amide, m.p. 88.6–90° was recovered. Its n.m.r. spectrum was identical to the starting *cis* isomer.

trans-**N,N-Diethyl-2,6-dichlorophenylcinnamide (IIb).**—A solution containing 16.5 g. (0.076 mole) of 2,6-dichlorocinnamic acid[22] (m.p. 193.7–194.2°) and 18.0 g. (0.152 mole) of thionyl chloride in 100 ml. of benzene was heated to reflux for 1 hr. The solvent was evaporated to dryness to give a colorless solid, m.p. 68–69°. The yield was 17.2 g. (96.3% yield). One recrystallization from hexane crystals, m.p. 69.2–70.1°.

Anal. Calcd. for $C_9H_5Cl_3O$: Cl, 42.25. Found: Cl, 42.68.

To a stirred solution of 16.0 g. (0.068 mole) of 2,6-dichlorocinnamoyl chloride in 120 ml. of ether was added 12.5 g. (0.17 mole) of diethylamine over a period of 10 min. Stirring at room temperature was continued for 1 hr. The diethylamine hydrochloride salt (7.8 g., theory) was removed and the filtrate was evaporated *in vacuo* to dryness to yield 17.8 g. of light brown viscous oil. The distilled product, b.p. 170–171° (0.5 mm.), $n^{25}D$ 1.5791, was obtained in 15.2 g. (82.2% yield). The compound was identified as *trans* from n.m.r. spectrum (Table II).

Anal. Calcd. for $C_{13}H_{15}Cl_2NO$: Cl, 26.05; N, 5.15. Found: Cl, 26.02; N, 4.64.

Attempted Epoxidation of *trans*-IIa with Monoperphthalic Acid.—The procedure of Wheeler[23] was followed. A solution of 610 ml. of an ether solution containing 0.44 mole of monoperphthalic acid[24] and 14.0 g. (0.07 mole) of *trans*-N,N-diethylcinnamamide (IIa) was allowed to stand at 5° for 35 days. Water was added to destroy the peracid and the filtered solution was evaporated to dryness *in vacuo*. The residue was extracted with chloroform and chloroform extract was washed with aqueous sodium bicarbonate solution. After being dried over anhydrous magnesium sulfate, solvent was removed to give 12.1 g. (86.5% recovery) of starting *trans*-cinnamamide (IIa), m.p. 70–71°.

Attempted Bromoacetoxylation of *trans*-IIa with N-Bromosuccinimide–Acetic Acid.—The procedure of Jovtscheff[13] was followed. A solution of 10.0 g. (0.05 mole) of *trans*-N,N-diethylcinnamide (IIa) an 18.0 g. (0.10 mole) of N-bromosuccinimide in 500 ml. of glacial acetic acid was stirred at room temperature in a dark flask for a period of 1.5 hr. The reaction mixture was poured into 500 ml. of water containing 30 g. of potassium iodide and the liberated iodine was destroyed by aqueous sodium thiosulfate. The mixture after being extracted with ether, dried over anhydrous magnesium sulfate, evaporated to dryness *in vacuo* gave a dark brown tarry material. Attempts to purify this material by crystallization and chromatography were unsuccessful.

(22) F. Böck, G. Lock and K. Schmidt, *Monatsh.*, **64**, 399 (1934).

(23) K. W. Wheeler, M. G. Van Campen, Jr., and R. S. Shelton, *J. Org. Chem.*, **25**, 1021 (1960).

(24) H. Böhme, *Org. Syn.*, **20**, 70 (1940).

Reaction of Amides and Esters of α,β-Dibromopropionic Acids with Triphenylphosphine

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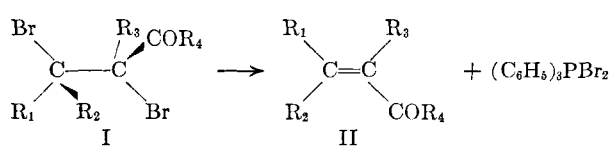
The debromination of the dibromides derived from ethyl methacrylate, methyl acrylate, and N,N-diethyl 3,3-dimethylacrylamide with triphenylphosphine is reported. However, 2,3-dibromopropionamide with triphenylphosphine underwent displacement of the α-bromine atom and dehydrohalogenation to produce the ylid (VI).

