Eluted with benzene and 0.5% ethyl acetate in benzene was 0.62 g. of a crystalline mixture. A paper chromatogram of these fractions showed two components to be present in roughly equal amounts. Partial separation of these compounds was effected by crystallization from methanol and from petroleum ether assisted by mechanical separation, giving rectangular plates, m.p. 126–128°, and prisms, m.p. 158–163°. The lower melting material was seen to be identical to the known 3,17α-dimethoxyestra-1,3,5(10)-trien-16-one (**6**)[9] by comparison of the infrared spectra. The second component was recrystallized from petroleum ether to give the pure 3,15β-dimethoxyestra-1,3,5(10)-trien-16-one (**7**), m.p. 165–168°; $[\alpha]D$ −15°; λ_{max} 5.75 mμ; 63 (C_{18}-CH_3), 210 (15-OCH_3) c.p.s.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.12; H, 8.50.

Also eluted with 1% ethyl acetate in benzene was 80 mg. of a crystalline mixture recrystallized from petroleum ether and then from methanol to yield 30 mg. of 3,15α-dimethoxyestra-1,3,5(10)-trien-16-one (**8**), m.p. 100–102°; λ_{max} 5.72 mμ; 57 (C_{18}-CH_3), 218 (15-OCH_3) c.p.s.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 77.09; H, 8.32.

At 5% ethyl acetate in benzene was eluted 0.19 g. of material, recrystallized from acetone–petroleum ether to yield 0.11 g. of the unsaturated ketone, **2**, m.p. 130–135° (spectral comparison satisfactory).

Reaction of the Bromo Ketone 1a with Potassium Carbonate.—To a solution of 0.6 g. of potassium carbonate in 6 ml. of water and 200 ml. of methanol was added 0.30 g. of the bromo ketone **1a**. After 72 hr. the solution was poured into water containing excess acetic acid. The resulting mixture was isolated with benzene in the usual way. The crude product (0.25 g.) was analyzed by paper chromatography and was seen to consist of 40–45% of the 15β-methoxy compound **7**, 35–40% of the 17α-methoxy compound **6** and 3–5% of the 15α-compound **8**. No bromo ketones were seen and less than 5% of the unsaturated ketone **2** was in evidence. Chromatography on silica led to isolation of the two major products as described for the sodium methoxide-catalyzed reaction.

In an earlier experiment, using similar conditions, the reaction was stopped after 18 hr. At that time, analysis of the product by paper chromatography showed 45% of the 17β-bromo ketone **4b**, 20% of the 17α-bromo ketone **1a**, and 15% each of the methoxy ketones **6** and **7**.

Equilibration of the Methoxy Ketones 7 and 8.—A solution of 40 mg. of the methoxy ketone **7** and 0.2 g. of potassium carbonate in 10 ml. of methanol and 2 ml. of water was heated at reflux for 1 hr. The solution was diluted with water and extracted with benzene. Isolation of the product in the usual way afforded 40 mg. of semicrystalline residue. This material was seen by paper chromatography and n.m.r. (methoxyl absorption at 210 and 218 c.p.s.) to consist of about 60% of ketone **8** and 40% of ketone **7**. Attempts at separation by fractional crystallization were only partially successful.

Retreatment of the equilibrium mixture with potassium carbonate in methanol for an additional 2 hr. led to no appreciable change in the proportion of isomers **7** and **8** as seen by paper chromatography.

Acyl Transfer during Chromium Trioxide Oxidation in the Pregnane Series. Some Reactions of 5 β-Androstane-16,17-ketols[1,2]

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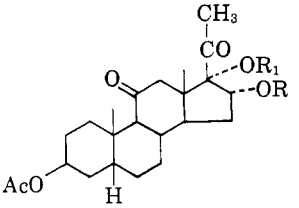
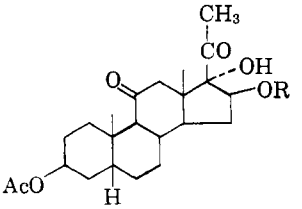
Reaction of 3α,16α-diacetoxy-17α-hydroxypregnane-11,20-dione (Ib) with chromium trioxide in acetic acid proceeded in part anomalously to give the 17α-acetoxy-11,16-20-trione V. The latter compound with base underwent β-ketonic cleavage or rearrangement to give primarily the δ-lactone VIII. Various reactions of the 17β-hydroxy ketol system VIIa are discussed.

In connection with work on the D-homoannulation of the 3α,16-17α-trihydroxy-11, 20-diketopregnanes Ia and IIa,[3] we had occasion to degrade the corresponding 16α- and 16β-acetates, Ib and IIb, to the respective 16-acetoxy 17-ketones by two routes in order to confirm that ring D in the parent compounds was five-membered. In each case, successive treatment with sodium borohydride in aqueous dimethylformamide[4] and sodium metaperiodate[3,5] led to the ketol acetates III and IV, respectively. Both ketol acetates III and IV gave positive blue tetrazolium tests and showed a characteristic shift in the 17-carbonyl infrared band to 5.70 μ from the normal 5.77 μ due to interaction with the 16-acetyl function. This shift was independent of configuration at C-16.[6]



Ia. R = R₁ = H
Ib. R = Ac, R₁ = H
Ic. R = R₁ = Ac



IIa. R = H
IIb. R = Ac

Although the second method of side chain degradation, namely, chromium trioxide in acetic acid, gave analogous results in the 16β-acetoxy series, similar treatment of the 16α-acetate Ib gave a second neutral tetrazolium positive substance (20–25% yield) in addition to the 16α-acetoxy 17-ketone III (30–35%)[7] plus a minor amount of 3α-acetoxy-11-ketoetiobilianic acid (VIb). The infrared spectrum of the new material [λ_{max}^{chf} 5.68, 5.79, 5.84, 8.00 μ] indicated the possible presence of an acetate function adjacent to a carbonyl group as in the ketol acetates III and IV. However, the high negative specific rotation of this substance,

(1) Presented in part before the American Chemical Society, North Jersey Section, Meeting-in-Miniature, February 1, 1960.

