solution. The crystalline product, which separated, was filtered with suction, washed well with water and cold ether and dried *in vacuo* (12.4 g., 62%). Recrystallization from methanol yielded an analytical sample, m.p. 170–172°.

Compound X (R = R_1 = C_6H_5).—Sodium borohydride (5.0 g., 0.135 mole) was added to a warm mixture of IX (R = R_1 = C_6H_5, 5.07 g., 0.0105 mole) in methanol (125 ml.). The mixture soon became homogeneous and a white crystalline solid separated. After 10 min., water (500 ml.) was added and the product was filtered with suction and dried *in vacuo* (4.11 g., 81%). An analytical sample, m.p. 210–212.5°, was obtained by recrystallization from a methanol–ethanol mixture.

Compound XI (R = R_1 = C_6H_5).—To a warm, stirred solution of IX (R = R_1 = C_6H_5, 5.0 g., 0.0105 mole) in 1-butanol (150 ml.), sodium (15.5 g., 0.67 g.-atom) was added in portions. The mixture was boiled at reflux for 2 hr. Hydrochloric acid (18%, 200 ml.) was added and the mixture was distilled until the distillate was clear and homogeneous. The residue was treated with additional HCl (10%, 200 ml.) and the acidic solution was extracted with three 70-ml. portions of ether. The aqueous layer was made alkaline with ammonia and the resultant white precipitate was filtered, washed with water, and dried *in vacuo* (2.2 g., 65%). Recrystallization from methanol yielded an analytical sample, m.p. 210–212°.

Compound XI (R = C_6H_5; R_1 = CH_2OH).—A mixture of IX (R = C_6H_5, R_1 = $CO_2C_2H_5$; 18.5 g., 0.039 mole), lithium aluminum hydride (25 g., 0.66 mole), and tetrahydrofuran (400 ml.) was stirred and boiled at reflux under a nitrogen atmosphere for 4 days. Ether (1 l.) was added and the stirred mixture was hydrolyzed by dropwise addition of water (200 ml.). Inorganic salts were separated by filtration with Celite. The filter cake was washed with ether, and HCl (18%, 800 ml.) was added to the combined organic layers. The aqueous layer was separated, washed with four 250-ml. portions of ether and made alkaline with concentrated ammonia. The mixture was extracted with chloroform and the organic extract was washed with saturated aqueous NaCl and dried (Na_2SO_4). Removal of solvent *in vacuo* yielded a viscous oil, which crystallized upon trituration with methylene chloride–ether. Recrystallization from the same solvent pair yielded an analytical sample, m.p. 156–158°.

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Steroidal Carbamic Acid γ-Lactones

EUGENE FARKAS AND JOHN A. SWALLOW

The Lilly Research Laboratories, Indianapolis 6, Indiana

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The reaction of steroidal 17α-ethynylcarbinols with alkyl isocyanates was used to prepare the 17-carbamoylcarbamate, carbamate, and carbamic acid γ-lactones in the aromatic A-ring, androstenone, and 19-norandrostenone series. The biological testing of these resultant compounds was performed and an interesting gradation in activity in the progestational area was observed.

Substitution of various functional groups at the 17-position of the steroid nucleus produces interesting and useful alterations in the pharmacological activity of the resultant compounds. While the well-documented 17α-alkyl substitution in the 4-androstene molecule increases the androgenic–anabolic activity, the 17α-ethynyl-17β-hydroxy substitution results in progestational activity.[1] The corresponding 17α-ethynyl-17β-hydroxy-19-nor steroids are especially important and useful progestational and anovulatory agents. The spirolactone grouping,[2] on the other hand, transforms these same androstene steroids into clinically useful antimineralocorticoid agents.

