797. N-*Substituted Glycosylamines. Part IV.** N-*Aryl*-D-*fructosylamines.*

By C. P. Barry and John Honeyman.

Unsuccessful attempts were made to condense D-fructose with aniline and *p*-toluidine under conditions used for preparing *N*-arylaldosylamines. *N*-Phenyl- and *N*-*p*-tolyl-D-fructosylamines have been prepared by boiling the amine and fructose in anhydrous ethanol in the presence of the amine hydrochloride. These products were acetylated and benzoylated to crystalline esters which were hydrolysed to D-fructose 1 : 3 : 4 : 5-tetra-acetate and 1 : 3 : 4 : 5-tetrabenzoate. The same *N*-phenylfructosylamine tetra-acetate has been prepared from aniline and fructopyranosyl chloride tetra-acetate. Thus, these *N*-aryl-D-fructosylamines react as pyranose compounds.

In contrast with the large number of *N*-arylaldosylamines which have been reported, only four *N*-arylketosylamines are known. Sorokin (*Ber.*, 1886, **19**, 513; *J. pr. Chem.*, 1888, **37**, 295) condensed aniline and D-fructose in boiling ethanol and obtained in very low yield crystalline *N*-phenyl-D-fructosylamine. Kuhn and Birkofer (*Ber.*, 1938, **71**, 621) found that for *p*-phenetidine to react with D-fructose or L-sorbose in alcohol ammonium chloride is required as catalyst. The *N*-*p*-ethoxyphenylketosylamines, isolated in 15% yield, were crystalline solids melting with decomposition. Since our work was carried out an abstract (*Chem. Abs.*, 1951, **45**, 9481) has appeared in which *N*-*p*-tolyl-D-fructosylamine is mentioned, but no details are given of its preparation: the original paper (Inoue and Onodera, *J. Agric. Chem. Soc., Japan*, 1948, **22**, 70) is not yet available to us. No esters or ethers of *N*-substituted ketosylamines have previously been recorded; indeed, Irvine and McNicoll (*J.*, 1910, **97**, 1450) report their failure to make aniline derivatives of methyl fructoses.

The less ready reaction of fructose with amines has been used by Weygand, Perkow, and Kuhner (*Ber.*, 1951, **84**, 594) to obtain crystalline fructose from invert sugar by precipitating the glucose as *N*-*p*-nitrophenyl-D-glucosylamine. We have confirmed the failure of aniline and *p*-toluidine to react with fructose under conditions usually successful for aldoses. At room temperature in aqueous alcohol, as described for aldoses by Ellis and Honeyman (*J.*, 1952, 1490), and in hot aqueous suspension (Weygand, *Ber.*, 1939, **72**, 1663) no condensation occurred. Unchanged fructose was recovered when the compounds were heated in boiling absolute alcohol, but the addition of ammonium chloride or, better, aniline hydrochloride catalysed the reaction and a small proportion of crystalline *N*-phenyl-D-fructosylamine was isolated as well as unchanged fructose. Increasing the

* Part III, Ellis and Honeyman, *J.*, 1952, 2053.

