the biological evaluation of the compounds described herein.

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Steroid Side-Chain Oxazolidines†,‡

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Steroid 20,21-glyoxals reacted selectively at C-21 with N-monosubstituted ethanolamines giving moderate yields of oxazolidines which appear to be mixtures of C_{21} epimers. *N*-Methyloxazolidines were obtained simply by heating the glyoxal in a solvent with 2 to 5 molar equivalents of substituted ethanolamine at 50 to 100° for 1–2 hr. The *N*-methyloxazolidine obtained from prednisolone 21-aldehyde was more active than hydrocortisone in the thymolytic assay; the corresponding compound "S" derivative was inactive. The product obtained from prednisolone 21-aldehyde and (−)-epinephrine was inactive in the thymolytic assay but exhibited significant adrenal-suppression activity.

Steroids modified by conversion of a functional group to a heterocyclic moiety may have their biological activities affected profoundly. Well-known examples include antiinflammatory[1] and anabolic[2] agents. The selectivity[3] with which the C-21 aldehyde group of polyfunctional steroids reacts with diazomethane prompted us to investigate other reactions which might provide access to steroid heterocycles *via* routes involving relatively mild reaction conditions. This paper describes our investigation of the reaction of some steroid 21-aldehydes with ethanolamines designed to provide side-chain oxazolidines for testing the group's effectiveness in changing the spectrum of activities of well-known corticoids.

The reaction of unsubstituted ethanolamine with aliphatic carbonyl compounds was reported some time ago by Knorr[4] and later by Cope and Hancock.[5] The results of those studies and of the extensive investigations of the Bergmann group[6] have shown that α,β-unsaturated carbonyl compounds form Schiff bases (I) and that saturated aldehydes and ketones form oxazolidines (II). Hindered ketones, however, such as methyl isobutyl ketone, give equilibrium mixtures of I and II.

The results obtained by Irmscher and his coworkers[7] with ethanolamine and a variety of steroid ketones are generally consistent with the pattern described by the earlier investigators for nonsteroidal compounds. Thus, various α,β-unsaturated 3-keto steroids afforded Schiff bases and saturated 3- and 6- keto steroids produced oxazolidines. However, saturated 17- and 20-ketones gave Schiff bases.

Our early experiments utilizing ethanolamine and 11β,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-al (prednisolone-21-aldehyde) (IIIa) gave intractable products consisting of several components (tlc evidence), indicating perhaps that the reactivity of the 21-aldehyde group toward this reagent was not sufficiently greater than the 3- and 20-keto groups

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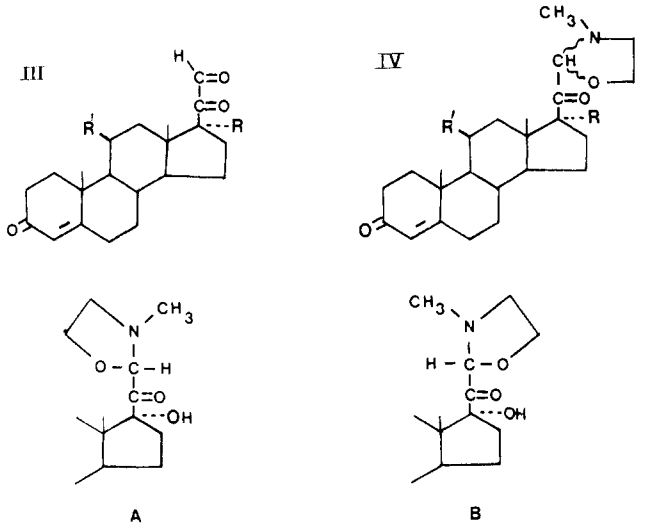
to allow for selective derivatization. In order to preclude Schiff base formation we confined our subsequent studies to the reactions of N-monosubstituted ethanolamines, primarily 2-(*N*-methylamino)ethanol. Reaction occurred with facility in all cases and gave readily isolable oxazolidines (IV) in fair yield in the 17-hydroxyl series. Assignment of the oxazolidine structure is based on elemental analyses, spectral data and by analogy with earlier investigations with nonsteroid compounds.[5,6] Thin-layer chromatographic evidence indicated the presence of other products in the crude



III and IV, a, R = R′ = OH; 1-dehydro
b, R = OH; R′ = H
c, R = R′ = H

reaction mixtures but attempts to isolate any of them, particularly the individual C_{21}-epimers of IV, have been unsuccessful thus far. Inspection of molecular models of the two epimers (A and B) and their likely intermediates did not disclose any obvious preference for one or the other stereoisomer. The products IVa and IVb appear to be single entities when examined by thin-layer and paper chromatography. However, their nmr spectra indicate they are mixtures, presumably of C_{21} epimers.

