TABLE I

DIELS–ALDER ADDUCTS OF HEXACHLOROCYCLOPENTADIENE WITH MONO- AND DIVINYL SUBSTITUTED BENZENES

Substituent R	Starting compound	Yield, %	M.p., °C.	Composition, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found
H	Styrene[a]	80	58–59 71.5–72.5[b]	...	...	..	..	...	...
ar-CH_3—	Vinyltoluenes[c]	94	163.5 (0.8[d] mm.)	43.01	43.29	2.58	2.65	54.41	54.25
ar-C_2H_5—	Ethylstyrenes[e]	75	194 (2.2[f] mm.)	44.48	44.62	2.99	2.90	52.53	52.42
4-*t*-C_4H_9—	4-*t*-Butylstyrene[g]	93	103.5–104	47.15	47.10	3.72	3.83	49.13	48.87
2,4-Cl_2—	2,4-Cl_2-styrene[h]	35	127–128	35.02	35.05	1.36	1.46	63.62	63.13
2-($C_7H_3Cl_6$)[i]	1,2-Divinylbenzene[j]	82	121–121.5	35.54	35.64	1.49	1.54	62.96	62.45
3-($C_7H_3Cl_6$)[i]	1,3-Divinylbenzene[k]	90	213–215	35.54	35.35	1.49	1.54	62.96	62.45
4-($C_7H_3Cl_6$)[i]	1,4-Divinylbenzene[k]	85	291	35.54	35.72	1.49	1.51	62.96	62.20

[a] The Dow Chemical Co. [b] Ref. 4, reported m.p. 73.7–74.5°. The compound isolated here was shown to be dimorphic; the compound recrystallized from heptane showed the indicated melting points. After melting at the lower temperature the compound resoldified and melted again at the higher temperature. [c] The Dow Chemical Co., an isomeric mixture containing 35% *meta* and 65% *para* compounds. [d] B.p., $n^{25}D$ 1.5828. [e] Mixed ethylstyrenes contained to 30% in the isomeric mixture of divinylbenzene (see footnote *k*); 30% *meta* and 70% *para* isomer distribution. Yields based upon original available ethylstyrenes. [f] B.p., $n^{25}D$ 1.5750. [g] Prepared by dehydration of 1-(4-*t*-butylphenyl)ethanol; b.p. 65–70° (6 mm.), $n^{25}D$ 1.5245. D. T. Mowry, M. Renoll, and W. F. Huber, *J. Am. Chem. Soc.*, **68**, 1105 (1946), reported b.p. 77–100° (14 mm.), $n^{22}D$ 1.5245. [h] From a mixture of isomeric dichlorostyrenes; yield based upon available 2,4-dichlorostyrene (45% in original mixture). [i] $C_7H_3Cl_6$ represents the substituent (1,4,5,6,7,7-hexachloro-5-norbornen-2-yl). [j] Prepared according to the published procedure, J. O. Halford and B. Weissmann, *J. Org. Chem.*, **17**, 1646 (1952), b.p. 78–79° (16 mm.). [k] The Dow Chemical Co. divinylbenzene; contains 55% divinyl compounds of which 65% is the 1,3-isomer. Yields in the 1,3- and 1,4-divinylbenzene reaction are based on potential available isomer.

Experimental[6]

Most of the preparations were run in a similar fashion; typical syntheses are described for the reaction of commercial divinylbenzene with hexachlorocyclopentadiene and 4-*t*-butylstyrene with hexachlorocyclopentadiene. Where isomeric mixtures of products were obtained or when a pure isomer was produced, infrared analysis was used for analysis of isomeric purity.

Preparation of 5-(4-*t*-Butylphenyl)-1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-ene.—A solution of 273 g. (1 mole) of hexachlorocyclopentadiene (Hooker) in 500 ml. of *n*-heptane was heated to reflux and 160 g. (1 mole; purity 90–95%) of 4-*t*-butylstyrene was added dropwise during 1 hr. The resulting mixture was heated under reflux for 70 hr. and then chilled. The resulting precipitate was removed by filtration and recrystallized from *n*-hexane to give 333 g. of product, m.p. 103.5–104°. The combined filtrates, on evaporation, gave additional product which, when recrystallized from *n*-hexane, gave 73.5 g., m.p. 103.5–104°, a 93% yield based on 100% 4-*t*-butylstyrene or nearly a quantitative yield based on estimated purity of the 4-*t*-butylstyrene used.

