Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.81; H, 7.54.

Chromatography over silica gel (Davison, grade 923, 100–200 mesh) of the mother liquor from the two crops of crystalline material gave 120 mg. of colorless crystals melting at 197–200° dec., in the benzene–ether (1:1) eluate. Recrystallization from ether did not change the melting point. This material, probably **4,16-pregnadien-3,11,20-trione (VII)**, had $\lambda_{\max}^{\mathrm{MeOH}}$ 238 mμ (ε 24,552).

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.26; H, 8.03. Found: C, 76.84; H, 7.73.

16α,21-Diacetoxy-4-pregnene-3,11,20-trione.—A 63-mg. sample of 16α-hydroxy-21-acetoxy-4-pregnene-3,11,20-trione was acetylated with 0.8 ml. of an acetic anhydride–pyridine mixture (1:3). The reaction mixture was heated at 40° for 15 minutes and then let stand at room temperature for five hours. The product was crystallized by cautious addition of water. There resulted 67 mg. of colorless needles melting at 189–191°. Two recrystallizations from acetone–ether afforded material melting at 190–192° dec.

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.61; H, 7.43.

17α-Hydroxy-21-acetoxy-4-pregnene-3,11,20-trione (Cortisone Acetate) (VIII).—Commercial Raney nickel catalyst was treated with acetic acid until acidic to phenolphthalein, but basic to litmus. The catalyst was washed by centrifugation with water, followed by methanol. Two grams (wet weight) of the catalyst was suspended in 32 ml. of methanol and refluxed with stirring for one hour. Then 160 mg. of 16β-bromocortisone acetate (m.p. 222–223° dec.) was added and refluxing continued for another hour. The hot mixture was filtered to remove catalyst. The catalyst was washed several times with hot methanol–methylene chloride. The combined filtrate was concentrated *in vacuo* to 10 ml. and then 20 ml. of hot water was added to the residue. The glistening plates which separated upon cooling were filtered, washed with methanol and dried. The crystalline product, 90 mg. (70%), melted at 228–231°. Recrystallization from acetone gave shiny white needles (solvated) melting at 240–242°, $\lambda_{\max}^{\mathrm{MeOH}}$ 238 mμ (ε 15,100). Upon admixture with an authentic sample of cortisone acetate (m.p. 245–246°, $\lambda_{\max}^{\mathrm{MeOH}}$ 238 mμ (ε 15,700)), no depression in melting point was observed.

NORTH CHICAGO, ILL.

[CONTRIBUTION FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH, UNIVERSITY OF CHICAGO, AND FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, KYÔTO UNIVERSITY]

Preparations of the Synthetic Estrogens. VI.[1] A New Synthesis of 1,1-Bis-(*p*-Alkoxyphenyl)-2-phenyl-2-bromoethylenes

BY KEIITI SISIDO, KÔITI OKANO AND HITOSI NOZAKI

RECEIVED FEBRUARY 23, 1955

Treatment of 1,1,2-triarylethanes with 2 moles of N-bromosuccinimide effected simultaneous dehydrogenation and bromination, giving triarylbromoethylenes in a single operation. 1,1-Bis-(*p*-methoxyphenyl)-2-phenyl-2-bromoethylene and 1,1-bis-(*p*-ethoxyphenyl)-2-phenyl-2-bromoethylene have been prepared in this way in 92 and 91% yields, respectively. The required 1,1-bis-(*p*-alkoxyphenyl)-2-phenylethanes were obtained in fair yields from the condensation of phenylacetaldehyde with anisole or phenetole in the presence of concentrated sulfuric acid as a catalyst.

A common defect of usual preparations of 1,1,2-triaryl-2-bromoethylenes,[2-4] for the purpose of large-scale production at least, is that the Grignard reaction is utilized for synthesizing the key intermediate, 1,1,2-triaryl-2-ethanol. Though some variations[5] have been reported in which the use of the Grignard reaction is avoided, the yields obtained are rather low. We have observed that the treatment of 1,1,2-triarylethane derivatives with 2 moles of N-bromosuccinimide results in the formation of 1,1,2-triaryl-2-bromoethylenes in good yields. This discovery constitutes a new synthesis which appears suitable for a large scale preparation of these potent estrogens.

