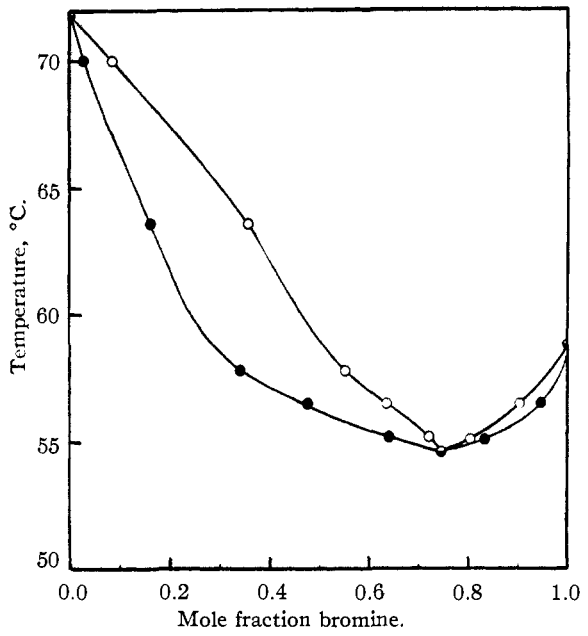

Fig. 3.—Temperature–composition diagram for the system Br_2–$CHCl_2CF_2Cl$ at 760 mm. pressure: O, vapor; ●, liquid; ◒, vapor and liquid.

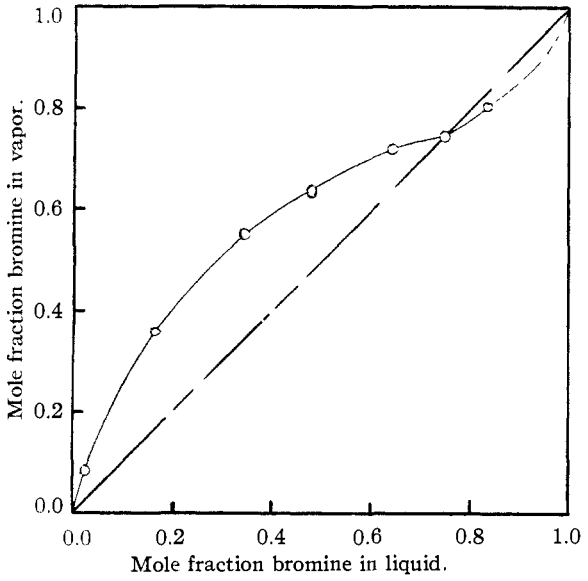

Fig. 4.—Vapor–liquid equilibrium diagram for the system Br_2–$CHCl_2CF_2Cl$ at 760 mm. pressure.

purified further by fractionation in a five-foot glass helix-packed column, taking a middle cut. The boiling point range of the $CHCl_2CHF_2$ was 58.4–59.5° at 735.2 mm. and that of the $CHCl_2CF_2Cl$ was 71.1–71.2° at 736.3 mm.

Vapor–liquid equilibrium data were obtained at 760 mm. as has been described previously.[1,2]

For each system exhibiting azeotrope formation, the azeotrope itself was prepared by fractionation at 760 mm. pressure of a liquid mixture of very nearly the azeotropic composition in a small glass helix-packed column (packed section 40 cm. in length and 2 cm. in diameter). After the column had reached equilibrium, the azeotropic temperature was read directly and the composition of the azeotrope determined by analyzing small samples of the condensed vapor.

To test the systems for evidence of reaction, although the likelihood of such was considered small, approximately 10% (by weight) bromine solutions were fractionated, the bromine being distilled off in the azeotrope. After removal of the bromine the refractive index of the residue in the still pot was determined and compared with that of the pure solvent at the same temperature. The index of the $CHCl_2CHF_2$ changed from 1.3769 to 1.3773 and that of the $CHCl_2CF_2Cl$ from 1.3900 to 1.3899. This slight change was felt to be due, not to reaction but to some slight fractionation of the solvents.

The azeotropic boiling points and compositions for these systems as obtained from the column mentioned above were found to be as follows: Br_2–$CHCl_2CHF_2$, 49.6°, 58.1 mole per cent. bromine and Br_2–$CHCl_2CF_2Cl$, 54.6°, 74.7 mole per cent. bromine.

The equilibrium data are plotted in the usual manners in the figures shown.