(2) In a recent publication entitled, "16-Bromo-D-Homo Steroids," by N. L. Wendler and H. L. Slates [*J. Org. Chem.*, **26**, 4738 (1961)], these authors inadvertently failed to make reference to the reports of C. Djerassi and T. Nakano [*Chem. Ind.* (London), 1385 (1960)] as well as M. Uskoković, M. Gut, and R. I. Dorfman [*J. Am. Chem. Soc.*, **82**, 958 (1960)] bearing on the isomerization and elimination reactions of A and D ring α-halo ketones in related steroid systems. Apologies are herewith expressed for this oversight.—N. L. W.

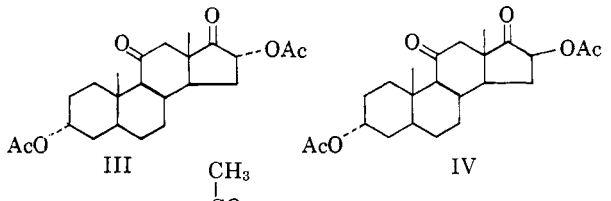
(3) N. L. Wendler, D. Taub, and C. H. Kuo, *ibid.*, **82**, 5701 (1960).

(4) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *ibid.*, **81**, 3291 (1959).

(5) G. Cooley, B. Ellis, F. Hartley, and V. Petrow, *J. Chem. Soc.*, 4373 (1955), utilized an analogous sodium borohydride-periodate sequence to degrade the side chain in the 3β,16-diacetoxy-5-pregnen-20-one series.

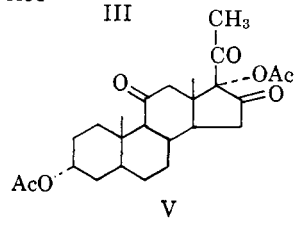
(6) *Cf.* R. N. Jones and G. Roberts, *Chem. Ind.* (London), 1269 (1957).

(7) Cooley, *et al.*, ref. 5, on chromium trioxide oxidation of 3β,16α-diacetoxy-17α-hydroxy-5α-pregnan-20-one observed formation of one neutral product, the expected 16α-acetoxyandrostan-17-one.

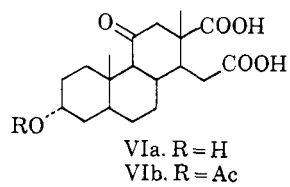


III

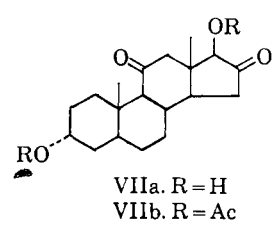
IV



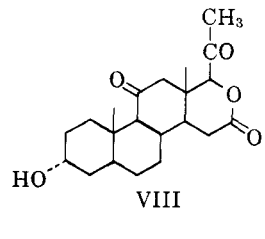
V



VIa. R = H
VIb. R = Ac

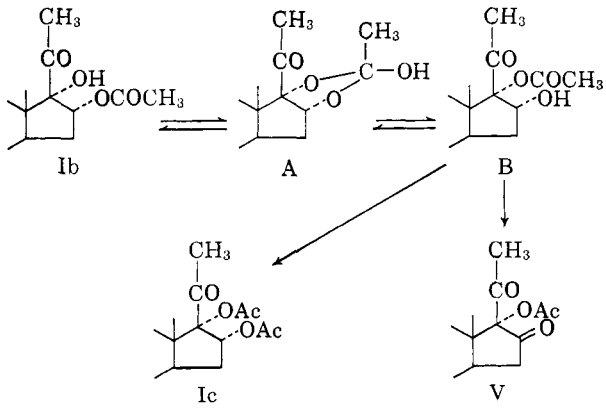


VIIa. R = H
VIIb. R = Ac



VIII

$[\alpha]_D^{Chf}$ −164°, contrasted with the positive rotations of Ia (+98°), III (+133°), and IV (+129°) and was suggestive of a marked structural change. In connection with this problem we had ascertained that the 3α,16α-diacetate Ib was converted in part to the 3α,-16α,17α-triacetate Ic under normal acetylation conditions (acetic anhydride–pyridine at 25°). Acetylation was complete at 90°, and its relative ease in comparison with acetylation of the 17α-hydroxyl group in the absence of the 16α-hydroxyl function suggested the operation of an acyl transfer process[8] in the formation of the triacetate Ic. As formulated below the acetyl group may undergo transfer from the C-16 to the C-17 hydroxyl group through the orthoacetate intermediate A to yield the 17α-acetate B which would be readily acetylated to Ic.

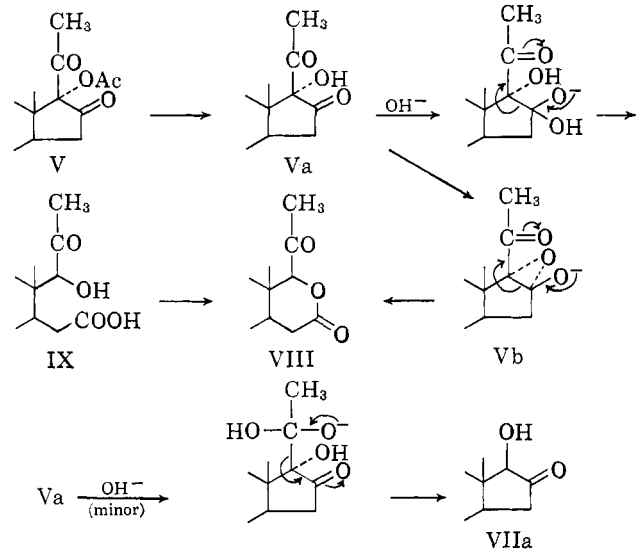


Ib A B

Ic V

The possibility that acyl transfer might also be involved in the chromium trioxide–acetic acid oxidation of Ib led to consideration of the 17α-acetoxy-16,20-diketo structure V for the new substance. Formula V is in accord with the elemental analysis ($C_{25}H_{34}O_6$), infrared spectrum and the n.m.r. spectrum which indicated the presence of three acyl methyl functions (7.65, 7.72 τ, 17-$COCH_3$, -$OCOCH_3$; 7.86 τ, 3-$OCOCH_3$).

