nated, at 16–17°, with a solution of 3.10 g. of bromine in 50 ml. of acetic acid containing 1.55 g. of sodium acetate. Excess water was then added, and crude VI was removed by filtration; wt. 8.0 g., m.p. 182–183° dec. Recrystallization from aqueous acetone gave m.p. 181–183°. This bromide was split in the usual fashion[16] using the semicarbazone; 3.86 g. of VI gave 2.20 g. (69%) of crude VII, m.p. 110–115°. The analytical sample crystallized from aqueous methanol as the monohydrate, m.p. 116–120°, $[\alpha]_D$ +141.2° (chl.), ϵ 15,100 at 240 mμ (methanol).

Anal. Calcd. for $C_{23}H_{32}O_5 \cdot H_2O$: C, 67.95; H, 8.43. Found: C, 67.65, 67.50; H, 8.66, 8.73.

Δ^4-Pregnen-11β,17α-diol-3,20-dione (prepared *via* bromination and dehydrobromination of pregnan-11β,17α-diol-3,20-dione[6]) had m.p. 223.0–224.5°, $[\alpha]_D$ +112.3° (chl.), ϵ 14,200 at 242 mμ (methanol).

Pregnan-3α,11β,17α,21-tetrol-11,21-Diacetate (IX).—A solution of 5.0 g. of IV in 50 ml. of C.P. chloroform was brominated at room temperature over a period of 20 min. with a solution of 2.20 g. of bromine in 22 ml. of C.P. chloroform. The chloroform was removed under reduced pressure, 10 g. of potassium acetate and 100 ml. of acetone were added and the mixture refluxed for 5 hr. Steam was then introduced to remove the acetone, and the organic residue was extracted with methylene chloride. Removal of the organic solvent left an oil which crystallized easily from ether to yield 4.0 g. of IX, m.p. 189–191°. The analytical sample, crystallized once more from ether, had a m.p. of 195.0–196.0°, $[\alpha]_D$ +88.4° (chl.).

Anal. Calcd. for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.45; H, 8.56.

Pregnan-11β,17α,21-triol-3,20-dione 11,21-Diacetate (X).—At ice-bath temperature, 51.0 g. of N-bromosuccinimide was added to a solution of 42.5 g. of IX in 760 ml. of acetone and 190 ml. of water. A temperature of about 3–5° was maintained for 2.5 hr., and the excess oxidizing agent was then destroyed by the addition of sodium sulfite solution. Water was then added to precipitate 39.8 g. (93.7%) of X, m.p. 199–201°. The analytical sample, crystallized from aqueous methanol, had a m.p. of 206.0–207.5°, $[\alpha]_D$ +92.8° (chl.).

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 67.00; H, 8.09. Found: C, 67.00; H, 8.09.

4-Bromopregnan-11β,17α,21-triol-3,20-dione 11,21-Diacetate (XI).—A solution of 50.0 g. of X in 340 ml. of acetic acid and 160 ml. of methylene chloride, and containing 10 ml. of 10% hydrogen bromide in acetic acid, was cooled to *ca.* 3–5° and then brominated at this temperature over a period of 20 min. with a solution of 18.0 g. of bromine and 9.0 g. of sodium acetate in 250 ml. of acetic acid. The methylene chloride was removed under reduced pressure, and water was then added to precipitate 57 g. (96.5%) of crude XI, m.p. 161–164° dec. The pure 4-bromide was obtained by first sludging the crude with ether, and then recrystallizing the residue from aqueous acetone: m.p. 185–187° dec., $[\alpha]_D$ +95.5° (chl.).

Anal. Calcd. for $C_{25}H_{35}O_7Br$: Br, 15.15. Found: Br, 15.05.

Δ^4-Pregnen-11β,17α,21-triol-3,20-dione 11,21-Diacetate (Compound F 11,21-Diacetate) (XII).—A solution of 14.75 g. of XI in 300 ml. of acetic acid was dehydrobrominated in the usual way[16] using 3.82 g. of semicarbazide hydrochloride. After splitting the semicarbazone with pyruvic acid, the crude XII was extracted into methylene chloride. Pure compound F 11,21-diacetate (7.50 g., 76.3%) was obtained by crystallization from aqueous methanol, m.p. 191.0–191.8°, $[\alpha]_D$ +167.1° (chl.), ϵ 17,200 at 240 mμ (95% ethanol).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.19; H, 7.47.

