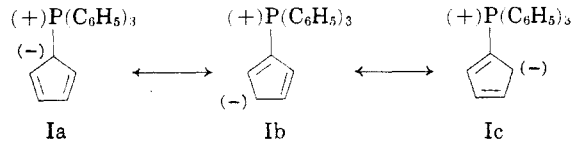
Communications TO THE EDITOR

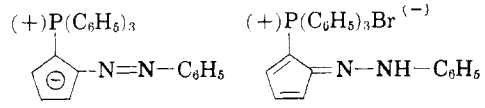
A New Type of Azo Compound by Coupling at the Cyclopentadienide Ring

Sir:

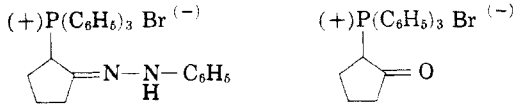
We wish to report the preparation of a new type of azo compound, triphenylphosphonium-(2-phenylazo)cyclopentadienylide [II, deep orange, m.p. 239–240°, from benzene; $\lambda_{max.}^{CH_3CN}$ 220 mμ (ε 49,700), 250 mμ (ε 17,000) and 452 mμ (ε 23,500); band at 7.00 μ but no bands at 3.0 or 4.0–6.6 μ; *Anal.* Calc'd for $C_{29}H_{23}N_2P$: C, 80.9; H, 5.4; N, 6.5; P, 7.2; M.W., 430. Found: C, 80.7; H, 5.8; N, 6.8; P, 7.5; M.W., 413]. II resulted, in high yield, from a coupling reaction between the phosphinemethylene[1] (I) and benzenediazonium chloride in an aqueous-methylene chloride system containing sodium acetate. II formed an orange-red *hydrobromide* best formulated as a derivative of cyclopentadienonephenylhydrazone, III [m.p. 232–233°; $\lambda_{max.}^{EtOH}$ 219 mμ (ε 50,800) 227 mμ (ε 46,200), 259 mμ (ε 17,100), 266 mμ (ε 15,700), 273 mμ (ε 10,100), and 446 mμ (ε 26,700); bands at 3.0 and 6.48 μ (strong); *Anal.* Calc'd for $C_{29}H_{24}BrN_2P$: N, 5.5. Found: N, 5.1].



Ia Ib Ic



II, etc. III



IV V

Catalytic hydrogenation of III in aqueous methanol afforded (2-phenylhydrazonocyclopentyl)triphenylphosphonium bromide [IV, colorless, m.p. 204–205°; $\lambda_{max.}^{EtOH}$ 217 mμ (ε 45,400), 225 mμ (ε 40,600), 269 mμ (ε 20,200), and 277 mμ (ε 20,600); bands at 2.92–3.02, 6.25, and 7.00 μ; *Anal.* Calc'd for $C_{29}H_{28}BrN_2P$: C, 67.6; H, 5.5; N, 5.4; Br, 15.5. Found: C, 67.4; H, 5.8; N, 5.8; Br, 16.0.] An authentic sample of IV was independently prepared from phenylhydrazine and (2-oxocyclopentyl)triphenylphosphonium bromide [V, colorless, m.p. 270–272°; $\lambda_{max.}^{EtOH}$ 217 mμ (ε 38,500), 225 mμ (ε 37,500), 257 mμ (ε 10,100), 266 mμ (ε 9,200), and 275 mμ (ε 6,700); bands at 5.80 and 7.00 μ; *Anal.*, Calc'd for $C_{23}H_{22}BrOP$: C, 65.0; H, 5.2. Found: C, 65.3; H, 5.5]. V was prepared from triphenylphosphine and 2-bromocyclopentanone.

This manifestation of aromaticity in the cyclopentadienide ring opens a route to a family of phosphorus-containing azo compounds of remarkably long wave length absorption (azobenzene: $\lambda_{max.}^{CH_3CN}$ 317 mμ (ε 18,100). The substitution on I occurs at a position which preserves the cyclopentadienide system and which gives rise to the longest of the possible conjugated systems terminating at a phosphorus atom. The dipole moment of II was found[2] to be 6.52 D, as compared with 6.99 D for I.

DEPARTMENT OF CHEMISTRY
COLUMBIA UNIVERSITY
NEW YORK 27, N. Y.

FAUSTO RAMIREZ
STEPHEN LEVY

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(1) F. Ramirez and S. Levy, *J. Org. Chem.*, 21, 488 (1956).

(2) The dipole moments were measured by Prof. M. T. Rogers of Michigan State University and will be the subject of a separate communication.