In connection with our work on the debromination of *erythro*-N,N-diethylcinnamamide dibromide with bases,[1] the reaction of amides and esters of α,β-dibromopropionic acid with triphenylphosphine was undertaken. Abramov and Ilyina[2] in their investigation of the mechanism of the Arbuzov rearrangement of methyl α,β-dibromopropionate with tributylphosphite, reported a small quantity of by-product whose constants agreed with those of methyl acrylate. Very recently, Dershowitz and Proskauer[3] reported the debromination of dibromides of cinnamic acid, chalcone and *trans*-dibenzoylethylene with one mole equivalent of trialkylphosphite. They also stated that diphosphonates were formed when two mole equivalents of trialkylphosphite were employed.

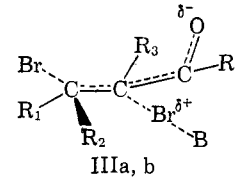
We have found that ethyl methacrylate dibromide (Ia) and methyl acrylate dibromide (Ib) with one mole equivalent of triphenylphosphine gave theoretical yields of triphenylphosphine dibromide and 49.5% yield of ethyl methacrylate (IIa) and 64.0% yield of methyl acrylate (IIb), respectively, were obtained.



I II

a. $R_1 = R_2 = H$; $R_3 = CH_3$; $R_4 = OC_2H_5$
b. $R_1 = R_2 = R_3 = H$; $R_4 = OCH_3$
c. $R_1 = R_2 = CH_3$; $R_3 = H$; $R_4 = N(C_2H_5)_2$

When two mole equivalents of triphenylphosphine were employed, the debromination of Ia,b to IIa,b proceeded with the recovery of one mole equivalent of the unchanged triphenylphosphine. The elimination of bromine can be reasonably explained[1] *via* a favored *trans*-coplanar transition state IIIa,b in which the incipient negative charge on the α-carbon atom can be stabilized by resonance with the carbonyl group.



IIIa, b

Dehydrobromination of Ib or SN2 displacement of the α or β-bromine atoms of Ia,b by triphenylphosphine was not observed. The elimination of hydrogen bromide from Ib would involve the unfavored conformer Ib'.[4]

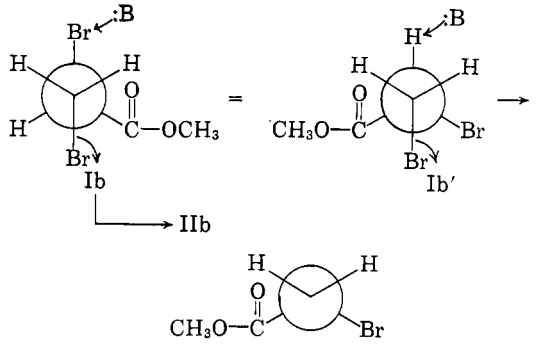
The reaction of N,N-diethyl 3,3-dimethylacrylamide dibromide (Ic) with triphenylphosphine was also found to give the debrominated product IIc. However, reaction of acrylamide dibromide IV with two moles of triphenylphosphine gave a product $C_{21}H_{19}BrNOP$ in 85% yield and triphenylphosphonium bromide in 90% yield. The product was water soluble and its aqueous

(1) A. J. Speziale and C. C. Tung, *J. Org. Chem.*, **28**, 1323 (1963).

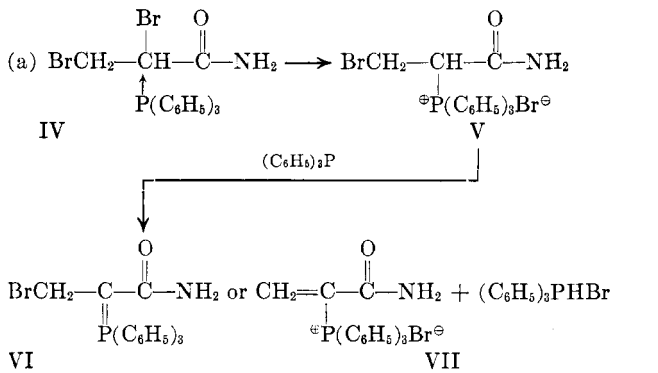
(2) V. S. Abramov and N. A. Ilyina, *J. Gen. Chem., USSR* (Eng. Trans.), **26**, 2245 (1956).

(3) S. Dershowitz and S. Proskauer, *J. Org. Chem.*, **26**, 3595 (1961).

