no skin irritation was observed from any of the compounds. All of the amides were colorless when perfectly pure.

It is noteworthy that the yields obtained from amine hydrochlorides in aqueous sodium hydroxide were comparable to those obtained from the free amine in anhydrous medium. This was not evident in the work on α-bromoacetamides, though otherwise the results were very similar.

Experimental

Reagents.—The α-bromopropionyl bromide, dimethylamine, ethylamine, diethylamine, allylamine, di-*n*-butylamine and the amine hydrochlorides were obtained from Eastman Kodak Company (white label), the isopropylamine from Commercial Solvents Corporation, and the ethylene dichloride from Carbide and Carbon Chemicals Corporation. The other amines used were generously supplied by Sharples Chemicals, Inc. None of the reagents was purified before use.

Methods.—The methods used have been described previously in detail.[1]

I. A solution of the amine in ethylene dichloride, maintained at −10°, was treated with the acid bromide. After filtering off the precipitated amine hydrobromide, the filtrate was washed with dilute hydrochloric acid, dried and distilled. When distillation was impracticable the compounds were recrystallized from aqueous ethanol after the ethylene dichloride had been removed.

II. Since the first members of the series were somewhat soluble in water, the filtrates were not washed with dilute hydrochloric acid.

III. When amine hydrochlorides were used, the reaction was run in the presence of 40% sodium hydroxide solution.

The mycological findings will be published elsewhere, but it can be stated here that the α-bromopropionamides are less fungicidal than the corresponding α-bromoacetamides.

Summary

Twenty-three α-bromopropionamides have been prepared preliminary to evaluation of their fungicidal activity. Twenty of these are new compounds.

WASHINGTON, D. C. RECEIVED FEBRUARY 7, 1947

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Evidence that Racemic Arabinose is β-D,L-Arabinopyranose

BY HEWITT G. FLETCHER, JR., AND C. S. HUDSON

In a previous note[1] it was pointed out that there is a hiatus in our knowledge of the structure of those racemates which are formed by the union of such enantiomorphic compounds as are capable of undergoing tautomeric change. As an example was cited the case of ordinary crystalline racemic arabinose which may conceivably be *rac.* α-arabinopyranose, *rac.* β-arabinopyranose, *rac.* α-arabinofuranose, *rac.* β-arabinofuranose or even *rac.* aldehydo-arabinose. It was the purpose of the present research to ascertain which of these various forms is actually represented by the long known "*rac.* arabinose," originally discovered by Ruff[2] in 1899.

The conversion of free mutarotating sugars into stable, nonmutarotating derivatives by acylation in pyridine was long ago introduced by Behrend and Roth[3] as a method for studying anomerism; they found that the acetylation of α-D-glucopyranose at low temperature with pyridine and acetic anhydride yielded the α-D-glucopyranose pentaacetate, whereas the β-pentaacetate resulted from the β-glucopyranose. For the present purpose recourse was had, not to the acetates of arabinose, but to the beautifully crystalline arabinose benzoates. Wolfrom and Christman[4] have reported two tetrabenzoates of L-arabinose. One of these, obtained by the benzoylation of an equilibrated solution of L-arabinose in pyridine, rotated +112.5° in chloroform at 29° and was shown by an unequivocal series of reactions to be a derivative of L-arabinopyranose. The other tetrabenzoate, formed by benzoylating L-arabinose at a low temperature in the presence of pyridine, rotated +325° in chloroform at 26° and the authors believed that it was the pyranose anomer of the lower rotating form. Following the established convention, the lower dextrorotatory form was designated α- and the higher rotating form β-L-arabinose tetrabenzoate. Evidence in support of the anomeric relationship between these two isomers has been obtained in the present investigation by the observation that β-L-arabinose tetrabenzoate affords 2,3,4-tribenzoyl-β-L-arabinosyl bromide having the same physical constants as that obtained by Wolfrom and Christman from α-L-arabinopyranose tetrabenzoate.

The two corresponding tetrabenzoates of the D-series were readily obtained and used in attempts to make authentic samples of the two possible pyranose racemates. Recrystallization of a mixture of equal quantities of α-D and α-L-arabinopyranose tetrabenzoate afforded material which melted lower than either of its components and gave an X-ray diffraction pattern indistinguishable from that of either of its components. It was, therefore, merely a racemic mixture. The two enantiomorphic β-arabinopyranose tetrabenzoates on the other hand readily furnished a true racemate, distinguishable from its components by its higher melting point and characteristic X-ray diffraction pattern.

(1) C. S. Hudson, THIS JOURNAL, **65**, 1239 (1943).

(2) O. Ruff, *Ber.*, **32**, 550 (1899).

(3) R. Behrend and P. Roth, *Ann.*, **331**, 359 (1904).

