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SOME REACTIONS OF TRIPHENYLPHOSPHINE DIBROMIDE WITH STEROIDS AND TRITERPENOIDS

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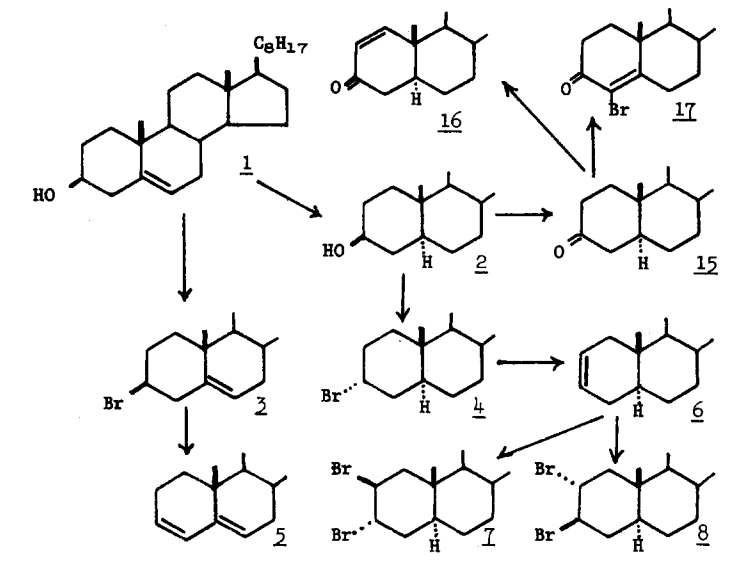
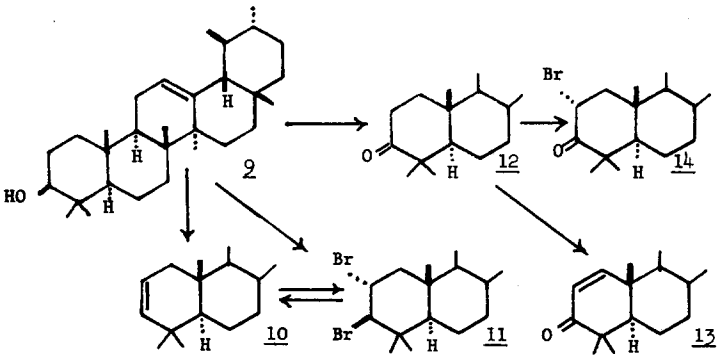
The formation of alkyl halides from alcohols and gem-dihalides from carbonyl compounds, by the action of triaryl- and trialkylphosphine dihalides has been described.[1] The considerable advantage of these reagents over phosphorus pentahalides in the C-OH → C-X reaction has been emphasized by Wiley and coworkers,[2] who have also discussed the gross features of the mechanism.[3]

The ready availability[4] of triphenylphosphine dibromide (Ph_3PBr_2) has prompted an examination of its reaction with some simple representative steroids and triterpenoids, to examine particularly its utility in the sequence -C-OH → C-Br → C-H in the presence of double bonds, carbonyl and less reactive hydroxyl groups, and its action on alcohols known to undergo molecular rearrangement on dehydration with phosphorus pentahalides.

The products from the action of Ph_3PBr_2 (10:1 molar ratio, 20 hr., 90°) on cholesterol (1) and cholestanol (2) have been identified respectively as 3β-bromocholest-5-ene (3, m.p. 96-98°, $[\alpha]_D$ -25°) and 3α-bromocholestane (4, m.p. 101-103°, $[\alpha]_D$ + 26°) in yields


