a and b rather than c or e, strengthening the deductions presented above for the predominance of forms IIa and b.

It is intended to make further detailed spectroscopic studies of these and closely related compounds in order to understand the conformational differences more fully.

Experimental

Solutions of II and III in $CDCl_3$ were obtained by hydrolysis of the acetals, $(EtO)_2CH \cdot CH_2CH(OEt)_2$ and $CH_3COCH(OMe)_2$, respectively, with an equal volume of dilute aqueous hydrochloric acid, followed by extraction with $CDCl_3$. The *trans*-β-ethoxyacrolein is obtained in small amount as a by-product of the hydrolysis of malondialdehyde tetraethyl acetal[17] and is preferentially extracted by the $CDCl_3$. A single n.m.r. tube was thus used to obtain the spectra of II and IV. This tube also contained a little ethanol, water, hydrochloric acid, and the original acetal. Similarly the $CDCl_3$ solution of III contained a little methanol, water, HCl, and the original acetal. In this case a small amount of the keto form (acetylacetaldehyde) could be detected. In both solutions only a single peak was observed for the protons of the water and hydrochloric acid together with the hydroxylic protons of the alcohol and the enol.

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Acknowledgment.—We are grateful to Drs. G. M. Grant, R. C. Hirst, G. H. Goldstein, and A. W. Douglas for information on the n.m.r. parameters of acrolein in advance of publication. Similarly we are indebted to Dr. S. L. Manatt for the coupling constants in cyclohexadiene. Computation in this research was done with the support of the U. S. Air Force Office of Scientific Research under Grant AF-AFOSR 199-63.

Formation of 17α-Ethyl-17-methyl-8ξ,9ξ,13ξ,14ξ-gona-1,3,5(10)-trien-3-ol from 17α-Ethyl-19-nortestosterone. An Unusual Transformation

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The dehydration of 17α-ethyl-19-nortestosterone with pyridine hydrohalides yields two crystalline products, 17α-ethyl-17-methylgona-4,13-dien-3-one and 17α-ethyl-17-methyl-8ξ,9ξ,13ξ,14ξ-gona-1,3,5(10)-trien-3-ol. The latter structure was established by ultraviolet, infrared, and n.m.r. spectra and by dehydrogenation to 3′-ethyl-3′-methyl-1,2-cyclopentanophenanthrene.

In the presence of acids, a 17-hydroxy-17-alkyl steroid undergoes dehydration with concomittant migration of the angular methyl group (I to II). The resulting double bond has been shown to be at C-13 and C-14,[1] but, where there is additional unsaturation in the molecule, the double bond may migrate further to become part of an extended conjugated system. Thus, Kaufmann found that treatment of 17β-hydroxy-17-methylandrosta-1,4,6-trien-3-one with *p*-toluenesulfonic acid in acetic anhydride affords 1,17,17-trimethyl-13ξ,14ξ-gona-1,3,5(10),6,8-pentaen-3-ol acetate.[2]

As part of a study on the dehydration–rearrangement of the steroids carried out in these laboratories,[3] we found that treatment of 17α-ethyl-19-nortestosterone (III)[4] or the enol ether, 17α-ethyl-3-methoxyestra-2,5-(10)-dien-17-ol (IV),[4] with either pyridine hydrochloride or pyridine hydrobromide at 230–240° affords 17α-ethyl-17-methylgona-4,13-dien-3-one (V), a product which previously had been obtained from III with hydrogen chloride in acetic acid.[5] Besides V, we obtained yet another crystalline product, m.p. 152–153.5°, $[\alpha]D$ −17°, λ_{max} 279.5 mμ (ε 2220) and 286 mμ (ε 2100), from the reaction of either III or IV with the pyridine hydro halide.

The formation of this product, to which we assign the 17α-ethyl-17-methyl-8ξ,9ξ,13ξ,14ξ-gona-1,3,5(10)-trien-3-ol structure (VIa) is analogous to the transformation observed by Kaufmann.[2] The double bond that is generated by the removal of the hydroxyl group at C-17 migrates into conjugation with the unsaturated carbonyl group in ring A. Enolization then results in the aromatization of this ring. The presence of the phenolic hydroxyl group in VIa is supported by spectroscopic evidence and is confirmed by the formation of the methyl ether, VIb.

