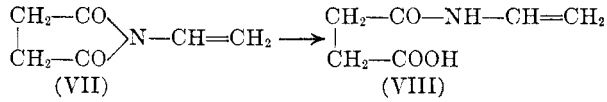
cating that the saponified product was IVa instead of IVb. In other words, a structure of the *N*-vinyl secondary amide type is stable.

By the similar saponification of *N*-vinylsuccinimide (VII), *N*-vinylsuccinamic acid (VIII), was obtained.



(VII) (VIII)

In the case of the saponification of *N*-vinylsaccharin, *o*-sulfamidobenzoic acid or saccharin was obtained.

## EXPERIMENTAL

*Materials.* *N*-Vinylphthalimide,[3] *N*-vinylsuccinamide,[4] and *N*-vinylsaccharin were prepared by the pyrolysis of *N*-2-acetoxyethylphthalimide, *N*-2-acetoxyethylsuccinimide, and *N*-2-acetoxyethylsaccharin respectively. *N*-Vinylsaccharin is a new compound, m.p. 131–132° (from ethanol).

*Anal.* Calcd. for $C_9H_7NO_3S$: C, 51.67; H, 3.37; N, 6.70. Found: C, 51.61; H, 3.36; N, 6.64.

*N-Vinylphthalamic acid* (IVa). Five grams of *N*-vinylphthalimide (III) was added to 50 ml. of 10% aqueous potassium or sodium hydroxide while stirring at room temperature, after which most of III was neutralized with 5% sulfuric acid under ice-cooling. The precipitate which was filtered and washed with water, was extracted with ethanol and the solvent was concentrated under reduced pressure and at room temperature, and then IVa was obtained, m.p. 110–111.5° (dec.). IVa was also obtained by saponification with ethanolic potassium hydroxide.

*Anal.* Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.32. Found: C, 62.72; H, 4.81; N, 7.25.

*Hydrogenation of* IVa. To 10 ml. of ethanol and 0.1 g. of Pd-black saturated with hydrogen in a hydrogenation vessel, 0.72 g. of IVa was added and hydrogenated with vigorous shaking under ordinary pressure and at room temperature. After hydrogenation was completed, the solution was filtered to remove the catalyst and the solvent was evaporated. Recrystallization of the residue from benzene gave 0.62 g. of *N*-ethylphthalamic acid (V), m.p. 133°. The mixed melting point of V with the authentic sample which was prepared by the saponification of *N*-ethylphthalimide was 132–133°.

*Anal.* Calcd. for $C_{10}H_{11}NO_3$: N, 7.25. Found: N, 7.13.

*Oxidation of* IVa *with potassium permanganate.* To the solution in which 1.7 g. of IVa was suspended by vigorous stirring in 30 ml. of water was added in 0.5 hr. another solution made by dissolving 0.86 g. of potassium permanganate in 60 ml. of water. Stirring was further continued for 20 min. after addition of potassium permanganate was completed. After addition of sodium hydrogen sulfide to the solution, the latter was extracted with 10 portions of 20 ml. of ethyl acetate. The extract was dried with anhydrous sodium sulfate and the solvent was evaporated. Recrystallization of the residue from ethanol gave 1.7 g. of VI, m.p. 150–151°.

*Anal.* Calcd. for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 55.77; H, 3.75; N, 6.98.

*N-Vinylsuccinamic acid* (VIII). Five grams of *N*-vinylsuccinimide (VII) was dissolved in 20 ml. of 10% aqueous sodium hydroxide. After the solution was filtered, the filtrate was neutralized with 5% sulfuric acid under ice-cooling. The solution was extracted with ether and the solvent was removed after the extract was dried with anhydrous calcium chloride. Recrystallization of the residue from ether gave VIII, m.p. 93–94°.

*Anal.* Calcd. for $C_6H_9NO_3$: N, 9.79. Found: N, 9.98. Hydrogenation of VIII gave *N*-ethylsuccinamic acid, m.p. 96–97°.

*Saponification of N-vinylsaccharin.* Two grams of *N*-vinylsaccharin was dissolved in a mixed solution of 10 ml. of ethanol and 10 ml. of aqueous potassium or sodium hydroxide, then the solution was filtered and the filtrate was neutralized with 5% hydrochloric or sulfuric acid and extracted with ethyl acetate. After drying the extract with anhydrous calcium chloride, the solvent was distilled under reduced pressure. Recrystallization of the residue from ethanol gave saccharin, m.p. 224°. The mixed melting point with an authentic sample was 222–223°. The infrared spectra of the two coincided. The product obtained by saponification with 10% ethanolic potassium hydroxide in a similar method was also saccharin. The product of saponification with 10% aqueous sodium hydroxide was *o*-sulfamidobenzoic acid, m.p. 164–165°. The mixed melting point with the authentic sample[5] was 164–165°. The infrared spectra of the two perfectly coincided.