Preparation of 1,4-Bis(1,2,3,4,7,7-hexachlorobicyclo[2.2.1]-hept-2-en-6-yl)benzene and 1,3-Bis(1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-en-6-yl)benzene (Fractional Crystallization and Method I).—A mixture of 900 g. (3.3 moles) of hexachlorocyclopentadiene, 264 g. (55% divinylbenzene, 45% ethylstyrene—70% *para*, 30% *meta;* approximately 3.3 moles of vinyl groups) and 1 l. of anhydrous toluene was allowed to stand at room temperature for 72 hr.; the mixture then was warmed and heated under reflux for 4 hr. and allowed to cool to room temperature and stand overnight. The precipitated solid was removed by filtration and the mother liquor partially evaporated at room temperature under vacuum; additional crops of crystalline products were obtained in this fashion. A total yield of solid product was obtained representing an 85% yield of bis-adducts of the isomeric divinylbenzenes. From this mixture was isolated a pure sample of each of the pure *para* and pure *meta* isomers (see Table I) by fractional crystallizations from mixtures of toluene and heptane; the pure isomers which resulted were recrystallized from 1,2-dibromoethane. The infrared spectra[6] of these pure isomeric compounds established the identity of the *para* and *meta* isomers, "using the well known correlation of the summation bands in the 1650–2000-cm.$^{-1}$ region.[7] The spectra were obtained as Nujol mulls. The isomer, m.p. 291°, showed weak absorption at 1910 cm.$^{-1}$, a very weak absorption at 1790 cm.$^{-1}$, and no other absorption in the 1700–200-cm.$^{-1}$ region; this is very typical of the *para*-disubstituted phenyl structure. The isomer, m.p. 213–215°, showed three weak absorptions at 1940 cm.$^{-1}$, 1870 cm.$^{-1}$, and 1790 cm.$^{-1}$, and no other significant absorption in the 1700–200-cm.$^{-1}$ region; this is very typical of the *meta*-substituted phenyl structure or the 1,3,5-trisubstituted phenyl structure; in these examples the latter structure is ruled out."

The mother liquors from several preparations of the bis-adducts were combined and evaporated to dryness under reduced pressure. The oily residue was distilled under reduced pressure to give the adducts of the isomeric *meta*- and *para*-ethylstyrenes (see Table I).

The experimental procedure for the preparation of the other adducts listed in Table I varied primarily in the duration of reflux. In most instances the best yields of product are obtained after a 24- to 48-hr. reflux time.

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[6] Analytical data kindly supplied by S. Shrader. Infrared spectra and interpretations by W. J. Potts.

[7] C. W. Young, R. B. DuVall, and N. Wright, *Anal. Chem.*, **23**, 709 (1951).

Condensation Derivatives in Corticosteroid Side Chains. IV. Aldosterone 20,21-Cyclic Acetals[1,2]

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In order to account for the low intensity of the 20-ketone band in the infrared spectrum of aldosterone, Ham, *et al.*,[3] suggested at automeric 20,21-dihydroxy-11,18;18,20-bisepoxide form (I) in equilibrium with the ketol–aldehyde and ketol–hemiacetal forms. Others[4] proposed a hydrogen bond between the 18-hydroxyl and the 20-ketone.

Now we wish to report the preparation of aldosterone acetals doubtless recognized as derivatives of form I. Interchange reaction between aldosterone and acetone diethyl acetal, carried out in a suitable solvent in the

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[1] Previous paper in this series, III, *Gazz. chim. ital.*, in press.

[2] This paper represents a part of the Round Table contribution by R. Gardi at the International Congress on Hormonal Steroids, Milan, May 14–19, 1962 (Excerpta Medica, International Congress Series No. 51, p. 57).

[3] E. A. Ham, R. E. Harmon, N. G. Brink, and L. H. Sarett, *J. Am. Chem. Soc.*, **77**, 1637 (1955).

