lization from hexane an additional 8.2 g of II, mp 129–131°, identical with that obtained above (total yield, 78.6%) as determined by tlc and infrared spectra.

3-(3α-Bromo-2β,17β-hydroxy-5α-androstan-17α-yl)propionic Acid γ-Lactone (VI).—To a cooled and stirred solution of II (16 g) in dioxane (250 ml, purified) was added dropwise a mixture of N-bromosuccinimide (9.6 g), H_2O (105 ml), and 60% $HClO_4$ (8.34 g) over 15 min. The reaction was stirred for 3 hr at room temperature and poured into H_2O. The oily product was extracted with ethyl acetate and the extract washed with aqueous HCl (5%) followed by $NaHCO_3$ (5%, aqueous) and water. After drying (Na_2SO_4, Darco), the solvent was removed *in vacuo* to leave a white solid. Recrystallization from methanol–H_2O afforded VI (15.7 g, 75.5%), mp 204–207°. Further recrystallization from methanol produced an analytical sample, mp 220–220°, $[\alpha]D$ +33°.

Anal. Calcd for $C_{22}H_{33}BrO_3$: C, 62.11; H, 7.82. Found: C, 62.54; H, 7.82.

3-(2,3α-Epoxy-17β-hydroxy-5α-andostan-17α-yl)propionic Acid γ-Lactone (III).—A solution of II (9 g) and *m*-chloroperbenzoic acid in benzene (1.2 *N*, 275 ml) was allowed to stand at 7° for 16 hr. The mixture was allowed to warm to room temperature and washed repeatedly with aqueous Na_2CO_3 solution (5%) followed by H_2O and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded an oil which gradually solidified. Recrystallization from methanol gave III (6.5 g, 68.8%), mp 164–166°, $[\alpha]D$ −9°.

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.46; H, 9.08.

3-(2,3β-Epoxy-17β-hydroxy-5α-androstan-17α-yl)propionic Acid γ-Lactone (VII).—A solution of VI (6.0 g) in DMF (100 ml) was heated with K_2CO_3 (2.0 g) in H_2O (10 ml) in a steam cabinet (40–60°) for 16 hr. The reaction was cooled and poured into ice and water. A precipitate formed and was collected, washed with H_2O, and air dried. Recrystallization from methanol afforded VII (3.0 g, 47.6%), mp 178.5–180.5°, $[\alpha]D$ +1.5°.

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.22; H, 9.02.

3-(3α,17β-Dihydroxy-2β-thiocyano-5α-androstan-17α-yl)propionic Acid γ-Lactone (IV).—To a mixture of KSCN (44 g) in ice-cold H_2O (21.6 ml) and ether (180 ml) in a separatory funnel was added with shaking H_3PO_4 (66.4 g) in small portions. The pink organic layer was separated, washed with two small portions of H_2O, and dried briefly (Na_2SO_4). The solution of HSCN in ether was decanted into a stirred slurry of III (4.0 g) in ether (30 ml). The mixture was allowed to stand at room temperature for 2 days. The homogeneous reaction was washed with 10% aqueous Na_2CO_3 until neutral. After washing with several portions of H_2O and drying (Na_2SO_4, Darco), the solvent was removed *in vacuo*. The remaining semisolid was recrystallized from methanol to give IV (2.2 g, 52.8%). Further recrystallization from the same solvent gave an analytical sample, mp 216–217.5°, $[\alpha]D$ −9°.

Anal. Calcd for $C_{23}H_{33}NSO_3$: C, 68.45; H, 8.24. Found: C, 68.87; H, 8.23.

3-(2β,17β-Dihydroxy-3α-thiocyano-5α-androstan-17α-yl)propionic Acid γ-Lactone (VIII).—A solution of VII (2.5 g) in ether (50 ml) was treated with HSCN in ether as described above. Rectification as above and recrystallization from methanol–H_2O afforded VIII (2.15 g, 73.5%), mp 239–240°, $[\alpha]D$ +20.0°.