The required intermediates, 1,1-bis-(*p*-alkoxyphenyl)-2-phenylethanes, were prepared by the condensation of alkyl phenyl ethers and phenylacetaldehyde in the presence of sulfuric acid. If the acidic catalyst was added dropwise to a solution of the reaction components in glacial acetic acid, there resulted a considerable quantity of tarry matter, which presumably might be composed of a polymer of the aldehyde. Substantially improved yields were realized, however, when the aldehyde was added quite slowly to a mixture of the phenol ether, glacial acetic acid and concentrated sulfuric acid in order to minimize the action of the mineral acid on the unchanged phenylacetaldehyde. 1,1-Bis-(*p*-methoxyphenyl)-2-phenylethane and 1,1-bis-(*p*-ethoxyphenyl)-2-phenylethane were prepared in this way in 51 and 58% yields, respectively. An attempted condensation of phenylacetaldehyde with benzene, fluorobenzene or *o*-fluoroanisole in the presence of concentrated sulfuric acid failed to afford the desired 1,1,2-triphenylethane.

When these 1,1-bis-(*p*-alkoxyphenyl)-2-phenylethanes were treated with 2 moles of N-bromosuccinimide in carbon tetrachloride solution at its boiling point, simultaneous dehydrogenation and bromination of the ethane derivatives occurred and the corresponding 1,1-bis-(*p*-alkoxyphenyl)-2-phenyl-2-bromoethylenes were obtained in excellent

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[1] Previous paper: K. Sisido, H. Nozaki and O. Kurihara, THIS JOURNAL, **72**, 2270 (1950).

[2] For the preparation of triarylethanols and triarylhaloethylenes therefrom which utilizes the Grignard reaction between benzylmagnesium halides and benzophenones see (a) C. F. Koelsch, THIS JOURNAL, **54**, 2487 (1932); (b) A. Schönberg, J. M. Robson, W. Tadros and H. A. Fanim, *J. Chem. Soc.*, 1327 (1940); (c) W. Tadros and A. Schönberg, *ibid.*, 394 (1943); (d) W. Tadros and A. Latif, *ibid.*, 3823 (1952); (e) R. S. Shelton, M. G. Van Campen, Jr., D. F. Meisner, S. M. Parmerter, E. R. Andrews, R. E. Allen and K. K. Wyckoff, THIS JOURNAL, **75**, 5491 (1953).

[3] For the preparation utilizing the Grignard reaction between phenylacetic esters and phenylmagnesium bromides see (a) ref. 2a; (b) P. R. Carter and D. H. Hey, *J. Chem. Soc.*, 150 (1948).

[4] For the preparation utilizing the Grignard reaction between desoxybenzoins and phenylmagnesium bromides see (a) F. R. Basford, British Patent 566,415 (Dec. 29, 1944); *C. A.*, **41**, 3929e (1947); (b) F. R. Basford, British Patent 567,807 (Mar. 5, 1945); *C. A.*, **41**, 2753g (1947); (c) Buu-Hoï, *Bull. soc. chim. France*, 117 (1946); *C. A.*, **41**, 5490a (1947); (d) Nguyen-Hoán and Buu-Hoï, *Compt. rend.*, **224**, 1228 (1947); *C. A.*, **41**, 6571b (1947); (e) ref. 3b.