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(3) W. E. Hanford and H. B. Stevenson, U. S. Patent **2,276,840**; *Chem. Abstr.*, **36**, 4637 (1942).

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# 16-Hydroxylated Steroids. VIII.[1] 5β-Dihydrocortisone Approach to the Synthesis of Triamcinolone

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In 1956, this laboratory[2] announced the synthesis of triamcinolone (9α-fluoro-16α-hydroxy-prednisolone), a compound which has found considerable use in the treatment of rheumatoid arthritis and other disorders.[3] The importance of triamcinolone therefore merited further work on its preparation.[4]

One of the original syntheses of triamcinolone proceeded *via* 16α,21-diacetoxy-17α-hydroxy-4,9-

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(2) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman, and R. H. Blank, *J. Am. Chem. Soc.*, **78**, 5693 (1956). A detailed paper on this work has been submitted for publication to the *Journal of the American Chemical Society*.

(3) L. Hellman, B. Zumoff, M. K. Schwartz, T. F. Gallagher, C. A. Berntsen, Jr., and R. H. Freyberg, Paper presented before Am. Rheumatism Assoc. Meeting, Bethesda, Md., Nov. 30, 1956; R. H. Freyberg, C. A. Berntsen, Jr., and L. Hellman, *Arthritis and Rheumatism*, **1**, 215 (1958).

(4) A synthesis of triamcinolone based essentially on the introduction of the 16α-hydroxyl group by *Streptomyces roseochromogenus* has been announced by R. W. Thoma, J. Fried, S. Bonanno, and P. Grabowich, *J. Am. Chem. Soc.*, **79**, 4818 (1957).

(11)-pregnadiene-3,20-dione (VII).[2] A synthesis of the latter has now been established which utilizes 5β-dihydrocortisone (I)[5] as the starting material rather than Reichstein's substance S or cortisone.[2]

Ketalization of 5β-dihydrocortisone (I) with ethylene glycol in benzene[6] gave 3,20-bis-ethylenedioxy-17α,21-dihydroxy-pregnan-11-one (IIa) in 50% yield. Reduction with sodium borohydride[7] gave the 11β-hydroxy compound IIb in 84% yield. Acetylation of IIb provided a 77% yield of the 21-acetate IIc. Treatment of the latter with thionyl chloride in pyridine[8] gave 21-acetoxy-3,20-bis-ethylenedioxy-9(11),16-pregnadiene (III). The ketal protective groupings were then removed by treatment with dilute acetic acid,[8] and 21-acetoxy-9(11),16-pregnadiene-3,20-dione (IV) was obtained (in an over-all yield of 55% from IIc). Hydroxylation of IV with osmium tetroxide[9] followed by acetylation gave 16α,21-diacetoxy-17α-hydroxy-9(11)-pregnene-3,20-dione (Vb) in 52% yield. Bromination of Vb in dimethylformamide gave 16α,21-diacetoxy-4-bromo-17α-hydroxy-9(11)-pregnene-3,20-dione.[10] Dehydrobromination with anhydrous lithium chloride in dimethylformamide[11] afforded 16α,21-diacetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (VII). Thereby, an alternate pathway to triamcinolone was established.

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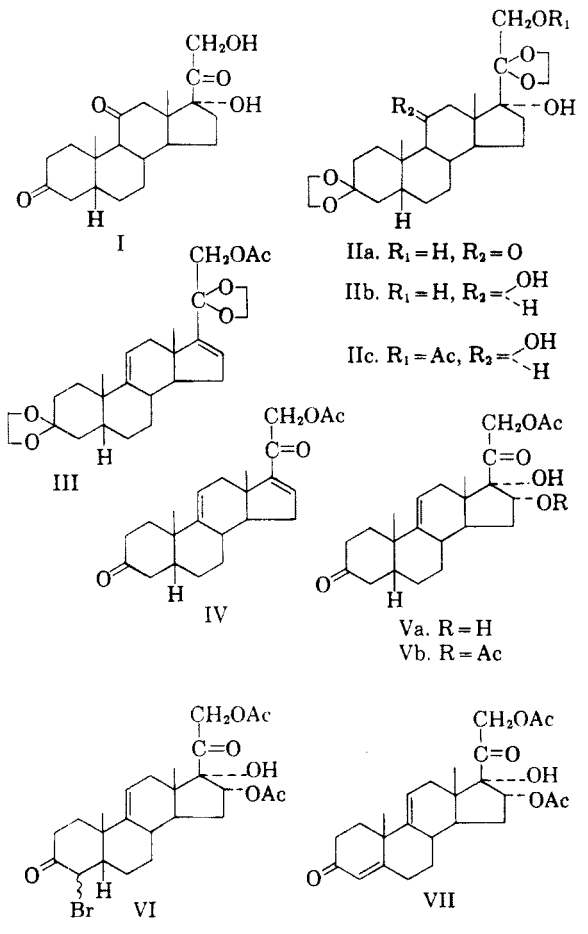