Utilizing the results of Easton, *et al.*,[3] of this laboratory, the reaction of various steroidal 17α-ethynyl-17β-carbinols with alkyl isocyanates was examined with the goal of introducing a C-17 spirocarbamic acid γ-lactone group. The reaction of 17α-ethynylestradiol-3-methyl and -ethyl isocyanate gave two products. The more polar product, obtained in the greater amount, was found to be the carbamate (IIA) as evidenced by the analysis and the infrared and n.m.r. spectra. The infrared spectrum showed two peaks at 2.9 and 3.04 μ which corresponded to -NH and acetylenic hydrogen, respectively. The carbonyl region revealed a broad band centered at 5.83 μ. The n.m.r. spectrum[4] supported the structure IIA by demonstrating the presence of a single N-ethyl grouping.

The minor, less polar product assigned structure IA apparently resulted from the reaction of the ethynyl carbinol with 2 molecules of isocyanate. The infrared spectrum indicated no free –NH but a band for weakly hydrogen-bonded –NH at 2.98 and also showed an acetylenic hydrogen at 3.04 μ. The carbonyl region contained an intense band at 5.84 μ for the –OCON– and medium intensity bands at 5.98 and 6.53 μ for –NCONH–. The n.m.r. spectra supported structure IA showing two methyl triplets nearly coincident at δ 1.17 (J = 7.0 c.p.s.) a ≡CH singlet at δ 2.68, an 8-component multiplet at δ 3.30 for NH-CH_2CH_3 in which coupling with NH is 9.0 c.p.s. and with methyl 7.0 c.p.s., a quartet at δ 3.78 for $-CH_2-N(CO)_2$, and a broad signal for hydrogen bonded NH at δ 8.5. These spectra and the analysis favor the assigned structure, IA.

As in the previous work,[3,5a,5b] treatment of the carbamate (IIA) with sodium methoxide yielded a new compound, IIIA, whose infrared spectrum had strong absorption at 5.65 μ in support of the carbamic acid γ-lactone structure. In the n.m.r. the exocyclic methylene gave an AB pattern centered at δ 4.18 for

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(2) J. A. Cella and C. M. Kagawa, *ibid.*, **79**, 4808 (1957).

(3) N. R. Easton, D. R. Cassady, and R. D. Dillard, *J. Org. Chem.*, **27**, 2927 (1962).

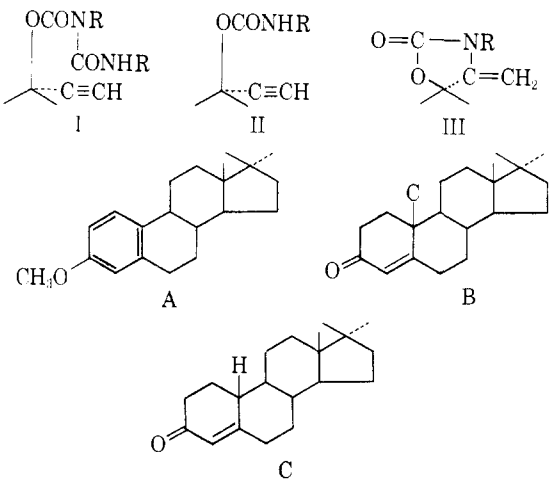
(4) The n.m.r. spectra were determined using a HR60 Varian instrument with $CDCl_3$ as solvent and TMS as an internal standard. The δ-values are reported as p.p.m.

(5) (a) R. Sisido, K. Hukuoka, M. Tuda, and H. Nozaki, *J. Org. Chem.*, **27**, 2663 (1962); (b) P. J. Stoffel and A. J. Speziale, *ibid.*, **28**, 2814 (1963).

which $\Delta\nu$ is 12.1 c.p.s. and J_{AB} = 3.5 c.p.s. The methylene attached to the nitrogen shows a nonequivalence corresponding to $\Delta\nu$ = 15.6 c.p.s., J_{AB} = 14 c.p.s., and $J_{CH_2CH_3}$ = 7 c.p.s. Although the available data do not completely eliminate the oxygen-closed structure, the nitrogen closure is favored since structure IIIA is completely consistent with the physical data and because of the closely analogous work of Easton[3] where this closure was established chemically.