(4) M. L. Wolfrom and C. C. Christman, THIS JOURNAL, **58**, 39 (1936); *cf.* M. Gehrke and F. X. Aichner, *Ber.*, **60**, 918 (1927).

The cautious benzoylation of *rac.* arabinose at ice-bath temperature led to a yield of *rac.* arabinose tetrabenzoate comparable in amount to the yields of optically active tetrabenzoate obtained from D- and L-arabinose under similar circumstances. Comparison of this *rac.* arabinose tetrabenzoate with authentic β-D,L-arabinopyranose tetrabenzoate proved their identity and demonstrated that ordinary crystalline *rac.* arabinose is actually β-D,L-arabinopyranose.

The authors are indebted to Mr. William C. White for X-ray diffraction measurements.

One of us (H. G. F.) held the Chemical Foundation Research Associateship while carrying out this research.

Experimental

The Tetrabenzoates of α-D- and α-L-Arabinopyranose.—Ten grams of pure D- or L-arabinose was dissolved in 75 ml. of boiling pyridine and the solution left at room temperature for twenty-four hours. The solution was then cooled in an ice-bath and vigorously agitated while 39 ml. (5 moles) of benzoyl chloride was gradually added. After standing at room temperature for twenty-four hours, the solution was treated with 76 ml. of ethylene dichloride and poured on finely chipped ice. After separation, the non-aqueous layer was washed twice with ice-cold 3 *N* sulfuric acid, twice with aqueous sodium bicarbonate solution and finally once with water. Calcium chloride was used to remove remaining traces of moisture; the solution was filtered through a funnel precoated with carbon and finally concentrated *in vacuo* (40–45° bath). The resulting sirup was dissolved in 100 ml. of absolute alcohol and reconcentrated *in vacuo*—a procedure which gave rise to spontaneous crystallization. The semi-crystalline mass, after solution in 700 ml. of boiling methanol, afforded a fluffy mass of fine, needle-shaped crystals; 11.1 g. (29%). This material melted at 163°[5] and rotated in U. S. P. chloroform +114.1°. Recrystallized once from 80 parts of hot methanol and once from 5.7 parts of warm glacial acetic acid, the tetrabenzoate melted at 164–165° and showed for the D-isomer $[\alpha]^{20}D$ −114.4° (chloroform, *c*, 0.848) and for the L-isomer an equal dextrorotation. Further recrystallization from glacial acetic acid failed to change these constants.

Wolfrom and Christman[4] record α-L-arabinopyranose tetrabenzoate as melting at 160–161° and showing in chloroform $[\alpha]^{29}D$ +112.5°.

Tetrabenzoates of β-D- and β-L-Arabinopyranose.—Ten grams of pure D- or L-arabinose was suspended in 60 ml. of dry pyridine, cooled in an ice-bath and stirred vigorously while 48 ml. of benzoyl chloride was added dropwise. The rate of addition of the acid halide was adjusted so that the temperature of the reaction mixture did not rise above 4°. After 3.5 hours the thin slurry was kept in the ice box overnight and then at room temperature for five hours. Seventy-six milliliters of ethylene dichloride was added and the solution poured in a thin stream onto finely chipped ice. After separation, the non-aqueous layer was washed twice with ice-cold 3 *N* sulfuric acid, twice with aqueous sodium bicarbonate solution and, finally, once with water. After desiccation with calcium chloride and filtration through a bed of decolorizing carbon the solution was concentrated *in vacuo* (40–45° bath). The resulting sirup was dissolved in 100 ml. of absolute alcohol and reconcentrated *in vacuo*, spontaneous crystallization taking place. Prolonged refluxing effected solution of the mixture in 300 ml. of methanol. The prism-shaped crystals which were deposited on cooling (20.0 g.; 53%) melted at 157–159°. Recrystallized twice from 33 parts of hot methanol, the material melted at 160–161° and showed, for the D-isomer, $[\alpha]^{20}D$ −322.7° ($CHCl_3$, *c*, 0.981). The L-isomer showed an equal dextrorotation.

Wolfrom and Christman[4] reported 173–174° for the melting point and $[\alpha]^{26}D$ +325° for β-L-arabinopyranose tetrabenzoate.