Δ^4-Pregnen-11β,17α,21-triol-3,20-dione 11-Acetate (Compound F 11-Acetate) (XIII).—A solution of 4.5 g. of XII in 40 ml. of C.P. chloroform, 140 ml. of C.P. methanol, 8.5 ml. of concd. hydrochloric acid and 14 ml. of water was allowed to react at 25° for 48 hr. Water was added, and the mixture was extracted with methylene chloride. Removal of the organic solvent under reduced pressure gave 4.2 g. of a white resin which crystallized on trituration with ether, m.p. 110–112° dec. Two further crystallizations gave 2.7 g. of compound F 11-acetate as the monohydrate, m.p. 113–118°, $[\alpha]_D$ +163.2° (chl.), ϵ 16,250 at 240 mμ (95% ethanol). The infrared spectrum confirmed the loss of one acetate group which had been adjacent to a ketone carbonyl.

Anal. Calcd. for $C_{23}H_{32}O_6 \cdot H_2O$: C, 65.38; H, 8.11. Found: C, 65.77, 65.32; H, 8.27, 8.27.

Compound F or its 21-acetate has λ_{max} at 242 mμ.[2a,8b]

BLOOMFIELD, N. J.

(16) W. F. McGuckin and E. C. Kendall, THIS JOURNAL, **74**, 5811 (1952); V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1951); B. Koechlin, T. Kritchevsky and T. F. Gallagher, *ibid.*, **184**, 393 (1950); E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Action of *t*-Butyl Hypochlorite on Organic Compounds. IV. Cholesterol[1]

BY DAVID GINSBURG[2]

RECEIVED JULY 13, 1953

t-Butyl hypochlorite adds to the double bond of cholesterol and oxidizes the secondary alcoholic function to a carbonyl group. The primary reaction product is 6β-chloro-Δ^4-cholesten-3-one. Dehydrochlorination of this compound gives Δ-4,6-cholestadien-3-one which is isolated as its 2,4-dinitrophenylhydrazone. The mechanism of the reaction is discussed.

In previous communications in this series[3] it has been indicated that in a molecule containing an olefinic double bond, *t*-butyl hypochlorite (TBH) introduces a chlorine atom by addition to the double bond rather than through substitutive chlorination in the allylic position, *i.e.*, through formulation A rather than B

$$\text{A, } RCH_2CH{=}CHR' \xrightarrow{TBH} RCH_2\overset{+}{C}HCHClR' \xrightarrow{-H^+} RCH{=}CHCHClR'$$

$$\text{B, } RCH_2CH{=}CHR' \xrightarrow{TBH} RCHClCH{=}CHR'$$

This point is of interest, as if it can be shown to hold in many cases, TBH could become as versatile a halogenating agent as N-bromosuccinimide. While the latter is an allylic halogenating agent in the majority of cases,[4] the former could perform halogenation concurrent with a *shift* of the double bond. In a system such as 1-phenylcyclohexene[5] it is not possible to distinguish between formulations A and B because of the inherent symmetry of the resulting chlorination product. Of several unsymmetrical systems which could be employed to investigate this problem, cholesterol

(1) A preliminary communication on this subject has appeared: D. Ginsburg, *Bull. Res. Council Israel*, **2**, 269 (1952).

(2) U. S. Public Health Service Fellow, Harvard University, 1952–1953. On leave of absence from the Weizmann Institute, Rehovoth, Israel.

(3) D. Ginsburg, THIS JOURNAL, **73**, 2723 (1951), and additional references given therein.

(4) C. Djerassi, *Chem. Revs.*, **43**, 271 (1948).

(5) D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 516 (1951).

seemed to be a particularly fruitful substance, because many of the potential intermediates and final products are known.

