Summary

The following 5,5-barbituric acid derivatives have been prepared: ethyl-acetanilido-, *n*-butyl-acetanilido-, isobutyl-acetanilido-, isoamyl-acetanilido- and allyl-acetanilido-.

NEW HAVEN, CONN. RECEIVED JULY 13, 1935

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

Studies in the Ketone Sugar Series. V. The Validity of Hudson's Rules of Isorotation in the Ketose Group. Preparation of the True α-Pentaacetylfructose<2,6>

BY EUGENE PACSU AND FRANCIS B. CRAMER

Twenty years ago Hudson and Brauns[1] prepared a positively rotating pentaacetylfructose by acetylation of β-tetraacetylfructose<2,6> in the presence of zinc chloride. Since this pentaacetate was different from the β-pentaacetylfructose<2,6> obtained[2] from the same tetraacetate by using sulfuric acid with acetic anhydride for the acetylation, it was allocated to the α-series. Five years later Brauns[3] prepared from β-tetraacetylfructose<2,6> two chloroacetylfructoses, designating the one having specific rotation[4] −161 in chloroform as the α-, and the one having 45.3 in chloroform as the β-form. Subsequently, Brauns' allocations were reversed at the suggestion of Hudson,[5] the dextrorotatory compound becoming the α-, and the levorotatory the β-chloroacetylfructose. On the assumption that these two isomers constituted an α,β-pair with the same ring which is present in the parent β-tetraacetylfructose, Hudson[5] calculated the rotation of carbon 2 to be $a_{\text{Cl}} = 37,800$, and that of the acetylated basal chain common to them, comprising asymmetric carbon atoms 3,4 and 5, to be $b_{\text{fruct. ac.}} = -21,200$. The fact that the constant a_{Cl} was found to be the same both in sign and magnitude as $A_{\text{Cl}} = 37,900$[6] for the aldoses was regarded as evidence that the substitution of $—CH_2OAc$ for —H does not change the rotation of carbon atom 2. This conclusion seemed to be confirmed by the additional fact that the values of a_{F} and a_{Br} in the ketose group also have been found to be practically equal to the corresponding values of A_{F} and A_{Br} for the aldose group. It appeared therefore, safe to assume that $a_{\text{Ac}} = A_{\text{Ac}} = 19,100$, which is the average value for the aldoses. However, combining $a_{\text{Ac}} = 19,100$ with the constant $b_{\text{fruct. ac.}} = -21,200$, the specific rotations for α-, and β-pentaacetylfructoses become −5 and −103°, respectively, in chloroform, whereas the two known pentaacetates of fructose show 34.7 and −121.0°, respectively. In view of this disagreement, Hudson concluded that "it seems very unlikely that the dextrorotatory pentaacetate can be the expected α-form." As to the other known pentaacetate, of specific rotation −121.0°, Hudson stated that "it may be the expected β-form, though the difference of 18° in specific rotation makes such a conclusion uncertain." However, it was recently proved[7] that neither "α-chloroacetylfructose" nor "α-pentaacetylfructose" possesses a ring structure in its molecule, but both of these "α"-isomers are derivatives of the open-chain fructose, the former being 1,3,4,5-tetraacetyl 6-chloro*keto*fructose, and the latter 1,3,4,5,6-pentaacetyl*keto*fructose. Consequently, all calculations and conclusions based on the assumption that either the two chloro acetates or the two pentaacetates of fructose constitute α,β-stereoisomeric pairs, are invalid. This discovery *ipso facto* invalidated the above inference that the values of the different A_{x} constants for the aldoses are equal to those of the corresponding a_{x} constants in the ketose group. It also reopened the problem of the validity of the principle of optical superposition in the ketose series for further investigation. In order to test this principle it is necessary to know the optical rotations of a true α,β-stereoisomeric pair of any ketose or ketose derivative. It is remarkable that in the ketose series, contrasting with the aldose, no such true, α,β-pair has hitherto been known with cer-

---

[1] Hudson and Brauns, THIS JOURNAL, **37**, 2736 (1915).