The spectra of the products are in good agreement with those expected for the assigned structures IV. The inertness of the unsaturated ketone in ring A to reaction conditions was indicated by normal uv spectra and normal C_4-vinylic proton resonances in the nmr spectra. The ir spectra of IVa and IVb exhibit normal, strong, sharp, saturated carbonyl absorption at about 1725 cm^{-1}; unsaturated carbonyl at about 1650 cm^{-1} and C=C from about 1595 to 1615 cm^{-1}. The nmr spectrum of IVa contains two C_{18}-methyl proton resonances (0.93 and 0.99 ppm; ratio approximately 1:2), a single C_{19}-methyl peak at 1.46 ppm (presumably due to accidental equivalence) and two peaks (4.69 and 4.84 ppm, assigned to the tertiary C_{21}-H adjacent to the C_{20}-carbonyl) whose relative intensities are approximately 1:2, consistent with the relative intensities of the two C_{18}-methyl peaks and the two NCH_3 peaks at 2.46 and 2.53 ppm. The spectrum of IVb contains C_{18}- and C_{19}-methyl peaks with normal chemical shifts. The C_{18}-methyl resonance appears as two peaks at 0.75 and 0.69 ppm; the C_{19}-methyl at 1.20 and 1.10 ppm and the tertiary C_{21}-H at 4.80 and 4.90 ppm. All have similar relative intensities (approximately 10:1).

The chemical shifts observed for the C_{18}- and C_{19}-methyl proton resonances of the products of *N*-(methylamino)ethanol and IIIa to IIIc are in good agreement with calculated chemical shifts obtained utilizing Zurcher's values.[8]

Attempts to extend this study to the 17-deoxy series by investigating the reaction of *N*-(methylamino)ethanol with IIIc yielded a product which could not be recrystallized for analysis.

A mixture of 2 components (approximately 1:1) is indicated by tlc and paper chromatography and confirmed by the presence of two saturated carbonyl absorptions of about equal intensity at 1724 and 1704 cm^{-1}. Assuming a normal reaction, the product should have structure IVc, which possesses only one saturated carbonyl group. Its nmr spectrum displays two pairs of peaks each indicative of a 1:1 mixture. One pair appears in the NCH_3 region (2.44 and 2.50 ppm) and the other in the C_{19}-methyl region (1.20 and 1.27 ppm). Surprisingly, only a single C_{18}-methyl peak is present (0.75 ppm). Additional structural studies will be required on the individual components, which have not yet been separated from the mixture.

The preparation of analogous oxazolidines derived from (−)-epinephrine and typical 21-aldehydes was successful when applied to prednisolone-21-aldehyde (IIIa), which afforded an apparently normal product V, but reaction of deoxycorticosterone (IIIc) with (−)-epinephrine gave an intractable product.

Biological Test Results.§ Compounds IVa, IVb, and V were tested in the thymolytic assay subcutaneously for 3 days in adrenalectomized female rats (with cotton pellet implantation). Compound IVa produced approximately the same response in thymus and granuloma reduction at 1.2 mg (total dose) as the standard (hydrocortisone) produced at 4.8 mg. Neither IVb nor V exhibited significant activity in the same assay. In other assays, compound V was significantly active (estimated 34% of hydrocortisone activity) in the adrenal suppression assay in female rats administered a total dose of 20 mg over 10 days, while it exhibited no significant activity in the mineralocorticoid assay in adrenalectomized male rats.

Experimental Section

The steroid 20,21-ketols were generously provided by the Medical Research Laboratories of Chas. Pfizer and Co., Inc. All C-21 aldehydes were prepared by cupric acetate oxidn of the corresponding 20,21-ketols by the method of Christensen, *et al.*[9]

The 2-(*N*-methylamino)ethanol used was Baker Lot 6-277, mp −6 to 4°; the (−)-epinephrine was K. and K. Laboratories, Lot 12381.

