608. *The Scope and Mechanism of Carbohydrate Osotriazole Formation. Part VII.*[1] *Some Osotriazoles having Reactive Groups.*

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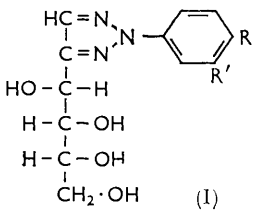
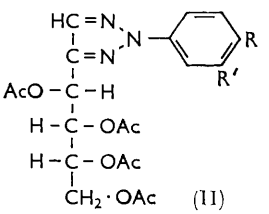
Some glucose arylosotriazoles with reactive groups such as NO_2, NH_2, NHAc, CHO, ·CH:CH·CO_2H, and α-naphthyl have been prepared with a view to their use for introduction of stable sugar residues into organic molecules.

Carbohydrate arylosotriazoles, unlike glycosides, have their sugar residues firmly bound and are unaffected by hydrolysis; they may therefore find application as a means of introducing sugar residues into the molecules of drugs and dyes to induce specificity or affinity to fibres. In this paper, we describe the preparation of some glucose arylosotriazoles having reactive groups which might prove useful for such syntheses.

Glucose *p*-acetamidophenyl- (I; R = NHAc, R′ = H), *p*-cyanophenyl- (I; R = CN, R′ = H), *m*-carboxyvinylphenyl- (I; R = H, R′ = CH:CH·CO_2H), 3,4-methylenedioxyphenyl- (I; RR′ = CH_2O_2), and α-naphthyl-osotriazole were prepared from the corresponding osazones by the action of copper sulphate. The time of reaction (Table 1) varied from 10 hours for the *p*-cyano-derivative to 15 minutes for the *p*-acetamidophenyl and methylenedioxyphenyl derivatives, affording further [2] evidences that osotriazole formation is inhibited by electron-attracting and facilitated by electron-releasing groups.



(I)



(II)

p-Aminophenylosotriazoles were also prepared by reducing the corresponding nitro-derivatives, obtained by nitrating phenylosotriazole tetra-acetates having a free *p*-position. Thus, glucose phenylosotriazole tetra-acetate (II; R = R′ = H) yielded on nitration and hydrolysis glucose *p*-nitrophenylosotriazole (I; R = NO_2, R′ = H), identical with a specimen obtained by the action of bromine water on glucose *p*-nitrophenylosazone. Henseke and Winter [3] obtained this nitro-osotriazole by the action of copper sulphate on the mixed osazone, glucose 1-phenyl-2-*p*-nitrophenylosazone, by the elimination of the 1-arylamine but recorded a lower melting point, possibly owing to contamination of their product by partial elimination of the 2-arylamine. Further proof of the position of the nitro-group in our osotriazole was obtained by oxidation with potassium permanganate to the known [4] 2-*p*-nitrophenyl-1,2,3-triazole-4-carboxylic acid. Glucose *m*-tolyl- and *m*-chlorophenyl-osotriazole tetra-acetates (II; R = H, R′ = Me and Cl) also yielded on nitration and hydrolysis glucose 3-methyl- and 3-chloro-4-nitrophenylosotriazole (I; R = NO_2, R′ = Me and R′ = Cl), respectively.

Reduction of the nitrophenylosotriazoles was best carried out catalytically on the acetates since the free nitrophenylosotriazoles, owing to their sparing solubilities, reacted very slowly. Thus, glucose *p*-nitrophenylosotriazole tetra-acetate yielded the *p*-aminophenylosotriazole tetra-acetate which was also obtained by hydrogenating glucose 3-chloro-4-nitrophenylosotriazole tetra-acetate (II; R = NO_2, R′ = Cl). The replacement of the

[1] Part VI, *J.*, 1961, 3146.
[2] El Khadem, El-Shafei, and Meshreki, *J.*, 1961, 2957.
[3] Henseke and Winter, *Chem. Ber.*, 1960, **93**, 45.
[4] Bischop, *Science*, 1953, **117**, 715.

halogen by hydrogen in the latter case should be attributed to the influence of the triazole ring and not to the *o*-nitro-group since 2-*m*-chlorophenyl-1,2,3-triazole-4-carboxylic acid also lost its chlorine atom readily on similar treatment.