[2] Hudson and Brauns, *ibid.*, **37**, 1283 (1915).

[3] Brauns, *ibid.*, **42**, 1846 (1920).

[4] Unless otherwise stated the rotations given are all for sodium light and 20°.

[5] Hudson, THIS JOURNAL, **46**, 477 (1924).

[6] The revised mean value of this constant is $A_{\text{Cl}} = 39,450$. It is obtained by using $A_{\text{Cl}} = 38,100$ found by Hudson and Kunz [THIS JOURNAL, **47**, 2052 (1925)] for chloroacetyllactose instead of the old value of $A_{\text{Cl}} = 30,300$ [Hudson, *ibid.*, **46**, 462 (1924)].

[7] Pacsu and Rich, *ibid.*, **54**, 1697 (1932); **55**, 3018 (1933).

tainty. To be sure, Schlubach and Schröter[8] prepared a crystalline methylfructoside tetraacetate, which they regarded as representing the α-isomeride of the known β-methylfructoside tetraacetate<2,6>. However, the allocation of their substance to the α-series was made on a premise that was shown in Part IV[9] of this series to be incorrect. It seemed, therefore, advisable to search for another α-derivative of fructose that might be used as a key substance to test the validity of the principle of optical superposition in the ketose group. Such a substance has now been provided by the discovery of the true α-pentaacetylfructose<2,6>. On replacement of the chlorine atom in β-acetochlorofructose<2,6> by an acetoxyl radical, no Walden inversion occurs on carbon atom 2, if the reaction be carried out in acetic anhydride solution with silver acetate.[10] The reaction product represents the pure β-pentaacetylfructose<2,6>. However, a partial Walden inversion does take place on carbon atom 2, if the same exchange reaction be carried out in boiling acetic anhydride solution with anhydrous sodium acetate. The mixture so obtained was found to consist of about 71% of the β-pentaacetate and 29% of the α-isomeride. After separation from the β-compound, the α-pentaacetylfructose<2,6> was isolated in pure, crystalline form; m. p. 122–123°; specific rotation 47.4° in chloroform. Using the molecular rotation of the β-pentaacetate ([M] −47,200) and the new acetate ([M] 18,500), the constants $a_{\text{Ac}} = 32{,}850$ and $b_{\text{fruct. ac.}} = -14{,}350$ were obtained from the two equations: $-47{,}200 = -a_{\text{Ac}} + b_{\text{fruct. ac.}}$ and $18{,}500 = +a_{\text{Ac}} + b_{\text{fruct. ac.}}$. It is seen that $a_{\text{Ac}} = 32{,}850$ for the ketoses is very much larger than $A_{\text{Ac}} = 19{,}100$ for the aldoses. Knowing the value of $b_{\text{fruct. ac.}}$, it is now possible to calculate the different a_{x} values for the ketoses, and the specific rotations of the α-isomerides from the corresponding β-derivatives. For instance, the value of a_{OMe} is calculated from the molecular rotation of the known β-methylfructoside tetraacetate<2,6> ([M] −45,200) to be $a_{\text{OMe}} = 45{,}200\text{–}14{,}350 = 30{,}850$. Hence, the specific rotation of α-methylfructoside tetraacetate<2,6> will be $(30{,}850-14{,}350)/362 = 45.5°$. Schlubach's crystalline tetraacetylmethylfructoside is recorded as having specific rotation 45.0° in chloroform. The excellent agreement between these two values indicates that Schlubach's compound is really the α-isomeride of the tetraacetyl-β-methylfructoside<2,6>. Fifteen years ago Brauns[11] prepared a crystalline β-ethylfructoside tetraacetate<2,6> from tetraacetyl-β-fructose-<2,6> by ethylation and reported for the pure substance m. p. 83° and specific rotation −127.6° in chloroform. From the molecular rotation ([M] −48,000) of this compound, and using the above constant of $b_{\text{fruct. ac.}} = -14{,}350$, the value of $a_{\text{OEt}} = 48{,}000-14{,}350 = 33{,}650$ is obtained. Hence, the specific rotation of the α-isomeride is calculated to be $(33{,}650-14{,}350)/376.2 = 51.3°$ in chloroform. In Part IV[9] of this series, there has been described a new crystalline ethylfructoside tetraacetate with m. p. 103–104°, and specific rotation 51.6° in chloroform. Here again, the agreement between the calculated and the observed value is excellent, and it supports the conclusion that the new fructoside represents the α-form of Brauns' β-ethylfructoside tetraacetate <2,6>.