[5] (a) D. Xuong, P. Cagniant and C. Mentzer, *Compt. rend.*, **226**, 1453 (1948); *C. A.*, **42**, 7279d (1948); (b) C. Mentzer and D. Xuong, French Patent 937,423 (Aug. 13, 1948); *C. A.*, **44**, 2030h (1950).

yields, *viz.*, 1,1-bis-(*p*-methoxyphenyl)-2-phenyl-2-bromoethylene in a 92% yield and 1,1-bis-(*p*-ethoxyphenyl)-2-phenyl-2-bromoethylene in a 91% yield. Dehydrogenation and bromination of 1,1,4-triphenylbutane to monobromo-1,1,4-triphenylbutadiene (with the bromine atom at an unknown position) was reported recently by Israelashvili and Bergmann.[6] The 1,1,2-triaryl-2-bromoethylenes described above constitute lower vinylogs of the butadiene derivative.

It should be added that the treatment of 1,1-bis-(*p*-alkoxyphenyl)-2-phenylethylene with one mole of N-bromosuccinimide proved to afford 1,1-bis-(*p*-alkoxyphenyl)-2-phenyl-2-bromoethylene in excellent yields. 1,1,2-Tris-(*p*-methoxyphenyl)-ethylene gave similarly 1,1,2-tris-(*p*-methoxyphenyl)-2-bromoethylene in a 93% yield. Accordingly the mechanism of the dehydrogenation and bromination of the ethane derivatives in a single operation may be represented as

$$C_6H_5CH_2CH(C_6H_4X)_2 + (CH_2CO)_2NBr \longrightarrow C_6H_5CH{=}C(C_6H_4X)_2 + (CH_2CO)_2NH + HBr \quad (1)$$

$$C_6H_5CH{=}C(C_6H_4X)_2 + (CH_2CO)_2NBr \longrightarrow C_6H_5CBr{=}C(C_6H_4X)_2 + (CH_2CO)_2NH \quad (2)$$

$$X = p\text{-}CH_3O;\ p\text{-}C_2H_5O$$

It seems of interest in this connection that the formation of free bromine was noticed at the initial stage of the reaction of the ethane derivatives with N-bromosuccinimide, whereas such was not the case in the reaction of the triarylethylenes. The free bromine, which is considered to be formed presumably from N-bromosuccinimide and hydrogen bromide[7] liberated during the dehydrogenation stage 1, can act as a brominating agent of triarylethylenes. Therefore following reactions 3 and 4 may take place, in part at least, in the treatment of the ethane derivatives with N-bromosuccinimide along with the direct bromination with the N-bromoamide (2).

$$HBr + (CH_2CO)_2NBr \rightleftharpoons Br_2 + (CH_2CO)_2NH \quad (3)$$

$$C_6H_5{-}CH{=}C(C_6H_4X)_2 + Br_2 \longrightarrow C_6H_5{-}CBr{=}C(C_6H_4X)_2 + HBr \quad (4)$$

$$X = p\text{-}CH_3O;\ p\text{-}C_2H_5O$$

An attempted adaptation of the present synthesis to the preparation of triarylchloroethylenes resulted in failure. Thus treatment of the triarylethanes with N-chlorosuccinimide[8] or with N,N-dichloro-*p*-toluenesulfonamide[9] in carbon tetrachloride or in chlorobenzene solution, afforded a noncrystalline tar, from which the desired triarylchloroethylenes could not be isolated.

Experimental[10]

1,1-Bis-(*p*-methoxyphenyl)-2-phenylethane.—To a mixture of 45 g. (0.40 mole) of anisole, 50 ml. of glacial acetic acid and 75 g. (41 ml.) of concentrated sulfuric acid, 18 g. (0.15 mole) of phenylacetaldehyde[11] was added dropwise with stirring. The addition required about 40 minutes, during which time the temperature of the mixture was maintained below 20°. The stirring was continued for an additional four hours at the same temperature and the mixture was allowed to stand overnight. The product was poured into crushed ice and the precipitated semi-solid material was extracted with benzene. The benzene solution was washed with water, dilute sodium hydroxide solution and water. After distilling off the solvent the residue was subjected to steam distillation in order to remove excess anisole. The residual semi-solid was taken up in benzene and dried over anhydrous sodium sulfate. Removal of the solvent, followed by several recrystallizations from ethanol, gave 24 g. (51%) of 1,1-bis-(*p*-methoxyphenyl)-2-phenylethane melting at 96–97°.[12]

Anal. Calcd. for $C_{22}H_{22}O_2$: C, 82.98; H, 6.96. Found: C, 83.01; H, 7.05.