Unless otherwise indicated, uv absorption spectra were detd in MeOH soln on a Beckman DU spectrophotometer, ir absorption spectra were taken in KBr using a Perkin-Elmer 137 spectrophotometer and mps were taken on a Fisher-Johns app and are uncor. The nmr spectra were determined on a Varian T60 in $CHCl_3$ using TMS as internal std.

Tlc was done on microscope slides coated with silica gel GF 254. EtOAc was the solvent of choice. Steroids were visualized by spraying with 20% H_2SO_4 and then charring on a hot plate.

11β,17α-Dihydroxy-17-[(3-methyl-2-oxazolidinyl)carbonyl]androsta-1,4-dien-3-one (IVa). A mixt of 5.0 g (12.8 mmoles) of 11β,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-al[3] (methanolate, mp 186–188° dec) (IIIa) and 1.5 ml (21.4 mmoles) of 2-(*N*-methylamino)ethanol in 170 ml of $CHCl_3$ was heated at reflux with stirring and constant H_2O sepn for 2 hr. The resultant yellow soln was evapd to dryness under reduced pressure and the glassy residue, upon trituration with EtOAc, yielded 5.0 g of light tan crystals, mp 165–167°. Recrystn first from C_6H_6 and then from EtOAc gave an analytical sample: mp 190.5–192.0; λ_{max} 242 mμ (15,860); ir (cm^{-1}); two broad bands, 3200, 3425 (OH); 1725 (C=O); 1650 (C=CC=O); 1615, 1595 (C=C); nmr (ppm), 0.93, 0.99 (C_{18}); 1.46 (C_{19}); 2.46, 2.52 (NCH_3); 4.69, 4.84 (C_{21}-H); 5.96 (C_4-H); 6.14, 6.24 (C_2-H); 7.22, 7.32 (C_1-H). *Anal.* ($C_{24}H_{33}NO_5$) C, H, N.

§ All biological tests were performed by the Cancer Chemotherapy National Service Center's Endocrine Evaluation Branch.

17α-Hydroxy-17-[(3-methyl-2-oxazolidinyl)carbonyl]androsta-4-en-3-one (IVb). A soln of 5.0 g (14.5 mmoles) of 17-hydroxy-3,-20-dioxopregna-4-en-21-al (IIIb) and 5.0 ml (72 mmoles) of 2-(*N*-methylamino)ethanol in 170 ml of $CHCl_3$ was heated under reflux for 2 hr. The residue, after evapn under reduced pressure and trituration with cold EtOAc, gave 1.9 g of tan crystals: mp 179–181°. Tlc indicated the presence of a single component, which was more polar than starting material. Recrystn to constant mp from EtOAc afforded 0.5 g of colorless crystals: mp 191–192°; λ_{max} 242 mμ (16,340); ir (cm^{-1}), 3400 (OH); 1730 (C=O); 1653 (C=CC=O); 1605 (C=C); nmr (ppm), 0.69, 0.75 (C_{18}-CH_3); 1.10, 1.20 (C_{19}-CH_3); 2.45, 2.50 (NCH_3); 4.80, 4.90 (C_{21}-H); 5.72 (C_4-H). *Anal.* ($C_{24}H_{35}NO_4$) C, H, N.

17α-Hydroxy-17-[(3-methyl-5-(3,4-dihydroxyphenyl)-2-oxazolidinyl)carbonyl]androsta-1,4-dien-3-one (V). A mixture of 750 mg (1.9 mmoles) of aldehyde IIIa[3] and 750 mg (4.2 mmoles) of (−)-epinephrine in 140 ml of DMF was heated on a hot plate until dissolution occurred and was then maintained at 70° for 1 hr. The dark red soln was evapd to dryness at reduced pressure. Addn of MeOH gave a soln of the product and left behind unreacted epinephrine, which was sepd by filtration. Concn of the filtrate, pptn of the product with saturated NaCl soln, and filtration afforded 940 mg of red crystals: mp 140–145° dec (prior darkening at 130–140°). Recrystn from EtOAc (3 times) and then from 3:2 C_6H_6-EtOAc (2 times) gave light tan crystals which were dried *in vacuo* at room temperature for analysis. The analytical sample exhibited mp 144–146° dec (prior change to dark red), λ_{max} 235 mμ (20,600). *Anal.* Found: C, 66.95; H, 7.16; N, 2.32. Calcd for $C_{30}H_{37}NO_7$: C, 68.83; H, 7.12; N, 2.67. Calcd for V + 1 mole of EtOAc: $C_{34}H_{45}NO_9$: C, 66.75; H, 7.42; N, 2.29.

