

mass having a strong phosphite odor. A small portion of the solid, washed with cold petroleum ether, and pressed dry on a porous plate, melted at 62–65°. The product was soluble in petroleum ether, hexane, benzene, ether, carbon tetrachloride, chloroform, acetone, and ethanol. The main portion of reaction product, recrystallized once from petroleum ether, gave 17.4 g. of crystalline solid, m.p. 63–66°; several additional recrystallizations from the same solvent raised the melting point to 66–67°.

Anal. Calcd. for $C_{28}H_{31}N_2O_3P$: C, 65.65; H, 7.76; N, 6.96; P, 7.70. Found: C, 65.84; H, 7.67; N, 6.79; P, 7.56. Mol. wt. (determined cryoscopically in benzene): Calcd.: 402. Found: 387.

Reaction of Diphenyldiazomethane with Triisopropyl Phosphite.—Triisopropyl phosphite (52 g., 0.25 mole) was added rapidly at ambient temperature to diphenyldiazomethane (13.0 g., 0.07 mole). After 45 min., the purple reaction mixture turned a clear yellow, and the reaction temperature rose to 37°. At the end of 16 hr. at ambient temperatures no low-boiling condensate was found in a Dry-Ice trap connected to the system.

The reaction mixture was heated slowly; at 150–170° gas was evolved and a low-boiling liquid condensed in the cold trap. After refluxing the reaction mixture for 20 hr. at 178 ± 3°, the cold trap contained 3.0 g. (0.072 mole) of propylene identified by boiling point and infrared spectrum. The main reaction mixture (60.6 g.) was distilled in vacuo to give: (a) 33.6 g. (0.16 mole) of triisopropyl phosphite, b.p. 67–67.5° (14.9 mm.), n_D^{20} 1.4104; (b) 2.1 g. of a clear colorless liquid, b.p. 40–68° (2.4 mm.), n_D^{20} 1.4082 (infrared indicated the presence of diisopropyl hydrogen phosphonate^{10a} and triisopropyl phosphate^{10b}); (c) 1.2 g. of triisopropyl phosphate, b.p. 68° (2.4 mm.), n_D^{20} 1.4068; and (d) 23 g. of a turbid residual oil.

The residual oil solidified on cooling; it was triturated with cold hexane and filtered. The faintly yellow crystalline filter cake (17.4 g., m.p. 91.5–95°), after recrystallizing several times from hexane, melted at 96.5–98°.

Anal. Calcd. for $C_{16}H_{22}N_2O_3P$: C, 63.32; H, 6.99; N, 7.77; P, 8.60. Found: C, 63.14; H, 6.60; N, 7.92; P, 8.52. Mol. wt. by cryoscopy in benzene: Calcd. 360. Found 360.

The hexane filtrate was concentrated; the acidic yellow mushy solid (5.3 g.) was recrystallized from hot absolute alcohol to give 2.1 g. of diphenylketazine, m.p. 160–164°. Admixture with the authentic azine¹¹ gave no depression in melting point. The alcohol soluble material was not identified.

Thermal Decomposition of Benzophenone Triisopropylphosphorazine.—A sample (1.0 g., 0.0025 mole) of the azine was heated at 181° for 40 min. Propylene (52.8 ml. at STP, 0.0023 mole) was collected in a gas buret and identified by I.R. The light yellow residual oil (0.89 g.) solidified on cooling, m.p. 91.5–95°. The m.p. of mixture with authentic diisopropyl *N*-diphenylmethylenephosphorohydrazide was not depressed.

Hydrolysis of Diisopropyl *N*-Diphenylmethylenephosphorohydrazide.—The hydrazide (5.0 g., 0.014 mole) was refluxed 24 hr. with 50 ml. of concentrated hydrochloric acid. Excess aqueous 20% sodium hydroxide was added and the immiscible oil extracted with ether. Distillation of the combined dried ether extracts left 2.3 g. (0.013 mole) of benzophenone, identified by m.p. and mixture m.p. The basic aqueous layer was acidified slightly and excess salicylaldehyde was added. The reaction mixture was shaken and the faint yellow solid present filtered, washed with low boiling petroleum ether, and air-dried to give 3.0 g. of

material, m.p. 224.5–226°. A mixture m.p. with authentic salicylaldehyde showed no depression.

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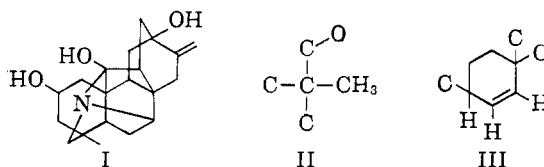
Aconite Alkaloids. The Structure of Hetisine

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Data presented below confirm certain features of structure I,^{1,2} but conflict with others, thus leading us to withdraw I as the tentative formulation for hetisine.