reaction time beyond an hour did not increase the yield of product, but decreased the amount of recovered fructose. The amount of condensation was increased by removing water during the reaction, but the method which gave the best yield involved anhydrous ethanol as solvent. With this, the optimum time was seven minutes at boiling point: longer heating did not lead to more product but increased the discoloration. These results taken together suggest the possibility of this being an equilibrium reaction and, therefore, differing from the aldose condensations. The same method has been used successfully to prepare crystalline *N*-*p*-tolyl-D-fructosylamine. No anomers have been obtained, although the compounds mutarotated in alcohol and in pyridine. The melting points of these compounds are really decomposition temperatures, of little value as a criterion of purity or for correlating the compounds with those obtained by Sorokin (*loc. cit.*) and Inoue and Onodera (*loc. cit.*). Comparison of the specific rotations is possible in the case of *N*-phenyl-D-fructosylamine only and indicates that our compound is the same as Sorokin's. Judgment is suspended in the case of the other compound until further information is available for Inoue and Onodera's *N*-*p*-tolyl-D-fructosylamine. Although they found that their compound is more readily hydrolysed by acid than a number of *N*-*p*-tolylaldosylamines, we found that both our compounds have excellent storage properties. Some samples have now been kept under ordinary laboratory conditions for over two years without deterioration, whereas arylaldosylamines decompose completely in a few months. *N*-Phenyl- and *N*-*p*-tolyl-D-fructosylamine have been acetylated and benzoylated by the method described by Ellis and Honeyman (*J.*, 1952, 2053), to give crystalline tetra-acetates and tetrabenzoates. The ease of hydrolysis of the amine residue in these esters is roughly the same as in the corresponding aldose compounds; the greater stability of the benzoates is again marked. The product obtained in this way from the two tetra-acetates was D-fructose 1 : 3 : 4 : 5-tetra-acetate, shown to be the same as that obtained by direct acetylation of fructose by Pacsu and Rich's process (*J. Amer. Chem. Soc.*, 1933, **55**, 3018). Similarly the two tetrabenzoates were converted into D-fructose 1 : 3 : 4 : 5-tetrabenzoate, identical with a specimen prepared by the direct benzoylation of fructose by Brigl and Schinle's method (*Ber.*, 1933, **66**, 325). This proves that the four *N*-aryl-D-fructosylamine esters which we have prepared have pyranose ring structures and that their acetyl or benzoyl groups are linked to oxygen. Confirmation of this was obtained by isolating the same *N*-phenyl-D-fructopyranosylamine tetra-acetate on condensing aniline with D-fructopyranosyl chloride tetra-acetate. In contrast with the aldose series, however, D-fructose 1 : 3 : 4 : 5-tetra-acetate was recovered after 30 minutes' boiling with aniline in anhydrous ethanol containing aniline hydrochloride as catalyst. Longer reaction resulted in much decomposition. Under similar conditions, no condensation took place between aniline and D-fructose 1 : 3 : 4 : 5-tetrabenzoate, 1 : 3 : 4 : 6-tetrabenzoate, or 1 : 3 : 4 : 5 : 6-pentabenzoate. The non-reactivity of the 1 : 3 : 4 : 6-tetrabenzoate was further indicated by the isolation of benzanilide. Attempts to obtain crystalline products by treating aniline with D-fructose 1 : 3 : 4 : 6-tetra-acetate and with D-fructofuranosyl bromide tetrabenzoate were unsuccessful. Methylation of *N*-phenyl-D-fructosylamine by Honeyman and Ellis's method (*loc. cit.*, p. 2053) led to extensive decomposition.

EXPERIMENTAL

Ethanol is used throughout to signify ordinary absolute alcohol. Anhydrous ethanol was prepared by drying ethanol with ethyl phthalate and sodium.

Volatile solvents were evaporated under reduced pressure. All initial values for $[\alpha]_D$ were obtained where necessary by extrapolation to zero time.

Attempted Reaction of Aniline with Fructose.—Fructose was recovered from the attempted condensation of fructose and aniline in boiling water (30 minutes) and in boiling ethanol (2 hours). Longer reaction times led to excessive decomposition.

Reaction of Aniline with Fructose, with Ammonium Chloride as Catalyst.—A solution of aniline (1·4 ml.), fructose (2 g.), and ammonium chloride (0·04 g.) in ethanol (8 ml.) was boiled under reflux for 1 hour. Ether (20 ml.) was then added, precipitating a dark syrup, from which fructose (60%) crystallised on trituration with alcohol. Addition of more ether (20 ml.) to the reaction solution precipitated a solid which, after recrystallisation from ethanol, formed colourless plates (0·3 g., 10%) of *N*-phenyl-D-fructosylamine, m. p. 150° (decomp.).

Preparation of N-*Phenyl*-D-*fructosylamine*.—(*a*) A solution of aniline (2·8 ml.), fructose (4 g.) and ammonium chloride (0·1 g.) in ethanol (16 ml.) and benzene (8 ml.) was boiled under reflux for 1½ hours, the condensate being returned to the reaction vessel through a column of quicklime. The dark solution, left at 0° for several days, deposited a solid which, after being washed with ether and recrystallised from ethanol, was *N*-phenyl-D-fructosylamine (1·7 g., 30%) m. p. 150°, $[\alpha]_D^{19}$ −203·6° → −161·0° (*c*. 0·2 in ethanol).

Fructose (1·6 g., 40%) was obtained by adding ether to the reaction mother-liquor.