Anal. Calcd for $C_{23}H_{33}NO_3S$: C, 68.45; H, 8.24. Found: C, 68.78; H, 8.23.

3-(2,3β-Epithio-17β-hydroxy-5α-androstan-17α-yl)propionic Acid γ-Lactone (V).—To a stirred solution of IV (1.2 g) in methanol (40 ml) was added KOH (0.6 g) in methanol (10 ml). The reaction mixture was allowed to stand at room temperature for 2 hr. Water (25 ml) was added and the solution was cooled in the refrigerator. The precipitate which formed was collected and recrystallized from methanol–H_2O to give V (0.4 g, 37.4%), mp 158.5–160°, $[\alpha]D$ −10.0°.

Anal. Calcd for $C_{22}H_{32}O_2S$: C, 73.28; H, 8.95. Found: C, 73.12; H, 8.85.

3-(2,3α-Epithio-17β-hydroxy-5α-androstan-17α-yl)propionic Acid γ-Lactone (IX).—A warm solution of VIII (1.5 g) in methanol (80 ml) was treated with methanolic KOH as above. Rectification and recrystallization from acetone–H_2O afforded IX (0.85 g, 63.5%), mp 175–177°, $[\alpha]D$ +26.5°.

Anal. Calcd for $C_{22}H_{32}O_2S$: C, 73.28; H, 8.95. Found: C, 73.36; H, 8.98.

3,4-Dihydro-1,3-oxazines from Dicyclohexylcarbodiimide

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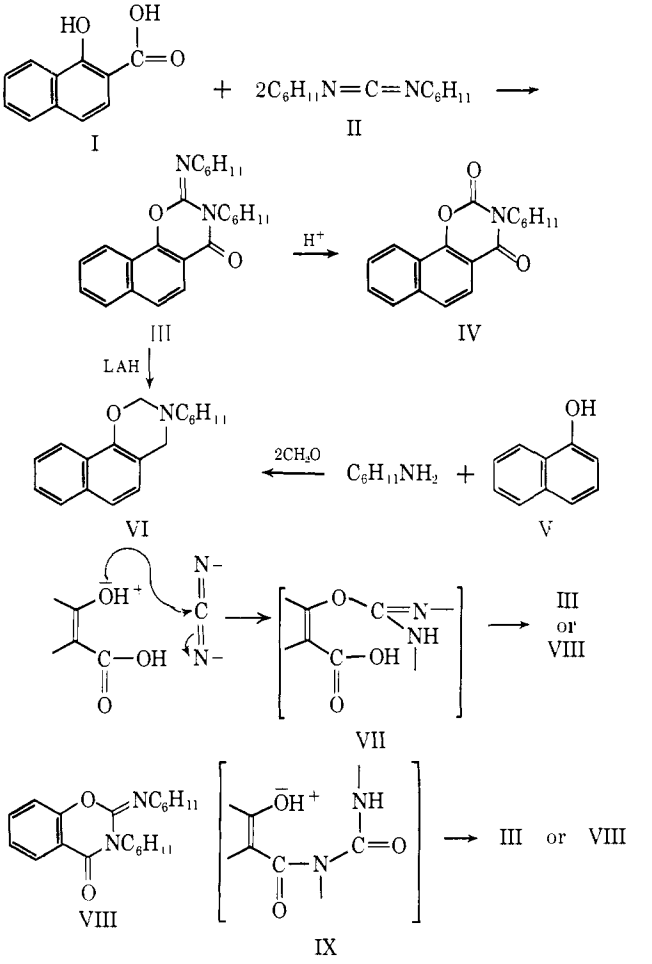
Several years ago, we attempted to prepare amides of 1-hydroxy-2-naphthalenecarboxylic acid (I) by the carbodiimide method using dry tetrahydrofuran (THF) as the solvent. Instead of the expected amides, a product containing the combined components of the two reagents minus the elements of H_2O was isolated whether or not an amine was used. 1,3-Dicyclohexylurea was also obtained in 70–80% yield. Analytical, infrared, and nmr data left little doubt that this product was 3-cyclohexyl-2-cyclohexylimino-3,4-dihydro-4-oxo-2H-naphth[2,1-*e*]-1,3-oxazine (III).