Since secondary alcohols may be oxidized to ketones by means of TBH[6-9] cholesterol was dissolved in *t*-butyl alcohol or in acetic acid and treated with two moles of TBH. The intermediate chloroketone began to lose hydrogen chloride even during concentration of the solution so that its isolation in good yield was not possible. Treatment of the crude intermediate with dimethylaniline yielded a product whose 2,4-dinitrophenylhydrazone was identical with that of authentic $\Delta^{4,6}$-cholestadien-3-one. Dehydrochlorination with 2,4-dinitrophenylhydrazine[10] yielded this derivative directly in about 75% yield. Addition to the double bond probably precedes oxidation of the alcoholic function in cholesterol as it has been our experience that allylic alcohols are oxidized at a much faster rate than the corresponding saturated alcohols.[11] This assumption is borne out by the observation that Δ^5-cholesten-3-one with TBH, followed by treatment with 2,4-dinitrophenylhydrazine yields the 2,4-dinitrophenylhydrazone of $\Delta^{4,6}$-cholestadien-3-one whereas Δ^4-cholesten-3-one is attacked with comparative difficulty and yields a different 2,4-dinitrophenylhydrazone, m.p. 257°, which was not investigated further. Had oxidation preceded chlorination, one would expect that the hydrogen chloride generated by the small amount of chlorine dissolved in TBH, would suffice to isomerize the Δ^5-cholesten-3-one formed to the more stable Δ^4-cholesten-3-one. The latter, however, is not a precursor of the 4,6-dien-3-one by this route.

If, on the other hand, chlorination through addition to the double bond occurs first, the intermediate 6-chloro-5-carbonium ion upon loss of a proton, creates the 4-en-3-ol allylic alcohol system which is then readily oxidized, at a very rapid rate, to the 6-chloro-4-en-3-one system.

The chlorination route was conclusively proved when 6β-chloro-Δ^4-cholesten-3-one was isolated from the chlorination mixture, albeit in low yield because of the difficulty in handling this substance. Crystallization from ethyl acetate–methanol below 20°[12] yielded a product m.p. 129–130°. Admixture with an authentic specimen of 6β-chloro-Δ^4-cholesten-3-one showed no m.p. depression and the infrared absorption spectra of both substances were identical.[13]

The stereochemistry of the addition of TBH to the cholesterol double bond parallels the addition of molecular chlorine which also proceeds through an ionic mechanism, *i.e.*, the 6β-configuration is obtained for the chlorine atom in both cases.[12]

(6) B. F. Clark, Ph.D. Thesis, M.I.T., 1931.

(7) Dr. A. Dreiding, personal communication.

(8) Dr. M. Cava, personal communication.

(9) D. Ginsburg, unpublished results.

(10) C. Djerassi, THIS JOURNAL, **71**, 1003 (1949).

(11) D. Ginsburg, unpublished work. For example, allyl alcohol itself is oxidized by means of TBH in *t*-butanol solution much more rapidly than 1-propanol.

(12) D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 370 (1950).

(13) We are grateful to Dr. D. H. R. Barton for authentic specimens of 6α- and 6β-chloro-Δ^4-cholesten-3-one.

Several reports in the literature[14] indicate that allylic chlorination of cholesteryl esters may be accomplished by means of TBH. Thus, 7-dehydrocholesteryl acetate was obtained when cholesteryl acetate was chlorinated with TBH in carbon tetrachloride in the presence of benzoyl peroxide. We have not been able to chlorinate cholesterol with TBH in carbon tetrachloride and even when peroxides were added the reaction was sluggish and incomplete. Undoubtedly, some of the 7-chloro derivative is obtained under the above free radical conditions, but the yield of 7-dehydrocholesterol reported[14] was of the order of 15%.

Although it is not inconceivable that allylic chlorination takes place also in the case of cholesterol in *t*-butyl alcohol or acetic acid and that an equilibrium mixture is obtained through an allylic shift, in which the components are 7-chloro-Δ^5-cholesten-3-ol and 5-chloro-Δ^6-cholesten-3-ol, yet, in view of our results, this possibility seems remote. One would not expect allylic chlorination to take place in *t*-butyl alcohol or in acetic acid, when it apparently occurs only to a minor extent in carbon tetrachloride containing peroxide. While it seems plausible that a free radical mechanism might be operative in the latter case, it seems clear from the evidence presented that in *t*-butyl alcohol and in acetic acid an ionic mechanism is operative through which addition of chloronium ion to the double bond takes place.

