In some cases the procedure described above proved unsuccessful or else resulted in very low yields of the desired ether. The preparation of these ethers by modified procedures is described below.

***n*-Propyl Octyl Ether.**—Only negligible yields of *n*-propyl octyl ether were formed by the addition of 1-bromopropane to sodium octoxide. A 30% yield of this ether was obtained by the addition of 1-bromoöctane to sodium propoxide.

Isopropyl Octyl Ether.—The same difficulty was encountered with isopropyl octyl ether as with its normal isomer. A 12% yield of this material was obtained by the addition of 1-bromoöctane to sodium isopropoxide.

Allyl Octyl Ether.—This ether was formed by the addition of allyl chloride to sodium octoxide. However, when distilling from sodium a reaction seemed to occur and a very low yield of the ether was obtained.[3] Acetyl chloride was then used instead of the sodium to remove any water and alcohol which might be present. A yield of 66% of allyl octyl ether was prepared by fractionation of this product.

Isobutyl Octyl Ether.—An 80% yield of this ether was obtained by the addition of 1-bromoöctane to the sodium derivative of 2-methyl-1-propanol; the reaction of sodium octoxide with 1-bromo-2-methylpropane did not prove to be very satisfactory.

***s*-Butyl Octyl Ether.**—A 56% yield of this ether was formed by the addition of 1-bromoöctane to the sodium derivative of 2-butanol. The addition of 2-bromobutane to sodium octoxide resulted in low yields of the desired ether.

(3) Letsinger and Traynham, THIS JOURNAL, **70**, 3342 (1948), report the reaction of diallyl ether with sodium to give allylsodium.

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Configuration of Steroid Bromoketones; a Correction

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RECEIVED JUNE 3, 1953

In contradiction of a report by Fieser and Dominguez,[1] Corey[2] has presented evidence that 2-bromocholestanone is the 2α-bromo epimer since on reduction it yields a bromohydrin that on hydrogenation gives cholestanol and on treatment with base gives 2β,3β-oxidocholestane. We have now found that by chromatography of the sodium borohydride reduction mixture it is possible to isolate two bromohydrins, one corresponding to that of Corey and giving the same reaction products, and the other identified as 2α-bromocholestane-3α-ol by hydrogenation to epicholestanol and by dehydrohalogenation to cholestanone. Corey's conclusion is thus fully substantiated. The material that Dominguez had in hand appears from the constants to have been a mixture of the two bromohydrins.

We also repeated the experiments[1] on the bromo derivative of testane-17β-ol-3-one acetate and again were able to isolate both C_3-epimeric bromohydrins. One gives the transformations described for the sole product previously isolated, which appears to have been reasonably homogeneous; the other gives reactions indicating that it is the 3β,4β-bromohydrin, hence the assignment of configuration is correct. Revised M_D differences between the methyl cholanate and 17β-acetoxytestane derivatives are as follows: 3-ketones, +46; 4β-bromo-3-ketones, +88; 3α-hydroxy-4β-bromides, +69; 3α-acetoxy-4β-bromides, +41; 3α,4α-oxides, +15; 3β-hydroxy-4β-bromides, +7; 3β-acetoxy-4β-bromides, +48.

(1) L. F. Fieser and J. A. Dominguez, THIS JOURNAL, **75**, 1704 (1953).

(2) E. J. Corey, *ibid.*, **75**, 4832 (1953).

Experimental

2α-Bromocholestane-3α-ol.—A mixture of 6.71 g. of 2α-bromocholestane-3-one and 0.6 g. of sodium borohydride in 250 cc. of absolute ethanol was let stand for 12 hr. at 25°, diluted with water and extracted with ether. The total product in 40 cc. of 1:1 petroleum ether–benzene was adsorbed on 150 g. of alumina, which was then eluted with 100-cc. portions of solvent mixture of composition adjusted each time to higher eluant potency; a plot of the weights of material eluted showed two well separated peaks indicative of a two-component system. The earlier petroleum ether–benzene (2:3 to 1:4) eluates gave a total of 2.12 g. of the 2α-epimer, m.p. 116–118°, after crystallization from ether–methanol. Rechromatographed and recrystallized, the substance formed big long blades, m.p. 117–118°, α_D +33° Chf (*c* 2.31), λ^{Chf} 2.78 μ.

Anal. Calcd. for $C_{27}H_{47}OBr$ (467.57): C, 69.35; H, 10.13; Br, 17.13. Found: C, 69.21; H, 9.98; Br, 17.25.

The acetate crystallized from chloroform–methanol in soft needles, m.p. 195–195.5°, α_D +57° Chf (*c* 2.35).

