methyl-3-pyrrolidinylmethylamino)quinazoline, m.p. 109–110.5°, undepressed on admixture with authentic material, m.p. 110.5–111.5°. The infrared spectra of the reduction product and authentic material were identical. In 0.1 N sodium hydroxide the ultraviolet spectrum exhibited maxima at 324, 314, 302, 289, 238, and 224 mμ (ε = 9,080, 12,100, 9,680, 10,820, 13,000, and 12,000) and in 0.1 *N* hydrochloric acid at 328, 314, 305 (shoulder), 243 and 220 mμ (ε = 17,150, 18,650, 12,100, 13,760, and 17,400). In ethanol, the 2-chloroprecursor exhibited maxima at 332, 318, 306, 289 and 238 mμ (ε = 8,260, 10,630, 8,260, 10,250 and 14,660) and in 0.1 *N* ethanolic hydrogen chloride at 332, 318, 306 (shoulder), 288 and 226 mμ (ε = 13,250, 15,020, 10,320, 6,900 and 23,850).

*Chlorination of 2,4-quinazolinedione with phosphorus oxychloride and triethylamine. 4-Chloro-2-diethylaminoquinazoline.* A mixture of 10.0 g. (0.062 mole) of 2,4-quinazolinedione, 140 ml. of phosphorus oxychloride, and 30 ml. of anhydrous triethylamine was refluxed for 75 min. The residue left after removal of phosphorus oxychloride by vacuum distillation was extracted three times with 120-ml. portions of hot *n*-heptane containing 5% triethylamine. The extracts were washed with water, 10% sodium hydroxide, and twice with water. The heptane was then removed *in vacuo* to leave 9.5 g. of an orange oil which was distilled to give 7.0 g. of yellow distillate, (48.5%) b.p. 118–120°/5 microns, $n^{24}D$ 1.6186. The ultraviolet spectrum in ethanol showed strong absorption between 230–290 mμ, the strongest peak being at 249 mμ (ε = 30,100). Beyond 350 mμ was a broad peak at 387 mμ (ε = 3,210). The oil was unstable, darkening slowly in a sealed ampoule and forming a white solid in the atmosphere.

*Anal.* Calcd. for $C_{12}H_{14}ClN_3$: C, 61.14; H, 5.99; Cl, 15.04; N, 17.83. Found: C, 61.13; H, 6.00; Cl, 15.24; N, 17.82.

*2-Chloro-4-diethylaminoquinazoline.* A slurry of 0.6 g. of 2,4-dichloroquinazoline in 15 ml. of ethanol was quickly brought into solution by the addition of 3 ml. of freshly distilled diethylamine. The solution was warmed on a steam bath briefly, poured into 50 ml. of water, and the resultant crystals were collected, m.p. 76.5–77°. After two recrystallizations of petroleum ether the white needles melted at 76.5–77.5°. In ethanol the ultraviolet spectrum exhibited maxima at 343, 328, 316, 296 and 232 mμ (ε = 8,930, 11,050 8,500, and 19,050) and in 0.1 *N* hydrochloric acid at 337, 323, 312–319 (shoulder), and 232 mμ (ε = 12,290, 14,590, 10,380, and 15,750).

*Anal.* Calcd. for $C_{12}H_{14}ClN_3$: Cl, 15.04; N, 17.83. Found Cl, 15.40; N, 17.93.

*Acknowledgment.* We are indebted to Dr. R. F. Feldkamp and to Dr. Y. H. Wu for their advice during the course of this work.

EVANSVILLE 21, IND.

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[CONTRIBUTION FROM MERCK SHARP & DOHME RESEARCH LABORATORIES]

# Some 21-Carbamates of Hydrocortisone and Related Compounds

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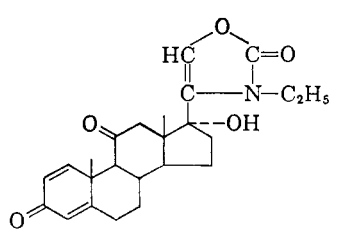
A series of 21-carbamate esters of hydrocortisone and some of its relatives was prepared and tested for biological activity. Most of these esters were quite active in the local granuloma inhibition assay but were less active in systemic tests.