(*b*) The same result was obtained when (*a*) was modified by using aniline hydrochloride (0·2 g.) instead of ammonium chloride and a time of 15 minutes.

(*c*) Aniline (1·5 ml.) was boiled for 15 minutes with fructose (2 g.) and aniline hydrochloride (0·1 g.) in ethanol (10 ml.) and benzene (5 ml.). A mixture of ethanol and benzene (1 : 1) was run in at the same rate as liquid distilled. The same product (35%) was purified as in (*a*).

(*d*) A solution of aniline (1·4 ml.), fructose (2 g.), and aniline hydrochloride (0·1 g.) in anhydrous ethanol (7 ml.) was boiled under reflux for 7 minutes. After being kept at 0° overnight, the crystalline precipitate (2 g.) was purified as before, and found to be *N*-phenyl-D-fructosylamine (1·35 g., 70%, calc. on fructose not recovered), m. p. 149° (decomp.), $[\alpha]_D^{17-19}$ −209·3° → −203·8° (*c*, 0·2 in ethanol), $[\alpha]_D^{19}$ −209·4° → −164·1° (*c*, 1·0 in pyridine), $[\alpha]_D$ −220·6° → −202·5° (*c*, 0·6 in 90% ethanol), $[\alpha]_D^{19}$ −206·8° → −175·6° (*c*, 0·2 in methanol) (Found : C, 56·7; H, 6·9; N, 5·7. Calc. for $C_{12}H_{17}O_5N$: C, 56·5; H, 6·7; N, 5·5%). Sorokin (*loc. cit.*) recorded for this compound m. p. about 147° (decomp.), $[\alpha]_D^{20-23}$ −185·5° (*c*, 1·7 in 90% ethanol), −215·7° (*c*, 0·6 in 90% ethanol), $[\alpha]_D^{20}$ −181·1° (*c*, 1·1 in dry methanol). Mutarotation was not mentioned.

Unchanged fructose (0·4 g.) was isolated from the reaction solution as previously described.

Reaction of p-*Toluidine with* D-*Fructose*.—(*a*) When *p*-toluidine (1·2 g.) was boiled under reflux for 2 hours with fructose (2 g.) and ammonium chloride (0·05 g.) in ethanol (13 ml.) fructose was recovered.

(*b*) Fructose (2 g.) in anhydrous ethanol (10 ml.) was treated with *p*-toluidine (1·5 g.) and *p*-toluidine hydrochloride (0·1 g.) under the conditions in (*d*) above. Recrystallisation of the crude solid from ethanol gave colourless needles (1·4 g., 47%) of N-p-*tolyl*-D-*fructosylamine*, m. p. 138° (decomp.), $[\alpha]_D^{19}$ −207·7° → −176·9° (*c*, 0·3 in ethanol), $[\alpha]_D^{18}$ −200·4° → −167·3° (*c*, 1·3 in pyridine) (Found : C, 57·9; H, 7·0; N, 5·5. $C_{13}H_{19}O_5N$ requires C, 58·0; H, 7·1; N, 5·2%). Inoue and Onodera (*loc. cit.*) record for their compound m. p. 154°, $[\alpha]_D$ −168° → −88° (*c* and solvent not specified).

Acetylation of N-*Phenyl*-D-*fructosylamine*,—A solution of *N*-phenyl-D-fructosylamine (1 g.) in pyridine (5 ml.) and acetic anhydride (5 ml.) was kept at 0° for an hour and overnight at room temperature, and then poured into ice and water and left for an hour. The product, recrystallised from ethanol as colourless crystals (60%), was N-*phenyl*-D-*fructosylamine* 1 : 3 : 4 : 5-*tetra-acetate*, m. p. 151° $[\alpha]_D$ −149·6° (*c*, 1·1 in chloroform) (Found : C, 57·4; H, 5·9; N, 3·1. $C_{20}H_{25}O_9N$ requires C, 56·7; H, 5·9; N, 3·3%).