Anal. Calcd. for $C_{29}H_{49}O_2Br$ (509.60): C, 68.35; H, 9.69. Found: C, 68.43; H, 9.85.

A mixture of 205 mg. of 2α-bromocholestane-3α-ol, 0.5 g. of potassium hydroxide, 25 cc. of methanol and 10 cc. of ether was warmed to effect solution, let stand at 25° for 48 hr., diluted and extracted with ether. Crystallization from ether–methanol gave 91 mg. of crude product, m.p. 118–120°, λ^{Chf} 5.84 μ. Chromatography and recrystallization gave cholestanone, m.p. 129–130°, α_D +42° Chf (*c* 2.12), undepressed on admixture with an authentic sample.

Hydrogenation of 222 mg. of 2α-bromocholestane-3α-ol in 30 cc. of 95% ethanol in the presence of 80 mg. of 10% palladium–charcoal and 0.6 g. of potassium hydroxide was complete in about 10 min. On concentration of a washed and dried ethereal extract of the reaction mixture **epicholestanol** crystallized (123 mg., m.p. 183–184°). Recrystallized from chloroform–methanol, the alcohol melted at 185–186°, α_D +23° Chf (*c* 2.41). **The acetate** crystallized from ether–methanol as small prisms, m.p. and mixed m.p. 97°, α_D +27° Chf (*c* 1.83).

2α-Bromocholestane-3β-ol was obtained from later fractions of the above chromatogram (benzene–ether, 49:1; 19:1; 9:1); crystallization from ether–methanol gave a total of 3.33 g. of prisms, m.p. in the range 95–110°. This was rechromatographed and then recrystallized from ether–methanol to the constant m.p. 113–114°, α_D +12° Chf (*c* 3.16), λ^{Chf} 2.79 μ.

Anal. Calcd. for $C_{27}H_{47}OBr \cdot {}^1/_2CH_3OH$ (483.59): C, 68.30; H, 10.21; Br, 16.53. Found: C, 68.15; H, 10.00; Br, 16.57.

Terminal elution of the column with ether gave about 0.5 g. of Beilstein-negative material, m.p. 125–145°, λ^{Chf} 2.78, 2.9 μ (crystallized from ether–methanol). This consisted mainly of cholestanol, as shown by digitonin precipitation and from the infrared spectrum.

The bromohydrin acetate separated from ether–methanol in needles, m.p. 106–107°, α_D −82° Chf (*c* 2.41).

Anal. Calcd. for $C_{29}H_{49}O_2Br$ (509.60): C, 68.35; H, 9.69; Br, 15.68. Found: C, 68.46; H, 9.77; Br, 15.85.

Treatment of 202 mg. of the 2α,3β-bromohydrin with base as described for the epimer gave material that showed no selective infrared absorption in either the hydroxyl or the carbonyl region. One crystallization from ether–methanol gave 103 mg. of needles of **2β,3β-oxidocholestane**, m.p. 87–89°; recrystallized: 89–91°, α_D +53° Chf (*c* 1.70).

Hydrogenation of 275 mg. of the bromohydrin as above gave 189 mg. of **cholestanol**, m.p. 140–142°, α_D +23° Chf (*c* 1.99), identified by mixed m.p. determination and comparison of infrared spectra.

4β-Bromotestane-17β-ol-3-one Acetate.—Bromination of 5.1 g. of testane-17β-ol-3-one acetate (m.p. 144–145°) in acetic acid in the presence of a trace of hydrobromic acid gave a first crop of 3.0 g., m.p. 180–181° dec., which separated directly from the reaction mixture. Dilution of the mother liquor, extraction with ether, and crystallization from ether gave a second crop of 2.0 g., m.p. 177–178°. Recrystallization from chloroform–ether gave material of m.p. 183–184°, α_D +41° Chf (*c* 2.47).

Evidence that the bromine atom is at C_4 was provided by conversion of the bromoketone to the 2,4-dinitrophenylhydrazone of testosterone acetate, which formed reddish orange microcrystals from chloroform–methanol, m.p. 216–217°, λ^{EtOH} 385 mμ (29,800), negative Beilstein test; identity established by mixed m.p. and ultraviolet comparisons with an authentic sample[3] prepared from testosterone acetate.