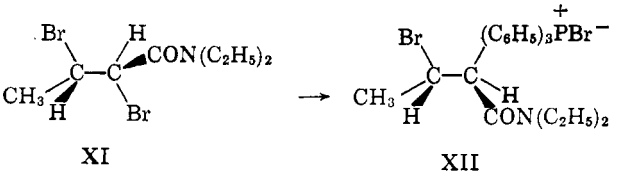
(4) The difference of 33 kcal./g.-bond between C–Br and C–H would favor C–Br bond breaking.



solution gave an equivalent of ionic bromide. Two paths can be formulated for the reaction of IV with triphenylphosphine. These involve an SN2 displacement of one of the bromine atoms together with the elimination of hydrogen bromide. Path a would involve the displacement of the α-bromine atom by triphenylphosphine with subsequent removal of hydrogen bromide by the second mole of phosphine to produce either VI or VII. Path b would involve the less likely displacement of the β-bromine atom with the formation of a mixture of the *cis–trans* isomers IX or the bromo ylid X. There were no bands attributable to a carbon–carbon double bond in the infrared spectrum of the product. Further, n.m.r. spectrum[5] of the product indicated no olefinic protons but showed a clean doublet for $-CH_2-$ protons resulting from spin–spin coupling with phosphorus. Therefore, the $C_{21}H_{19}BrNOP$ compound has the ylid structure VI.



The reaction of *erythro*-N,N-diethyl 3-methylacrylamide dibromide (XI) with two mole equivalents of triphenylphosphine gave the phosphonium bromide XII as the only identified product. The failure of XII to eliminate hydrogen bromide as did V may indicate



that the α-hydrogen atom in XII is less acidic than that of V.

Experimental

Reaction of Ethyl Methacrylate Dibromide (Ia) with Triphenylphosphine.—To a solution of 15.80 g. (0.060 mole) of triphenylphosphine in 85 ml. of ether was added 16.44 g. (0.06 mole) of ethyl methacrylate dibromide. Solid material precipitated immediately and the reaction mixture was heated to reflux temperature for 3 hr. The product, distilled at 40–41°, 68 ml., was found both from infrared analysis and vapor phase chromatography to contain 5% of ethyl methacrylate (3.4 g., 50% yield). The residue 25.2 g. (theory) was identified as triphenylphosphine dibromide by infrared analysis and by its conversion to triphenylphosphine oxide.

When the reaction was carried out in benzene solution at room temperature for 3 hr., same results were obtained.

Reaction of Methyl Acrylate Dibromide (Ib) with Triphenylphosphine.—The reaction was carried out under conditions described for Ia. From 14.75 g. (0.060 mole) of methyl acrylate dibromide and 15.80 g. (0.060 mole) of triphenylphosphine was obtained 3.3 g. (64.0% yield) of methyl acrylate and 25.1 g. (98% yield) of triphenylphosphine dibromide.

Reaction of N,N-Diethyl 3,3-Dimethylacrylamide Dibromide (Ic) with Triphenylphosphine.—To a stirred solution of 26.2 g. (0.10 mole) of triphenylphosphine in 130 ml. of benzene was added 15.75 g. (0.05 mole) of N,N-diethyl 1,2-dibromo-2-methyl butyramide in 20 ml. of benzene. Solid was precipitated immediately and the temperature of reaction rose from 24° to 30°. The reaction was heated at reflux temperature for 3 hr. After cooling to room temperature, the triphenylphosphine dibromide was collected by filtration and dried immediately *in vacuo*. The weight of dried triphenylphosphine dibromide was 20.5 g. (97%) and was converted to triphenylphosphine oxide in quantitative yield. The benzene filtrate was evaporated to dryness and the residue distilled *in vacuo* to give 6.51 g. (84%) of N,N-diethyl 2,2-dimethylacrylamide and 13.07 g. (0.05 mole) of unchanged triphenylphosphine.

When the reaction was carried out at room temperature, the same results were obtained.

Reaction of Acrylamide Dibromide (IV) with Triphenylphosphine.—To a stirred solution of 11.6 g. (0.05 mole) of acrylamide dibromide in 70 ml. of dioxane at 24° was added dropwise a solution of 26.2 g. (0.10 mole) of triphenylphosphine in 80 ml. of dioxane over a period of 1 hr. The temperature of the reaction mixture was maintained at 20–25° by external cooling and stirring continued for an additional 3 hr. The colorless solid was collected by filtration and dried *in vacuo*. One crystallization from chloroform–hexane mixture gave 17.6 g. (85% yield) of colorless solid VI, m.p. 241–242°. The compound was soluble in water and gave a positive test for ionic bromide.

Anal. Calcd. for $C_{21}H_{19}BrNOP$: C, 61.30; H, 4.65; N, 3.40; P, 7.54; Br, 19.45; mol. wt., 412. Found: C, 60.68; H, 4.70; N, 3.31; P, 7.58; Br, 19.48; mol. wt., 424.