Hydrolysis of N-*Phenyl*-D-*fructosylamine Tetra-acetate*.—Aqueous formic acid (0·5%; 40 ml.) was added to the tetra-acetate (1 g.) in acetone (30 ml.) and the solution boiled under reflux for 6 hours in nitrogen. The solution was extracted with chloroform, and the extract dried and evaporated. Addition of ether precipitated a solid which, after recrystallisation from ethanol, was identified as β-D-fructose 1 : 3 : 4 : 5-tetra-acetate (60%), m. p. 132°, $[\alpha]_D$ −91·0° (*c*, 0·5 in chloroform), undepressed on admixture with authentic substance prepared directly from fructose. Brauns (*Proc. Roy. Acad. Amsterdam*, 1907—1908, **10**, 563) gives m. p. 131—132°, $[\alpha]_D^{20}$ −91·6° (*c*, 3 in chloroform).

Attempted Condensation of Aniline with D-*Fructose Tetra-acetates*.—Aniline (1·1 ml.) and aniline hydrochloride (0·1 g.) were boiled under reflux for 30 minutes with D-fructose 1 : 3 : 4 : 5-tetra-acetate (2 g.) in anhydrous ethanol (10 ml.). Unchanged tetra-acetate (1·4 g., 70%) was the only compound isolated.

No crystalline product was obtained when aniline (1·1 ml.), aniline hydrochloride (0·1 g.), and D-fructose 1 : 3 : 4 : 6-tetra-acetate (2 g.) were boiled under reflux for from 30 minutes to 5 hours in anhydrous ethanol (10 ml.).

Reaction of D-*Fructosyl Chloride* 1 : 3 : 4 : 5-*Tetra-acetate with Aniline*.—A solution of aniline (1·1 ml.) and D-fructosyl chloride 1 : 3 : 4 : 5-tetra-acetate (2 g.) in dry benzene (20 ml.) was kept at 0° overnight. Aniline hydrochloride was filtered off and the solution evaporated to a syrup. On addition of ethanol, this deposited crystals of *N*-phenyl-D-fructosylamine tetra-acetate (0·22 g., 10%), m. p. 147—148°. After recrystallisation from ethanol the substance had m. p. 151°, undepressed on admixture with the sample prepared as above.

Benzoylation of N-*Phenyl*-D-*fructosylamine.*—Benzoyl chloride (8 ml.) in pyridine (10 ml.) was added at 0° to *N*-phenyl-D-fructosylamine (2·5 g.) in pyridine (10 ml.). After 24 hours at 0°, chloroform (50 ml.) was added and the mixture extracted several times with dilute hydrochloric acid, then dilute sodium carbonate solution, and water. After being dried, the solvent was evaporated, leaving a syrup which crystallised on trituration with ethanol. The product, recrystallised from ethanol as colourless needles (6·2 g., 90%), was N-*phenyl*-D-*fructosylamine* 1 : 3 : 4 : 5-*tetrabenzoate*, m. p. 100—102°, $[\alpha]_D^{20}$ $-132{\cdot}0°$ (*c*, 0·5 in chloroform) (Found : C, 70·9; H, 5·0; N, 2·4. $C_{40}H_{33}O_9N$ requires C, 71·6; H, 4·9; N, 2·1%).

Hydrolysis of N-*Phenyl*-D-*Fructosylamine Tetrabenzoate.*—(*a*) The tetrabenzoate (1 g.) was recovered after being heated in acetone (25 ml.) for 6 hours in nitrogen with aqueous formic acid (0·5%; 25 ml.).

(*b*) The tetrabenzoate (1 g.) in acetone (25 ml.) was boiled under reflux for 6 hours with concentrated hydrochloric acid (2 ml.) and water (25 ml.). After cooling, water was added and the solution left overnight at room temperature. A solid was deposited, which recrystallised from ethanol as colourless prisms (0·8 g., 90%) of D-fructose 1 : 3 : 4 : 5-tetrabenzoate, m. p. 175—177°, undepressed on admixture with authentic substance, $[\alpha]_D^{19}$ $-169{\cdot}6° \longrightarrow -165{\cdot}2°$ (*c*, 0·67 in chloroform). For this compound Brigl and Schinle (*loc. cit.*) record $[\alpha]_D^{20}$ $-164{\cdot}9°$ (*c*, 0·4 in chloroform).