The presence of a methyl group on a fully substituted carbon atom is confirmed by NMR, the methyl group appearing as a sharp singlet at 9.02 τ in hetisine, 9.02 τ in dihydrohetisine,^{3,4} and 9.06 τ in hetisine diacetate.² Similarly, the presence of the exocyclic methylene group is demonstrated by peaks which occur at 5.16 τ and 5.36 τ (vinyl hydrogen) in the spectrum of hetisine and do not occur in the spectrum of dihydrohetisine. However, the spectrum of dihydrohetisine does contain a new peak (apparently a doublet, partially obscured by the original methyl) at $\tau \approx 9.00$ attributable to a methyl group substituted on a carbon bearing a hydrogen.

The NMR spectrum of Jacobs' des-*N*-methyl-hetisine⁴ has singlets at 9.06 τ and 8.80 τ and no peaks in the range 5.0 τ to 5.4 τ , which is consistent with the presence of the original methyl plus a new methyl group of the type II, presumably arising from the exocyclic methylene of hetisine by *alkyl* migration.^{1,2} The *N*-methyl group appears as a singlet at 7.59 τ . Absorption at 4.37 τ (s) and 4.84 τ (d., $J \approx 5$ c.p.s.) suggests the presence of a new double bond of type III.

The spectrum of hetisine diacetate has peaks at 4.82 τ , 4.98 τ , 5.1 τ , and 5.24 τ corresponding in area to four protons. This indicates the presence, in addition to the exocyclic methylene group, of two protons on carbon atoms bearing acetoxy groups, a feature *not* in accord with structure I.

(10)(a) Reported b.p. 79° (14 mm.). H. McCombie, B. C. Saunders, and G. J. Stacey, *J. Chem. Soc.*, 380 (1945). (b) Reported b.p. 83.5° (5 mm.), n_D^{20} 1.40573, A. I. Vogel and D. M. Cowan, *ibid.*, 16 (1943).

(11) Diphenylketazine was prepared from benzophenone and diphenylmethyl hydrazine, m.p. 164.5–165.5°, reported m.p. 164°. H. Szmant and C. McGinnis, *J. Am. Chem. Soc.*, 72, 2890 (1950).

(1) A. J. Solo and S. W. Pelletier, *J. Am. Chem. Soc.*, 81, 4439 (1959).

(2) S. W. Pelletier, *Tetrahedron*, 14, 98 (1961).

(3) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, 143, 605 (1942).

(4) W. A. Jacobs and C. F. Huebner, *ibid.*, 170, 189 (1947).

In confirmation of this finding, the spectrum of the keto diacetate,² obtained by chromium trioxide-acetic acid oxidation of hetisine diacetate, has peaks at 4.80 τ , 4.95 τ , 5.02 τ , and 5.18 τ corresponding in area to four protons while the spectrum of the hydrolysis product² has peaks at 5.13 τ and 5.32 τ corresponding in area to two protons.

NOTE ADDED IN PROOF: After this note had been submitted for publication, a new structure,⁵ based on X-ray studies was advanced for hetisine.

Experimental

The NMR spectra were determined at 60 Mc. on Model HR-60 and A-60 Varian spectrometers. Deuteriochloroform was used as solvent and tetramethylsilane served as internal standard.

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(5) M. Przybylska, *Can. J. Chem.*, **40**, 566 (1962).

1,4,17 α -Trimethylestra-1,3,5(10)-trien-17 β -ol

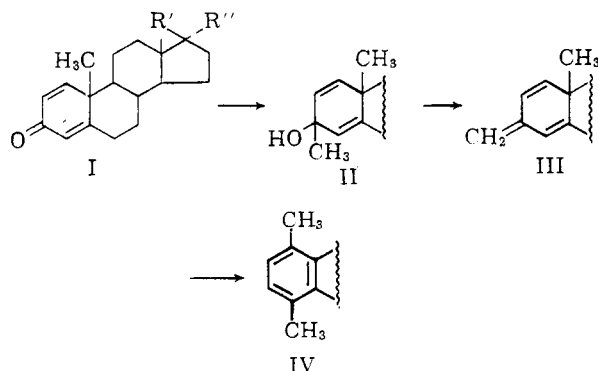
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Recently Dannenberg and Neumann¹ reported the results of their study on the dienol-benzene rearrangement.² They observed that the addition of methylmagnesium iodide to a compound possessing a $\Delta^{1,4}$ -dienone system I gives a tertiary carbinol II, which dehydrates to a "semibenzenes" III, that rearranges to a substance whose ring A is in the form of a 1,2,3,4-tetrasubstituted benzene IV.