Experimental[15]

Chlorination of Cholesterol.—Cholesterol (1.93 g.) was dissolved in *t*-butyl alcohol (15 ml.) and *t*-butyl hypochlorite (1.5 ml.) was added in one portion at 60°. An exothermic reaction set in almost immediately. After standing for two hours the solution was concentrated *in vacuo*. A portion of the oily product was dissolved in methanol–ethyl acetate and after seeding with an authentic specimen of 6β-chloro-Δ^4-cholesten-3-one[12,13] and standing in the refrigerator for several days, crystals of this substance, m.p. 127–128°, deposited. Recrystallization from methanol–ethyl acetate below 20° raised the m.p. to 129–130°, $[M]_D$ +62°. The product did not depress the m.p. of authentic 6β-chloro-Δ^4-cholesten-3-one. The infrared spectra of both specimens were identical. Seeding of a similar portion of product with 6α-chloro-Δ^4-cholesten-3-one[12,13] did not cause crystallization.

Dehydrochlorination. (a) **With Dimethylaniline.**—Another portion of the oily product was treated with boiling dimethylaniline for 2 hours. After cooling, chloroform was added and the extract was washed with dilute hydrochloric acid to remove the base. The chloroform was evaporated and the residue was taken up in ethanol and treated with an alcoholic solution of 2,4-dinitrophenylhydrazine. The 2,4-dinitrophenylhydrazone of $\Delta^{4,6}$-cholestadien-3-one was obtained as crimson needles, m.p. 230–231° (from ethanol–ethyl acetate); 40% yield. This compound was identical with the product described below.

(b) **With 2,4-Dinitrophenylhydrazine.**—Another portion of the chlorination product was taken up in acetic acid and boiled with a solution of 2,4-dinitrophenylhydrazine in acetic acid for 1 hour. The brick red precipitate was recrystallized from ethanol–ethyl acetate to yield beautiful crimson needles, m.p. 230–232°; $\lambda\lambda_{max}$ 309; 404 mμ; $\epsilon\epsilon_{max}$ 18,300; 37,500 (chloroform); yield 75%. Djerassi and Ryan[16] report m.p. 227–229° for the 2,4-dinitrophenylhydrazone of $\Delta^{4,6}$-cholestadien-3-one with identical ultraviolet absorption.

(14) E. R. H. Jones, A. E. Bide and R. J. Nicholls, U. S. Patent 2,531,688; British patent 608,482. See also E. R. H. Jones, *et al.*, *J. Chem. Soc.*, 1783 (1948), and following.

(15) M.p.'s are uncorrected.

(16) C. Djerassi and E. Ryan, THIS JOURNAL, **71**, 1000 (1949); *cf.* Ref. 12.

Anal. Calcd. for $C_{33}H_{46}O_4N_4$: C, 70.43; H, 8.24; N, 9.96. Found: C, 70.61; H, 8.19; N, 10.01.

Chlorination of Δ^5-Cholesten-3-one.—Δ^5-Cholesten-3-one (1.92 g.) was dissolved in acetic acid (15 ml.) and treated with one portion of *t*-butyl hypochlorite (0.7 ml.). The mixture was allowed to stand overnight. To the yellow solution was added a solution of 2,4-dinitrophenylhydrazine in acetic acid and the mixture was boiled for 30 minutes. The 2,4-dinitrophenylhydrazone of $\Delta^{4,6}$-cholestadien-3-one, m.p. 231–232° (from ethanol–ethyl acetate) was obtained, identical with the product described above.

Chlorination of Δ^4-Cholesten-3-one.—Δ^4-Cholesten-3-one (0.9 g.) was dissolved in acetic acid (7 ml.) and treated with *t*-butyl hypochlorite (0.4 ml.). After the mixture had stood overnight, a solution of 2,4-dinitrophenylhydrazine in acetic acid was added and the mixture was boiled for 30 minutes. The precipitate was filtered, dissolved in chloroform and chromatographed over alumina. The 2,4-dinitrophenylhydrazone of Δ^4-cholesten-3-one, m.p. 232–233°, was obtained as the major product, identical with an authentic sample, showing that very little chlorination had taken place. A second 2,4-dinitrophenylhydrazone was obtained, m.p. 257° dec. (from ethanol–chloroform) and was not investigated further. No 2,4-dinitrophenylhydrazone of $\Delta^{4,6}$-cholestadien-3-one was obtained.