The dioxane filtrate was evaporated to dryness to give 18.4 g. of a viscous light yellow liquid which upon treatment with water gave 12.70 g., 90% yield (0.046 mole) of triphenylphosphine oxide. The formation of the triphenylphosphine oxide resulted from the reaction of triphenylphosphine hydrobromide with glycolaldehyde which was an impurity in the dioxane used. When the dioxane used in this experiment was evaporated to dryness, a viscous colorless syrup was obtained which had infrared absorption at 3550 cm.$^{-1}$ (—OH) and 1725 cm.$^{-1}$ (—C=O). Treatment of this syrup with alcoholic 2,4-dinitrophenylhydrazine gave the deep yellow glyoxal bis(2,4-dinitrophenylhydrazone), m.p. 285–87°.[6]

(5) Spectra were measured at 60 Mc./sec. on a modified Varian Mode A-60 spectrometer in dimethyl sulfoxide solution with tetramethylsilane as an internal reference. Chemical shifts observed are: for acrylamide (IV) amide protons (wide band) at τ 2.6 and olefinic protons (multiplet) at τ 3.7–4.5 in an intensity ratio of 2:3; for VI ring protons (doublet) at τ 1.8, amide protons (wide band) at τ 2.6 and β-methylene protons at τ 6.0 (doublet with a coupling constant of 8.0 c.p.s.) in an intensity ratio of 15:2:2.

(6) T. Banks, C. Vaughan, and L. M. Marshall, *Anal. Chem.*, **27**, 1348 (1955). Reported m.p. for glyoxal bis(2,4-dinitrophenylhydrazone) is 290–300°.

Reaction of Triphenylphosphine Hydrobromide with Crude Dioxane.—A suspension of 10.0 g. (0.0292 mole) of triphenylphosphine hydrobromide in 250 ml. of crude dioxane was stirred at room temperature for 2 hr. The unchanged triphenylphosphine hydrobromide (6.1 g.) was removed by filtration and the filtrate was evaporated to dryness to give 5.9 g. of viscous liquid. The viscous liquid, upon stirring with water, gave 3.01 g. (96% yield based on the used triphenylphosphine hydrobromide) of triphenylphosphine oxide, m.p. 155–56°.

Reaction of N,N-Diethyl 3-Methylacrylamide Dibromide (XI) with Triphenylphosphine.—A solution containing 30.1 g. (0.10 mole) of XI and 52.4 g. (0.20 mole) of triphenylphosphine in 470 ml. of anhydrous acetone was stirred at room temperature for 12 hr. The solid material, 6.1 g., was collected by filtration. The filtrate was evaporated under reduced pressure to about 250 ml. and additional 11.5 g. of solid was collected. The combined solid after recrystallization from chloroform–ether gave an unidentified colorless solid, m.p. 149–150°, with the following analysis: C, 66.30; H, 5.19; P, 9.65; Br, 11.95. This solid, upon treatment with water, gave triphenylphosphine oxide. The acetone filtrate was evaporated to dryness and the residue recrystallized from acetone–ether. There was obtained 27.6 g. of a colorless solid, m.p. 97–98°. The elemental analysis indicated the compound to be the monohydrate of XII. The yield was 47%.

Anal. Calcd. for $C_{26}H_{32}Br_2NO_2P \cdot H_2O$: C, 53.70; H, 5.50; N, 2.41; Br, 27.50; P, 5.34; mol. wt., 581. Found: C, 53.58; H, 5.45; N, 2.42; Br, 27.05; P, 5.29; mol. wt., 606.

The Preparation of 14β,21-Epoxy Steroids

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The 14β,21-epoxy steroidal moiety has been synthesized by a basic displacement cyclization reaction of a C-20-methoxyimino derivative of a 14β-hydroxy-21-methanesulfonyloxy-20-ketopregnane. Mineral acid hydrolysis removed the C-20 protective grouping to provide the desired 14β,21-epoxy-20-ketopregnane. 14β,21-Epoxy-14β-pregn-4-ene-3,20-dione has been prepared by a multi-stage synthesis from digitoxigenin acetate.

This laboratory[1] has been concerned for some time in the preparation of epoxy steroids, more particularly in the ether formed by attachment of the C-21 hydroxymethyl grouping to the various positions on the steroid D ring. In this connection we became interested in the suggestion of Tschesche and Buschauer[2] that a 14β,21-epoxy moiety constituted a part of the structure of diginigenin.[3] This paper describes a synthetic pathway to the 14β,21-epoxy-20-ketone grouping.

