Experimental

General.—Melting points were taken in an open capillary tube and are corrected. The ultraviolet spectra were determined in methanol on a Cary recording spectrophotometer and infrared spectra (pressed potassium bromide disks) were carried out with a Perkin-Elmer spectrophotometer (Model 21). N.m.r. data were determined with tetramethylsilane as an internal standard in deuteriochloroform with a Varian Model DP-60 spectrometer at 56.4 Mc. All evaporations were carried out under reduced pressure, and the petroleum ether used was that fraction boiling at 60–70°. Nitrogen analyses were by the Dumas method.

16β-Cyano-3-methoxy-16α-methylestra-1,3,5(10)-trien-17-one (II).—To a solution of 500 mg. of 16-cyano-3-methoxyestra-1,3,5(10)-trien-17-one[5] (I) in 25 ml. of reagent acetone, through which nitrogen was bubbled, was added 1 g. of anhydrous potassium carbonate and 2 ml. of methyl iodide. The mixture was allowed to stir under a nitrogen atmosphere for 2 days after which time another 2 ml. of methyl iodide was added and stirring was continued for an additional 5 days. The mixture then was filtered and the mother liquor was evaporated to dryness. The residue was recrystallized from acetone–water to give 442 mg. (85%) of product, m.p. 173–176°. Recrystallization from acetone–petroleum ether and then from ether–petroleum ether gave white crystals, m.p. 185–186°; $[\alpha]^{25}\text{D}$ +108° (c 0.58, $CHCl_3$); λ_{max} 221 mμ (ϵ 9400), 279 (2100), 288 (1940); λ_{max} 4.48, 5.68, 6.18, 6.34, 6.66, 6.86, 7.96 μ; n.m.r.,[26] τ 8.90 (C-18 CH_3), 8.50 (C-16 CH_3), 6.26 (OCH_3).

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.77; H, 8.28; N, 4.22.

16β-Cyano-16α-fluoro-3-methoxyestra-1,3,5(10)-trien-17-one (III).—Perchloryl fluoride was bubbled briskly into a cold (−4°) stirred solution of 16-cyano-3-methoxyestra-1,3,5(10)-trien-17-one[5] and 3.3 ml. of 1 N methanolic sodium methoxide in 20 ml. of methanol until neutral (4 min.). After flushing with nitrogen, the solution was concentrated to a small volume, diluted with water, and extracted twice with methylene chloride. The combined extracts were washed with water, dried with anhydrous magnesium sulfate, and evaporated to dryness. Recrystallization of the residue from ether–petroleum ether gave 308 mg. (58%) of product, m.p. 153–155°. Recrystallization from the same solvent pair furnished white crystals, m.p. 154–155°; $[\alpha]^{25}\text{D}$ +185° (c 1.1, $CHCl_3$); λ_{max} 222 mμ (ϵ 9000), 279 (1960), 288 (1960); λ_{max} 4.45, 5.63, 6.19, 6.34, 6.65, 7.98 μ; n.m.r.,[26] τ 8.90 (C-18 CH_3), 6.25 (OCH_3).

Anal. Calcd. for $C_{20}H_{22}FNO_2$: C, 73.37; H, 6.77; F, 5.80; N, 4.28. Found: C, 73.09; H, 6.90; F, 5.63; N, 4.40.

16β-Cyano-3-methoxy-16α-methylthioestra-1,3,5(10)-trien-17-one (IV).[12]—16-Cyano-3-methoxyestra-1,3,5(10)-trien-17-one (1.54 g., 5 mmoles) was dissoved in 20 ml. of methanol and 5 ml. of a 1 N methanolic sodium methoxide solution. The yellow solution was evaporated at 40° and the residue was evaporated with 10 ml. of dry dioxane to remove traces of methanol. The residue was mixed with 30 ml. of dioxane and to the yellow suspension was added 470 mg. (theory, 450 mg.) of methanesulfenyl chloride.[27] Most of the solid went into solution within a few minutes and the faintly yellow solution was evaporated at 40°. The residue was dissolved in benzene and the solution was washed with water till neutral and then dried, decolorized, and evaporated. The residue was crystallized from ether to afford 755 mg., m.p. 113–115°; $[\alpha]^{25}\text{D}$ +115° (c 1.05, $CHCl_3$); λ_{max} 225 mμ (ϵ 7453), 278 (2134), 288 (1952); λ_{max} 4.44, 5.73 μ; n.m.r.,[26] τ 8.95 (C-18 CH_3), 7.59 (S–CH_3), 6.25 (OCH_3).