Steroids. LXXXIII.[1] Synthesis of 2-Methyl and 2,2-Dimethyl Hormone Analogs

Sir:

The discovery that profound changes in biological activity may be effected by removal of the steroid *C*-10 angular methyl group[2] or by shift of the group from C-10 to C-1[3] prompted us to investigate steroid analogs with additional alkyl substituents in other parts of the molecule. This communication is concerned with the synthesis of a number of 2-methyl and 2,2-dimethyl substituted testosterone and dihydrotestosterone derivatives,[4] compounds of great interest due to the discovery that certain members of this series have been found to be mass-

(1) Paper LXXXII. H. J. Ringold, E. Batres, O. Mancera, and G. Rosenkranz, *J. Org. Chem.*, 21, December 1956.

(2) *Cf.* (a) C. Djerassi, L. Miramontes, and G. Rosenkranz, *J. Am. Chem. Soc.*, 75, 4440 (1953); (b) C. Djerassi, L. Miramontes, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, 76, 4092 (1954); (c) C. Huggins, E. V. Jensen and A. S. Cleveland, *J. Exp. Med.*, 100, 225 (1954); (d) A. Sandoval, G. H. Thomas, C. Djerassi, G. Rosenkranz and F. Sondheimer, *J. Am. Chem. Soc.*, 77, 148 (1955).

(3) (a) H. J. Ringold, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, 78, 2477 (1956); (b) C. Djerassi, A. E. Lippman, and J. Grossman, *J. Am. Chem. Soc.*, 78, 2479 (1956).

(4) Presented in part at the 129th meeting of the American Chemical Society, Dallas, April 1956.

ive inhibitors of the development of a transplantable rat mammary tumor.[5]

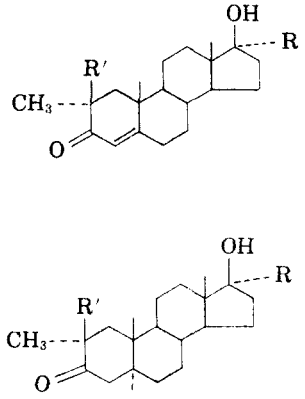
The sodium hydride catalyzed condensation, in benzene solution, of ethyl oxalate with testosterone, androstan-17β-ol-3-one, 17α-methyltestosterone, and 17α-methylandrostan-17β-ol-3-one gave the corresponding 2-ethoxyoxalates (amorphous solids) after acid precipitation of the water-soluble sodio salts. Methylation of the crude free ethoxyoxalates with methyl iodide in boiling acetone containing potassium carbonate gave the corresponding 2-methyl-2-ethoxyoxalates which underwent reversal of oxalate condensation on treatment with ethanolic sodium ethoxide furnishing the 2α-methyl hormone analogs of: testosterone (Ia) (m.p. 155–157°, $[\alpha]_D$ +116°, $\lambda_{max.}$ 242 mμ, log ϵ 4.19.[6] Found: C, 79.33; H, 10.28). 17α-Methyltestosterone (Ib) (m.p. 150–152°, $[\alpha]_D$ +82°, $\lambda_{max.}$ 240 mμ, log ϵ 4.21. Found: C, 79.68; H, 10.03). Androstan-17β-ol-3-one (IIa) (m.p. 152–154°, $[\alpha]_D$ +32° (ethanol). Found: C, 78.70; H, 10.77). 2α,17α-Dimethylandrostan-17β-ol-3-one (IIb) (m.p. 151–154°, $(\alpha)_D$ +8°. Found: C, 79.29; H, 10.82).

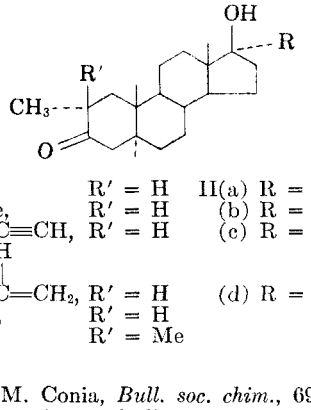
Assignment of the 2-methyl structure in the case of the 3-keto-Δ^4-compounds follows from the established position of oxalate and formate condensation on α,β-unsaturated steroid ketones.[7] The 2α (equatorial) position is assumed from the mode of preparation involving treatment of the final product with strongly alkaline reagent.[8]

That condensation had occurred at C-2 in the dihydroallo series was established by conversion of Ia to its C-3 ketal (2α-methyl-3,3-cycloethylenedioxy-Δ^5-androsten-17β-ol, m.p. 175–178°, $[\alpha]_D$ +41° (pyridine). Found: C, 76.11; H, 9.78) which after hydrogenation in methanol solution over a palladium-carbon catalyst followed by ketal hydrolysis, gave authentic IIa.