1,1-Bis-(*p*-ethoxyphenyl)-2-phenylethane.—A mixture of 61 g. (0.50 mole) of phenetole, 100 ml. of glacial acetic acid and 100 g. (55 ml.) of concentrated sulfuric acid was treated with 24 g. (0.20 mole) of phenylacetaldehyde under exactly the same conditions as above and the product was worked up as usual. After several recrystallizations from ethanol, 40 g. (58%) of 1,1-bis-(*p*-ethoxyphenyl)-2-phenylethane, m.p. 83°, was obtained.

Anal. Calcd. for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56. Found: C, 83.21; H, 7.74.

1,1-Bis-(*p*-methoxyphenyl)-2-phenyl-2-bromoethylene.—To a solution of 6.3 g. (0.02 mole) of 1,1-bis-(*p*-methoxyphenyl)-2-phenylethane in 70 ml. of carbon tetrachloride, 7.1 g. (0.04 mole) of N-bromosuccinimide and 50 mg. of benzoyl peroxide were added all at once. The mixture was stirred and heated to reflux while under irradiation with a photographic reflector spot light lamp for five hours. The refluxing of bromine was observed during the initial stage of the reaction; thereafter the evolution of hydrogen bromide occurred. The reaction mixture was cooled to 0°, filtered to remove the precipitated succinimide and the solids were washed twice with 50 ml. of carbon tetrachloride cooled at 0°. The filtrate and washings were combined, washed with water, dilute sodium hydroxide solution and water, and dried over anhydrous sodium sulfate. After removing the solvent on a water-bath, the residue was recrystallized from ethanol. Thus was obtained 7.2 g. (92%) of 1,1-bis-(*p*-methoxyphenyl)-2-phenyl-2-bromoethylene melting at 110–111° which showed no depression when admixed with an authentic specimen.[13]

Another route to 1,1-bis-(*p*-methoxyphenyl)-2-phenyl-2-bromoethylene is as follows. To a solution of 3.0 g. (0.0095 mole) of 1,1-bis-(*p*-methoxyphenyl)-2-phenylethylene in 50 ml. of carbon tetrachloride, 1.7 g. (0.0095 mole) of N-bromosuccinimide and 50 mg. of benzoyl peroxide were added. The mixture was stirred under irradiation with a photo lamp to refluxing temperature for one hour. Neither the formation of bromine nor of hydrogen bromide could be observed. Work up of the product in the usual way, followed by two recrystallizations from ethanol, gave 3.4 g. (92%) of 1,1-bis-(*p*-methoxyphenyl)-2-phenyl-2-bromoethylene melting at 110–111°, which showed no depression when admixed with the product prepared from the ethane derivative.

1,1-Bis-(*p*-ethoxyphenyl)-2-phenyl-2-bromoethylene.—A mixture of 6.9 g. (0.02 mole) of 1,1-bis-(*p*-ethoxyphenyl)-2-phenylethane, 70 ml. of carbon tetrachloride, 7.1 g. (0.04 mole) of N-bromosuccinimide and 50 mg. of benzoyl peroxide was heated under irradiation in the manner described above to yield 7.7 g. (91%) of 1,1-bis-(*p*-ethoxyphenyl)-2-phenyl-2-bromoethylene, m.p. 97–98°. A mixed melting point with a known sample prepared according to the method of W. Tadros[2c] showed no depression.