Compound III was essentially unchanged by refluxing (3 hr), alcoholic KOH. It was also resistant to hydrogenation with PtO_2, but $LiAlH_4$ effected hydrogenolysis of the cyclohexylimino and carbonyl groups, producing 3-cyclohexyl-3,4-dihydro-2H-naphth[2,1-*e*]-1,3-oxazine (VI), isolated in 20–40% yields as the hydrochloride salt[1] (see Scheme I). It proved to be identical with VI obtained by synthesis from 1-naphthol,

SCHEME I



(1) Also detected was N,N′-dicyclohexylformamidine providing evidence of some ring rupture.

formaldehyde, and cyclohexylamine[2] and isolated as the rather unstable base.

Similar reaction of salicylic acid and II gave 3-cyclohexyl-2-cyclohexylimino-3,4-dihydro-4-oxo-2H-1,3-benzoxazine (VIII) in 15–20% yield. No other tractable products could be isolated.

The formation of III and VIII may be *via* intermediate VII which would undergo instantaneous lactamization. Hawtrey[3] has characterized the product analogous to VII resulting from the addition of 2,4,6-trinitrophenol and II. Alternatively, the naphthoxide ion may add to the urea carbonyl function of the "activated acid" (IX)[4] with subsequent loss of H_2O. In any event, the reaction is strongly exothermic and rapid as indicated by the immediate precipitation of 1,3-dicyclohexylurea.

Compound VI (ED_{50} = 25 mg/kg) is about one-third as potent as codeine (ED_{50} = 7.5) as an analgetic agent in mice (subcutaneous administration).[5] Compounds III and VI were ineffective at 100 mg/kg in inhibiting ultraviolet erythema in guinea pigs. At this dose phenylbutazone gives 95% protection.[6]

Experimental Section

Melting points (capillary) were determined with total-immersion thermometers, and infrared measurements with the Perkin-Elmer Infracord. Nmr data ($CDCl_3$) were obtained with a Varian Associates Model A-60, with Me_4Si as an internal reference standard. Complete spectral data are available on request.

3-Cyclohexyl-2-cyclohexylimino-3,4-dihydro-4-oxo-2H-naphth[2,1-*e*]-1,3-oxazine (III).—Acid I (5.0 g), 12 g (2.1 molar equiv) of dicyclohexylcarbodiimide (II), and 50 ml of THF (dried over Molecular Sieve, Type 4A) were warmed briefly on the steam bath (after the initial, exothermic reaction had subsided), left for 1 hr to 2 days at 25°, and filtered to give 4.9 g (80%) of 1,3-dicyclohexylurea. The filtrate was evaporated to dryness, and the oil was digested with 125 ml of boiling ether. Decantation and evaporation of the ether left a residue which crystallized from 75–80 ml of absolute ethanol in a yield of 2.9 g (29%); mp 173–178°; needles from ethyl acetate, mp 183–184°; $\lambda_{max}^{CHCl_3}$ 5.9 (C=N), 6.0 (lactam) μ.

Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 76.6; H, 7.5; N, 7.4. Found: C, 76.6; H, 7.4; N, 7.4.

Dioxane, ethyl acetate, $CHCl_3$, or C_6H_6 instead of THF gave inferior yields; with absolute ethanol, no III was obtained.

3-Cyclohexyl-2,4-dioxo-3,4-dihydro-2H-naphth[2,1-*e*]-1,3-oxazine (IV).—Compound III (0.5 g), 2 ml of concentrated HCl, and 15 ml of absolute ethanol, kept on the steam bath overnight, concentrated *in vacuo*, and cooled, gave 0.3 g (85%) of IV: mp 160–165°; needles from ethanol or ethyl acetate, mp 165–166; $\lambda_{max}^{CHCl_3}$ 5.67 (lactone), 5.93 (lactam) μ.