Because of the stability of carbamate esters to hydrolysis, some 21-carbamates of corticosteroids were prepared and examined for biological activity. Preparation of the *N*-alkyl carbamates was accomplished in straightforward fashion using either an isocyanate in dry refluxing hydrocarbon solvents or a carbamyl chloride in pyridine. Similarly no difficulties were experienced in obtaining good yields of the corresponding *N*-arylurethans. However separation from the arylureas obtained as by-products was difficult and could best be done by chromatography. Fractional crystallization failed to separate the by-product ureas apparently because of co-precipitation or complex formation.

Reaction of ethyl isocyanate (in dimethoxyethane) with prednisone gave what is apparently the oxazolidone (I). The structure is assigned on the basis of physical data (I is very high melting and quite insoluble even by comparison with the sparingly soluble carbamates), elemental analysis, infrared spectra (the N—H bending at 6.5 μ is missing in I), and a negative blue tetrazolium test.



I

In accord with the known decreased reactivity of isothiocyanates the steroid alcohols were recovered unchanged after treatment with phenyl isothiocyanate in boiling toluene. Allyl isothiocyanate under similar conditions likewise gave no thiocarbamate ester of hydrocortisone.

For comparison in the biological tests, the 21-ethyl carbonate ester of hydrocortisone was synthesized using ethyl chlorocarbonte in pyridine. Similarly the 21-hippurate was obtained from 2-phenyloxazolone and hydrocortisone.

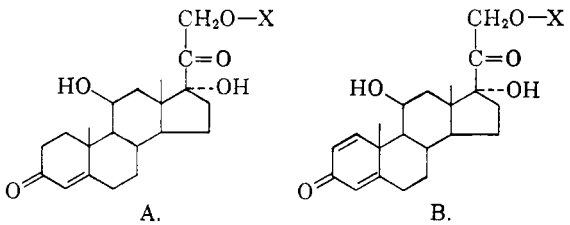
*Biological activity.* The carbamate esters were highly active in the local granuloma inhibition assay.[1] They were poorly absorbed after subcutaneous injection and little systemic activity was noted with this route of administration. However even with a water soluble carbamate (VII) local

(1) C. A. Winter, C. G. Porter, *J. Am. Pharm. Assoc.*, **46**, 515–519 (1957).

(and no systemic) activity was still observed. The 21-hippurate (XI) of hydrocortisone was quite active locally and showed some systemic activity in spite of poor absorption. By contrast with the carbamates, the 21-ethyl carbonate of hydrocortisone (XII) was comparable to the free alcohol in systemic activity.

TABLE I

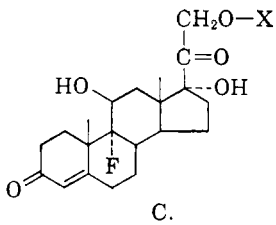
21-ESTERS OF CORTICOSTEROIDS



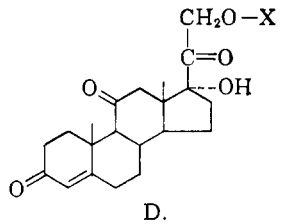

A.




B.

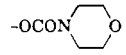
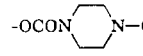
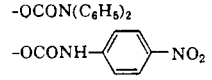



C.




D.

A. Derivatives of hydrocortisone

| | |
|---|---|
| X = —O—CONHCH₃ | (II) |
| —OCONHC₂H₅ | (III) |
| —OCONHC₃H₇(n) | (IV) |
| —OCONHC₁₈H₃₇(n) | (V) |
|  | (VI) |
|  | (VII) |
| -OCONHC₆H₅ | (VIII) |
| -OCON(C₆H₅)₂ | (IX) |
|  | (X) |
| —OCOCH₂NHCOC₆H₅ | (XI) |
| —OCO₂C₂H₅ | (XII) |