When 3.1 g. (0.0090 mole) of 1,1-bis-(*p*-ethoxyphenyl)-2-phenylethylene was treated with 1.6 g. (0.0090 mole) of N-bromosuccinimide and 50 mg. of benzoyl peroxide in 50 ml. of carbon tetrachloride as above, 3.5 g. (92%) of 1,1-bis-(*p*-ethoxyphenyl)-2-phenyl-2-bromoethylene, whose m.p. and mixed m.p. with the specimen prepared from the ethane derivative are 97–98°, was obtained.

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[6] S. Israelashvili and F. Bergmann, *J. Chem. Soc.*, 1070 (1953). See also E. Buchta and H. Weidinger, *Ann.*, **580**, 83 (1953).

[7] R. A. Barnes, THIS JOURNAL, **70**, 145 (1948).

[8] J. Tscherniac, *Ber.*, **34**, 4209 (1901).

[9] S. Akiyoshi and K. Okuno, THIS JOURNAL, **76**, 693 (1954).

[10] All temperatures are uncorrected.

[11] A redistilled commercial product was used; b.p. 88–89° (14 mm.).

[12] M. A. Orèkhoff, *Bull. soc. chim. France*, [4] **25**, 174 (1919), reported a m.p. of 89–90°.

[13] The specimen was prepared by the method of C. F. Koelsch, who reported a m.p. of 109–111°; *cf.* ref. 2a.

1,1,2-Tris-(*p*-methoxyphenyl)-2-bromoethylene.—Treatment of 3.5 g. (0.01 mole) of tris-(*p*-methoxyphenyl)-ethylene[14] in 50 ml. of carbon tetrachloride with 1.8 g. (0.01 mole) of N-bromosuccinimide and 50 mg. of benzoyl peroxide in the manner described above gave 4.0 g. (93%) of 1,1,2-tris-(*p*-methoxyphenyl)-2-bromoethylene melting at 118–119°[15] after two recrystallizations from ethanol.

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[14] This compound, m.p. 97–98.5°, was prepared by a new method to be reported shortly.

[15] R. S. Shelton and M. G. Van Campen, Jr., U. S. Patent 2,430,-891 (Nov. 18, 1947); *C. A.*, **42**, 1968g (1948), reported a m.p. of 119–120.5°.

[16] After January, 1956, communications regarding this paper should be sent to Kyôto, Japan.

[CONTRIBUTION NO. 148 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Reduction of Gossypol with Lithium Aluminum Hydride[1]

BY DAVID A. SHIRLEY AND WILLIAM C. SHEEHAN

RECEIVED MARCH 11, 1955

The reduction of gossypol with lithium aluminum hydride followed by acetylation yields a product, designated as methylapogossypol hexaacetate (II), in which the aldehyde groups of gossypol have been reduced to methyl groups and all hydroxyl groups acetylated. Oxidation of methylapogossypol hexaacetate yields methylapogossypolone tetraacetate (IV). Reductive acetylation of this latter product leads to methylapohydrogossypolone octaacetate (V).

We have undertaken a study of new reactions and reaction products of gossypol (I), the principal pigment of cottonseed. Of initial interest was an examination of the reduction of gossypol with lithium aluminum hydride. Earlier work on reduction of gossypol and gossypol derivatives has been largely limited to catalytic hydrogenation.[2] The only report of the use of lithium aluminum hydride with gossypol or its derivatives is its use in determination of active hydrogen content.[2c] It was anticipated that a study of the reduction products would throw additional light on the problem of the structure of gossypol.[3]

A solution of gossypol in ether was treated with excess lithium aluminum hydride in ether. No substance could be isolated from the reaction mixture and the crude product was acetylated. Chromatographic separation on "Florisil" absorbent allowed isolation, in about 10% yield, of a white crystalline product, m.p. 277–280°. Analysis showed a molecular formula of $C_{42}H_{46}O_{12}$ containing six acetyl groups. Infrared and ultraviolet (see Table I and Fig. 1) absorption spectra showed the absence of the bands characteristic for the presence of aldehyde carbonyl groups in gossypol at 358 mμ and 6.19 μ.[4] The infrared spectrum of the new compound (Table I) resembled very closely that of gossypol hexaacetate[4b] (VI) in the range 2–9 μ. Gossypol hexaacetate (white form) is reported to melt at 276–279°.[5] That the new product is not gossypol hexaacetate is indicated by the following evidence: (1) a mixture melting point between the new product and gossypol hexaacetate shows a sharp depression; (2) the infrared spectra of the two materials are different in the fingerprint region above 9 μ; (3) solubilities of the two compounds in several solvents are significantly different; and (4) elementary analyses on the new material differ appreciably from the values for gossypol hexaacetate.

