep purple color with aqueous ferric chloride.

*Anal.* Calcd. for $C_3H_7NO_3$: C, 34.28; H, 6.72; N, 13.33. Found: C, 34.47; H, 6.49; N, 13.72.

*Ethyl methoxythionocarbamate.* An aqueous solution of 0.30 mole sodium ethyl xanthate was prepared according to Davies and Maclaren.[7] To this was added an ice cold solution of sodium chloroacetate prepared by slowly neutralizing 39 g. (0.42 mole) of chloroacetic acid with 17 g. (0.42 mole) of sodium hydroxide in 180 ml. of cold water. After having stood overnight this mixture was evaporated to about 150 ml. on a water bath at reduced pressure. Methoxyamine (21 g., 0.45 mole) was added and the mixture kept at room temperature overnight. After being neutralized with acetic acid, it was extracted with ether. After the extract had been dried over sodium sulfate and the ether removed by evaporation at room temperature, a low melting solid remained; yield 37 g. (66%). Upon recrystallization from petroleum ether (30–60°), long needles were obtained, m.p. 33–36°.

(7) W. Davies and J. A. Maclaren, *J. Chem. Soc. (London)*, 1434 (1951).

(8) (a) B. J. Ludwig and E. C. Piech, *J. Am. Chem. Soc.*, **73**, 5779 (1951); (b) U. S. Patent **2,724,720**; (c) R. E. Oesper, W. Broker, W. A. Cook, *J. Am. Chem. Soc.*, **47**, 2609 (1925).

(9) R. T. Major and E. E. Fleck, *J. Am. Chem. Soc.*, **50**, 1479 (1928).

*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]

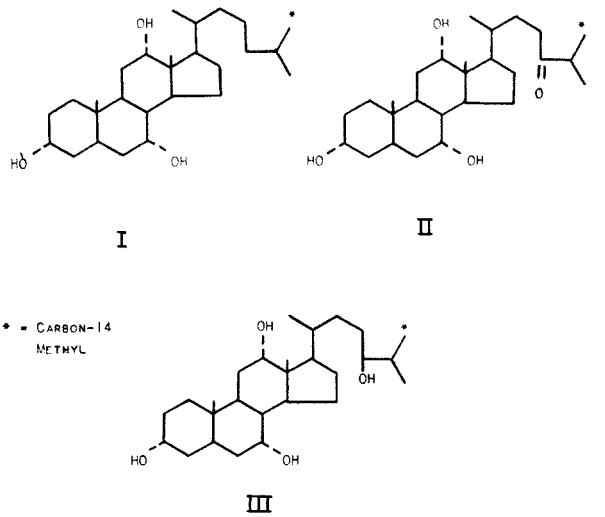


Figure 1.

### 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-

(1) This work was done during the tenure of an Established Investigatorship of the American Heart Association.

(2) T. Kazuno and A. Mori, *Proc. Japan Acad.*, **30**, 486 (1954).

(3) S. Bergström, K. Paäbo, and J. A. Rumpf, *Acta Chem. Scand.*, **8**, 1109 (1954).

(4) H. Seno, *Proc. Japan Acad.*, **30**, 887 (1954).

(5) W. Cole and P. L. Julian, *J. Am. Chem. Soc.*, **67**, 1369 (1945).

(6) E. Staple and M. W. Whitehouse, *Federation Proc.*, **16**, 254 (1957).

(7) F. Cortese and L. Bauman, *J. Am. Chem. Soc.*, **57**, 1393 (1935).

(8) Obtained from Nuclear Instrument and Chemical Corp., Chicago, Ill.