Reaction of 3,20-Dioxopregn-4-en-21-al (IIIc) and 2-(*N*-Methylamino)ethanol. A soln of 3.0 g (9.5 mmoles) of IIIc (mp 104–105) and 1.5 ml (19 mmoles) of 2-(*N*-methylamino)ethanol in 150 ml of $CHCl_3$ was heated at reflux with constant water sepn for 1.5 hr. Evapn to dryness *in vacuo* gave a yellow oil. Trituration with EtOAc gave 1.1 g of white crystals, mp 104–110°. Recrystn from hexane gave crystals: mp 107–111°; ir (cm^{-1}); 1724, 1704 (C=O) (barely resolved doublet in either KBr or $CHCl_3$ soln); 1667 (C=CC=O); 1610 (C=C); nmr (ppm), 0.75 (C_{18}-CH_3); 1.27, 1.20 (C_{19}-CH_3); 2.44, 2.50 (NCH_3); 5.77 (C_4-H); unassigned peaks at 4.33 and 5.57 (each about one-half proton intensity).

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Novel Anthelmintic Agents. 6. Pyrantel Analogs with Activity against Whipworm

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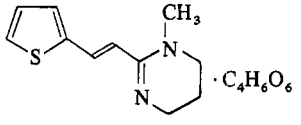
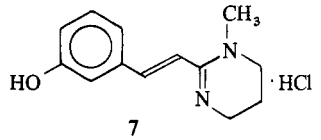
Although the broad-spectrum anthelmintic agent pyrantel is inactive against adult whipworms (*Trichuris* spp.), a number of its *m*-oxyphenyl analogs are very effective against these refractory helminths. The following compounds exhibit high potency in mice against *T. muris*: *trans*-1,4,5,6-tetrahydro-2-(3-hydroxystyryl)-1-methylpyrimidine (**7**), *trans*-1-(3-hydroxystyryl)pyridinium bromide (**33**), *trans*-1-(3-benzoyloxystyryl)pyridinium bromide (**34**), *trans*-2-(3-benzyloxystyryl)-1,4,5,6-tetrahydro-1-methylpyrimidine (**12**), and *trans*-3-hydroxy-*N,N*-dimethylcinnamamidine (**22**). The methods of preparing these compounds, the technique of evaluating them as whipworm control agents, and structure–activity relationships are discussed.

Pyrantel is a highly effective broad spectrum nematocide, but as with many other commercially important anthelmintics, it is of no practical value against adult whipworms.



pyrantel tartrate (**25**)



7

In the course of exploiting this series of compounds,[1-4] it was discovered that *trans*-1,4,5,6-tetrahydro-2-(3-hydroxystyryl)-1-methylpyrimidine hydrochloride (**7**) is highly effective against the adult whipworms of mice (*Trichuris muris*),[5] and dogs (*T. vulpis*).[5] There are 2 surprising features in this discovery: (1) although **7** is highly potent against *T. muris*, it is active only at high doses (125 mg/kg) against our primary screening organism, *Nematospiroides dubius;* pyrantel has no practical effect on adult *T. muris*, but is highly potent against *N. dubius;* (2) the structure–activity relationships developed previously in this series[1,6] would suggest that **7** should not be active, meta substitution and OH substituents in the aryl rings being usually unfavorable for activity.

Because **7** is at least 10 times more potent that dichlorvos, the leading agent for the control of whipworms in dogs and swine,[7] it seemed logical to pursue this compound as a structure lead.

Although several analogs were discovered to have activity against *T. muris*, none were more potent than **7** itself. The results of these studies are given in this report. The compounds prepared and their activities against *T. muris* are summarized in Tables I–IV. The activities of some related compounds are given in Tables V and VI.

Chemistry. The general methods for preparing the new compounds mentioned in Tables I–IV have been described previously;[1,3] specific details for the preparation of typical entities are given in the Experimental Section. The use of formate esters as water scavengers[8] in the condensation of hydroxybenzaldehydes with 2-methyl cyclic amidines was decisive to the success of this research. Attempts to effect these reactions by distilling the by-product H_2O were often unsatisfactory.

The stereochemistry of **7** was established by nmr spec-