The ability of the tertiary ketol system V to give a positive tetrazolium test characteristic of primary or secondary ketols may appear on first inspection to be inconsistent with its structure. However, under the alkaline conditions of the test, secondary ketol systems are generated. Thus treatment of V with dilute methanolic sodium hydroxide followed by acidification led primarily to a new tetrazolium-positive substance. This substance, $C_{21}H_{30}O_5$, had the base solubility properties of a lactone and absorbed in the infrared at 2.76, 2.94 (OH), 5.74 (δ-lactone), 5.85 (11 C=O) and 9.3 μ (lactone ether oxygen). It was consequently formulated as VIII; the n.m.r. spectrum confirmed the presence of the CH_3CO grouping attached to C-17a (7.60 τ). The above reaction sequence evidently involves cleavage of the β-diketone system of V as formulated below [V → IX → VIII]. Alternatively, an internal rearrangement pathway *via* Vb is also possible.



V Va Vb

IX VIII

Va $\xrightarrow[\text{(minor)}]{OH^-}$ VIIa

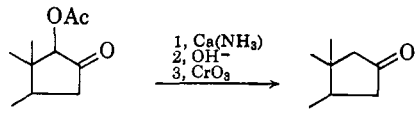
The lactone VIII contains a potential secondary ketol system and would be expected to give a positive tetrazolium test by conversion in alkali to the anion of the corresponding acid IX. The ability of V to give a positive test, therefore, is due to cleavage of its β-diketone system to the secondary ketol system IX. Paper chromatographic evidence indicated the presence of a minor amount of the 17β-hydroxy 16-ketone VIIa which may be formed by the indicated alternate cleavage of the β-diketone system (Va → VIIa).

We previously had prepared the 17β-hydroxy 16-ketone VIIa by equilibration of the ketol acetates III and IV in methanolic sodium hydroxide in the absence of oxygen.[3] Acetylation of VIIa gave the corresponding 3α-17β-diacetate VIIb[3] which clearly differed from III and IV and must, therefore, be a 17-acetoxy 16-ketone. Calcium and liquid ammonia reduction[9] of VIIb gave the corresponding 16-ketone Xa which on hydrolysis and oxidation at C-3 gave 5β-androstane-3,11,16-trione (Xc), identical with an authentic sample.[10] The 17β, quasi equatorial configuration for the

(8) For examples of acyl transfer in the steroid series, see for example: (a) D. K. Fukushima, N. S. Leeds, H. L. Bradlow, T. H. Kritchevsky, M. B. Stokem, and T. F. Gallagher, *J. Biol. Chem.*, **212**, 449 (1955) [C-17 → C-20]; (b) P. Wieland, K. Heusler, and A. Wettstein, *Helv. Chim. Acta*, **41**, 1657 (1958) [C-18 → C-17]; (c) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *J. Am. Chem. Soc.*, **81**, 3291 (1959) [C-21 → C-20]; (d) R. Gardi, R. Vitali, and A. Ercoli, *Tetrahedron Letters*, **13**, 448 (1961) [C-17 → C-21].

(9) Method of J. H. Chapman, J. Elks, G. H. Phillips, and L. J. Wyman, *J. Chem. Soc.*, 4344 (1956).

(10) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *J. Org. Chem.*, **26**, 2849 (1961).

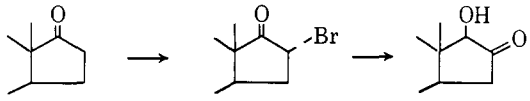


VIIb

Xa, 3α-acetate
Xb, 3α-ol
Xc, 3-one

17-hydroxyl group in VIIa is the predicted one for a thermodynamically equilibrated product and is in accord with results in the estrane and 5α-androstane series.[11]

The ketol VIIa was best prepared from the readily available 17-ketone XI by a new and simple route. Bromination of the latter in chloroform–acetic acid produced the bromo compound XII (probably mainly

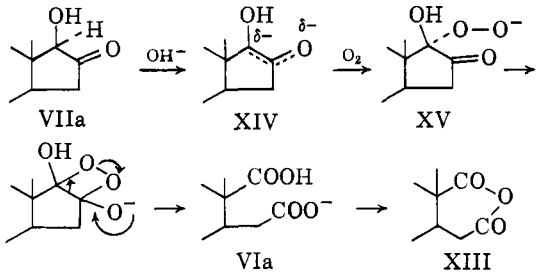


XI
$[\alpha]_D^{chf}$ +150°

XII
$[\alpha]_D^{chf}$ +135°

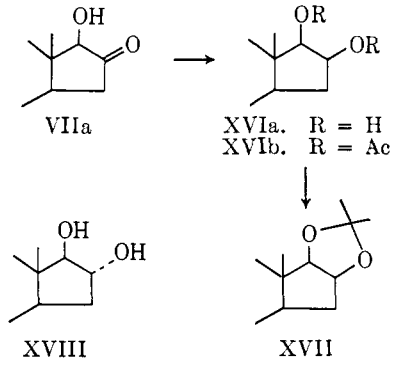
VIIa

16α[12]). Treatment of the latter with dilute potassium hydroxide in *t*-butyl alcohol in the absence of air produced the ketol VIIa in moderate (45–50%) over-all yield from the 17-ketone XI.[13] In the presence of air 3α-hydroxy-11-ketoetiobilianic acid VIa was an important by-product and in some runs the major product. Its structure was secured by conversion to the corresponding 3α-acetoxy anhydride XIII.[14] The reaction may be formulated as involving addition of oxygen to the anion XIV to give an intermediate 17-hydroperoxide XV, which can rearrange as indicated to the diacid VIa. The ketol acetates III and IV similarly were oxidized in part to the diacid VIa on treatment with alcoholic alkali in the presence of air.[15]



Some further reactions of the ketol VIIa are now discussed.

Sodium borohydride reduction of VIIa in aqueous dimethylformamide[4] led to the 16,17-*cis*-β-glycol XVIa the structure of which was confirmed by conversion to the isopropylidene derivative XVII and to the 3α,16β,-17β-triacetate XVIb. Treatment of VIIa with benzaldehyde and alkali did not lead to the expected 15-benzylidene derivative. The crude product which had slight ultraviolet absorption in the 290-mμ region and weak absorption in the 5.70-μ region in the infrared was more polar than VIIa on paper [benzene–chloroform(1:3)–formamide system]. It is believed to consist primarily of the *trans* glycol XVIII formed by crossed Canizzaro reaction,[16,17] together with a small amount of unchanged ketol.