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 73.2; H, 5.8. Found: C, 73.1; H, 6.1.

3-Cyclohexyl-3,4-dihydro-2H-naphth[2,1-*e*]-1,3-oxazine (V). Hydrochloride.—A mixture of 2.5 g of III, 1.5 g of $LiAlH_4$, and 50 ml of dry ether was refluxed for 2 hr and treated carefully with water. The filtered ether solution was dried (Na_2SO_4) and evaporated to dryness. The residue[7] in dry ether was acidified with dry HCl. The ether was decanted, and the residual amorphous material was triturated in 5–10 ml of acetone to give, after cooling to 0°, 1.01 g (50%) of crystals, mp 160–190°, which were dissolved in 3 ml of hot methanol. Addition of 4 ml of ethyl acetate and cooling, finally to 0°, gave pure VI·HCl (needles), mp 185–187°,[8] whose infrared spectrum was transparent from 5.5–6.2 μ.

Anal. Calcd for $C_{19}H_{22}ClNO$: C, 71.2; H, 7.3; Cl, 11.7; N, 4.6. Found: C, 70.9; H, 7.2; Cl, 11.8; N, 4.6.

The picrate of VI (prepared with alcoholic picric acid) crystallized from methanol in yellow prisms of mp 129–132°.

Anal. Calcd for $C_{31}H_{34}N_4O_8$: C, 58.1; H, 4.9; N, 11.3. Found: C, 57.9; H, 5.3; N, 11.3.

Exactly according to Burke, *et al.*,[2] VI was synthesized from V, formaldehyde, and cyclohexylamine. The free base, hydrochloride salt, and picrate proved to be identical with those obtained in the $LiAlH_4$ reduction of III.

3-Cyclohexyl-2-cyclohexylimino-3,4-dihydro-4-oxo-2H-1,3-benzoxazine (VIII). A mixture of 5.0 g of salicylic acid 15 g (2 molar equiv) of II and 50 ml of dry THF was shaken briefly and left for 1 hr to 2 days. Filtration gave 6.9 g (63%) of 1,3-dicyclohexylurea. The filtrate was evaporated to dryness giving a residue that crystallized from methanol during 24 hr: yield 2.1 g (18%), mp 75–95°. Two recrystallizations from methanol did not change the melting point. After drying at 38° (house vacuum), VIII melted at 99–104°, $\lambda_{max}^{CHCl_3}$ 5.87 (imine) and 6.01 (lactam) μ. The material is dimorphic, crystallizing either in long, well-defined or short, poorly defined needles.

Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.6; H, 8.0; N, 8.6. Found: C, 73.7; H, 8.1; N, 8.4.

Acknowledgment. We are indebted to Paula Parisius, Alice Wong, and Byron Baer of the Section on Instrumentation of this institute, Dr. W. C. Alford, Chief, for the microanalyses and to Louise Atwell for performing analgetic assays.

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(3) A. O. Hawtrey, *Tetrahedron Letters*, 6103 (1966).

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(5) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).

(6) We are indebted to Dr. Frank Clarke, Geigy Pharmaceutical Co., Ardsley, N. Y., for these data.

(7) Invariably, the infrared spectrum of this residue showed a maximum at 5.9 μ indicative of N,N'-dicyclohexylformamidine which was actually isolated (in low yield) and characterized as the hydrochloride salt: mp 235–237°; λ_{max}^{Nujol} 3.15, 5.92 μ. *Anal.* Calcd for $C_{27}H_{53}ClN_2$: C, 63.8; H, 10.3; Cl, 14.5; N, 11.5. Found: C, 63.9; H, 10.3; Cl, 14.6; N, 11.2. It proved to be identical (melting point, glpc, infrared data) with material prepared by $LiAlH_4$ reduction of dicyclohexylcarbodiimide; *cf.* M. T. Leplawy, D. S. Jones, G. W. Kenner, and R. C. Sheppard, *Tetrahedron*, **11**, 39 (1960).

(8) II crystallizes also as parallelograms, mp 175–178°.