In Table I there are shown the values of the different a_{x} constants for the ketoses calculated from the known β-derivatives of fructose, and the corresponding A_{x} values for the aldoses. It is seen that these constants, with the exception of a_{OH}, are throughout larger in the ketose than in the aldose series. Table I also shows the calculated specific rotations of the α-isomerides. The very satisfactory agreement between calculated and observed rotations in the case of methyl- and ethylfructoside tetraacetate leads to the conclusion that Hudson's rules of isorotation hold closely in the ketose series. It will be attempted to prepare some of the unknown α-derivatives from the new fructose pentaacetate.

Experimental Part

Preparation of α-Pentaacetylfructose <2,6>.—To a gently boiling mixture of 7 g. of anhydrous sodium acetate and 70 g. of freshly distilled acetic anhydride there was added 13.7 g. of β-acetochlorofructose<2,6> in one portion. A rapid reaction took place and sodium chloride precipitated. After thirty minutes of boiling, the solution was filtered from the sodium salts and the filtrate was concentrated *in vacuo* to a sirup which was mixed with 300 cc. of ice-cold water. The oily precipitate obtained soon turned into a crystalline solid (10.8 g.) which showed specific rotation −71.6° in chloroform solution. The filtrate was neutralized with solid sodium bicarbonate, extracted with chloroform, the chloroform layer dried with calcium chloride and evaporated *in vacuo* to a thick sirup. The ether solution of the latter soon deposited crystals at 0°;

---

[8] Schlubach and Schröter, *Ber.*, **61**, 1216 (1928).

[9] Pacsu, THIS JOURNAL, **57**, 745 (1935).

[10] Pacsu and Rich, *ibid.*, **55**, 3023 (1933).

[11] Brauns, *ibid.*, **42**, 1846 (1920).

TABLE I

Comparison of the calculated a_x values for the ketoses with the corresponding A_x values for the aldoses; calculated and observed rotations of the α-isomerides of some β-fructose derivatives.

Substance	Mol. wt.	M. p., °C.	$[\alpha]_D$ in $CHCl_3$	Mol. rot. in $CHCl_3$	a_x for ketoses	A_x for aldoses	$[\alpha]_D$ of the α-isomers in $CHCl_3$ Calcd.	$[\alpha]_D$ of the α-isomers in $CHCl_3$ Obsd.
β-Tetraacetylmethylfructoside<2,6>	362	76	−125.0°	−45,200	a_{OMe} = 30,850	A_{OMe} = 26,900	+ 45.5°	+45.0°
β-Tetraacetylethylfructoside<2,6>	376.2	83	−127.6°	−48,000	a_{OEt} = 33,650	A_{OEt} = 29,100[a]	+ 51.3°	+51.6°
β-Acetofluorofructose<2,6>	350	112	− 90.0°	−31,500	a_F = 17,150	A_F = 9,800	+ 8.0°	Unknown
β-Acetochlorofructose<2,6>	367	83	−161.0°	−59,100	a_{Cl} = 44,750	A_{Cl} = 39,450[b]	+ 82.0°	Unknown
β-Acetobromofructose<2,6>	411	65	−189.0°	−77,700	a_{Br} = 63,350	A_{Br} = 60,000[c]	+119.2°	Unknown
β-Tetraacetylfructose<2,6>	348	132	− 91.6°	−31,900	a_{OH} = 17,750	A_{OH} = 20,700	+ 9.2°	Unknown
β-Pentaacetylfructose<2,6>	390	109	−121.0°	−47,200	a_{OAc} = 32,850	A_{OAc} = 19,100	......	+47.4°