An appropriate starting material for this investigation was selected from the cardiac aglycones which contain a 14β-hydroxyl group. Accordingly, digitoxigenin acetate was ozonized by the procedure of Oliveto and coworkers[4] to give the desired 3β-acetoxy-14β,21-dihydroxy-14β-pregnan-20-one (I). The latter was evidently less contaminated with 17-iso compound than the preparation described by Meyer and Reichstein.[6]

Since cyclizing reactions that might be utilized to prepare a 14β,21-epoxide from I would involve basic conditions, it was considered desirable to protect the base sensitive ketol grouping in I by preparing a C-20 carbonyl derivative which would withstand these conditions. The first consideration was given to the ethylene ketal grouping because of its well known base stability properties. Since it is also evident that the 14β-hydroxyl group is quite acid sensitive, various methods of ketalization were attempted. While it was possible to produce a 20-ketal by any of several methods, it was not possible to maintain the 14β-hydroxyl function. In every case dehydration occurred to give 3β-acetoxy-20-ethylenedioxypregn-14-en-21-ol (II). That the unsaturation was at position 14:15 and not the alternatively possible 8:14 position was determined by ultraviolet absorption measurements in the 190–225-mμ region and also by a proton magnetic resonance spectrum of II. As pointed out by Bladon, Henbest, and Wood[7a] and later expanded by Ellington and Meakins[7b] it is possible in the ultraviolet spectrum to distinguish by the shape of the curves[8] between a doubly exocyclic tetrasubstituted ethylenic linkage as in a $\Delta^{8(14)}$-compound and an exocyclic trisubstituted double bond as in a Δ^{14}-compound. The n.m.r. spectrum of II clearly showed the vinyl proton at C-15, thereby eliminating any consideration of a $\Delta^{8(14)}$-compound. The ketal II was hydrolyzed in acid to afford 3β-acetoxy-21-hydroxypregn-14-en-20-one (III), which also revealed a vinyl proton in the n.m.r. spectrum.

The 20-carbonyl group of I was protected successfully by reaction with methoxyamine hydrochloride in the presence of potassium acetate without concomitant destruction of the 14β-hydroxyl function. The resultant methoxyimino[9] derivative IVa was an uncrystallizable glass which, however, could be smoothly converted into the crystalline 3β-acetoxy-21-methanesulfonyloxy-20-methoxyimino-14β-pregnan-14β-ol (IVb). The desired displacement cyclization and simultaneous deacetylation was then readily achieved by treatment of the mesylate IVb with potassium hydroxide in methanol. The methoxyimino group of the cyclic product Va was

(1) W. S. Allen, S. Bernstein, M. Heller, and R. Littell, *J. Am. Chem. Soc.*, **77**, 4784 (1955); W. S. Allen and S. Bernstein, *ibid.*, **78**, 3223 (1956).

(2) R. Tschesche and G. Buschauer, *Ann.*, **603**, 59 (1957).

(3) C. W. Schoppee, R. Lack, and A. V. Robertson, *J. Chem. Soc.*, 3610 (1962), have disclosed that the structure of diginigenin is 12α,20α-epoxy-3β-hydroxy-14β,17α-pregn-5-ene-11,15-dione.

(4) E. P. Oliveto, L. Weber, C. G. Finckenor, M. M. Pechet, and E. B. Herschberg, *J. Am. Chem. Soc.*, **81**, 2831 (1959), have described an ozonolysis procedure which eliminates the bicarbonate[5] treatment of the intermediate 21-glyoxylic ester.

(5) C. P. Balant and M. Ehrenstein, *J. Org. Chem.*, **17**, 1576 (1952), have shown that bicarbonate hydrolysis invites considerable isomerization at C-17 in this type of compound.

(6) K. Meyer and T. Reichstein, *Helv. Chim. Acta*, **30**, 1508 (1947).

(7) (a) P. Bladon, H. B. Henbest, and G. W. Wood, *J. Chem. Soc.*, 2739 (1952); (b) P. S. Ellington and G. D. Meakins, *ibid.*, 697 (1960).

(8) Subsequent papers considering techniques to determine the exact maximum of an isolated double bond in the ultraviolet absorption spectrum have led to considerable discussion. *Cf.*, D. W. Turner, *ibid.*, 30 (1959); K. Stich, G. Rotzler, and T. Reichstein, *Helv. Chim. Acta*, **42**, 1480 (1959); Ref. 7b; J. H. Chapman and A. C. Parker, *J. Chem. Soc.*, 2075 (1961); T. H. Applewhite and R. A. Micheli, *J. Org. Chem.*, **27**, 345 (1962); R. Bührer and T. Reichstein, *Helv. Chim. Acta*, **45**, 389 (1962).

(9) The bismethoxyimino derivatives of certain corticoids have been described[10a] and a patent application[10b] describing the use of this protective grouping has been printed.