TABLE I

INFRARED ABSORPTION BANDS[a]

Compound	Bands, μ
Methylapogossypol hexaacetate[b]	3.39 (M),[c] 5.64 (VS), 6.14 (W), 6.23 (W), 6.95 (M), 7.27 (VS), 8.07 (W), 8.40 (VS), 8.73 (S), 8.95 (W), 9.60 (S), 9.85 (W), 10.6 (W), 11.0 (M), 11.25 (M)
Methylapogossypolone tetraacetate[d]	3.28 (W), 5.60 (S), 6.02 (S), 6.43 (W), 6.94 (W), 7.28 (M), 7.39 (W), 7.58 (S), 7.70 (M), 7.80 (W), 8.40 (VS), 8.88 (W), 9.18 (M), 9.50 (W), 9.82 (W), 10.38 (W), 10.80 (W), 11.13 (W), 11.38 (W)

[a] These spectra were determined by Mr. R. T. O'Connor and co-workers. For details on equipment and method used, see reference 4b. [b] Measured in chloroform solution at a concn. of 14.24 g. per l. in a 0.4 mm. cell. [c] The letters in parentheses represent the intensity of absorption in qualitative fashion (W = weak, M = medium, S = strong, VS = very strong). [d] Measured at 8.20 g. per l. of chloroform in a 0.4 mm. cell.

On the basis of analytical data, similarity of infrared spectrum below 9 μ to gossypol hexaacetate and the known properties of lithium aluminum hydride we propose that the new reduction product is 3,3′,8,8′-tetramethyl-5,5′-diisopropyl-1,1′,6,6′,7,7′-hexaacetoxy-2-2′-binaphthyl as indicated by structure II. Continuing the common nomenclature used by Adams and by Clark in their extensive work on gossypol we designate this material as methylapogossypol hexaacetate. Formation of II depends on the reduction of the aldehyde group of the gossypol structure proposed by Adams[6] (I) to a

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[1] A report of work carried out under contract with the U. S. Department of Agriculture and authorized by the Research and Marketing Act. The contract is being supervised by the Southern Regional Research Laboratory of the Agricultural Research Service.

[2] (a) R. Adams and W. R. Dial, THIS JOURNAL, **61**, 2077 (1939); (b) L. Schmid and S. Margulies, *Monatsh.*, **65**, 391 (1934); (c) V. L. Frampton, J. D. Edwards and H. R. Henze, paper presented before Combined Southeast and Southwest Regional Meeting of the American Chemical Society, New Orleans, December 12, 1953.

[3] C. H. Boatner in A. E. Bailey, editor, "Cottonseed and Cottonseed Products," Interscience Publishers, Inc., New York, N. Y., 1948.

[4] (a) W. A. Pons, M. D. Murray, R. T. O'Connor and J. D. Guthrie, *J. Am. Oil Chemists Soc.*, **25**, 308 (1948); (b) R. T. O'Connor, P. Von der Haar, E. F. DuPre, L. E. Brown and C. H. Pominski, THIS JOURNAL, **76**, 2368 (1954).

[5] R. F. Miller, D. J. Butterbaugh and R. Adams, *ibid.*, **59**, 1729 (1937).

[6] R. Adams, R. C. Morris, T. A. Geissman, D. J. Butterbaugh and E. C. Kirkpatrick, *ibid.*, **60**, 2193 (1938).