Attempted Condensation of Aniline with D-*Fructose Benzoates.*—(*a*) A solution of aniline (40 mg.), aniline hydrochloride (4 mg.), and D-fructose 1 : 3 : 4 : 5-tetrabenzoate (100 mg.) in anhydrous ethanol (0·5 ml.) was boiled under reflux for 6 hours. After addition of light petroleum (b. p. 40—60°) (2 ml.) the solution slowly deposited D-fructose 1 : 3 : 4 : 5-tetrabenzoate (80 mg.), m. p. 169—170°, mixed m. p. 173—174°, $[\alpha]_D^{19}$ $-157{\cdot}2°$ (*c*, 0·3 in chloroform).

(*b*) Under similar conditions, D-fructose 1 : 3 : 4 : 6-tetrabenzoate was recovered from an attempt to condense it with aniline.

(*c*) Similarly, *keto*-D-fructose 1 : 3 : 4 : 5 : 6-pentabenzoate (75 mg., 75%) was recovered from an attempt to condense it with aniline.

Attempted Condensation of Aniline and D-*Fructofuranosyl Bromide Tetrabenzoate.*—Crude, liquid D-fructofuranosyl bromide tetrabenzoate, prepared as described by Klages and Niemann (*Annalen*, 1937, **529**, 185) from D-fructofuranose 1 : 3 : 4 : 6-tetrabenzoate (5 g.), was dissolved in ether (100 ml.), and aniline (1·7 ml.; 2 eq.) was added. The solution was left overnight, and the deposit of aniline hydrobromide removed. Evaporation of the solvent yielded a dark syrup which could not be purified.

Acetylation of N-p-*Tolyl*-D-*fructosylamine.*—This was achieved by the method used for the *N*-phenyl derivative. The product, recrystallised from ethanol or light petroleum (b. p. 60—80°) as colourless crystals (50%), was N-p-*tolyl*-D-*fructosylamine* 1 : 3 : 4 : 5-*tetra-acetate*, m. p. 129°, $[\alpha]_D$ $-141{\cdot}0°$ (*c*, 1·5 in chloroform) (Found: C, 57·7; H, 6·1; N, 3·5. $C_{21}H_{27}O_9N$ requires C, 57·7; H, 6·2; N, 3·2%).

Hydrolysis of N-p-*Tolyl*-D-*fructosylamine Tetra-acetate.*—This, carried out as for the *N*-phenyl derivative, gave D-fructose 1 : 3 : 4 : 5-tetra-acetate (*ca.* 50 mg., from 0·2 g.), m. p. 128—130°, mixed m. p. with that prepared from the corresponding *N*-phenyl compound, 131—132°, mixed m. p. with starting substance, 110°.

Benzoylation of N-p-*Tolyl*-D-*fructosylamine.*—Benzoyl chloride (3·2 ml.) in pyridine (4 ml.) was added at −10° to *N*-*p*-tolyl-D-fructosylamine (1 g.) in pyridine (8 ml.). The solution was kept at −10° for ½ hour, then at 0° for 4 hours. The product, isolated in the same way as for the *N*-phenyl derivative, and recrystallised from light petroleum (b. p. 60—80°) and ethylene dichloride as colourless needles (0·8 g., 30%), was N-p-*tolyl*-D-*fructosylamine* 1 : 3 : 4 : 5-*tetrabenzoate*, m. p. 167·5°, $[\alpha]_D^{20}$ $-131{\cdot}4°$ (*c*, 1·1 in chloroform) (Found : C, 71·7; H, 5·2; N, 1·9. $C_{41}H_{35}O_9N$ requires C, 71·8; H, 5·1; N, 2·0%).

Hydrolysis of N-p-*Tolyl*-D-*fructosylamine Tetrabenzoate.*—When this tetrabenzoate was hydrolysed by the method used for the *N*-phenyl derivative, the product was D-fructose 1 : 3 : 4 : 5-tetrabenzoate (0·16 g., from 0·2 g.), m. p. 173°, mixed m. p. with that prepared from *N*-phenyl-D-fructosylamine, 175°, $[\alpha]_D^{19}$ $-163{\cdot}3°$ (*c*, 0·5 in chloroform).

The authors thank the Chemical Society and the University of London for grants from their Research Funds, and Professor B. Helferich and Herr Bottenbruch, University of Bonn, for generously preparing and providing a sample of fructopyranose tetrabenzoate. The work was carried out during the tenure of a State Scholarship by C. P. B.

KING'S COLLEGE (UNIVERSITY OF LONDON),
STRAND, LONDON, W.C.2.

[*Received, July* 10*th*, 1952.]