C_8H_{17}
HO
1
16
17
Br
2
15
3
4
6
5
7
8

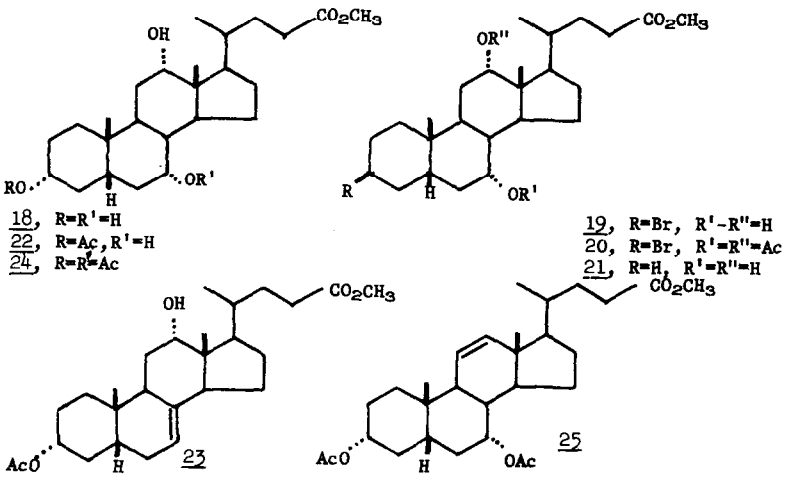

HO
9
12
14
10
11
13
Br

surpassing 80%; the stereochemical consequence of these displacements is unexceptional,[5] being that effected by both phosphorus pentahalides and phosphite halides.[6] When the products of these reactions were isolated by chromatography on acid alumina (Woelm), there were obtained instead, in high purity, the respective hydrocarbons, cholesta-3,5-diene (5, m.p. 77-79°, $[\alpha]_D$ -117°, 86% yield) and cholest-2-ene (6, m.p.73-75°, $[\alpha]_D$+ 64°, 90% yield).[7] The latter was characterized by its addition of bromine, yielding the 2β,3α-(dieq.)dibromo-(7, m.p. 123-125°, $[\alpha]_D$ + 78°) and 2α, 3β-(diax.)dibromo-(8, m.p. 142-144°, $[\alpha]_D$-26°) derivatives in a 4:1 ratio, when separated by chromatography on Spence alumina (Type H); isolation by chromatography on Woelm acid alumina gave only the diaxial dihalide (8), isolated in over 90% yield.

In contrast, the 4,4-dimethyl-3β-ol system, which is characteristic of many naturally-occurring triterpenoids and trimethyl steroids, and which undergoes molecular rearrangement (retropinacolic dehydration with ring contraction[8]) on treatment with phosphorus pentahalides, behaves differently with Ph_3PBr_2. From treatment of α-amyrin (9) with Ph_3PBr_2 under the same conditions, we have isolated the hydrocarbon ursa-2,12-diene (10, m.p. 120-121°, $[\alpha]_D$ + 130°, 58% yield) and a dibromide, $C_{30}H_{48}Br_2$ to which we assign the structure 2α, 3β-dibromours-12-ene (11, m.p.295-297°, $[\alpha]_D$ + 37°, stable to acid Al_2O_3, 12% yield). No monobromoursane product was observed. The dibromide (11) is also obtained from the presumed intermediate hydrocarbon (10) in 18% yield by the action of Ph_3PBr_2, or by the addition of bromine (1 mole); zinc debromination of 11 gave 10. We have also shown that the ketone, α-amyrenone (12), reacts under the same conditions with Ph_3PBr_2 to yield the αβ-unsaturated ketone, ursa-1,12-dien-3-one (13, m.p.

177-178°, $[\alpha]_D$ + 36°, λ 232 mμ (ε 10,200), 6.01 μ, 45% yield) and the bromoketone, 2α-bromours-12-en-3-one (14, m.p. 184-187°, $[\alpha]_D$ + 26°, λ 5.80 μ, 30% yield). Treatment of 12 with bromine in acetic acid at room temperature also gave 14. That Ph_3PBr_2 has some generality as a reagent for conversion of cyclohexanones to conjugated cyclohexenones is further demonstrated by its reaction with cholestanone (15). Under the usual conditions, in addition to 25% unchanged ketone and 12% unidentified product (lacking carbonyl group in infrared spectrum), there were obtained two unsaturated ketones, identified as cholest-1-en-3-one (16, m.p. 97-98°, $[\alpha]_D$ + 50°, λ 232 mμ (ε 10,500), 25% yield)[9] and 4-bromocholest-4-en-3-one (17, m.p. 112-114°, $[\alpha]_D$ + 104°, λ 261 mμ (ε 10,500), 20% yield).[10]