Pyridinium chromate oxidation of the ketal of Ia yielded 2α-methyl-3,3-cycloethylenedioxy-Δ^5-androsten-17-one (m.p. 206–210°, $[\alpha]_D$ +51° (pyr.). Found: C, 76.92; H, 9.38), which was converted to 2α-methyl-17α-ethinyl-3,3-cycloethylenedioxy-Δ^5-androsten-17β-ol (m.p. 224–227°, $[\alpha]_D$ −63° (pyr.). Found: C, 77.85; H, 9.31) by treatment with potassium acetylide and 2α-methyl-17α-ethinyltestosterone (Ic) (m.p. 175–178°, $[\alpha]_D$ +3°, $\lambda_{max.}$ 240 mμ, log ϵ 4.19. Found: C, 81.02; H, 9.33) was derived by ketal hydrolysis. Hydrogenation of Ic over palladium-calcium carbonate in pyridine solution gave 2α-methyl-17α-vinyltestosterone (Id) (m.p. 159–162°, $[\alpha]_D$ +89°, $\lambda_{max.}$ 240 mμ, log ϵ 4.20. Found: C, 80.54; H, 9.61) while hydrogenation of Ic in dioxane over the same catalyst, interrupted at two moles, gave 2α-methyl-17α-ethyltestosterone (Ie) (m.p. 141–143°, $[\alpha]_D$ +88°, $\lambda_{max.}$ 240 mμ, log ϵ 4.21. Found: C, 79.95; H, 10.23).

The 2,2-dimethyl compounds were prepared by direct alkylation of androstan-17β-ol-3-one and of 17α-methylandrostan-17β-ol-3-one with excess methyl iodide and potassium *tert*-butoxide in *tert*-butanol.[9] The mixtures so obtained, in each case, contained about 10% of the 2-monomethyl derivatives IIa and IIb, and 50% of 2,2-dimethylandrostan-17β-ol-3-one (IIc) (m.p. 134–136°, $[\alpha]_D$ +72°. Found: C, 78.84; H, 10.43) and 2,2,17α-trimethylandrostan-17β-ol-3-one (IId) (m.p. 117–120°, $[\alpha]_D$ +53°. Found: C, 78.92; H, 11.12). That these are the 2,2-dimethyl compounds and not the 2,4 or tri- or tetra-methyl derivatives was proven by the following reactions carried out on the C-17 acetate of IIc (m.p. 138–140°). Bromine-acetic acid titration showed uptake of just two moles of bromine. The crystalline dibromo compound (m.p. 180–181°, $[\alpha]_D$ +100°. Found: C, 53.60; H, 6.83; Br, 30.15) on collidine dehydrobromination gave a 4-bromo-Δ^4-3-ketone (2,2-dimethyl-4-bromotestosterone acetate, m.p. 151–153°, $[\alpha]_D$ +82°, $\lambda_{max.}$ 262 mμ, log ϵ 4.07. Found: Br, 17.92). The monobromo compound [m.p. 146–148°, $[\alpha]_D$ +13° (ethanol). Found: C, 62.59; H, 7.86; Br, 18.47] from treatment of IIc acetate with one equivalent of bromine provided, on collidine dehydrobromination, 2,2-di-





I(a) R = H, R′ = H II(a) R = H, R′ = H
(b) R = Me, R′ = H (b) R = Me, R′ = H
(c) R = —C(H)≡CH, R′ = H (c) R = H, R′ = Me
(d) R = —C(H)=CH$_2$, R′ = H (d) R = Me, R′ = Me
(e) R = Et, R′ = H
(f) R = H, R′ = Me

(5) Dr. Charles Huggins, The Ben May Laboratory for Cancer Research, private communication (to be published subsequently).

(6) All melting points are uncorrected. Unless specified otherwise, rotations were determined at 20° in chloroform and the ultraviolet absorption spectra in 95% ethanol. Thanks are due Mr. A. Mijares and Mrs. E. Necoechea for able technical assistance and to Mr. A. Erlin for rotations and spectra.

(7) *Cf.* (a) F. Weisenborn, D. Remy, and T. Jacobs, *J. Am. Chem. Soc.*, **76**, 552 (1954); (b) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, B. J. Magerlein, W. P. Schneider, P. F. Beal, and J. Korman, *J. Am. Chem. Soc.*, **77**, 4438 (1955).

(8) See J. A. Hogg, F. H. Lincoln, R. W. Jackson, and W. P. Schneider, *J. Am. Chem. Soc.*, **77**, 6401 (1955).

(9) *Cf.* J. M. Conia, *Bull. soc. chim.*, 690, 943 (1954), for a discussion of related alkylations.

methyltestosterone acetate (If acetate) (m.p. 171–173°, $[\alpha]_D$ +44°, $\lambda_{max.}$ 240 mμ, log ε 4.19. Found: C, 77.23; H, 9.81).

While anti-tumor screening of the above described 2-methyl hormones is still in progress, Ia and IIa have already been shown to be very effective tumor inhibitors.