The n.m.r. spectra of both VIa and VIb show a signal at 57.5 c.p.s., which we attribute to the methyl group at C-17, as well as a pair of signals at *ca.* 51.5 and 48.5 c.p.s. Because the latter signals could not be unambiguously assigned to the methyl portion of the ethyl side chain, the possibility that the product was a D-homo steroid containing a pair of methyl group had to be considered.

In order to determine the size of ring D, VIa was dehydrogenated with palladium on charcoal between 210 and 285°.[2] In the process, elimination of the hydroxyl group also occurred, and 3′-ethyl-3′-methyl-1,2-cyclopentanophenanthrene (VII), m.p. 97–98.5°, $[\alpha]D$ −28.5, was obtained. The physical constants of this substance and the melting point of its trinitrobenzene complex are essentially identical with those of a product isolated from the selenium dehydrogenation of 3β-acetoxypregn-5-en-20-one, for which VII has been proposed as its most likely structure.[6]

The infrared and n.m.r. spectra of our sample of VII unequivocally establish its identity with that obtained

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(2) S. Kaufmann, *J. Org. Chem.*, **28**, 1390 (1963).

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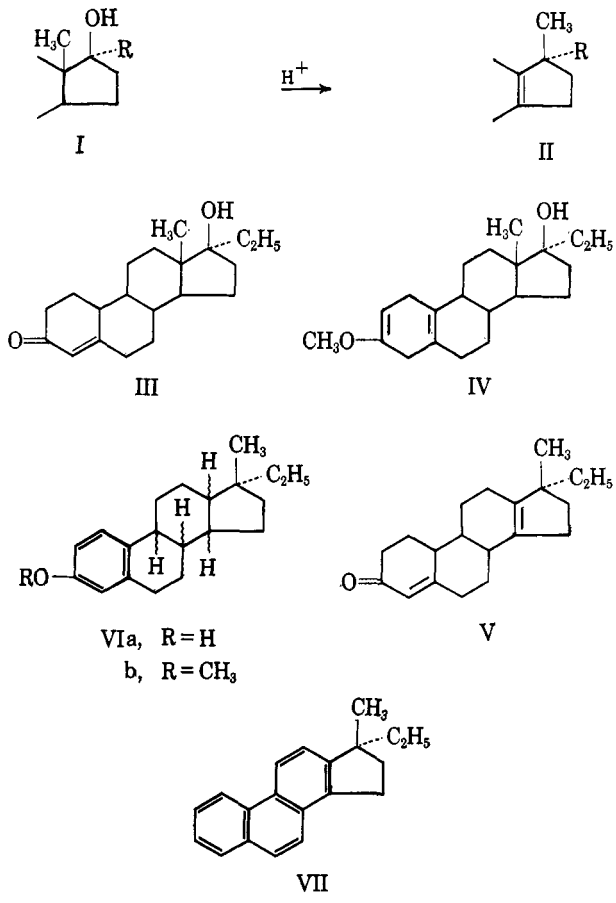
CHART I



by Reichstein and his associates.[6] As they noted, the methyl group of VII appears as a singlet in the n.m.r. spectrum while the methyl portion of the ethyl side chain gives rise to a triplet with a coupling constant of *ca.* 7 c.p.s. The dehydrogenation experiment clearly indicates that enlargement of ring D had not occurred during the dehydration–rearrangement of III or IV to give the aromatic product isolated and that the latter, indeed, has the structure formulated as VIa.[7]

Experimental[8]

17α-Ethyl-17-methylgona-4,13-dien-3-one (V)[5] and 17α-Ethyl-17-methyl-8ξ,9ξ,13ξ,14ξ-gona-1,3,5(10)-trien-3-ol (VIa). A. With Pyridine Hydrochloride.—A mixture of 485 g. (3.1 moles) of pyridine hydrochloride and 100 g. (0.33 mole) of 17α-ethyl-19-nortestosterone (III)[4] was maintained at 240° in an atmosphere of nitrogen for 1.5 hr. The cooled reaction mixture was extracted with ether. The combined ether extracts were successively washed with water, dried over anhydrous sodium sulfate, and distilled to dryness under reduced pressure. The residue was dissolved in hexane and chromatographed on silica gel. The column was eluted with varying proportions of hexane, benzene, and ethyl acetate. Elution with 50% benzene in hexane gave 17α-ethyl-17-methyl-8ξ,9ξ,13ξ,14ξ-gona-1,3,5(10)-trien-3-ol (VIa), which crystallized from hexane as colorless plates: yield 8.0 g. (8%); m.p. 152–153.5°; $[\alpha]^{27}D$ −17°; λ_{max}^{MeOH} 279.5 mμ (ε 2220) and 286 mμ (ε 2100); λ^{KBr} 3.07, 6.22, and 6.32 μ; n.m.r. 435.5, 427.5, 400.5, 392.5, 293 (disappeared when D_2O was added), 57.5, 51.5, and 48.5 c.p.s.