2,3,4-Tribenzoyl-β-L-arabinosyl bromide from β-L-arabinopyranose tetrabenzoate.—Five grams of pure β-L-arabinopyranose tetrabenzoate was dissolved in 5 ml. of ethylene dichloride and the solution treated with 10 ml. of a chilled solution of glacial acetic acid containing 30% hydrobromic acid. After standing for two hours at room temperature the reaction mixture was diluted with 50 ml. of dry toluene and concentrated *in vacuo* (40–45° bath) to a thin sirup which crystallized spontaneously. The semi-crystalline mass was dissolved in 12 ml. of methanol. After scratching the cooled solution to initiate crystallization, the characteristic spherical masses of needle-like crystals were allowed to develop at 3°. Removed by filtration and washed liberally with chilled methanol the 2,3,4-tribenzoyl-β-L-arabinosyl bromide (3.085 g.; 66%) melted at 144–145° and showed in U. S. P. chloroform +201.8° (*c*, 1.7364). Wolfrom and Christman[4] reported a melting point of 144–145° and a rotation of +203° ($CHCl_3$) for the compound which they made by a similar procedure from α-L-arabinopyranose tetrabenzoate.

α-D,L-Arabinopyranose Tetrabenzoate.—Half-gram samples of each of the enantiomorphs were separately dissolved in 25-ml. portions of boiling alcohol and the solutions then combined. Scratching the cool solution initiated the formation of crystals as long, flexible needles. After washing thoroughly with fresh alcohol these melted at 140–141°. An X-ray diffraction picture from these crystals proved indistinguishable from that from the component enantiomorphs and demonstrated that this material represents a racemic mixture.

β-D,L-Arabinopyranose Tetrabenzoate.—Precisely the same procedure was used as for the α-isomer and crystals were obtained as thin, quadrilateral plates melting at 165–166°. The X-ray diffraction picture from these crystals was strikingly different from that from its component enantiomorphs and indicates that the compound is a true racemate.

The Benzoylation of D,L-Arabinose at 0–4°.—Ten grams of D,L-arabinose[6] was suspended in 60 ml. of dry pyridine, cooled in an ice-bath and stirred vigorously while 48 ml. of benzoyl chloride was added at such a rate that the temperature of the mixture did not rise above 4°. After several days in the ice box and a few hours at room temperature the slurry was diluted with 76 ml. of ethylene dichloride and poured on chipped ice. After separation, the non-aqueous layer was washed twice with ice-cold 3 *N* sulfuric acid, twice with aqueous sodium bicarbonate solution and once with water. After desiccation with calcium chloride and filtration through a bed of carbon the solution was concentrated *in vacuo* (45–55° bath). One hundred milliliters of absolute alcohol was similarly evaporated from the resulting sirup. The crystalline magma which remained was digested with 250 ml. of boiling methanol and, without filtration, cooled in the ice box forty-eight hours. The microcrystalline mass, removed by filtration, weighed 20.0 g. (53%) and melted at 162–164°. Recrystallized twice from 40 parts of hot alcohol the melting point became constant. Either alone or in admixture with authentic β-D,L-arabinopyranose tetrabenzoate, it melted at 165–166°.

Summary

Benzoylation of D- and of L-arabinose readily

(5) All melting points reported here are corrected for stem exposure. Specific rotations are for the D-line of sodium at 20° while concentrations are expressed in grams of substance to 100 ml. of solution.

(6) Equal quantities of D- and L-arabinose (10 g. of each) were dissolved in 20 ml. of warm water and the solution treated with 100 ml. of glacial acetic acid. The hard, colorless prisms which developed at room temperature were removed by filtration, washed with 5 ml. of glacial acetic acid and then 10 ml. of absolute alcohol; wt. 16.48 g., m. p. 153–155°. Recrystallized from a mixture of 2 parts of water and 18 parts of absolute alcohol the D,L-arabinose melted at 159–160°. Ruff[2] reported a value of 163.5–164.5° (cor.).

furnishes the expected four possible arabinopyranose tetrabenzoates. X-Ray diffraction measurements and melting point determinations show that the enantiomorphic α-arabinopyranose tetrabenzoates form a racemic mixture, while the β-arabinopyranose tetrabenzoates form a true racemate.

Benzoylation of the long known *rac.* arabinose at 0–4° affords β-D,L-arabinopyranose tetrabenzoate in substantial yield, which demonstrates that ordinary crystalline D,L-arabinose, like its individual components, exists as β-D,L-arabinopyranose.

BETHESDA 14, MARYLAND RECEIVED JANUARY 24, 1947

[CONTRIBUTION FROM THE DIVISION OF MEDICINAL CHEMISTRY, THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

I. Derivatives of Aminopyridines[1]

BY JACK BERNSTEIN, BARBARA STEARNS, MARTIN DEXTER[2] AND W. A. LOTT

Since the common antimalarial agents contain a heterocyclic nitrogen ring, it was thought desirable to prepare and test many of the readily available substituted pyridines as antiparasitic agents. The isomeric aminopyridines and their acetyl derivatives were prepared by known procedures[3] and found to be inactive,[4] as were the isomeric 2-acetylamido-methylpyridines. Alkylated derivatives of 2-aminopyridine, which were also inactive, were prepared by the reaction of 2-bromopyridine with the appropriate amines.[5]