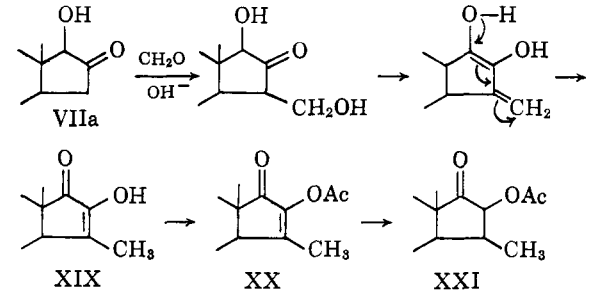
VIIa

XVIa. R = H
XVIb. R = Ac

XVIII

XVII

By contrast with the benzaldehyde case, the ketol VIIa did condense with formaldehyde in the presence of potassium hydroxide in aqueous *t*-butyl alcohol to give in part a base-soluble substance with λ_{max}^{MeOH} 272 mμ, ε 6800, which is formulated as the 15-methyldiosphenol XIX on the basis of its properties and by



analogy with the same reaction in the D-homo series.[18] Acetylation of XIX gave the enol acetate XX, λ_{max}^{MeOH} 244 mμ (9700). Hydrogenation of XX over palladium on charcoal reduced the double bond to form the 15-methylketol acetate XXI which gave a characteristic

(11) M. N. Huffman and M. H. Lott, *J. Am. Chem. Soc.*, **71**, 719 (1949), see footnote 9, ref. 11b; N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *ibid.*, **76**, 2943 (1954); (c) W. S. Johnson, B. Gastambide, and R. Pappo, *ibid.*, **79**, 1991 (1957); (d) J. Fishman, *ibid.*, **82**, 6143 (1960).

(12) The 17-carbonyl group of XII absorbed in the infrared at 5.71 μ, but the shift from the normal 5.75 μ cannot be used in structural arguments concerned with the configuration of the 16-bromine substituent. J. Fajkos, *Collection Czech. Chem. Commun.*, **20**, 312 (1955), found in a related series that both 16α- and 16β-bromo 17-ketones absorb at 5.70 μ. See also C. W. Shoppee, R. H. Jenkins, and G. H. R. Summers, *J. Chem. Soc.*, 3048 (1958). The 16α-bromo assignment in the present case is based on analogy with the work of Fajkos and Shoppee, *et al.*, and is supported by the optical rotation data.

(13) The procedure of Leeds, Fukushima, and Gallagher (rearrangement of the 16α,17α-epoxy-17β-acetate, ref. 11b) proceeded poorly in the present 11-keto-5β-androstane series. Alternate procedures, acyloin condensation of the dimethyl ester of VI [*cf.* J. C. Sheehan, R. E. Coderre, and P. A. Cruikshank, *J. Am. Chem. Soc.*, **75**, 6231 (1953)] and reduction of the 16-oximino 17-ketone [*cf.* M. N. Huffman, *J. Biol. Chem.*, **169**, 167 (1947); F. H. Stodola, E. C. Kendall, and B. F. McKenzie, *J. Org. Chem.*, **6**, 841 (1941)] were not investigated.

(14) N. L. Wendler, D. Taub, S. Dobriner, and D. K. Fukushima, *J. Am. Chem. Soc.*, **78**, 5027 (1956).

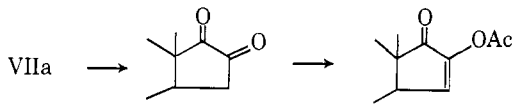
(15) Autoxidation of the above 16,17-ketols in air with aqueous base appears to be considerably more facile than that of simple ketones which in general require *t*-alkoxide and oxygen. *Cf.* W. E. Doering and W. M. Haines, *ibid.*, **76**, 482 (1954); E. Elkik, *Bull. soc. chim. France*, 933 (1959); E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1578 (1962). It is of interest that autoxidation of 2α- or 2β-hydroxytestosterone in aqueous potassium hydroxide proceeded only to the $\Delta^{1,4}$-2-hydroxy-3-keto stage [R. L. Clarke, *J. Am. Chem. Soc.*, **82**, 4629 (1960)].

(16) For an example of reduction on attempted benzylidene derivative formation in the D-homo series and a discussion of mechanism, see N. L. Wendler and D. Taub, *J. Org. Chem.*, **23**, 953 (1958).

(17) The characterization and additional chemistry of the present product is under study.

(18) N. L. Wendler, D. Taub, and R. P. Graber, *Tetrahedron*, **7**, 173 (1959).

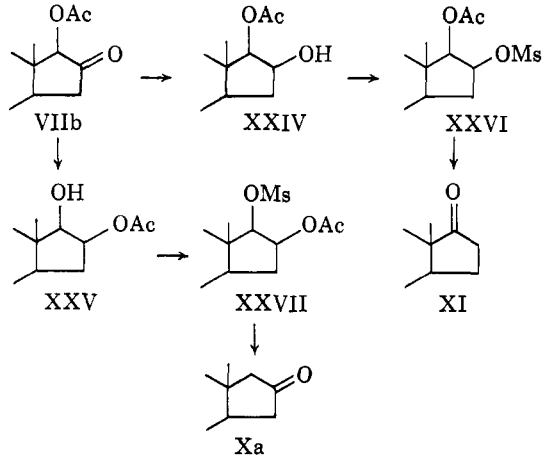
blue tetrazolium test. Under the assumption that hydrogenation occurred from the rear face of ring D the groups at C-15 and C-16 in XXI may be formulated as β.



XXII XXIII

Cupric acetate–methanol oxidation[19] of VIIa provided, in part, the alkali soluble 16,17-dione XXII as an amorphous yellow solid, m.p. ~155–170°, which was not obtained analytically pure. The dione XXII had negligible ultraviolet absorption in methanol and must exist, correspondingly, almost entirely in the α-diketone (or hemiacetal of the diketone) form in this solvent. In methanolic alkali XXII absorbed at 300 mμ (ϵ ~1500) showing the presence of the corresponding enolate anion. By contrast the 15-methyl-16,17-dione XIX exists in methanol in the diosphenol form as shown by strong absorption at 272 mμ. On acetylation XXII was converted into the amorphous enol acetate XXIII, λ_{max}^{MeOH} 236 mμ (5000).