Anal. Calcd. for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.42; H, 9.73.

Further elution of the column with 2% ethyl acetate in benzene afforded 17α-ethyl-17-methylgona-4,13-dien-3-one (V),[5] which was crystallized from hexane: yield 25.2 g. (25%); m.p. 82–84°; $[\alpha]^{26}D$ −31.5°; λ_{max}^{MeOH} 237.5 mμ (ε 15,800); lit.[5] m.p. 83–85°, λ_{max} 250 mμ[9] (ε 16,800).

B. With Pyridine Hydrobromide.—Comparable yields of V and VIa were obtained when pyridine hydrobromide was used instead of pyridine hydrochloride.

C. From 17α-Ethyl-3-methoxyestra-2,5(10)-dien-17-ol.—A mixture of 22 g. (0.07 mole) of 17α-ethyl-3-methoxyestra-2,5(10)-dien-17-ol (IV)[4] and 100 g. (0.87 mole) of pyridine hydrochloride was maintained at 230–235° in an atmosphere of nitrogen for 1.5 hr. The cooled reaction mixture was worked up as before to yield 1.1 g. (5%) of 17α-ethyl-17-methyl-8ξ,9ξ,13ξ,14ξ-gona-1,3,5(10)-trien-3-ol (VIa), m.p. 153.3–154°, and 8.0 g. (36%) of 17α-ethyl-17-methylgona-4,13-dien-3-one (V), m.p. 83–84°.

17α-Ethyl-17-methyl-8ξ,9ξ,13ξ,14ξ-gona-1,3,5(10)-trien-3-ol-3-Methyl Ether (VIb).—To a solution of 0.211 g. of 17α-ethyl-17-methyl-8ξ,9ξ,13ξ,14ξ-gona-1,3,5(10)-trien-3-ol (VIa) in 5 ml. of methanol, stirred at room temperature, was added 2 ml. of an aqueous methanolic solution of potassium hydroxide prepared from 2 g. of 85% potassium hydroxide pellets, 5 ml. of methanol, and 2 ml. of water. Then 3 ml. of dimethyl sulfate and the rest of the above aqueous methanolic solution of potassium hydroxide were added portionwise and alternately to the solution of VIa over a period of 10 min. After 0.19 g. of solid potassium hydroxide was added, the reaction mixture was stirred at room temperature for an additional 0.5 hr. The reaction mixture was diluted with water and extracted with ether. The combined ether extracts were washed successively with water and a saturated solution of sodium chloride, dried over anhydrous sodium sulfate, and distilled to dryness under reduced pressure. Thin layer chromatography revealed that the residual, viscous, colorless oil contained only a trace of starting material, VIa, and that the only other product present was one which was considerably less polar than VIa. Trituration of the oil with methanol gave 0.200 g. of a colorless crystalline product, m.p. *ca.* 30–56°. After several crystallizations from ether–methanol, the methyl ether VIb was obtained as colorless prisms: m.p. 71–72°; $[\alpha]^{22}D$ −20.5°; λ_{max}^{MeOH} 277 mμ (ε 2000) and 287 mμ (ε 1880); λ^{KBr} 6.21 and 6.36 μ (OH band was absent); n.m.r. 437, 428.5, 404, 397, 225.5, 57.5, 51, and 48.5 c.p.s. An analytical sample of VIb was evaporatively distilled at 125–135° (0.1 mm.).

Anal. Calcd. for $C_{21}H_{30}O$: C, 84.51; H, 10.13. Found: C, 84.37; H, 10.14.