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Molecular Rotation Differences for 17-Hydroxy-20-ketosteroids

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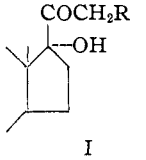
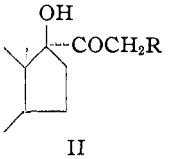
The method of molecular rotation differences[1] has been employed with outstanding success by Barton, Klyne and others in the elucidation of stereochemical and related structural problems encountered in investigations of a wide variety of steroids. An important application has been the correlation of configuration of hydroxyl substituents with the change in molecular rotation accompanying acetylation of these groups.[2] Recent development of procedures for acetylation of the hitherto refractory 17α-hydroxy-20-ketosteroids (I)[3] makes possible extension of the method to this important group of substances. Results of correlations in



I



II

this series are summarized in Table I, which includes also available data for three epimeric 17β-hydroxy-20-keto derivatives (II).

It is at once apparent that conversion of compounds possessing an α-oriented hydroxyl group at C-17 into the corresponding tertiary acetates involves a large negative shift in molecular rotation. The effect is enhanced in those products (Nos. 7–11) that possess an additional acetoxyl group at C-21 and is particularly pronounced in S acetate (No. 10) and in cortisone acetate (No. 11), which contain an α,β-unsaturated ketonic grouping as well. A negative increment of intermediate magnitude is observed for the 17α-hydroxy ester (No. 6),

(1) A discussion of the method as developed by Barton, together with literature citations, is given in "Natural Products Related to Phenanthrene," 3rd ed., L. F. Fieser and M. Fieser, Reinhold Publ. Corp., New York, N. Y., 1949, p. 206. See also D. H. R. Barton, *Angew. Chem.*, **61**, 57 (1949), and D. H. R. Barton and W. Klyne, *Chemistry and Industry*, 755 (1948).

(2) D. H. R. Barton, *J. Chem. Soc.*, 813 (1945); W. Klyne and D. H. R. Barton, THIS JOURNAL, **71**, 1500 (1949).

(3) Huang-Minlon, E. Wilson, N. L. Wendler and M. Tishler, *ibid.*, **74**, 5394 (1952); R. B. Turner, *ibid.*, **74**, 4220 (1952); *ibid.*, **75**, 3484 (1953).

TABLE I[a]

MOLECULAR ROTATION DIFFERENCES (Δ^{Ac}) FOR 17-HYDROXY-20-KETOSTEROIDS

No.	Compound	M_D 17-Alcohol	17-Acetate	Δ^A
1	3β,17α-Dihydroxy-5-pregnen-20-one[b,c]	−114 Di	−254 Di	−140
2	3β,17α-Dihydroxy-5-pregnen-20-one 3-monoacetate[c,d]	− 94 Di	−271 Di	−177
3	17α-Hydroxy-4-pregnene-3,20-dione[c,d]	+354 Di	+208 Di	−146
4	3β,17α-Dihydroxyallopregnan-20-one 3-monoacetate[c,d]	+ 71 Di	− 39 Di	−110
5	3α,17α-Dihydroxypregnane-11,20-dione 3-monoacetate[e,f]	+327 An	+202 Chf	(−125)
6	Methyl 3α-acetoxy-17α-hydroxy-11-ketoetiocholane-17-carboxylate[f,g]	+289 Chf	+ 98 Chf	−191
7	3α,17α,21-Trihydroxypregnane-11,20-dione 3,21-diacetate[e,f]	+416 An	+201 Chf	(−215)
8	17α,21-Dihydroxypregnane-3,11,20-trione 21-monoacetate[e,f]	+333 An	+123 Chf	(−210)
9	17α,21-Dihydroxyallopregnane-3,11,20-trione 21-monoacetate[e,f]	+406 Chf	+197 Chf	−209
10	17α,21-Dihydroxy-4-pregnene-3,20-dione 21-monoacetate[c,d]	+512 Di	+213 Di	−299
11	17α,21-Dihydroxy-4-pregnene-3,11,20-trione 21-monoacetate[c,d]	+852 Di	+591 Di	−261
12	3β,17β-Dihydroxyallopregnan-20-one 3-monoacetate[d,h]	−120 Di	+ 6 Di	+126
13	3β,17β-Dihydroxy-5-pregnen-20-one[i,j]	−199 Chf	−198 Di	(+ 1)
14	3β,17β-Dihydroxy-5-pregnen-20-one 3-monoacetate[i,k]	−229 Chf	−225 Di	(+ 4)