Finally, an additional example of acyl transfer was observed in the following sequence.



Sodium borohydride–aqueous dimethylformamide reduction of the ketol acetate VIIb led to a glycol monoacetate which was mesylated and treated with ethanolic potassium hydroxide. The product, which should have been the 17-ketone XI, was in fact a 40:60 mixture of the 17-ketone and the 16-ketone Xa as indicated by paper chromatography and infrared spectroscopy, from which a small quantity of XI was isolated by crystallization. Evidently acetyl transfer occurred during the reduction step[7b,c] to give a mixture of glycol monoacetates XXIV and XXV which was capable of resolution on paper at the acetate mesylate (XXVI and XXVII) and ketone (XI and Xa) stages.

Experimental[20]

Chromium Trioxide Oxidation of 3α,16α-Diacetoxy-17α-hydroxypregnane-11,20-dione (Ib). 3α,16α-Diacetoxy-5β-androstane-11,17-dione (III), 3α,17α-Diacetoxy-5β-pregnane-11,16,20-trione (V), and 3α-Acetoxy-11-keto etiobilianic Acid (VIb).—To a stirred solution of 2.0 g. of the 16α-acetate Ib in 40 ml. of acetic acid was added 1.0 g. of chromium trioxide in 40 ml. of acetic acid and 0.8 ml. of water. After 20 hr. at 25°, water was added and the mixture was extracted with chloroform The latter extract was washed with water, aqueous potassium bicarbonate, saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated to dryness. The residue (1.8 g.) was chromatographed over 85 g. of Florisil. From the benzene–chloroform eluates was obtained 500 mg. of **3α,17α-diacetoxy-5β-pregnane-11,16,20-trione** (V), crystallized from acetone–ether, m.p. 201–203°; $[\alpha]_D$ −164°; λ_{max}^{chf} 5.68, 5.79, 5.84, 8.00 μ. N.m.r. spectra: 7.65, 7.72 τ (17-$COCH_3$, $OCOCH_3$), 7.86 τ (3-$OCOCH_3$), 8.70 τ (C_{19}-methyl), 9.14 τ (C_{18}-methyl).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.23; H, 7.62. Found: C, 67.08; H, 7.30.

From the later benzene–chloroform and chloroform eluates was obtained 720 mg. of the known **3α,17α-diacetoxy-5β-androstane-11,17-dione** (III), double m.p. 194–198°, 208–212° (from acetone–ether), identical with an authentic sample[3] by mixture melting point and infrared comparison.

On acidification of the original bicarbonate extract with dilute hydrochloric acid 106 mg. of **3α-acetoxy-11-ketoetiobilianic acid** (VIb)[14], m.p. 247–250°, was obtained.

Chromium Trioxide Oxidation of 3α,16β-Diacetoxy-17α-hydroxypregnane-11,20-dione (IIb). 3α,16β-Diacetoxy-5β-androstane-11,17-dione (IV).—Treatment of 1.0 g. of the 16β-acetate IIb in 20 ml. of acetic acid with 500 mg. of chromium trioxide in 20 ml. of acetic acid and 0.4 ml. of water as previously described, led to **3α,16β-diacetoxy-5β-androstane-11,17-dione** (IV), m.p. 176–180, undepressed mixture melting point with an authentic sample[3] as the only observed product.

3α,16α,17α-Triacetoxypregnane-11,20-dione (Ic).—Treatment of 200 mg. of 3α,16α-diacetoxy-17α-hydroxypregnane-11,20-dione (Ib) with 1 ml. of acetic anhydride in 2 ml. of pyridine at 90–95° (steam bath) for 18 hr. and crystallization of the residue from ether–benzene led to the **3α,16α,17α-triacetate Ic** (144 mg.), m.p. 244–245°; λ_{max}^{Nujol} 5.70–5.85, 7.9–8.0 μ [no −OH].

Anal. Calcd. for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81. Found: C, 65.79; H, 7.71.

A similar experiment at 25° led to a mixture of Ib (major) and Ic (minor) as evidenced by paper chromatography [benzene–cyclohexane (1:10)–formamide system]. At 90° for 1 hr. Ic was the major component.

Reaction of V with Methanolic Sodium Hydroxide. 3α-Hydroxy-17a-acetyl-17-oxa-D-homo-5β-androstane-11,16-dione (VIII).—To a solution of 150 mg. of the 11,16,20-trione V in 10 ml. of methanol (under nitrogen) was added 150 mg. of sodium hydroxide in 2 ml. of water. After 1 hr. at 25° the mixture was acidified with dilute hydrochloric acid and the methanol removed by concentration under vacuum. Water was added and the mixture extracted with ether. The ether extract was washed with 5% aqueous potassium bicarbonate, 2% aqueous sodium hydroxide, salt solution, dried over magnesium sulfate, and concentrated to dryness. The basic extracts were acidified with dilute hydrochloric acid, extracted with chloroform, the latter extracts dried over magnesium sulfate, and concentrated to dryness. The bicarbonate extracted material (white solid, 53 mg.) was recrystallized from acetone–ether to give the **lactone VIII** 34 mg., m.p. 252–256°; $[\alpha]_D$ −106°; λ_{max}^{chf} 2.76, 2.94 μ (3α-OH), 5.74 μ (δ-lactone), 5.85 μ (11,20-C=O), 9.3 μ (lactone ether oxygen); in morpholine the 5.74-μ band slowly diminished with concomitant formation of a carboxylate anion band at 6.15–6.20 μ. N.m.r. spectra: 5.36 τ (17aα-H), 7.60 τ (17aβ-$COCH_3$), 8.80 τ (19-CH_3), 8.85 τ (18-CH_3).

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.35. Found: C, 69.68; H, 8.31.

The sodium hydroxide extracted material (46 mg.) crystallized with difficulty and probably contained additional lactone VIII as evidenced by paper chromatography (benzene–chloroform (1:5)–formamide system) along with polar components.