4β-Bromotestane-3β,17β-diol 17-Acetate.—A mixture of 8.37 g. of 4β-bromotestane-17β-ol-3-one acetate, 1.2 g. of sodium borohydride and 100 cc. of absolute ethanol was let stand at 25° for 6 hr., diluted with water, extracted with ether, and the product adsorbed onto 200 g. of alumina from 20 cc. of 1:1 petroleum ether–benzene. Chromatography was conducted as in the above series and each fraction was crystallized from petroleum ether. Early eluates (petroleum ether–benzene: 200 cc. of 1:1, 300 cc. of 1:3, followed by 300 cc. of benzene) gave 2.13 g. of the 3β,4β-bromohydrin, m.p. 145–154°. On recrystallization to constant m.p. from aqueous methanol the substance was obtained as prisms (1.85 g.), m.p. 155–156°, α_D +72° Chf (*c* 2.41), λ^{Chf} 2.79, 5.79, 7.9, 10.34 μ.

Anal. Calcd. for $C_{21}H_{33}O_3Br \cdot H_2O$ (431.41): C, 59.82; H, 8.18. Found: C, 59.87; H, 7.92.

The acetate, crystallized from aqueous methanol, formed prisms, m.p. 164–165°, α_D +68° Chf (*c* 2.03).

Anal. Calcd. for $C_{23}H_{35}O_4Br$ (455.43): C, 60.65; H, 7.74. Found: C, 60.71; H, 7.94.

A mixture of 407 mg. of 4β-bromotestane-3β,17β-diol 17-acetate, 0.9 g. of potassium hydroxide and 15 cc. of methanol was heated under a stream of nitrogen to effect solution and let stand at 25° for 48 hr. The reaction product crystallized poorly from aqueous acetone to give impure testane-17β-ol-3-one, m.p. 138–139°, α_D +30° EtOH (*c* 1.17), no depression in mixed m.p. with authentic material, m.p. 142–143°. However, acetylation and crystallization from ether gave 178 mg. of prismatic plates of **testane-17β-ol-3-one acetate**, m.p. and mixed m.p. 145–146°.

Hydrogenation of 486 mg. of 4β-bromotestane-3β,17β-diol 17-acetate (245 mg. palladium–charcoal, 1 g. potassium hydroxide, 50 cc. 95% ethanol; complete in a few minutes) and crystallization of the product from ether–petroleum ether afforded in the first crop 127 mg. of **testane-3β,17β-diol**, m.p. 175–178°, λ^{Chf} 2.78, 2.9 μ, Beilstein test negative; recrystallized from ether–petroleum ether, m.p. 162–164°, α_D +15° EtOH (*c* 1.38). This material is solvated; on oxidation it gave **testane-3,17-dione**, m.p. and mixed m.p. 131–132°, α_D +103° Chf (*c* 2.21), λ^{Chf} 5.78, 5.86μ.

4β-Bromotestane-3α,17β-diol 17-acetate was isolated from late fractions of the above chromatogram; 200-cc. portions of 19:1, 9:1 and 4:1 benzene–ether eluates afforded, on crystallization from petroleum ether, a total of 2.85 g. of bromohydrin melting in the range 138–144°. Recrystallization from aqueous methanol gave prismatic needles, m.p. 143–144°, α_D +47° Chf (*c* 1.91), λ^{Chf} 2.79, 5.79, 7.95 μ.

The acetate formed prismatic needles from aqueous methanol, m.p. 164–165°, α_D +34° Chf (*c* 2.18); mixed m.p. with the 3β-epimer, 135–145°.

Intermediate chromatogram fractions (0.62 g.) seemed to consist of mixtures of the two bromohydrins, m.p. 130–132°, 137–139°, 138–145°. Ether–methanol (9:1) eluted **testane-3α,17β-diol 17-acetate**, which crystallized from ether as thin needles (20 mg.), m.p. 173–175°, λ^{Chf} 2.9, 5.79, 8.0 μ, negative Beilstein test. Acid hydrolysis gave testane-3α,17β-diol, m.p. (from methanol) and mixed m.p. 230–231°.

Treatment of 408 mg. of 4β-bromotestane-3α,17β-diol 17-acetate with methanolic potassium hydroxide as described above gave 155 mg. of crude **3α,4α-oxidotestane-17β-ol**, m.p. about 155°. Recrystallization from aqueous methanol gave small prisms, m.p. 157–159°, α_D +13° Chf (*c* 2.38) λ^{Chf} 2.77, 2.9 μ, Beilstein test negative.

Hydrogenation of 495 mg. of 4β-bromotestane-3α,17β-diol 17-acetate gave 166 mg. of crude **testane-3α,17β-diol**, m.p. 220–225°; twice recrystallized from methanol: m.p. 230–231°, α_D +26° EtOH (*c* 1.66).[4]

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(3) B. A. Koechlin, T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **184**, 393 (1950).