Unlike halogenation, which takes place exclusively in the 4-position, nitration occurs in the 3-position of *p*-substituted phenylosotriazoles. Thus, glucose *p*-tolylosotriazole tetra-acetate yielded the 4-methyl-3-nitrophenyl derivative (I; R = Me, R′ = NO_2) identical with a specimen obtained from glucose 4-methyl-3-nitrophenylosazone by the action of bromine water; and glucose *p*-chlorophenylosotriazole tetra-acetate gave on nitration and hydrolysis glucose 4-chloro-3-nitrophenylosotriazole (I; R = Cl, R′ = NO_2). On the other hand, glucose *p*-bromophenylosotriazole tetra-acetate (II; R = Br, R′ = H) lost its bromine atom during nitration and afforded glucose *p*-nitrophenylosotriazole (I; R = NO_2, R′ = H).

Oxidation of the sugar residues of glucose nitrophenylosotriazoles (I; R = NO_2, R′ = H, Cl, or Me; R = Cl, R′ = NO_2) with potassium permanganate led to the corresponding nitrophenyl-1,2,3-triazole-4-carboxylic acids. Here the methyl group, being *ortho* to the nitro-group, resisted oxidation owing to hydrogen bonding similar to that in *o*-nitrotoluene. 2-*p*-Aminophenyl- and 2-(3-methyl-4-aminophenyl)-1,2,3-triazole-4-carboxylic acid were prepared from the corresponding nitro-acids by reduction. The former acid showed slight bacteriostatic activity against pneumoccocus *in vitro*.

Glucose *p*-formylphenylosotriazole (I; R = CHO, R′ = H) was readily obtained from glucose *p*-tolylosotriazole tetra-acetate (II; R = Me, R′ = H) by oxidation with chromyl chloride, followed by hydrolysis, first, with methanolic ammonia and then with dilute acid. Potassium permanganate oxidised the *p*-tolylosotriazole tetra-acetate to glucose *p*-carboxyphenylosotriazole tetra-acetate (II; R = CO_2H, R′ = H) but the yield was somewhat poor.

The ultraviolet absorption spectra of some of the above osotriazoles (I and II) and triazole-4-carboxylic acids were determined. Like the halogeno-derivatives investigated previously, they are characterised by a single peak (except that of glucose 3,4-methylenedioxyphenyloso-triazole which has 3 peaks) and, as expected, their absorption maxima are shifted to a much greater extent.

The dissociation constants of the substituted triazole-4-carboxylic acids show the expected variations and are in agreement with previous values.[1]

Experimental

Absorption spectra were determined for ethanolic solutions with a Unicam S.P. 500 spectrophotometer.

Dissociation constants were determined in 4 : 1 w/w methylcellosolve–water according to a previously described procedure.[1]

Osazones were prepared by heating glucose (10 g.) and the calculated amounts of the desired hydrazine hydrochloride and sodium acetate in water (400 ml.) on the water-bath for 2 hr.

Glucose Arylosotriazoles.—(*A*) *Oxidation with copper sulphate.* A solution of the osazone (5 g.) in hot dioxan (100 ml.) was refluxed with copper sulphate (5 g.) in water (100 ml.) for the period shown and filtered. To remove dioxan, the filtrate was distilled off until 100 ml. were collected and the residue was allowed to cool. The *osotriazole* which separated recrystallised from water–ethanol (see Table 1); it was soluble in ethanol or methanol and insoluble in water.

(*B*) *Oxidation with bromine.* The osazone (5 g.), suspended in water (250 ml.), was treated in the cold with bromine (8 ml.) and left at room temperature for the period shown with occasional shaking. The *osotriazole* was filtered off, washed, and recrystallised from water–ethanol (see Table 1).

(*C*) *Nitration of arylosotriazole tetra-acetates.* To a well-stirred cooled solution of the osotriazole tetra-acetate (20 g.), in glacial acetic acid (40 ml.), sulphuric acid (*d* 1·84) (40 ml.)

was added. Nitric acid (*d* 1·52) (8 ml.) was then added dropwise to the mixture during 1 hr., the temperature being kept below 20°. After a further hour's stirring, the mixture was poured on ice and extracted with chloroform. The chloroform layer was washed, dried, and distilled. The residue was hydrolysed by boiling 10% alcoholic sodium hydroxide (100 ml.) for 20 min.

TABLE 1.

Formation of glucose osotriazoles by copper sulphate or bromine.