The original neutral ether extract (30 mg.) probably contained the ketol VIIa as indicated by paper chromatography.

3α-Acetoxy-5β-androstane-11,16-dione (Xa).—To a stirred solution of 300 mg. of calcium turnings in 30 ml. of liquid ammonia[9] was added (5 min.) 400 mg. of 3α,17β-diacetoxy-5β-androstane-11,16-dione (VIIb) in 5 ml. of dry toluene. After an additional 10 min. 0.5 ml. of bromobenzene was added dropwise followed

(19) *Cf.* M. N. Huffman, *J. Biol. Chem.*, **167**, 273 (1947).

(20) Melting points were taken on a micro hot stage and are corrected. Paper chromatograms were run on strips of Whatman no. 4 filter paper using the formamide based systems of A. Zaffaroni, R. B. Burton, and E. H. Keutmann, *Science*, **111**, 6 (1950). N.m.r. spectra were run in deuteriochloroform at 60 Mc. [see N. R. Trenner, B. H. Arison, D. Taub, and N. L. Wendler, *Proc. Chem. Soc.*, 214 (1961), for procedural details].

by 1.0 ml. of water, and the ammonia was allowed to evaporate. Water (50 ml.) was added and the mixture extracted with chloroform. The latter extract was washed with salt water, dried over magnesium sulfate, and concentrated to dryness under vacuum. The residue (~300 mg.) was chromatographed over 15 g. of neutral alumina. Recrystallization of the crystalline and single spot [benzene–cyclohexane (1:5)–formamide system] petroleum ether–benzene eluates (104 mg.) from ether–petroleum ether gave analytically pure Xa, m.p. 135–137°; λ_{max}^{chf} 5.74, 5.83, 7.99 μ; negative tetrazolium test.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.51; H, 8.43.

Attempted deacetylation of VIIb by refluxing with zinc in acetic acid failed.[21]

5β-Androstane-3,11,16-trione (Xc).—To a solution of 50 mg. of Xa in 2.5 ml. of methanol was added 50 mg. of sodium hydroxide in 1 ml. of water. After 30 min. at 25°, 0.3 ml. of acetic acid was added and the methanol removed under vacuum. Water was added and the mixture was extracted with chloroform. The latter extract was dried over magnesium sulfate and concentrated to dryness. The residue crystallized from ether to give **3α-hydroxy-5β-androstane-11,16-dione (Xb)**, m.p. 130–133°; λ_{max}^{chf} 2.71, 2.8–2.9, 5.74, 5.84 μ. To a solution of 50 mg. of Xb in 1 ml. of acetic acid was added 30 mg. of chromium trioxide in 1 ml. of 90% acetic acid. After 17 hr. at 25° water was added and the mixture extracted with chloroform. The latter extract was washed with 5% aqueous potassium bicarbonate, salt water, dried over magnesium sulfate, and concentrated to dryness. Crystallization of the residue from acetone–ether gave Xc, m.p. 185–190°, undepressed on mixture melting point with an authentic sample, m.p. 189–191°.[10] The respective paper chromatographic mobilities [benzene–cyclohexane (1:1)–formamide system] and infrared spectra were identical.

3α-Acetoxy-16α-bromo-5β-androstane-11,17-dione (XII).—To a stirred solution (*t*, 10°) of 25.3 g. (73 mmoles) of 3α-acetoxy-5β-androstane-11,17-dione (XI) in 400 ml. of chloroform and 1 drop of 15% hydrogen bromide in acetic acid was added dropwise 11.7 g. (73 mmoles) of bromine in chloroform. Addition was complete in 90 min. After an additional 5 min. the pale yellow solution was concentrated to dryness under vacuum and the residue crystallized from ether to give 28.8 g. (93%) of XII, m.p. 191–195°. Recrystallization from ether–acetone raised the m.p. to 198–202°; $[\alpha]_D$ +135°; λ_{max}^{chf} 5.71, 5.80, 5.84, 8.0 μ.

Anal. Calcd. for $C_{21}H_{29}O_4Br$: C, 59.29, H, 6.87, Br, 18.79. Found: C, 58.96; H, 6.49; Br, 18.61.

3α,17β-Dihydroxy-5β-androstane-11,16-dione VIIa.—To a stirred solution of 28 g. of the 16α-bromo 17-ketone XII (m.p. 191–195°) in 1800 ml. of *t*-butyl alcohol maintained under nitrogen was added 1800 ml. of 2% aqueous potassium hydroxide. After 17 hr. at 25° the mixture was neutralized with cold 2 *N* hydrochloric acid and the *t*-butyl alcohol was removed under vacuum. The mixture was extracted with 1:1 benzene–ethyl acetate and the latter extract washed with saturated salt solution, dried over magnesium sulfate, and concentrated to dryness. Two crystallizations of the residue from acetone–ether gave 10.5 g. (50%) pure VIIa, m.p. 199–202°,[3] with additional material in the mother liquors.

Pyridine–acetic anhydride acetylation of VIIa (200 mg.) gave the corresponding 3α,17β-diacetate VIIb,[3] m.p. 184–186°.

3α-Hydroxy-11-ketoetiobilianic acid (VIa). (A) From XII.—A solution of the 16α-bromo 17-ketone XII (1.0 g.) in 6 ml. of tetrahydrofuran and 6 ml. of 2% aqueous potassium hydroxide was kept exposed to air at 25° overnight. The tetrahydrofuran was removed under vacuum and the alkaline solution extracted with ethyl acetate. The latter extract was washed with saturated salt solution, dried over magnesium sulfate and concentrated to dryness. Trituration of the residue with ether gave 200 mg. of the 17β-hydroxy-16-ketone VIIa. Acidification of the basic aqueous layer and extraction with ethyl acetate gave 3α-hydroxy-11-ketoetiobilianic acid VIa (360 mg.), m.p. 227–232; λ_{max}^{Nujol} 3.0–3.6 (broad), 5.82, 5.91 μ.

Anal. Calcd. for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.26; H, 7.75.

Reaction of VIa (100 mg.) with 0.5 ml. of acetic anhydride and 1 ml. of pyridine overnight at room temperature gave the known 3α-acetoxy-11-ketoetiobilianic acid anhydride (XIII), m.p. 207–215° (reported m.p. 213–215°[14]), undepressed on mixture melting point with an authentic sample.