From cholesta-1,4-dien-3-one (I.R' = C₈H₁₇, R'' =



(1) H. Dannenberg and H.-G. Neumann, *Ann.*, **646**, 148 (1961).

(2) M. J. Gentles, J. B. Moss, H. L. Herzog, and E. B. Hershberg, *J. Am. Chem. Soc.*, **80**, 3702 (1958); H. Plieninger and G. Keilich, *Ber.*, **91**, 1891 (1958).

= H) and 17 β -hydroxyandrosta-1,4-dien-3-one (I.R' = OH, R'' = H) they obtained 1,4-dimethyl-19-norcholesta-1,3,5(10)-triene (IV.R' = C₈H₁₇, R'' = H) and 1,4-dimethylestra-1,3,5(10)-trien-17 β -ol (IV.R' = OH, R'' = H), respectively. When androsta-1,4-diene-3,17-dione (I.R', R'' = O) was treated in the same manner, they were not able to isolate 1,4,17 α -trimethylestra-1,3,5(10)-trien-17 β -ol (IV.R' = OH, R'' = CH₃) as a homogeneous product.

In our investigation of the dehydration-rearrangement of the steroids,³ which partly parallels theirs, we found that 1,4,17 α -trimethylestra-1,3,5(10)-trien-17 β -ol (IV. R' = OH, R'' = CH₃) can be obtained readily if the reaction mixture is acidified with dilute hydrochloric acid and the crude reaction product is chromatographed afterward on silica gel. The physical constants of our pure product support the structure formulated for it.

Acetylation of the hydroxyl group at C-17 can be accomplished with isopropenyl acetate in the presence of *p*-toluenesulfonic acid to give IV (R' = OAc, R'' = CH₃).

Experimental⁴

1,4,17 α -Trimethylestra-1,3,5(10)-trien-17 β -ol (IV. R' = OH, R'' = CH₃).—To a solution of 8.00 g. (0.0281 mole) androsta-1,4-diene-3,17-dione, m.p. 136.5–142°, in 200 ml. of anhydrous ether, stirred, and heated under reflux, was added a solution of 40 ml. of a 3 M solution of methylmagnesium bromide. The reaction mixture was stirred and heated under reflux for 6 hr. and then stirred at room temperature for 15 hr. The reaction mixture was decomposed with water and acidified with 1.7 N hydrochloric acid. The ethereal phase was separated, washed successively with water and a saturated solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled to dryness under reduced pressure to afford a viscous orange oil. The oil was chromatographed on 800 g. of silica gel.

Elution of the column with 2% ethyl acetate in benzene gave 3.00 g. (36%) of a solid, which melted at 143–145° after crystallization from ether-hexane. The analytical sample of IV (R' = OH, R'' = CH₃) was obtained as colorless laths after another crystallization from hexane, m.p. 143–145.5°; $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ 269.5 m μ (ϵ 287); λ_{KBr} 2.88, 2.98, 12.47 μ ; $[\alpha]_{\text{D}}^{25} +127.5^\circ$ (CHCl₃). Admixed with the starting material, it melted at 97.5–124°.

Anal. Calcd. for C₂₁H₃₀O: C, 84.51; H, 10.13. Found: C, 84.35; H, 9.85.

1,4,17 α -Trimethylestra-1,3,5(10)-trien-17 β -ol acetate (IV. R' = OAc, R'' = CH₃).—A solution of 0.55 g. of IV (R' = OH, R'' = CH₃), m.p. 138–142°, 10 ml. of isopropenyl acetate, and ca. 0.1 g. of *p*-toluenesulfonic acid monohydrate was heated under reflux for 1 hr. After ca. 0.1 g. of sodium acetate was added, the reaction mixture was distilled nearly to dryness under reduced pressure. The residue was diluted with water and cooled in an ice bath. The solid was collected, washed well with water, and dried. It was crystallized first from acetone-hexane and then from hexane alone to yield 0.31 g. (47%) of IV (R' = OAc, R'' = CH₃) as colorless dense crystals, m.p. 166.5–167°; $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ 270 m μ (ϵ 286); λ_{KBr} 5.82, 7.90, 7.98, 12.42 μ ; $[\alpha]_{\text{D}}^{25} +133^\circ$ (CHCl₃).

Anal. Calcd. for C₂₂H₃₂O₂: C, 81.13; H, 9.47. Found: C, 80.96; H, 9.49.

(3) L. J. Chinn and R. M. Dodson, *J. Org. Chem.*, **24**, 879 (1959); C. G. Bergstrom and R. M. Dodson, *Chem. and Ind.* (London), 1530 (1961).

(4) Melting points were determined on a Fisher-Johns melting block.