Dehydrogenation[2] of 17α-Ethyl-17-methyl-8ξ,9ξ,13ξ,14ξ-gona-1,3,5(10)-trien-3-ol (VIa).—An intimate mixture of 0.285 g. of VIa and 0.285 g. of 5% palladium on charcoal was maintained at 210 to 285° for 4.5 hr. The cooled reaction mixture was extracted with ethyl acetate. The combined ethyl acetate extracts were evaporated to dryness to afford 0.191 g. (73.5%) of 3′-ethyl-3′-methyl-1,2-cyclopentanophenanthrene (VII),[6] m.p. 90.5–94°. Vapor phase chromatography indicated that the sample was 97% pure. Two crystallizations from ether–methanol gave VII as colorless plates: m.p. 97–98.5°; $[\alpha]^{25}D$ −28.5°; λ_{max}^{MeOH} 223 mμ (sh) (ε 29,900), 252 (sh) (ε 52,700), 257.5–258 (ε 65,000), 278.5–279 (ε 15,000), 286 (ε 12,000), 298 (ε 14,300), 319 (ε 780), 334 (ε 780); λ_{min} 230.5–231 mμ (ε 8560), 274–274.5 (ε 12,900), 284.5 (ε 10,500), 293.5–294 (ε 6220), *ca.* 330 (ε 625); λ^{CS_2} 3.25, 3.37, 5.20, *ca.* 5.65, 7.23, 7.90, 8.36, 8.81, 9.67, 9.92, 10.57, 11.57, 12.23, *ca.* 13.30, 13.88, and 14.37 μ; n.m.r. 135.5, 128.5, 122, 115 (quartet for CH_2—CH_3), 79.5 (CH_3), and 57.5, 51, 43 (triplet for CH_2—CH_3) c.p.s.; lit.[6] m.p. 94–96°, $[\alpha]^{25}D$ −28° (cyclohexane).

Anal. Calcd. for $C_{20}H_{20}$: C, 92.26; H, 7.29. Found: C, 92.06; H, 7.58.

3′-Ethyl-3′-methyl-1,2-cyclopentanophenanthrene Trinitro-

(7) The ethyl group of VIa is assigned the α-configuration on the basis that the C-17 carbonium ion derived from III undergoes a Wagner–Meerwein rearrangement in which the angular methyl group migrates from the 13- to the 17β-position [*cf.* K. Heusler and A. Wettstein, *Ber.* **87**, 1301 (1954); H. L. Herzog, C. V. Joyner, M. J. Gentles, M. T. Hughes, E. P. Oliveto, E. B. Hershberg, and D. H. R. Barton, *J. Org. Chem.*, **22**, 1413 (1957)]. The subsequent step may involve successive, discrete carbonium ions at C-14, -8, and -9, which would lead to rings C and D of VIa being *fused cis*.[2] Alternatively, it may proceed by a concerted mechanism, in which case VIa then would have the 9β,8α,14β,13α-configuration [*cf.* A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955)]. The data are insufficient to permit assignment of configuration with any degree of certainty to the ring junctions of VIa at this time.

(8) Melting points are corrected. Optical rotations were determined in $CHCl_3$ at a concentration of 1%. N.m.r. signals are reported as downfield with reference to internal tetramethylsilane at 60 Mc/sec. as determined in $CDCl_3$ on a Varian A-60 instrument.

(9) This figure, undoubtedly, is a misprint as simple 3-keto Δ⁴-steroids do not absorb significantly beyond 240 mμ.

benzene[6]—To a warm solution of 0.040 g. of VII in 2 ml. of 95% ethanol was added a warm solution of 0.040 g. of 1,3,5-trinitrobenzene in 2 ml. of 95% ethanol. The reaction mixture was allowed to stand at room temperature for 0.5 hr. The yellow crystalline product was collected and dried: yield 0.050 g. (68.5%); m.p. 162–162.5°. Crystallization from 95% ethanol gave the trinitrobenzene complex of VII as yellow stout needles. m.p. 162.5–163°, $[\alpha]^{26}D$ −15°, lit.[5] m.p. 158–163.

Anal. Calcd. for $C_{26}H_{23}N_9O_6$: C, 65.95; H, 4.90; N, 8.88. Found: C, 66.12; H, 5.04; N, 8.54.