Aryl in osotriazole	Time (hr.)	Yield (%)	Found (%) M. p.	C	H	N	Formula	Required (%) C	H	N	Procedure
1-$C_{10}H_7$	2	33·3	155—157°	60·8	5·4	13·5	$C_{16}H_{17}N_3O_4$	61·0	5·4	13·3	A
m-$HO_2C{\cdot}CH{:}CH{\cdot}C_6H_4$	2	30·3	206	53·5	5·1	12·1	$C_{15}H_{17}N_3O_6$	53·7	5·1	12·5	A
p-$NHAc{\cdot}C_6H_4$ *	¼	37·0	224—225	49·6	5·9	16·4	$C_{14}H_{18}N_4O_5,H_2O$	49·4	5·9	16·5	A
3,4-$CH_2O_2{:}C_6H_3$ *.....	¼	29·5	212—213	51·0	5·0	13·5	$C_{13}H_{15}N_3O_6$	50·5	4·9	13·6	A
p-$NC{\cdot}C_6H_4$	10	24·0	211—212	54·0	4·9	19·1	$C_{13}H_{14}N_4O_4$	53·8	4·8	19·3	A
p-$NO_2{\cdot}C_6H_4$	24	8·0	250—253	46·7	4·5	17·9	$C_{12}H_{14}N_4O_6$	46·5	4·5	18·1	B
3,4-$NO_2{\cdot}C_6H_3Me$	24	60·0	204—206	—	—	17·7	$C_{13}H_{16}N_4O_6$	—	—	17·3	B

* Reaction was carried out without dioxan.

TABLE 2.

Formation of osotriazoles by nitration.

Aryl *	Subst. of aryl in product	Yield (%)	Found (%) M. p.	C	H	N	Formula	Required (%) C	H	N
Ph [5]	*p*-NO_2	82	250—253°	46·6	4·4	18·0	$C_{12}H_{14}N_4O_6$	46·5	4·5	18·1
p-C_6H_4Br [6] ...	*p*-NO_2	66	250—253	46·9	4·6	17·9	$C_{12}H_{14}N_4O_6$	46·5	4·5	18·1
m-C_6H_4Me † ...	3-Me-4-NO_2	47	228	48·2	5·2	17·6	$C_{13}H_{16}N_4O_6$	48·1	4·9	17·3
p-C_6H_4Me [7] ...	4-Me-3-NO_2	40	204—206	48·3	5·0	17·4	$C_{13}H_{16}N_4O_6$	48·1	4·9	17·3
m-C_6H_4Cl † ...	3-Cl-4-NO_2	59	210—212	41·5	3·9	15·9	$C_{12}H_{13}ClN_4O_6$ ‡	41·8	3·8	16·3
p-C_6H_4Cl [2].....	4-Cl-3-NO_2	43	150—152	42·3	4·0	—	$C_{12}H_{13}ClN_4O_6$	41·8	3·8	—

* In glucose arylosotriazole tetra-acetate was used as starting material. † See Table 3. ‡ Found: Cl, 10·3. Reqd.: Cl, 10·3%.

or by saturated methanolic ammonia (100 ml.) at room temperature for 24 hr. The osotriazole which separated recrystallised from ethanol (see Table 2).

Glucose p-*Formylphenylosotriazole.*—Glucose *p*-tolylosotriazole tetra-acetate [7] (5 g.) in carbon tetrachloride (120 ml.) was treated with chromyl chloride (5 ml.) in portions and the mixture left for 3 hr. with occasional shaking. The precipitate was filtered off, washed with carbon tetrachloride, decomposed with sulphurous acid, and extracted with ether. The ethereal layer was separated, washed, and dried. *Glucose* p-*formylphenylosotriazole tetra-acetate* (4 g.), left after evaporation of ether, crystallised from methanol and had m. p. 90° (Found: C, 54·5; H, 5·3; N, 8·6. $C_{21}H_{23}N_3O_9$ requires C, 54·7; H, 5·0; N, 9·1%).

Hydrolysis. The acetate (2 g.) was suspended in methanolic ammonia and left overnight at room temperature. The product was then boiled with dilute hydrochloric acid for 15 min. and allowed to cool. *Glucose* p-*formylphenylosotriazole*, crystallised from water–ethanol, had m. p. 217°, soluble in ethanol and methanol and insoluble in water (Found: C, 53·5; H, 5·3; N, 14·2. $C_{13}H_{15}N_3O_5$ requires C, 53·2; H, 5·1; N, 14·3%).