To assay the selectivity of Ph_3PBr_2 in attack on the three hydroxyl groups of cholic acid, methyl cholate (18) was treated with the reagent (1:1 molar ratio, 2 hr., 90°) and gave an amorphous bromodihydroxy methyl ester (19) characterized as the diacetate derivative, methyl 3-bromo-7α, 12α-dihydroxycholanate (20, m.p. 176-177°, $[\alpha]_D$ + 45°, 85% yield). The structure of 19 was established by debromination with Raney nickel in ethanol solution to the known methyl 7α, 12α-dihydroxycholanate (21, m.p. 148-150°, $[\alpha]_D$ + 22°, 95% yield, further characterized as the free acid, m.p. 206-208°, $[\alpha]_D$ + 28°).[11] Under these conditions, the methyl ester 3-acetate (22) was recovered unchanged, but with the conditions generally used (10:1 molar ratio, 20 hr., 90°), the 7α-hydroxyl group was eliminated to give the known methyl 3α-acetoxy-12α-hydroxychol-7-enate (23, m.p. 172-173°, $[\alpha]_D$ + 104°, 68% yield)[12] further characterized as the methyl ester diol and free acid diol. Treatment of the methyl ester 3,7-diacetate (24) under



still more forcing conditions (25:1 molar ratio; 50 hr., 90°) successfully eliminated the 12α-hydroxyl group to give methyl 3α, 7α-diacetoxychol-11-enate (25, m.p. 138-139°, $[\alpha]_D$ + 4°, 50% yield)[13] characterized as the derived dihydroxy acid (m.p. 203-205°, $[\alpha]_D$ + 5°). The reactivity order towards this reagent is consequently 3α > 7α > 12α, i.e. the same as for acylation.

These preliminary experiments indicate that Ph_3PBr_2 is potentially useful for selective bromination or elimination of polyhydric alcohols, and that it has synthetic utility in converting cyclohexanones to their α-bromo and αβ-unsaturated derivatives. The prior indication[2] of its superiority over other reagents in the substitution or elimination of alcohols without molecular rearrangement is supported by the dimethylcyclohexanol elimination reaction (9→10) here reported.

Satisfactory analyses have been obtained for the new compounds 11,

13, 14 and 20. Specific rotations were measured in chloroform and ultraviolet spectra in ethanol solution.

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REFERENCES

1. L. Horner, H. Oediger and H. Hoffman, Ann., 626, 26 (1959).
2. G. A. Wiley, R. L. Hershkowitz, B. M. Rein and B. C. Chung, J. Amer. Chem. Soc., 86, 964 (1964).
3. G. A. Wiley, B. M. Rein and R. L. Hershkowitz, Tetrahedron Letters, 2509 (1964).
4. Available from Eastman Organic Chemicals, or prepared as described in ref. 2.
5. Reviewed by L. F. Fieser and M. Fieser, "Steroids", p. 322, Reinhold, New York, 1959.
6. a) S. R. Landauer and H. N. Rydon, J. Chem. Soc., 2224 (1953).
   b) D. G. Coe, S. R. Landauer and H. N. Rydon, J. Chem. Soc., 2281 (1954).
7. D. H. R. Barton and W. J. Rosenfelder, J. Chem. Soc., 1048 (1951).
8. Reviewed by J. F. King and P. de Mayo, "Molecular Rearrangements" Vol. 2, 822-827, Interscience, New York, 1964.
9. C. Djerassi and C. R. Scholz, J. Amer. Chem. Soc., 69, 2404 (1947).
10. J. I. Shaw and R. Stevenson, J. Chem. Soc., 3549 (1955).
11. S. Kuwada and S. Morimoto, Bull. Chem. Soc. Japan, 17, 147 (1942).
12. E. Berner, A. Lardon and T. Reichstein, Helv. Chim. Acta, 30 1542 (1947).
13. F. Nakada and K. Yamsaki, Steroids, 1, 13 (1963).