Anal. Calcd. for $C_{21}H_{25}NO_2S \cdot 0.1H_2O$: C, 70.57; H, 7.11; N, 3.92; S, 8.93; H_2O, 0.5. Found: C, 70.46; H, 6.93; N, 4.15 (Kjeldahl); S, 9.23; H_2O, 0.5.

16β-Cyano-3-methoxy-16α-methylsulfinylestra-1,3,5(10)-trien-17-one (V).—To a solution of 300 mg. of 16β-cyano-3-methoxy-16α-methylthioestra-1,3,5(10)-trien-17-one (IV) in 7.5 ml. of methylene chloride was added 1.05 mole equivalents of ethereal monoperphthalic acid. The reaction mixture, protected from moisture, was allowed to stand at room temperature for 24 hr. during which period phthalic acid separated. The phthalic acid was filtered and the filtrate was washed with dilute sodium carbonate solution and water, dried with anhydrous magnesium sulfate, and evaporated to dryness. Trituration of the residue with petroleum ether and filtration afforded 254 mg. (81%) of product, m.p. 148–150° (gas). Recrystallization from methylene chloride–ether gave white crystals, m.p. 149–151° (gas); $[\alpha]^{25}\text{D}$ +125° (c 0.97, $CHCl_3$); λ_{max} 221 mμ (ϵ 10,800), 279 (2040), 288 (2040); λ_{max} 4.48, 5.71, 6.18, 6.34, 6.65, 7.96, 9.22 μ.

Anal. Calcd. for $C_{21}H_{25}NO_3S$: C, 67.89; H, 6.78; N, 3.77; S, 8.63. Found: C, 67.16; H, 6.86; N, 3.78; S, 8.92.

16β-Cyano-3-methoxy-16α-methylsulfonylestra-1,3,5(10)-trien-17-one (VI).—16β-Cyano-3-methoxy-16α-methylsulfinylestra-1,-3,5(10)-trien-17-one (V, 110 mg.) was treated with monoperphthalic acid according to the procedure described above for the sulfoxide (V) preparation, except that the time was extended to 48 hr. Evaporation of methylene chloride solvent gave a semisolid which was recrystallized twice from acetone–petroleum ether to furnish 70 mg. (61%) of product, m.p. 164–166° (gas); λ_{max} 222 mμ (ϵ 4300), 279 (2130), 288 (2130); λ_{max} 4.46, 5.67, 6.18, 6.33, 6.65, 7.50, 7.98, 8.49 μ.

Anal. Calcd. for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61; S, 8.27. Found: C, 64.91; H, 6.58; N, 3.29; S, 8.06.

16β-Cyano-17β-hydroxy-3-methoxy-16α-methylestra-1,3,5(10)-triene (VII).—Treatment of 200 mg. of 16β-cyano-3-methoxy-16α-methylestra-1,3,5(10)-trien-17-one (II) in 20 ml. of purified tetrahydrofuran with 100 mg. of lithium borohydride for 3 hr. according to the procedure described below for the preparation of 16β-cyano-17β-hydroxy-3-methoxy-16α-methylthioestra-1,3,5-(10)-triene (VIII) afforded 150 mg. (75%) of product, m.p. 205–207°. Recrystallization from methylene chloride–ether gave white crystals, m.p. 208–210°; $[\alpha]^{25}\text{D}$ +51.5° (c 0.53, $CHCl_3$); λ_{max} 220 mμ (ϵ 8000), 279 (1870), 288 (1790); λ_{max} 2.90, 4.96, 6.19, 6.34, 6.66, 7.97 μ; n.m.r.,[28] τ 9.05 (C-18 CH_3), 8.48 (C-16 CH_3), 6.29 (OCH_3).

Anal. Calcd. for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.55; H, 8.10; N, 4.29.

16β-Cyano-17β-hydroxy-3-methoxy-16α-methylthioestra-1,3,5-(10)-triene (VIII).—To a solution containing 200 mg. of 16β-cyano-3-methoxy-16α-methylthioestra-1,3,5(10)-trien-17-one (IV) in 20 ml. of absolute ethanol was added 200 mg. of sodium borohydride and the resulting suspension was stirred at room temperature for 1 hr. Acetic acid was added carefully, followed by water. The resulting solution was evaporated to near dryness and the wet residue was extracted twice with methylene chloride. The combined extracts were washed with water, dried with anhydrous magnesium sulfate, and evaporated to dryness. Recrystallization of the residue from ether–petroleum ether furnished 140 mg. (70%) of product, m.p. 185–190°. Recrystallization from methylene chloride–ether–petroleum ether gave white crystals, m.p. 190–193°; $[\alpha]^{25}\text{D}$ +59° (c 0.29, $CHCl_3$); λ_{max} 220 mμ (ϵ 8600), 279 (1960), 288 (1880); λ_{max} 2.90, 4.46, 6.18, 6.38, 6.66, 7.98 μ; n.m.r.,[8] τ 9.05 (C–18 CH_3), 7.64 (SCH_3), 6.25 (OCH_3).