(B) From Ketol VIIa.—Treatment of 3α,17β-dihydroxy-5β-androstane-11,16-dione (VIIa) (100 mg.) in 4 ml. of methanol with 4 ml. of 2.5% aqueous sodium hydroxide in air for 2 hr. at room temperature led to 70 mg. of acid VIa.

Analogous treatment of the ketol acetates III and IV with aqueous methanolic sodium hydroxide in air also led to the etiobilianic acid VIa.

3α,16β,17β-Trihydroxy-5β-androstane-11-one (XVIa).—To a stirred solution of 400 mg. of ketol VIIa in 10 ml. of dimethylformamide was added 100 mg. of sodium borohydride in 5 ml. of water. After 3 hr. (negative tetrazolium test) 2 ml. of 10% aqueous acetic acid was added dropwise followed by saturated salt water. The mixture was extracted with chloroform, the latter extract washed with saturated salt solution, dried over magnesium sulfate and concentrated to dryness. The residue was crystallized from aqueous methanol, 287 mg., m.p. 262–268°, raised to 270–274° on repeated crystallization; λ_{max}^{Nujol} 2.9–3.0, 5.89 μ.

Anal. Calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.53; H, 9.20.

3α-16β,17β-Triacetoxy-5β-androstane-11-one (XVIb).—The triol XVIa (120 mg.) was acetylated in 2 ml. of acetic anhydride and 3 ml. of pyridine overnight at 25°. The mixture was concentrated to dryness under vacuum, flushing twice with benzene. Crystallization of the residue from acetone–ether gave the triacetate XVIb, m.p. 204–207°; λ_{max}^{chf} 5.75, 5.85, 8.0 μ.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.41; H, 8.03.

Isopropylidene Derivative (XVII).—A solution of 100 mg. of triol XVIa in 10 ml. of acetone and 0.1 ml. of concentrated sulfuric acid was kept at 25° overnight. A small quantity of solid was removed by filtration, the filtrate was neutralized with potassium bicarbonate and the acetone removed under vacuum. Water was added and the mixture extracted with chloroform. The latter extract was dried over magnesium sulfate and concentrated to dryness. Crystallization of the residue from acetone–ether gave the isopropylidene derivative XVII (110 mg.), m.p. 182–184°.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.84; H, 9.65.

Reaction of Ketol VIIa with Benzaldehyde.—To a solution of 2.0 g. of VIIa in 25 ml. of ethanol was added 1.40 g. of benzaldehyde and 13 ml. of 15% aqueous potassium hydroxide. The solution was stirred at room temperature under nitrogen for 18 hr. and most of the ethanol removed under vacuum. On addition of water a gum precipitated which crystallized on chilling and stirring. It was filtered and dried in air (1.66 g.), m.p. 138–146°; λ_{max}^{chf} 2.7–2.9 (strong), 5.72 (weak), 5.85 μ (strong). Crystallization from methanol–water did not raise the melting point. On paper chromatography (benzene–chloroform (1:3)–formamide) the material showed a major spot ($R_f \sim 0.4$) with nearly the same mobility as the triol XVIa and a minor, more mobile spot (+ tetrazolium test) of identical mobility as VIIa.

3α,16-Dihydroxy-15-methyl-5β-androst-15-ene-11,17-dione (XIX).—To a solution of 250 mg. of ketol VIIa in 10 ml. of *t*-butyl alcohol was added 1.0 g. of potassium hydroxide in 1 ml. of water and 0.5 ml. of 37% aqueous formaldehyde. The mixture was refluxed under nitrogen for 1 hr., the *t*-butyl alcohol removed under vacuum, water added and the mixture extracted with chloroform. The aqueous phase was acidified with dilute hydrochloric acid, extracted with chloroform, and the latter extract washed with dilute sodium bicarbonate, saturated salt solution, dried over magnesium sulfate, and concentrated to dryness. Trituration with ether gave 75 mg. of the diosphenol XIX, m.p. 158–169°, unchanged on crystallization from chloroform–ether; λ_{max}^{MeOH} 272 mμ (6800); λ_{max}^{chf} 2.78, 2.9, 5.85, 6.05 μ.

The original chloroform extract contained 50 mg. of crude starting ketol VIIa, m.p. 178–190°.

3α,16-Diacetoxy-15-methyl-5β-androst-15-ene-11,17-dione (XX).—The diosphenol XIX (80 mg.) was kept overnight at 25° in 2 ml. of pyridine and 1 ml. of acetic anhydride. The mixture was concentrated to dryness under vacuum and the residue crystallized from ether to give the enol acetate XX, 50 mg. with additional material in the mother liquor, m.p. 200–203°; λ_{max}^{MeOH} 244 mμ (9700); λ_{max}^{chf} 5.66, 5.78, 5.84 (shoulder), 6.05 μ.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.11; H, 7.52.

(21) *Cf.* R. S. Rosenfeld and T. F. Gallagher, *J. Am. Chem. Soc.*, **77**, 4367 (1955). Clemmensen reduction of 17-hydroxy-16-keto systems has given 16-keto steroids [M. N. Huffman and M. H. Lott, *ibid.*, **73**, 878 (1951)].

3α,16-Diacetoxy-15-methyl-5β-androstane-11,17-dione (XXI).—A solution of the enol acetate XX (250 mg.) in 12 ml. of ethyl acetate was hydrogenated at 25° and 1 atm. over 150 mg. of 10% palladium on charcoal catalyst. Uptake of one molar equivalent of hydrogen was complete in 2 hr. The mixture was filtered, the filtrate taken to dryness, and the residue crystallized from ether–petroleum ether to give the saturated diacetate XXI, m.p. 176–178°; λ_{max}^{chf} 5.70, 5.78, 5.83 μ; positive tetrazolium test.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.72; H, 8.38.