B. Derivatives of prednisolone

| | |
|---|---|
| X = —OCONHC₂H₅ | (XIII) |

C. Derivatives of 9α-fluorohydrocortisone

| | |
|---|---|
| X = —OCONHC₂H₅ | (XIV) |

D. Derivatives of cortisone

| | |
|---|---|
| X = —OCONHC₆H₅ | (XV) |

## EXPERIMENTAL[2]

The compounds described in this manuscript were prepared by two general procedures: *A*. Reaction of the steroid alcohols with an isocyanate; *B*. Reaction of the steroid alcohol with a carbamoyl chloride in the presence of a tertiary amine, such as pyridine. The compounds were all crystalline solids and, in general, were fairly readily purified either by recrystallization from the appropriate solvent and/or chromatography on acid-washed alumina. Where sizeable quantities of substituted ureas were obtained as by-products, chromatography was the preferred method of purification. Apparently complex formation made separation of the urea difficult by direct crystallization.

*Procedure A.* The general method used to treat an isocyanate with a steroid alcohol will be illustrated by the method used to prepare Compound III. Hydrocortisone (723 mg., 0.002 mole) was dried by azeotropic distillation in 15 ml. of benzene and heated under reflux with stirring for 5 hr. with 5 ml. of ethyl isocyanate. A solid separated and was collected by filtration. After washing the residue with water and a little acetone the yield was 729 mg. Several recrystallizations from ethyl acetate gave a product which melted at 200–203°.

*Procedure B.* The general procedure for reaction of a carbamoyl chloride with the steroid alcohol will be illustrated by the method used to prepare VI. Morpholyl carbamoyl chloride was prepared from morpholine and phosgene in dry toluene. A 1.5-g. portion was treated with 1.08 g. (0.003 mole) of hydrocortisone in 10 ml. of pyridine at 25° for 2 days. At this point the solution was poured onto crushed ice and extracted into chloroform. After washing with 1 *N* hydrochloric acid, 5% sodium bicarbonate, and water, drying over sodium sulfate, and filtering, the solvent was removed *in vacuo*. The residue was crystalline but colored and melted over a range. Hence the material was chromatographed on 6.5 g. of acid-washed alumina. In the region of 1:1 ether-chloroform 1 g. of material was collected which melted at 212–215° (negative B.T.).

*Reaction of prednisone with ethyl isocyanate*-(I) Dry prednisone (716 mg.) in 15 ml. benzene was mixed with 5 ml. of ethyl isocyanate in 15 ml. of dimethoxyethane. After 6 hr. of stirring at reflux temperature, the solvents and excess isocyanate were removed *in vacuo*. The crystalline residue was washed successively with benzene, water, and acetone. The residue weighed 434 mg., dark >300°, dec. 338–345°. Recrystallization from dimethylformamide-water gave a sample which decomposed at 340–350°. $\lambda_{max}$ $H_2SO_4$ (2 hr.) 303 $\mu$, $\epsilon$ % 391; 260 $\mu$, $\epsilon$ % 4.5. I.R. 3.05, 5.75, 5.89, 6.05, 6.21 (s) $\mu$.

*Anal.* Calcd. for $C_{24}H_{29}O_5N$: C, 70.05; H, 7.10; N, 3.40. Found: C, 69.51; H, 6.76; N, 3.70.

Table II contains the pertinent physical constants, spectra and analytical data for compounds II through XV.

*Acknowledgment.* The authors are indebted to Mr. Robert Walker for the infrared spectra, to Mr. R. N. Boos for the microanalytical determinations and to Dr. C. A. Winter and his associates for the biological assays. We are also happy to acknowledge the helpful suggestions of Dr. Karl Folkers.

RAHWAY, N. J.

(2) All melting points were taken on a Kofler micro hot stage. Ultraviolet absorption spectra were obtained in methanol solution unless otherwise specified. Infrared curves were secured from Nujol mulls (except where noted) using a Baird double beam instrument. Analytical samples were dried at room temperature *in vacuo* unless otherwise indicated.