[4] S. A. Simpson, J. F. Tait, A. Wettstein, R. Neher, J. Van Euw, O. Schindler, and T. Reichstein, *Helv. Chim. Acta*, **37**, 1163 (1954).

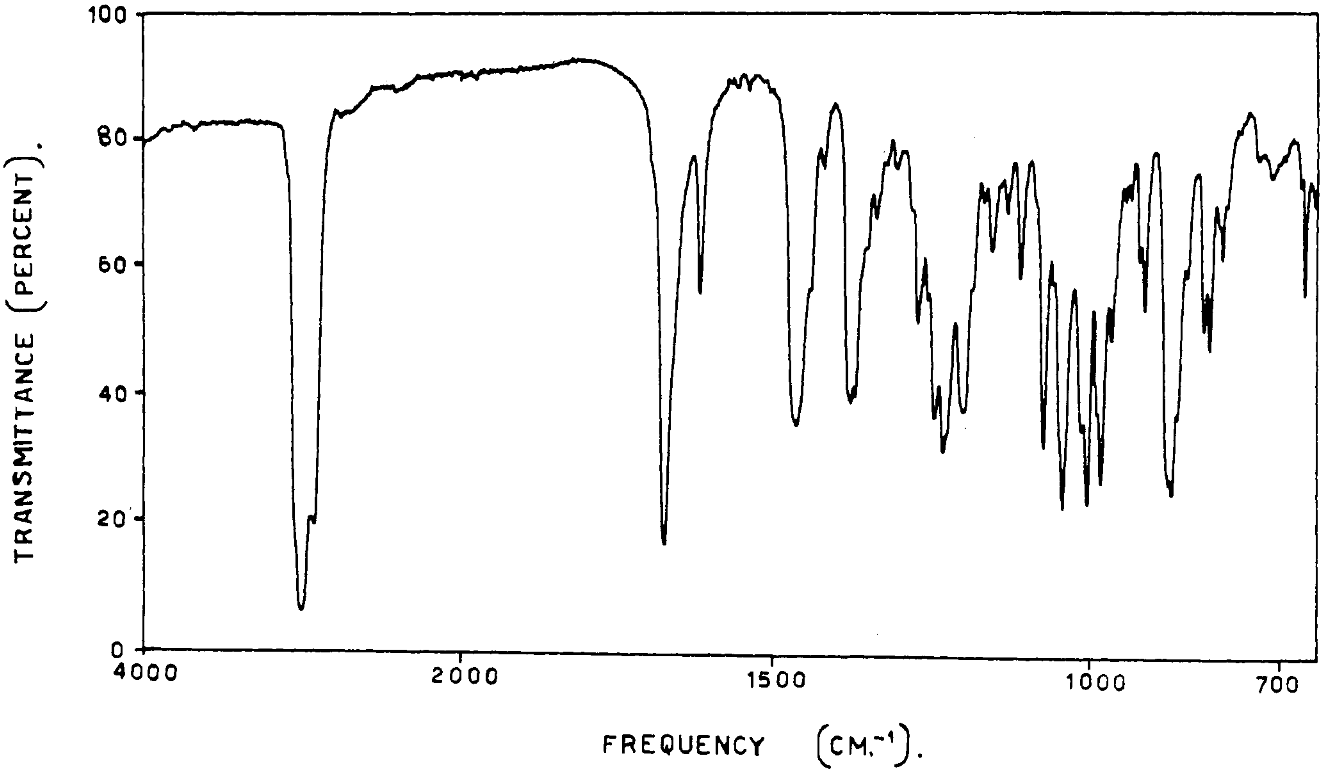
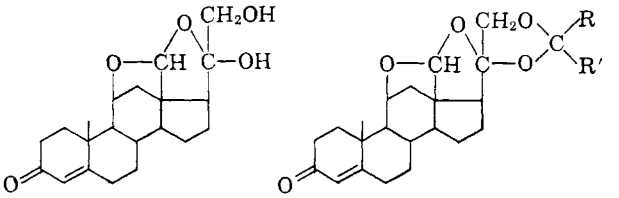


Fig. 1.—Infrared spectrum (Nujol mull) of aldosterone 20,21-acetonide (IIa).