[a] An = acetone, Chf = chloroform, Di = dioxane. Figures in the last column that are enclosed in parentheses indicate determinations made in different solvents. [b] P. L. Julian, E. W. Meyer and I. Ryden, THIS JOURNAL, **72**, 367 (1950). [c] R. B. Turner, *ibid.*, **75**, 3489 (1953). [d] R. B. Turner, this investigation. [e] L. H. Sarett, THIS JOURNAL, **70**, 1454 (1948). [f] Huang-Minlon, E. Wilson, N. L. Wendler and M. Tishler, *ibid.*, **74**, 5394 (1952). [g] E. Wilson and M. Tishler, *ibid.*, **74**, 1609 (1952). [h] C. W. Shoppee and D. A. Prins, *Helv. Chim. Acta*, **26**, 185 (1943). [i] C. W. Shoppee and D. A. Prins, *ibid.*, **26**, 201 (1943). [j] L. Ruzicka, M. W. Goldberg and F. Hunziker, *ibid.*, **22**, 707 (1939). [k] L. Ruzicka and H. F. Meldahl, *ibid.*, **21**, 1760 (1938).

which differs from other members of the series in the nature of the carbonyl function. The shift in molecular rotation occasioned by acetylation of 17β-hydroxy-20-keto derivatives (Nos. 12, 13 and 14), on the other hand, is either small or in a *positive* direction. The Δ values recorded for compounds 13 and 14, both of which possess 5,6-unsaturation, are zero, within the limits of the method. Although this result may be significant, it should be noted that the optical measurements in these cases were obtained in different solvents and hence are less reliable than those for which the same solvent was employed.

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Preparation of Crystalline Anhydrous β-Gentiobiose

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RECEIVED MARCH 17, 1953

Crystalline anhydrous β-gentiobiose has heretofore been difficult to obtain because of crystallization difficulties. Consequently, the more easily crystallized but unstable bis-(methyl alcoholate), an α-D form, is usually prepared. We wish to report herein an improved procedure for the preparation of crystalline anhydrous β-gentiobiose based upon the finding that this crystalline phase forms quite readily at elevated temperatures. A similar temperature effect has been noted in the crystallization of the trisaccharide panose, 4-α-(isomaltopyranosyl)-D-glucose.[2]

Both of the above-mentioned crystalline forms of gentiobiose were first obtained by Bourquelot and Hérissey,[3] who reported for the crystalline anhydrous form, the constants: m.p. 190–195°, $[\alpha]_D$ −6° (6 min.) → +9.8° (final). Hudson[4,5] calculated that the initial specific rotation of β-gentiobiose should be −11°. Extrapolation of Bourquelot and Hérissey's data to zero time gives a value near −11°. For our preparation we find the constants: m.p. 188–190° (cor.), $[\alpha]^{25}_D$ −3.0° (initial, extrapolated) → +10.5° (final, *c* 4, water). This divergence of 8° between the calculated and determined rotations for β-gentiobiose appears to be real. It is interesting to compare it with the determined value of +166° (calculated[4] +175°) found by Fletcher and Diehl[6] for the related (1 → 6)-linked disaccharide α-melibiose. That the crystalline form of gentiobiose herein described is a molecular compound containing a small amount of the α-anomer is possible but no evidence of this could be obtained.

It is convenient to isolate and purify gentiobiose, regardless of its source, in the form of its β-octaacetate because of the fine crystallizing properties of this substance. One of the better sources of this sugar is hydrol (the mother liquor or "molasses" from the commercial production of α-D-glucopyranose monohydrate) from which it can be isolated as the acetate by the method of Berlin.[7] We consider the presently described directions as the procedure of choice for preparing gentiobiose should the α-D form not be required.

Experimental

β-Gentiobiose.—β-Gentiobiose octaacetate[7] (15 g.) was suspended in 180 ml. of 0.05 *N* sodium methoxide in dry methanol and allowed to stand, with occasional shaking, at room temperature for 1 hr. It was then diluted with water to dissolve the suspended material and passed through columns of Amberlite IR-120[8] and Duolite A-4.[9] The re-

(1) Corn Industries Research Foundation Associate.

(2) S. C. Pan, L. W. Nicholson and P. Kolachov, THIS JOURNAL, **73**, 2549 (1951).

(3) E. Bourquelot and H. Hérissey, *Compt. rend.*, **135**, 290 (1902); *J. pharm. chim.*, [6] **16**, 417 (1902).

(4) C. S. Hudson, THIS JOURNAL, **38**, 1566 (1916).

(5) C. S. Hudson, *ibid.*, **46**, 483 (1924).

(6) H. G. Fletcher, Jr., and H. W. Diehl, *ibid.*, **74**, 5774 (1952).

(7) H. Berlin, *ibid.*, **48**, 2627 (1926); F. J. Bates and Associates, "Polarimetry, Saccharimetry and the Sugars," Circular of the Natl. Bur. Standards C440, 1942, p. 463.

(8) A product of Rohm and Haas Co., Philadelphia, Pa.

(9) A product of the Chemical Process Co., Redwood City, Calif.