TABLE II

21-CARBAMATES OF STEROID ALCOHOLS

| Compound | Method of Synthesis | M.P. | Ultraviolet Spectra $CH_3OH$ $\lambda_{max}$ mμ | ε | % | Infrared Spectra μ | Solvent for Rexing | Molecular Formula | Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | A | 340–350 (dec.) | 303 $H_2SO_4$ | 391 | | 3.05, 5.75, 5.89, 6.05, 6.21(s) | DMF-$H_2O$ | $C_{24}H_{29}O_5N$ | 70.05 | 69.51 | 7.10 | 6.76 | 3.40 | 3.70 |
| | | | 260 $H_2SO_4$ | 4.5 | | | | | | | | | | |
| II | A | 226–232 | — | — | | — | Ethyl Ac. | $C_{23}H_{33}O_6N$ | 65.85 | 65.74 | 7.93 | 7.96 | 3.34 | 3.47 |
| III | A | 200–203 | — | — | | 2.98, 5.85, 6.06–6.1, 6.85(s), 7.25(m), 8.1(w) | Ethyl Ac. | $C_{24}H_{35}O_6N$ | 66.49 | 66.69 | 8.14 | 8.13 | — | — |
| IV | A | 197–201 | 241 | 363 | | 2.98, 5.85, 6.08, 6.5 | Ethyl Ac. | $C_{25}H_{37}O_6N$ | 67.09 | 66.95 | 8.33 | 8.21 | 3.13 | 3.20 |
| V | A | 86–96 | 241 | 244 | | 2.9–3.0, 5.83 (shoulder 5.78), 6.01, 6.17, 6.5 | Ethyl Ac. Pet. Ether | $C_{40}H_{67}O_6N$ | 73.06 | 73.45 | 10.27 | 10.03 | 2.13 | 2.05 |
| VI | B | 212–215 | 241 | 315 | | 3.01, 5.80, 6.0, 6.2 | Acetone | $C_{26}H_{37}O_7N$ | 65.66 | 65.44 | 7.84 | 7.70 | 2.95 | 3.23 |
| VII | B | 175–185 | 241 | 302 | | 2.9–3.0, 5.97, 6.01, 6.19 | Ethyl Ac. | $C_{27}H_{40}O_6N_2$ | 66.36 | 66.47 | 8.25 | 8.05 | 5.73 | 6.20 |
| VIII | A | 204–206 | 237 | 651 | | — | Acetone E. | $C_{28}H_{35}O_6N$ | 69.83 | 69.50 | 7.33 | 7.53 | 2.91 | 2.89 |
| IX | B | 228–232 | 239 | 545 | | 2.95, 5.80, 5.92, 6.03, 6.18, 6.25, 6.67 | Ethyl Ac. | $C_{34}H_{39}O_3N$ | | | — | | | |
| X | A | 274–281 (dec.) | — | — | | — | Acetone | $C_{28}H_{34}O_8N_2$ | 63.86 | 63.71 | 6.51 | 6.49 | 5.32 | 5.62 |
| XI[a] | B | 133–136 | 235 | 449 | | 2.9, 5.70, 5.78, 6.01, 6.15, 6.26, 6.48, 6.67 | Ethyl Ac. | $C_{30}H_{37}O_7N$ | 68.81 | 68.69 | 7.12 | 6.97 | 2.68 | 2.69 |
| XII | B | 201–204 | 242 | 372 | | 2.97, 5.88, 6.0, 6.19, 7.7, 9.8, 11.6, 12.6 | Ethyl Ac. | $C_{24}H_{34}O_7$ | 66.34 | 66.32 | 7.89 | 7.74 | — | — |
| XIII | A | 227–230 | — | — | | 2.9, 2.99, 5.85, 6.02, 6.12, 6.52, 11.28 | Methanol-DMF | $C_{24}H_{33}O_6N$ | 66.80 | 66.30 | 7.71 | 7.84 | — | — |
| XXIV | A | 232–238 | — | — | | — | Ethyl Ac. | $C_{24}H_{34}NO_6F$ | 63.84 | 63.99 | 7.59 | 7.75 | 3.10 | 3.14 |
| XV | A | 232–237 | 234 | 650 | | — | " | $C_{28}H_{33}O_6N$ | 70.12 | 70.61 | 6.94 | 6.94 | — | — |

[a] Prepared from 2-phenyloxazolone. *Cf.* Roger Adams, *Org. Reactions*, III, 214 (1946).