In addition to these compounds, various halogenated aminopyridines were also prepared of which only 2-amino-5-iodopyridine showed slight antiparasitic activity. A number of alkylated and acylated derivatives of this compound were prepared to determine if further modification of the molecule would increase this activity. Alkylated derivatives were prepared by the reaction of 2-chloro-5-iodopyridine[6] with the desired amine. The inertness of a β-halogen as compared with an α- or γ-halogen in the pyridine ring made this method feasible and no replacement of the β-iodine was observed in any case (negative qualitative test). By the reaction of 2-amino-5-iodopyridine with diethylaminoethyl chloride, N-diethylaminoethyl-5-iodo-2-pyridone-imide was prepared. The ultraviolet absorption[7] of this compound in strongly basic solution showed one maximum at 245 mμ (ϵ = 15,900) and a second maximum at 330 mμ (ϵ = 3,180). The absorption of 2-diethylaminoethylamino-5-iodopyridine, also in strongly basic solution, likewise showed two maxima; at 253 mμ (ϵ = 22,000) and at 320 mμ (ϵ = 3,620). The difference in absorption indicates that the compounds are not identical, and since the structure of the latter one is clearly established by the method of synthesis, the alkylation reaction of the 2-amino-5-iodopyridine must have resulted in the N-substituted-2-pyridone-imide structure. The *p*-methoxybenzyl derivative was prepared by the condensation of 2-amino-5-iodopyridine with anisaldehyde in the presence of formic acid.[8] The acylated derivatives of 2-amino-5-iodopyridine were prepared by the usual procedures; reaction with an acyl chloride, acid anhydride or with an isocyanate. None of the derivatives of 2-amino-5-iodopyridine prepared showed the slight activity of the parent compound.

A number of alkoxy derivatives of 2- or 3-aminopyridine were also synthesized. The 2-amino-6-alkoxy derivatives were prepared by the reaction of 2-amino-6-bromopyridine with the sodium derivative of the desired alcohol.[9] The 2-amino-3-alkoxy derivatives were prepared by the procedure of Koenigs[10]; 3-bromopyridine was converted to 3-alkoxypyridine, nitrated to give 2-nitro-3-alkoxypyridine, followed by reduction to the 2-amino-3-alkoxypyridine. 2-Methoxy-5-aminopyridine was prepared by the conversion of 5-nitro-2-chloropyridine to 5-nitro-2-methoxypyridine followed by reduction to the corresponding amino compound.[11] None of these derivatives showed any antimalarial activity.

Condensation of 2-pyridylhydrazine with the appropriate β-keto ester yielded pyrazolones; from ethyl acetoacetate, 1-(2-pyridyl)-3-methyl-5-pyrazolone was formed while from diethyl α,β-diacetylsuccinate, 1,1′-di-(2-pyridyl)-3,3′-dimethyl-4,4′-bipyrazole-5,5′-dione was obtained. An attempt to prepare this latter compound by the reaction of phenylhydrazine with 1-(2-pyridyl)-3-methyl-5-pyrazolone was unsuccessful, although phenylhydrazine does convert 1-phenyl-3-methyl-

(1) Presented in part before the Division of Medicinal Chemistry of the American Chemical Society, Atlantic City, N. J., April 8–12, 1946.

(2) Present address: Specific Pharmaceuticals, Inc., 329 4th Avenue, New York, N. Y.

(3) Unless otherwise noted, the preparation of known pyridine derivatives is indicated in Maier-Bode and Altpeter, "Das Pyridin und seine Derivative," Wilhelm Knapp, Halle (Saale), 1934; photolithoprint reproduction by Edwards Brothers, Inc., Ann Arbor, Michigan, 1943.

(4) The antiparasitic activity of the compounds as suppressive agents for *Plasmodium lophurae* in ducklings was determined. These determinations were carried out by the Division of Pharmacology of this Institute. Some of the pharmacological results will be described in the forthcoming monograph by the Survey of Antimalarial Drugs.

(5) Subsequently described by Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945); also British Patent 265,167.

(6) Magidson and Menschikoff, *Ber.*, **58**, 113 (1925).

(7) Absorption spectra were measured by Dr. N. H. Coy of the Biological Laboratories, E. R. Squibb and Sons.

(8) Tschitschibabin and Knunjanz, *Ber.*, **64**, 2839 (1931).

(9) Hertog and Wilbaut, *Rec. trav. chim.*, **55**, 126 (1936).

(10) Koenigs, Gerdes and Sirot, *Ber.*, **61**, 1022 (1928). As indicated by Schickh, Binz and Schulz, *ibid.*, **69**, 2595 (1936), the product described by Koenigs as 2-amino-5-ethoxypyridine was actually 2-amino-3-ethoxypyridine.

(11) U. S. Patent 2,145,579.