Novel Preparation of Benzimidazoles from N-Arylamidines. New Synthesis of Thiabendazole[1]

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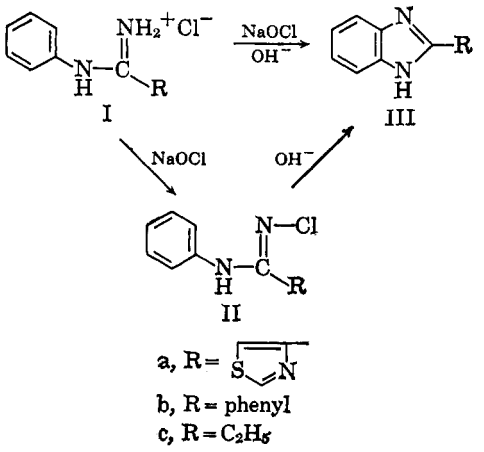
A new, efficient procedure for the conversion of N-arylamidines with hypochlorite and base to benzimidazoles has been devised. Using this technique, a new synthesis of thiabendazole has been realized.

Because of the increasing importance of benzimidazoles in recent chemical literature,[2] we felt that a simpler approach to the synthesis of these heterocyclics other than that described by Brown, *et al.*,[2] would be of great value. The procedure for preparing benzimidazoles usually involves the condensation of *o*-phenylenediamine or *o*-nitroaniline with a carboxylic acid derivative.[3] In each case, the cyclization directly involves a coupling at the *o*-phenylene nitrogens.

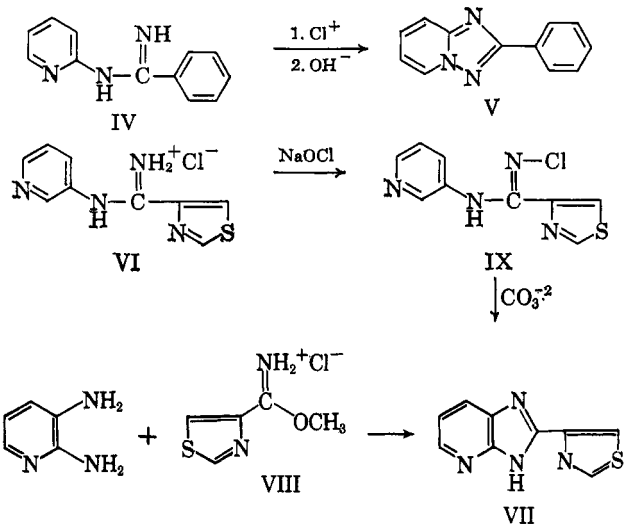
Since N-arylamidines are available[4] by the reaction of an aromatic amine with a nitrile or imidate, it appeared that substituted amidines I were potential precursors for benzimidazoles if they could be induced to cyclize by some oxidative process. A previous method[5] for the conversion of some amidines to benzimidazoles required the preparation of N-hydroxyamidines from amidines and hydroxylamine with the subsequent benzimidazole formation after treatment with benzenesulfonyl chloride and pyridine.

It was found that the N-arylamidine hydrochlorides I could, indeed, be transformed to benzimidazoles with 1 mole of sodium hypochlorite and base in excellent yields under mild conditions. The N-chloroamidine II might be isolated as a discrete intermediate, if desired prior to the addition of base. For example, in the preparation of 2-(4-thiazolyl)benzimidazole (IIIa, generic name thiabendazole),[1] an aqueous methanolic solution of N′-phenyl-4-thiazolecarboxamidine hydrochloride (Ia) was treated with 1 mole of sodium hypochlorite to form the crystalline N-chloroamidine IIa which could be isolated or processed directly with 1 equiv. of base in refluxing aqueous methanol to the benzimidazole IIIa in 98% yield. The benzimidazole formation could be followed by the disappearance of the positive halogen with potassium iodide–starch paper.



In a similar manner, N-phenylbenzamidine[5] (Ib) and N-phenylpropionamidine[6] (Ic) yielded 2-phenylbenzimidazole (IIIb, 94% yield) and 2-ethylbenzimidazole[7] (IIIc, 70% yield), respectively.

In order to extend our oxidative cyclization process to the preparation of azabenzimidazoles, we synthesized N-(2-pyridyl)benzamidine[8] (IV) and N′-(3-pyridyl)-4-thiazolecarboxamidine (VI). The amidines IV and VI were converted as hydrochlorides to their N-chloroamidines, respectively, and cyclized upon treatment with caustic. It is interesting to note that in the case of N-(2-pyridyl)benzamidine (IV) cyclization occurred at the pyridine nitrogen to produce 2-phenyl-1,3,3a-tri-



(1) United States Accepted Nomenclature approved generic name. The registered trade-mark of Merck & Co., Inc., for this anthelmintic is Thibenzole®.

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