(4) L. Ruzicka, M. W. Goldberg and W. Boshard, *Helv. Chim. Acta*, **20**, 541 (1937), report m.p. 236–236.5°, α_D +24.8° EtOH.

Compounds for Cancer Studies[1]

BY CARL TABB BAHNER, LEE ROY BARCLAY, GEORGE BIGGERSTAFF, DOROTHY ELLIS BILANCIO, GAY WALDEN BLANC, MARGUERITE CLOSE, MARY MARGUERITE ISENBERG AND EDWIN PACE

RECEIVED MAY 8, 1953

The quaternary salts listed in Table I have been synthesized by the methods cited, for screening as potential antitumor agents.

TABLE I

QUATERNARY SALTS

Salt	Empirical formula	M.p., °C.	Ionic halogen, % Calcd.	Found
Methyl *p*-toluenesulfonate salt of Quinoxaline[a]	$C_{16}H_{16}N_2O_3S$	150	[b]	
Allyl bromide salt of Quinoxaline[a]	$C_{11}H_{11}BrN_2$	111	31.85	31.86
n-Propyl iodide salt of Quinoxaline[a]	$C_{11}H_{13}IN_2$	145	42.29	42.43
Methyl iodide salt of 2-(*p*-Acetylamino-styryl)-pyridine[c]	$C_{16}H_{17}IN_2O$	298	33.38	33.26
Decyl iodide salt of 4-(*p*-Dimethylamino-styryl)-pyridine[c]	$C_{25}H_{37}IN_2$	209	25.77	25.85
2,5-Diiodohexane salt of 3-Acetylpyridine[d]	$C_{20}H_{28}I_2N_2O_2$	222–225	43.76	43.78
3-Cyanopyridine[d]	$C_{18}H_{20}I_2N_4$	243	46.38	46.30
Iodoacetonitrile salt of γ-Picoline	$C_8H_9IN_2O$	169	48.80	48.51
p-Fluorophenacyl bromide salt of Lepidine[e]	$C_{18}H_{15}BrFNO$	218	22.19	22.04
4-Methyl-5-(β-hydroxyethyl)-thiazole[f]	$C_{14}H_{15}BrFNO_2S$	209	22.19	22.28
β-Naphthacyl bromide salt of 4-Methyl-5-(β-hydroxyethyl)-thiazole[f]	$C_{18}H_{18}BrNO_2S$	213	20.39	20.20
2,5-Dichlorophenacyl bromide salt of Hexamethylene-tetramine[g]	$C_{14}H_{17}BrCl_2N_4O$	174	19.58	19.52

[a] C. T. Bahner and Wm. K. Easley, THIS JOURNAL, **72**, 3803 (1950). [b] Calcd.: C, 60.74; H, 5.09. Found: C, 60.86; H, 5.25. We are indebted to the National Cancer Institute for carbon and hydrogen analyses. [c] C. T. Bahner, E. S. Pace and Robert Prevost, *ibid.*, **73**, 3407 (1951). [d] C. T. Bahner, Wm. K. Easley, M. D. Pickens, H. D. Lyons, L. L. Norton, B. G. Walden and G. E. Biggerstaff, *ibid.*, **73**, 3499 (1951). [e] C. T. Bahner, Wm. K. Easley, B. G. Walden, H. D. Lyons and G. E. Biggerstaff, *ibid.*, **74**, 3960 (1952). [f] C. T. Bahner, Donald Pickens and D. B. Bales, *ibid.*, **70**, 1652 (1948). [g] C. T. Bahner, M. D. Pickens, Donald Pickens and Wm. K. Easley, *ibid.*, **72**, 3266 (1950.)

The fact that quaternary salts of hexamethylenetetramine are unstable in aqueous solution has raised the question whether the biological effects of such solutions[2] are due to products derived from the salts within the blood stream. Since it is known that under certain conditions quaternary hexamethylenetetraminium salts form amines[3] or aldehydes,[4] a number of amines and aryl glyoxals which might be formed from the corresponding salts have been synthesized in order to determine whether they would have the same activity against sarcoma cells as the quaternary salts. Active compounds were found among all three types.

Among the aryl glyoxals prepared by selenium

(1) This research was supported in part by a research grant from the National Institutes of Health, U. S. Public Health Service, and in part by a grant from the Damon Runyon Memorial Fund for Cancer Research.

(2) C. T. Bahner, M. D. Pickens, D. Pickens and W. K. Easley, THIS JOURNAL, **72**, 2266 (1950).

(3) T. Immediata and A. R. Day, *J. Org. Chem.*, **5**, 512 (1940).

(4) Sommelet, *Compt. rend.*, **157**, 852 (1913).