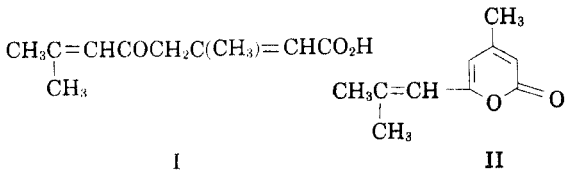
RESEARCH LABORATORIES
SYNTEX, S. A.
APARTADO 2679
MEXICO, D. F.

H. J. RINGOLD
G. ROSENKRANZ

2-Pyrones. XXIII. 4-Methyl-6-(2′-methylpropenyl)-2-pyrone

Sir:

We wish to report the synthesis of a new ten carbon isoprenoid lactone which is of interest as a simple multiple of senecioic acid in studies of the biosynthesis of cholestrol from acetate.[1–7] 4-Methyl-6-(2′-methylpropenyl)-2-pyrone (II), the lactone of the enol form of γ-senecioylsenecioic acid (I) has been prepared by the acylation of β-methylglu-



I II

taconic anhydride with senecioyl chloride followed by decarboxylative rearrangement. This is a modification of a synthetic route previously described,[8] but successfully applied here for the first time to an aliphatic acid chloride having over four carbon atoms.

A solution of β-methylglutaconic anhydride in pyridine and ether was treated with senecioyl chloride. Ether extraction of the acidified reaction mixture gave a red oil which was decarboxylated by flash distillation and refractionated to give 12% yield of 4-methyl-6-(2′-methylpropenyl)-2-pyrone, m.p. 46.5–47.5°, (*Anal.* Calc'd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.08; H, 7.37) showing the 2-pyrone carbonyl absorption band at 1730 cm.$^{-1}$ and the trisubstituted ethylenic absorption band at 840 cm.$^{-1}$. Reaction with bromine gave 3-bromo-4-methyl-6-(2′-methyl-2′,3′-dibromopropyl)-2-pyrone, m.p. 119–120°. (*Anal.* Calc'd for $C_{10}H_{11}Br_3O_2$: C, 29.80; H, 2.75. Found: C, 29.88; H, 3.10) showing the 2-pyrone carbonyl absorption band at 1724 cm.$^{-1}$ shifted slightly as with other 3-substituted types.[9]

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DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES
UNIVERSITY OF LOUISVILLE
LOUISVILLE 8, KENTUCKY

RICHARD H. WILEY
J. G. ESTERLE

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Ozonolysis of Phenanthrene in Chloroform

Sir:

Schmitt, Moriconi, and O'Connor[1] recently claimed the preparation of the first stable monomeric ozonide of an aromatic hydrocarbon. The material was obtained by the ozonolysis of phenanthrene in either chloroform or acetic acid. It melted at 65–90°. It was assigned a monoozonide structure on the basis of elementary analyses, a Rast molecular weight determination, catalytic hydrogenation to 2,2′-biphenyldicarboxaldehyde, and infrared spectra which showed strong bands in the region 5.7–5.9 μ, which Briner[2] had originally ascribed to ozonides.

Criegee[3] has shown that pure simple ozonides, such as the monoozonide of phenanthrene would be, do not absorb in the 5.6–6.2 μ region, which is the carbonyl region. Briner[4] has recently acknowledged the findings of Criegee and ascribed his results to the formation of aldehydes or ketones during the passage of ozone through the reaction mixture.

We have ozonized phenanthrene (5.9 g.) in chloroform (60 ml.) at −60° and have immediately precipitated the product (7.3 g., 98% yield, m.p. 129–130°) by addition of either ligroin or methanol. Several recrystallizations from benzene by addition of ligroin gave an 80% recovery of material melting at 139–141° (*Anal.* Calcd. for $C_{14}H_{10}O_3$: C,[5] 74.33; H, 4.46; Active 0, 7.07. Found: C, 74.58; H, 4.80; Active 0, 6.95). The material was

(1) Schmitt, Moriconi, and O'Connor, *J. Am. Chem. Soc.*, **77**, 5640 (1955).
(2) Briner, *et al.*, *Helv. Chim. Acta*, **35**, 340, 345, 353, 1377, (1952); *Helv. Chim. Acta*, **36**, 1166, 1757 (1953); *Helv. Chim. Acta.*, **37**, 620, 1558, 1561 (1954); *Compt. rend.*, **234**, 1932 (1952); *Compt. rend.*, **237**, 504 (1953).
(3) Criegee, Kerckow, and Zinke, *Chem. Ber.*, **88**, 1878 (1955).
(4) Briner and Dallwigk, *Compt. rend.*, **243**, 630 (1956); *Helv. Chim. Acta*, **39**, 1446 (1956).
(5) Schmitt, Moriconi, and O'Connor[1] erred in this calculation. Their product, therefore, analyzed 1% low in carbon.