IIa. $R=R'=CH_3$

b. $R=R'=(CH_2)_4$

c. $R=H;R'=C_6H_5$

presence of an acid catalyst,[5] gave in satisfactory yield a product, which afforded analytical data in agreement with the formula of an acetal $C_{24}H_{32}O_5$. Its infrared spectrum (Fig. 1) showed lack of hydroxyl and 20-carbonyl bands, clearly supporting the structure of 20,21-acetonide (IIa). In a similar manner we prepared the corresponding 20,21-cyclopentylidene and benzylidene derivatives (IIb and IIc).

The new acetals proved to be stable to base, remaining unchanged after refluxing in methanolic *N* potassium hydroxide while, by hydrolysis with aqueous hydrochloric acid in dioxane, they readily regenerated aldosterone. The possible usefulness of such compounds in protecting both hemiacetal and ketol groups of aldosterone is apparent.

The results of the interchange reactions between aldosterone and trialkyl ortho esters[6] will be reported later.

Experimental[7]

Aldosterone 20,21-Acetonide (IIa).—To an anhydrous boiling solution of 5 ml. of acetone diethyl acetal and 3 mg. of pyridine *p*-toluenesulfonate in 300 ml. of benzene, 300 mg. of aldosteron was added and the mixture was heated with rapid solvent distillation for 20 min. After complete solvent evaporation under vacuum, digestion with ether-petroleum ether yielded 170 mg. of IIa, m.p. 227–232°. One crystallization from ethanol raised the melting point to 235–237°, $[\alpha]^{23}D$ +170° (di); λ_{max}^{EtOH} 240–241 mμ (ε 16.000); ν_{max}^{Nujol} 1672, 1618, 1076, 1045, 1006, 985, 917, 871 cm.⁻¹.

Anal. Calcd. for $C_{24}H_{32}O_5$; C, 71.97; H, 8.05. Found: C, 71.86; H, 8.03.

By reaction of aldosterone with cyclopentanone diethyl acetal and benzaldehyde diethyl acetal, carried out according to the above described procedure, and followed by chromatography on Florisil, we prepared the following compounds, respectively.

Aldosterone 20,21-cyclopentanonide (IIb), m.p. 202–205°e $[\alpha]^{23}D$ +162° (di); λ_{max}^{EtOH} 241 mμ (ε 15.900); ν_{max}^{Nujol} 1672, 1622, 1045, 1015, 985, 966, 928, 876, 865 cm.⁻¹.

Anal. Calcd. for $C_{26}H_{34}O_5$; C, 73.21; H, 8.04. Found: C, 72.94; H, 8.05.

20,21-Benzylidenealdosterone (IIc), m.p. 224–226°, $[\alpha]^{23}D$ +115° (di); λ_{max}^{EtOH} 240–241 mμ (ε 17.000); ν_{max}^{Nujol} 1675, 1619, 1090, 1052, 1011, 985, 965, 886, 867 cm.⁻¹.

Anal. Calcd. for $C_{28}H_{32}O_5$; C, 74.94; H, 7.19. Found: C, 74.75; H, 7.21.

Acid Hydrolysis.—The following example is given to describe the acid hydrolysis of the acetals II. Aldosterone 20,21-acetonide (IIa) (50 mg.) was dissolved by stirring in 1 ml. of a mixture of dioxane–*N* hydrochloric acid 10:1. After standing for 4 hr. at room temperature, ether was added and the solution washed with saturated natrium hydrogen carbonate solution and then with water. Evaporation of the dehydrated extract gave a residue (35 mg.) which crystallized from acetone–ether yielding 25 mg. of aldosterone, m.p. 112–115° to 160–162° $[\alpha]^{23}D$ +151° (chf.).

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(5) *Cf.* R. Gardi, R. Vitali, and A. Ercoli, *J. Org. Chem.*, **27**, 668 (1962).

(6) *Cf.* R. Gardi, R. Vitali, and A. Ercoli, *Tetrahedron Letters*, 448 (1961).

(7) Melting points are uncorrected. We are indebted to Dr. Sergio Cairoli for the microanalyses and to Dr. Cesare Pedrali for the infrared spectra.