[a] From α- and β-ethylglucoside tetraacetate [J. H. Ferguson, THIS JOURNAL, **54**, 4086 (1932)]. [b] See Footnote 6. [c] This revised mean value is obtained by using A_{Br} = 59,300 [Hudson and Kunz, *ibid.*, **47**, 2052 (1925)] for bromoacetyllactose instead of A_{Br} = 56,500 [Hudson, *ibid.*, **46**, 462 (1924) .

yield, 1.1 g.; specific rotation −110.0° in chloroform. Since pure β-pentaacetylfructose<2,6> has the value of −120.9° in chloroform, and the pure α-pentaacetate has later been found to show specific rotation 47.4° in chloroform, the first crop (10.8 g.) of the reaction product obtained consisted of about 28.8% (3.1 g.) of the α- and 71.2% (7.7 g.) of the β-pentaacetate. The isolation of the isomerides was accomplished by a rough mechanical separation followed by one recrystallization from alcohol. The mixture (10.8 g.) was dissolved at room temperature in 250 cc. of absolute ether, and the solution was kept undisturbed in the icebox for several days. During this time 4 g. of crystalline material separated consisting of large crystals of the β-pentaacetate and small crystals of different appearance of the α-isomeride. The large crystals were sorted out (2.6 g.) and showed specific rotation −111.3° in chloroform; the small prismatic crystals of the α-isomeride (1.4 g.) showed the value of 26.5° in the same solvent. After one recrystallization from 10 cc. of absolute alcohol, the latter substance had m. p. 122–123°, $[\alpha]^{20}_{D}$ 47.4°; $[\alpha]^{20}_{6563}$ 38.0°; $[\alpha]^{20}_{5463}$ 56.0°; $[\alpha]^{20}_{4861}$ 73.0° and $[\alpha]^{20}_{4358}$ 94.3° in chloroform (0.2774 g. of substance, 10 cc. of solution; 2-dm. semi-micro tube; rotations, 2.63, 2.11, 3.11, 4.05 and 5.23° to the right, respectively); yield, 1.1 g. Another recrystallization from alcohol and a final one from chloroform by addition of ether at 0° did not change the rotation or melting point. The new acetate is soluble in most organic solvents except petroleum ether and cold alcohol. It is fairly soluble in hot water. In an acetyl estimation 0.2228 g. of the substance required 28.5 cc. of 0.1 *N* sodium hydroxide solution. The value calculated for the hydrolysis of five acetyl groups is 28.5 cc. The titrated solution (56.5 cc.) which contained 0.1028 g. of *d*-fructose, rotated sodium light 0.67° to the left in a 4-dm. tube at 20°, corresponding to specific rotation −92.0°, which is the constant rotation of *d*-fructose in water solution.

Summary

1. The true α-pentaacetylfructose<2,6> with m. p. 122–123° and specific rotation 47.4° in chloroform has been prepared. By the aid of this key substance it has been possible to calculate the correct a_x values for the ketone sugar derivatives.

2. The different a_x values for the ketoses are, with the exception of a_{OH}, throughout larger than the corresponding A_x values for the aldoses.

3. From the a_x values, the specific rotations of several α-fructose derivatives have been calculated. The excellent agreement between calculated and observed values of the methylfructoside tetraacetate of Schlubach as well as the ethylfructoside tetraacetate of Pacsu leads to the conclusion that (a) both compounds belong to the α-series (b) Hudson's rules of isorotation hold closely in the ketose group.

PRINCETON, NEW JERSEY
RECEIVED AUGUST 5, 1935