The exocyclic double bond in the spiro-4-methyleneoxazolidone is hindered since this olefinic bond resisted hydrogenation under a variety of conditions. Only conditions which were vigorous enough to reduce the aromatic A-ring, Pd–C catalyst, pressure, and heat, would effect reduction.

Analogous compounds were obtained using 17α-ethynyltestosterone and 17α-ethynyl-19-nortestosterone as starting materials. The reactions of the former compound proceeded with difficulty because of the relative insolubility of this compound. Although the lower isocyanates gave some reaction, best yields were obtained using *n*-propyl isocyanate leading to the carbamoylcarbamate, the carbamate, and the carbamic acid spirolactone. In the 19-nor series the carbamoylcarbamate was not obtained in any appreciable amount. However, the carbamate and the carbamic acid lactone were readily prepared using both methyl and ethyl isocyanate. The infrared and n.m.r. spectra were completely analogous to those discussed in series A.



Pharmacological Activity.—The biological activity of these new compounds, particularly the carbamic acid lactones, mirrored the activity of the parent ethynyl carbinols. Surprisingly, none of the various spiro compounds showed any appreciable antideoxycorticosterone activity.

In the A or aromatic series, compounds IIA and IIIA had about $^1/_{300}$ the estrogenic activity of estradiol while the carbamoylcarbamate IA was almost devoid of estrogenic properties at these same doses.

The substituted androstenone compounds, series B, possessed only a low order of activity in all assays studied. The 19-norandrostenone or series C compounds proved to be of the most interest. In the antiestrogen assay,[6] although the carbamate IIC (R = CH_3) showed no activity, the lactone IIIC had one-half the activity of 17α-ethynyl-19-nortestosterone. Further, in the progestational assay, as measured by the McPhail procedure,[7] only the lactones (IIIC) showed good activity. By injection, compound IIIC (R = CH_3) was found to be twice as active as 17α-ethynyl-19-nortestosterone but was only one-half as active orally. Surprisingly, the spirolactone with R = C_2H_5 showed only one-half the activity of 17α-ethynyl-19-nortestosterone by injection and no activity orally. Since the precursor of the carbamic acid lactone, the carbamate, had no appreciable progestational activity, this activity appears to be uniquely associated with the ring-closed compounds. The structure–activity relationships of these latter compounds indicate more stringent structural requirements operating here than in the parent ethynylcarbinols where the corresponding ethynyl-21-methyl-[8] and -21-chloro[9]-19-nor steroids show somewhat greater activity than the parent compound.

It is of further interest that in contrast to the 17-acetate[10] and the 17-tetrahydropyranyl ether[11] of the 17α-ethynyl-17β-hydroxy compounds, the 17-carbamate in each of the series, A, B, or C, leads to a diminution in biological activity.

Experimental[12]

17α-Ethynyl Carbamoylcarbamate (IA) and 17α-Ethynyl Carbamate (IIA).—A solution of 2.0 g. of 17α-ethynylestradiol 3-methyl ether, 23 ml. of ethyl isocyanate, and 0.15 g. of Dabco[13] was heated at reflux for 62 hr. with an additional 5 ml. of ethyl isocyanate being added after an initial elapse of 24 hr. The solvent was removed under vacuum, and the residue was chromatographed on 75 g. of neutral alumina using benzene as the initial solvent. The carbamoylcarbamate was eluted with 10% ether–benzene and recrystallized from methanol to give 0.11 g., m.p. 214–215°.

Anal. Calcd. for $C_{27}H_{36}N_2O_4$: C, 71.65; H, 8.02; N, 6.18. Found: C, 71.27; H, 7.99; N, 6.12.

Further elution with 25–50% ether–benzene gave the carbamate (IIA) which was recrystallized from methanol to give 0.62 g., m.p. 89–91°.

Anal. Calcd. for $C_{24}H_{31}NO_3$: C, 75.55; H, 8.19; N, 3.67. Found: C, 75.28; H, 8.14; N, 3.57.