Anal. Calcd. for $C_{21}H_{27}NO_2S$: C, 70.55; H, 7.61; N, 3.91; S, 8.97. Found: C, 70.83; H, 7.92; N, 3.88; S, 8.63.

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(26) N.m.r. of estrone 3-methyl ether: τ 9.11 (C-18 CH_3), 6.25 (OCH_3).

(27) I. B. Douglass, *J. Org. Chem.*, **24**, 2004 (1959).

(28) N.m.r. of estradiol 3-methyl ether: τ 9.25 (C-18 CH_3), 6.25 (OCH_3).

Synthesis of 3,5-Disubstituted Tetrahydro-4H-1,3,5-oxadiazin-4-ones

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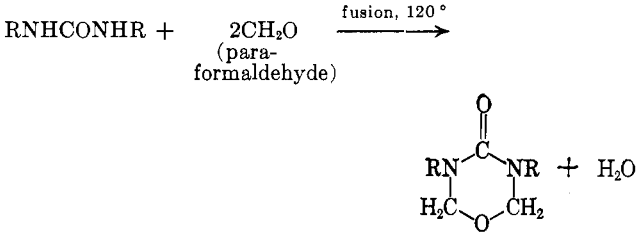
Recently, interest has been shown in the use of tetrahydro-4H-1,3,5-oxadiazin-4-ones as imparting crease resistance to cotton fabrics without causing yellowing in the presence of chlorine bleaches.[1] Kadowaki[2] obtained tetrahydro-3,5-dimethyl-4H-oxadiazin-4-one (I) in 27% yield by the action of aqueous formaldehyde on 1,3-dimethylurea followed by treatment with methanol and hydrochloric acid. When he substituted urea for 1,3-dimethylurea, he obtained tetrahydro-3,5-bis(methoxymethyl)-4H-1,3,5-oxadiazin-4-one (II). Beachem, *et al.*,[3] repeated Kadowaki's procedure but were unable to reproduce his results. Pure II could be isolated only by vapor phase chromatography of the mixture, and I was obtained by hydrogenolysis of II.

Zigeuner[4] prepared various tetrahydro-3,5-dibenzyl-4H-1,3,5-oxadiazin-4-ones using a modification of Kadowaki's method, but yields were largely unreported.

A practical method of preparing these compounds is now reported. In this laboratory, fusion of 1,3-disubstituted ureas with paraformaldehyde at 120° gave high yields of the corresponding tetrahydro-4H-1,3,5-oxadiazin-4-ones and also made possible the preparation of these compounds with acid-susceptible groups.



When the substituent was an alkyl group the reaction proceeded in almost quantitative yield. For ureas substituted by electronegative groups the use of boric acid catalyst proved necessary. Thus, ring closure of 1,3-bis(carbethoxymethyl)urea to tetrahydro-3,5-bis-(carbethoxymethyl)-4H-1,3,5-oxadiazin-4-one failed in the absence of boric acid, but, when boric acid catalyst was used, yields up to 82% were obtained, the yields varying directly with catalyst concentration.

Starting materials for the synthesis of tetrahydro-4H-1,3,5-oxadiazin-4-ones, *viz.*, 1,3-bis(ω-alkoxyalkyl)-ureas, were prepared from 2:1 mole ratio of amino acid ester hydrochlorides and phosgene by a modification of the Emil Fischer method,[5] in which potassium carbonate was used to absorb hydrogen chloride formed in the reaction.

Experimental

1,3-Bis(ω-carboalkoxyalkyl)ureas.—Phosgene (49 g., 0.5 mole) in benzene (500 g.), was added dropwise over a period of 1 hr. to a stirred mixture of amino acid ester hydrochloride (2 moles), benzene (440 g.), and KOH (112 g., 2 moles), in water (300 g.). Temperature was maintained at 5–10°. A solution of K_2CO_3 (139 g., 1 mole) and $KHCO_3$ (50 g. 0.5 mole) in water (300 g.) was added. Additional phosgene (49 g. 0.5 mole), in benzene, (350 g.), was added dropwise over a period of 1 hr. The mixture was stirred for another 1.5 hr. and allowed to warm to room temperature. Solids were isolated by filtration, washed with water (1000 g.), and recrystallized from appropriate solvents.