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RESEARCH LABORATORIES, THE WM. S. MERRELL COMPANY]

Synthetic Estrogens. Halotriphenylethylene Derivatives

BY R. S. SHELTON, M. G. VAN CAMPEN, JR., D. F. MEISNER, S. M. PARMERTER, E. R. ANDREWS, R. E. ALLEN AND K. K. WYCKOFF

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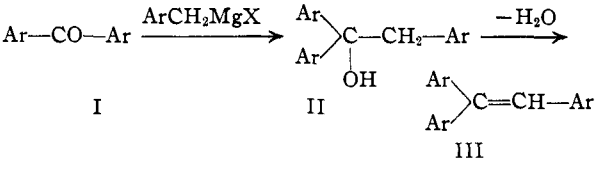
A series of halotriphenylethylene derivatives has been prepared and screened for estrogenic activity. Several of the products obtained showed a high order of estrogenic activity combined with a long duration of action.

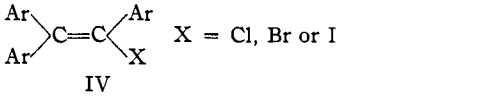
A number of non-steroidal compounds have been shown to have estrogenic activity.[1a,b] Hydroxy or alkoxy substitution is one means of obtaining highly potent, short-acting, synthetic estrogens.[2] Robson and Schönberg[3] reported that triphenylethylene and chlorotriphenylethylene were estrogens of low potency but of unusual duration of action. The authors, as well as Robson, Schönberg, Dodds and others,[4-13] have shown that increased potency is obtained in various alkoxy-substituted halotriphenylethylenes.

The work reported here deals principally with the synthesis and estrogenic activity of triphenylethylene derivatives having hydroxy or alkoxy substituents on all three benzene nuclei.

Most of the compounds were prepared by the reaction of appropriate benzylmagnesium halides with suitable diaryl ketones I followed by dehydration of the resulting carbinols II to triarylethylenes III



The triarylethylenes were then halogenated to obtain halotriarylethylenes IV.



In a few cases, the halogen was replaced by hydroxy, carboxy or alkyl substituents.

Tris-(*p*-alkoxyphenyl)- and tris-(*p*-aralkoxyphenyl)-ethylenes were converted to hydroxy derivatives by three types of dealkylation reactions: (1) demethylation with potassium hydroxide at elevated temperatures, (2) debenzylation by hydrogenolysis and (3) debenzylation with methylmagnesium iodide. In some cases, the hydroxy derivatives were then esterified.

The first debenzylation reactions were carried out with hydrogen and 10% palladium on charcoal. Recent work has shown, however, that this reaction can be effected more smoothly and consistently if a catalytic amount of hydrochloric acid is added to the reaction mixture as a promoter. For example, catalytic debenzylation of 1,1-bis-(*p*-benzyloxyphenyl)-2-(*p*-methoxyphenyl)-ethanol (compound 4), with concurrent or subsequent dehydration, gave 1,1-bis-(*p*-hydroxyphenyl)-2-(*p*-methoxyphenyl)-ethylene (compound 12) in a higher yield than did the Grignard cleavage of 1,1-bis-(*p*-benzyloxyphenyl)-2-(*p*-methoxyphenyl)-ethylene (compound 24). The controlled hydrogenolysis of bromo-2,2-bis-(*p*-benzyloxyphenyl)-1-(*p*-methoxyphenyl)-ethylene (compound 26) gave bromo-2,2-bis-(*p*-hydroxyphenyl)-1-(*p*-

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(2) E. C. Dodds and W. Lawson, *ibid.*, **137**, 996 (1936).

(3) J. M. Robson and A. Schönberg, *ibid.*, **140**, 196 (1937).

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(6) J. M. Robson and A. Schönberg, *Nature*, **150**, 22 (1942).

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