Carbamic Acid Lactone (IIIA).—A solution of 0.2 g. of IIA, 5 ml. of sodium methoxide solution (0.1 g. of sodium in 10 ml. of methanol), and 17 ml. of reagent methanol was heated at reflux overnight. Some of the solvent was evaporated, and the solution was poured into excess water. The mixture was extracted with ethyl ether, and the combined ethereal solutions were washed with sodium chloride solution, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was recrystallized from methanol to give 0.12 g., m.p. 148–149°.

Anal. Calcd. for $C_{24}H_{31}NO_3$: C, 75.55; H, 8.19; N, 3.67. Found: C, 75.52; H, 8.38; N, 3.48.

Hydrogenation Studies.—Since no reduction had occurred under milder conditions, 0.2 g. of IIIA was reduced using 0.2 g. of 5% Pd–C in 70 ml. of ethanol with 63.72 kg./cm.^{2} (900 p.s.i.) of hydrogen at 70° for 5 hr. After filtration the solvent was evaporated, and since the residue did not readily crystallize, it was examined spectrally. The ultraviolet spectrum revealed only 25% of methoxy aromatic remaining, and the infrared

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(12) All melting points were obtained on Fisher-Johns block and are corrected. All chromatography was carried out using Woelm neutral alumina with the solvents as specified.

(13) A. Farkas and K. G. Flynn, *J. Am. Chem. Soc.*, **82**, 642 (1960).

spectra showed the exocyclic methylene absorption at 6.0 μ was completely removed while the carbonyl was shifted slightly to 5.70 μ.

Carbamoylcarbamate (IB).—A mixture of 0.5 g. of 17α-ethynyl-4-androsten-17β-ol-3-one, 12 ml. of *n*-propyl isocyanate, and 0.05 g. of Dabco was heated at reflux using a magnetic stirrer for 94 hr. After 24 hr. an additional 2 ml. of isocyanate was added. The solvent was evaporated, and the residue was chromatographed on 30 g. of neutral alumina using 1:1 benzene–petroleum ether (b.p. 30–60°) as the initial solvent. The carbamoylcarbamate (IB) was eluted with benzene and recrystallized from ethyl ether to give 0.31 g., m.p. 132–133°.

Anal. Calcd. for $C_{29}H_{42}N_2O_4$: C, 72.16; H, 8.77; N, 5.80. Found: C, 72.15; H, 8.84; N, 5.83.

Carbamate (IIB).—While being agitated with a magnetic stirrer, a mixture of 0.5 g. of 17α-ethynyl-Δ^4-androsten-17β-ol-3-one, 10 ml. of *n*-propyl isocyanate, and 0.05 g. of Dabco was heated at reflux for 114 hr. The solvent was evaporated and the residue was chromatographed on 25 g. of neutral alumina using 2:1 benzene–petroleum ether (b.p. 30–60°) as solvent. Elution with benzene and recrystallization from ethyl ether–petroleum ether gave 0.33 g. of IIB, m.p. 184–185°.

Anal. Calcd. for $C_{25}H_{35}NO_3$: C, 75.52; H, 8.87; N, 3.52. Found: C, 75.94; H, 8.68; N, 3.32.

Carbamic Acid Lactone (IIC).—A solution of 0.2 g. of carbamate (IIB), 20 ml. of methanol, and 4 ml. of sodium methoxide solution (0.1 g. of sodium in 10 ml. of methanol) was heated at reflux for 12 hr. Most of the solvent was removed under vacuum, and the residue was poured into excess water. The mixture was extracted thoroughly with methylene chloride, and this latter combined solution was washed with sodium chloride solution. After drying (Na_2SO_4) the solution was concentrated and recrystallized from ethyl ether to give 0.11 g. of IIC, m.p. 197–199°.

Anal. Calcd. for $C_{25}H_{35}NO_3$: C, 75.52; H, 8.87; N. 3.52. Found: C, 75.43; H, 8.90; N, 3.28.