1,3-Bis(carbethoxymethyl)urea was prepared in 71% yield, m.p. 147–148°, lit. m.p. 144°, recrystallized from water.

Anal. Calcd. for $C_9H_{16}N_2O_5$: C, 46.55; H, 6.94; N, 12.07. Found: C, 46.02; H, 7.05; N, 11.76.

1,3-Bis(carbomethoxypentyl)urea was prepared in 46% yield, m.p. 100°, lit.[6] m.p. 101°, recrystallized from aqueous methanol.

Anal. Calcd. for $C_{15}H_{28}N_2O_5$: C, 56.94; H, 8.92; N, 8.85. Found: C, 56.78; H, 8.86; N, 9.07.

Tetrahydro-3,5-dibutyl-4H-1,3,5-oxadiazin-4-one.—Paraformaldehyde, 21.0 g. (0.682 mole of CH_2O), and 1,3-dibutylurea, 42.1 g. (0.244 mole), were thoroughly mixed and heated slowly until the temperature of the mixture reached 124°. Water and formaldehyde distilled during the heating step and the mixture became a clear melt. The product, a colorless liquid, was purified by distillation under reduced pressure, yielding 49.3 g. (94.4%), b.p. 100° (0.1 mm.), n^{27}_D 1.4678.

Anal. Calcd. for $C_{11}H_{22}N_2O_2$: C, 61.65; H, 10.34; N, 13.07. Found: C, 61.89; H, 10.50; N, 12.88.

Tetrahydro-3,5-bis(carboalkoxyalkyl)-4H-1,3,5-oxadiazin-4-ones from 1,3-Disubstituted Urea. Paraformaldehyde, 45.0 g. (1.46 moles of CH_2O), 1,3-bis(carboalkoxyalkyl)urea (0.50 mole), and boric acid (10.0 g., 0.16 mole) were mixed and heated slowly until the reaction mixture reached a temperature of 120–124°. Water and formaldehyde distilled during the heating step and the mixture finally became a clear melt which solidified on cooling. The crude product was slurried with 40 ml. of water.

Tetrahydro-3,5-bis(carbethoxymethyl)-4H-1,3,5-oxadiazin-4-one was prepared in 82% yield, m.p. 86–87°, recrystallized from water.

Anal. Calcd. for $C_{11}H_{18}N_2O_6$: C, 48.15; H, 6.62; N, 10.22. Found: C, 47.89; H, 6.68; N, 10.11.

Tetrahydro-3,5-bis(carbomethoxypentyl)-4H-1,3,5-oxadiazin-4-one, was prepared in 89% yield, m.p. 57–58°, recrystallized from aqueous methanol.

Anal. Calcd. for $C_{17}H_{30}N_2O_6$: C, 56.96; H, 8.44; N, 7.82. Found: C, 57.37; H, 8.63; N, 7.51.

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Substituted γ-Lactones. XV.[1] Condensation between Phthalide and Benzaldehyde

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Recently it was reported[3] that phthalide underwent an aldol-type condensation with equimolar quantities of aromatic aldehydes to yield a mixture of diastereoisomeric *dl-erythro-* and *dl-threo*-3-(α-hydroxybenzyl)-phthalides. If 2 equiv. of benzaldehyde are used in this condensation, a different compound, I, is obtained.[4] I also resulted, although at a slower rate, from the reaction of benzaldehyde with *dl-erythro-* and *dl-threo*-3-(α-hydroxybenzyl)phthalide. Physical and chemical evidence (Scheme I) reported in this Note establishes the structure of I as spiro-1-keto-1,3-dihydrobenzo(*c*)furan-3,5′,2′,4′,6′-triphenyl-1′-3′-dioxane.

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[1] Part XIV of this series: *J. prakt. Chem.*, in press.

[2] Taken in part from the Ph.D. Thesis of R. D. Barry, University of Cincinnati, 1960; Chattanooga Medicine Co. Fellow, 1957-1959; Ethyl Corp. Fellow, 1959-1960.

[3] H. Zimmer and R. D. Barry, *J. Org. Chem.*, **27**, 1602 (1962).

[4] The formation of I requires 3 moles of benzaldehyde. When the reaction was tried with a 3-mole amount, however, less than 10% of pure I was obtained. There was a large amount of oil, indicating that several side reactions occurred.