3α-Hydroxy-5β-androstane-11,16,17-trione (XXII).—A stirred mixture of ketol VIIa (150 mg.), cupric acetate monohydrate (440 mg.) in 20 ml. of methanol was refluxed for 3 hr., cooled, and the methanol removed under vacuum. Dilute hydrochloric acid was added and the mixture extracted with 1:1 benzene–ether. The latter extract was washed with dilute sodium bicarbonate and 1 *N* sodium hydroxide. The sodium hydroxide extract was washed with 1:1 benzene–ether, acidified with dilute hydrochloric acid, and extracted with 1:1 benzene–ether. The latter extract was washed with saturated salt solution, dried over magnesium sulfate and concentrated to dryness to give the base soluble 11,16,17-trione XXII, which on trituration with ether was obtained as an amorphous yellow solid, 60 mg., m.p. 127–130°; ultraviolet in methanol, no maximum; in methanol containing 0.1% sodium hydroxide, λ_{max} 300 mμ (1500); λ_{max}^{chf} 2.75, 2.8–2.9, 5.72, 5.85 μ; negative tetrazolium test.

An analytically pure specimen was not obtained.

Acetylation of XXII (20 mg.) in 0.5 ml. of acetic anhydride and 1 ml. of pyridine overnight at room temperature gave the noncrystalline **3α,16-diacetoxy-5β-androst-15-ene-11,17-dione** (XXIII); λ_{max}^{MeOH} 236 mμ (5000).

Conversion of 3α,17β-Diacetoxy-5β-androstane-11,16-dione (VIIb) to 40:60 Mixture of 3α-Acetoxy-5β-androstane-11,17-dione (XI) and 3α-Acetoxy-5β-androstane-11,16-dione (Xa).—The ketol acetate VIIb (360 mg.) in 10 ml. of dimethylformamide was treated with 70 mg. of sodium borohydride in 3.5 ml. of water as described above for the reduction of VIIa. The amorphous product [XXIV and XXV (350 mg.) negative tetrazolium test; λ_{max}^{chf} 2.75, 5.75, 5.84 μ] in 2 ml. of pyridine at 0°] was treated with 0.3 ml. of methanesulfonyl chloride for 17 hr. Iced water was added and the mixture extracted with chloroform. The latter extract was washed successively with dilute hydrochloric acid, dilute aqueous potassium bicarbonate, saturated salt solution, dried over magnesium sulfate and concentrated to dryness under vacuum to give an amorphous mixture of 16,17-acetate–mesylates XXVI and XXVII (430 mg.) as evidenced by paper chromatography [two spots $R_f \sim 0.3$ and ~0.7; benzene–cyclohexane (1:1)–formamide system]. The acetate–mesylate mixture in 20 ml. of ethanol and 20 ml. of 1 *N* aqueous potassium hydroxide was refluxed for 1 hr. The ethanol was removed under vacuum, water added, and the mixture extracted with chloroform. The chloroform extract was washed with saturated salt solution, dried over magnesium sulfate, and concentrated to dryness. The residue (340 mg.) crystallized slowly from ether to yield 14 mg. of **3α-hydroxy-5β-androstane-11,17-dione,** m.p. 182–187°, identical infrared spectrum and undepressed mixture melting point with authentic sample, m.p. 186–189°. Remainder of product was acetylated (2 ml. of pyridine, 1 ml. of acetic anhydride at 25° overnight). Paper chromatography (ligroin–formamide) along with samples of the individual compounds, showed the acetylation product to consist of a nearly equivalent mixture of 3α-acetoxy-5β-androstane-11,17-dione (XI) and 3α-acetoxy-5β-androstane-11,16-dione (Xa). Infrared spectroscopy *vs.* known mixtures of XI and Xa indicated the mixture to consist of 40% XI and 60% Xa.

In a second run the sodium borohydride reduction product (350 mg.) of VIIb was in part acetylated to give in good yield the triacetate XVIb, m.p. 204–206°, and in part saponified (dilute aqueous methanolic sodium hydroxide, 25° for 40 min.) to give a good yield of the triol XVIa, m.p. 265–270°, indicating the reduction product to be a clean mixture of 16β,17β-glycol monoacetates.

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Synthesis of 2,2-Diarylpropanes by Hydride Transfer[1]

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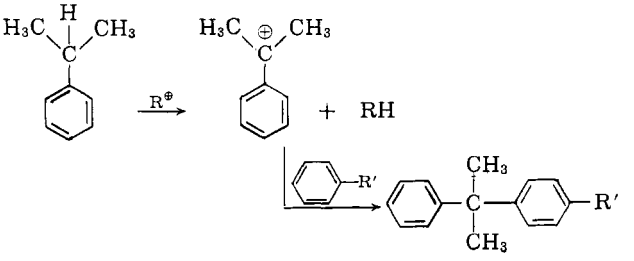
2,2-Diarylpropanes were prepared by hydride transfer reactions of 2-arylpropanes, arenes, and hydride ion acceptors. Hydride ion transfer and alkylation by the cumyl carbonium ion compete with alkylation by the hydride ion acceptors, isomerization, and transalkylation. Conversions of 2-arylpropanes to 2,2-diarylpropanes were surprisingly good in view of all these competing reactions.

Introduction

2,2-Diarylpropanes were needed in this laboratory as intermediates in oxidation studies. This led to a study of their synthesis as they are difficult to prepare by known methods. Most methods depend on alkylation of arenes with a cumyl cation formed from such reagents as α-methylstyrenes,[2] 2-chloro-2-phenylpropanes,[3] or 2-phenylpropanol-2.[4] Unfortunately these reagents readily dimerize to indanes and, except for one reaction,[3] give only a small amount of the alkylation products. Furthermore, ring-substituted α-methyl styrenes, 2-phenyl-2-chloropropanes, or 2-phenyl-2-propanols are not readily available, whereas a large number of ring-substituted cumenes can be easily prepared.

We wished to form the cumyl cations directly from 2-arylpropanes by hydride transfer to another carbonium ion in the following way.



The formation of many types of hydrocarbons by hydride transfer reactions has been reported, such as alkylation of arenes with paraffins,[5] formation of diaryl-

(1) Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

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(3) A. T. Coscia, J. T. Penniston, and J. C. Petropoulos, *J. Org. Chem.*, **26**, 1398 (1961).

(4) K. T. Serijan and P. H. Wise, *J. Am. Chem. Soc.*, **73**, 4766 (1951).

(5) J. T. Kelly and R. J. Lee, *Ind. Eng. Chem.*, **47**, 757 (1955).