## EXPERIMENTAL

*3,20-Bisethylenedioxy-17α,21-dihydroxypregnan-11-one* (IIa). A mixture of 5β-dihydrocortisone (17α,21-dihydroxypregnane-3,11,20-trione) (I, 1.60 g.), *p*-toluenesulfonic acid monohydrate (45 mg.), ethylene glycol (12 ml.), and benzene (100 ml.) was stirred and refluxed with continuous water removal for 5 hr. After the reaction mixture was neutralized with sodium bicarbonate, it was extracted with ethyl acetate. The solution was washed to neutrality with water, treated with magnesium sulfate and activated carbon, filtered through diatomaceous earth, and evaporated. Addition of ether gave 540 mg. of a white powder, m.p. 190–192°. A portion was crystallized twice from acetone-ether to give pure IIa, m.p. 190.5–191.5°; $[\alpha]_D^{25}$ +41° (*c*, 1.85 chloroform).

*Anal.* Calcd. for $C_{25}H_{38}O_7$ (450.55): C, 66.64; H, 8.50. Found: C, 66.75; H, 8.66.

In another run, 5.10 g. of I gave 3.15 g. (50%) of IIa, m.p. 186–188°.

*3,20-Bisethylenedioxypregnane-11β,17α,21-triol* (IIb). A mixture of 3,20-bisethylenedioxy-17α,21-dihydroxypregnan-11-one (IIa, 2.0 g.), tetrahydrofuran (100 ml.), 2.5% aqueous sodium hydroxide (15 ml.), and sodium borohydride (2.7 g.) was refluxed for 20 hr. The tetrahydrofuran was distilled under reduced pressure, and the resulting solution extracted with water to neutrality. Treatment with magnesium sulfate and activated carbon, filtration through diatomaceous earth, and evaporation gave a glass which, upon addition of petroleum ether, gave 1.52 g. of product, m.p. 170.5–171.5°. Crystallization of a 150-mg. portion from acetone–petroleum ether gave 100 mg. of pure IIb, m.p. 171–172°.

*Anal.* Calcd. for $C_{25}H_{40}O_7$ (452.57): C, 66.45; H, 8.91. Found: C, 66.58; H, 8.97.

In another run, with 3.10 g. of IIa there was obtained 2.6 g. (84%) of IIb, m.p. 162–168°.

*21-Acetoxy-3,20-bisethylenedioxypregnane-11β,17α-diol* (IIc). To a cooled solution of 3,20-bisethylenedioxypregnane-11α,17α,21-triol (IIb, 125 mg.) in pyridine (3 ml.) was added 1 ml. of acetic anhydride, and the solution was allowed to stand at room temperature overnight. Addition of methanol, and evaporation gave 90 mg. of a white powder, m.p. 166–168°. Two crystallizations from ether–petroleum ether gave 56 mg. of IIc, m.p. 166.5–167°; $[\alpha]_D^{25}$ +25° (*c*, 0.89, chloroform).

*Anal.* Calcd. for $C_{27}H_{42}O_8$ (494.61): C, 65.56; H, 8.56. Found: C, 65.51; H, 8.70.

In another run, a 77% yield of IIc, m.p. 166.5–167.5°, was obtained.

*21-Acetoxy-9(11),16-pregnadiene-3,20-dione* (IV). To a cooled (−5°) solution of 21-acetoxy-3,20-bisethylenedioxypregnane-11α,17α-diol (IIc, 5.6 g.) in 25 ml. of pyridine was added 3.0 ml. of thionyl chloride, and the solution was allowed to stand at −5° for 16 hr. The mixture was poured into ice water, and an oil was formed from which the water

(5) L. H. Sarett, *J. Am. Chem. Soc.*, **70**, 1454 (1948).

(6) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(7) W. S. Allen, S. Bernstein, and R. Littell, *J. Am. Chem. Soc.*, **76**, 6116 (1954).

(8) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **77**, 1028 (1955).

(9) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 1909 (1956).

(10) R. P. Graber, A. C. Haven, Jr., and N. L. Wendler, *J. Am. Chem. Soc.*, **75**, 4722 (1953).

(11) R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

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).