17α-Ethynyl Carbamate (IIC).—A mixture of 1.0 g. of 17α-ethynyl-19-nor-Δ^4-androsten-17β-ol-3-one, 35 ml. of methyl isocyanate, and 0.066 g. of Dabco was heated at reflux for 42 hr. while being agitated with a magnetic stirrer. At this time, solution had resulted. The solvent was evaporated, and the residue was taken up in 4:3 chloroform–ethyl ether and chromatographed on 40 g. of neutral alumina. Fractions 2 through 4 using the above solvent mixture were combined and recrystallized from ethyl ether to give 0.41 g., m.p. 130–132°.

Anal. Calcd. for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.21; H, 8.33; N, 4.22.

Carbamic Acid Lactone (IIIC).—A solution of 0.3 g. of carbamate IIC, 4 ml. of sodium methoxide solution (0.1 g. of sodium in 10 ml. of methanol), and 25 ml. of methanol was heated at reflux overnight. Some of the solvent was evaporated, and the solution was poured into excess water. The mixture was extracted thoroughly with ethyl ether, and the combined solution was washed with bicarbonate and sodium chloride solutions. After drying (Na_2SO_4) the solution was concentrated and recrystallized from methanol–water to give 0.11 g., m.p. 189–190°.

Anal. Calcd. for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.29; H, 8.34; N, 3.93.

Ethyl Carbamic Acid Lactone (IIIC).—A solution of 0.5 g. of 17α-ethynyl-19-nor-Δ^4-androsten-17β-ol-3-one, 20 ml. of ethyl isocyanate, and 0.04 g. of Dabco was heated at reflux for 87 hr. The solvent was evaporated, and the residue was taken up in 2:1 benzene–petroleum ether (b.p. 30–60°) and chromatographed on 30 g. of neutral alumina. The carbamate was eluted with 25% ethyl ether in benzene, and since it would not crystallize under a variety of conditions the oil was used directly for ring closure.

The residue was dissolved in 50 ml. of methanol and 10 ml. of the sodium methoxide solution was added. After heating at reflux overnight, some of the solvent was evaporated, and the solution was poured into an excess of water. The mixture was extracted thoroughly with methylene chloride–ethyl ether and after the usual washings was dried. The solvent was evaporated, and the residue was recrystallized from ethyl ether to give 0.15 g., m.p. 187–190°.

Anal. Calcd. for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.45; N, 3.79. Found: C, 74.78; H, 8.51; N, 3.88.

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The Synthesis and Myotrophic Activity of 1-Halo-4-methylestra-1,3,5(10)-trienes

G. W. MOERSCH, T. P. CULBERTSON, D. F. MORROW, E. L. WITTLE, R. R. HUMPHREY, W. A. NEUKLIS, M. E. BUTLER, AND M. M. CREGER

Research Laboratories, Parke, Davis and Co., Ann Arbor, Michigan

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A large series of variously substituted 1-halo-4-methylestra-1,3,5(10)-trienes was prepared. Some of these compounds possessed oral myotrophic activity with little or no accompanying androgenicity.

We have previously reported two different syntheses of 17-substituted 1-halo-4-methylestra-1,3,5(10)-trienes.[1,2] Some of these compounds were found to possess oral myotrophic activity, and the present paper describes certain related compounds which were prepared (see Table I) together with a record of their pharmacological activities.

The parent compound of this series, 1-chloro-4-methylestra-1,3,5(10)-trien-17-one (**11**), was prepared in 87% yield from the reaction of androsta-1,4-diene-3,17-dione with oxalyl chloride and oxalic acid in benzene at room temperature.[1] Fifteen related compounds (**14**, **22**, **25**, **28**, **31**, **43**, **48–51**, **53–55**, **57**, and **58**) were prepared by the same reaction on the corresponding substituted 1,4-dienones (Ia → II).[3] Seven of these androsta-1,4-dien-3-ones (**4–10**) were new compounds, synthesized from the Δ^4-3-ketones by dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone.[4] The yields of the 1-chloro-4-methylestra-1,3,5(10)-trienes prepared in this manner were generally good, ranging from 30 to 90%.

The addition of ethinylmagnesium bromide to the 17-ketone of **11** gave the 17α-ethinyl compound (**39**), and subsequent partial catalytic reduction of the

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