Glucose Arylosotriazole Tetra-acetates.—A solution of the osotriazole (2 g.) in dry pyridine (30 ml.) was treated with acetic anhydride (30 ml.) and left for 24 hr., then poured on ice and extracted with ether. The ether layer was washed, dried, and evaporated. Unless otherwise stated, the *products* (Table 3) crystallised from methanol and were soluble in boiling ethanol, methanol, and ether and insoluble in water.

Glucose p-*Aminophenylosotriazole Tetra-acetate.*—(a) Glucose *p*-nitrophenylosotriazole tetra-acetate (5 g.) in ethanol (100 ml.) was hydrogenated at ordinary pressure [8] over palladium–barium sulphate [9] (2 g.) within 4 hr.; 600 ml. of hydrogen were absorbed. The mixture was

[5] Hann and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 735.
[6] Hardegger, El Khadem, and Schreier, *Helv. Chim. Acta*, 1951, **34**, 253.
[7] Hardegger and El Khadem, *Helv. chim. Acta*, 1947, **30**, 1478.
[8] Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., Ltd., London, 1959, p. 472.
[9] *Org. Synth.*, Coll. Vol. III, p. 685.

TABLE 3.

Substituted glucose phenylosotriazole tetra-acetates.

Subst. in aryl	M. p.	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
p-NO_2	114°	80	50·0	4·7	11·9	$C_{20}H_{22}N_4O_{10}$	50·2	4·6	11·7
3-Me-4-NO_2	107—108	57	51·7	5·0	11·4	$C_{21}H_{24}N_4O_{10}$	51·2	4·9	11·4
4-Me-3-NO_2	114	50	—	—	—	—	—	—	—
m-Me	93	80	56·6	5·7	9·5	$C_{21}H_{25}N_3O_8$	56·4	5·6	9·4
m-CO_2H	175	81	53·0	5·0	8·9	$C_{21}H_{23}N_3O_{10}$	52·8	4·8	8·8
m-Cl	91	79	52·0	4·9	9·1	$C_{20}H_{22}ClN_3O_8$	51·4	4·7	9·0
3-Cl-4-NO_2	114	65	47·3	4·3	10·8	$C_{20}H_{21}ClN_4O_{10}$	46·8	4·1	10·9
4-Cl-3-NO_2	126	66	—	—	10·9	$C_{20}H_{21}ClN_4O_{10}$	—	—	10·9
4-Br-3-Me	114—115	51	—	—	7·7	$C_{21}H_{24}BrN_3O_8$ †	—	—	8·0
p-NHAc *	105	66	53·6	5·3	11·4	$C_{22}H_{26}N_4O_9$	53·8	5·3	11·4

* Crystallised from ether–light petroleum. † Found: Br, 14·8. Reqd.: Br, 15·2%.

TABLE 4.

Aryl-1,2,3-triazole-4-carboxylic acids.

Subst. in Ph	M. p.	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
p-NO_2	237°	76	46·3	2·5	23·6	$C_9H_6N_4O_4$	46·1	2·6	23·9
3-Me-4-NO_2	250	40	48·3	3·4	22·4	$C_{10}H_8N_4O_4$	48·4	3·2	22·6
3-Cl-4-NO_2	228—230	50	40·6	2·3	20·4	$C_9H_5ClN_4O_4$ *	40·2	1·9	20·9
4-Cl-3-NO_2	220—222	30	40·6	1·9	20·6	$C_9H_5ClN_4O_4$	40·2	1·9	20·9
p-NHAc	328 (decomp.)	66	53·6	4·2	22·8	$C_{11}H_{10}N_4O_3$	53·6	4·1	22·8

* Found: Cl, 13·5. Reqd.: Cl, 13·2%.

TABLE 5.

Ultraviolet spectra and dissociation constants.

R	R′	*o*-Subst.	$\lambda_{max.}$	log ε	$\lambda_{min.}$	log ε	pK_a
Osotriazole (I)							
NO_2	H	H	310	3·49	270	3·14	—
Me	NO_2	H	270	4·26	—	—	—
Cl	NO_2	H	245	3·87	—	—	—
NHAc	H	H	286—288	4·38	240—244	3·72	—
CN	H	H	286	4·78	235—236	3·63	—
O–CH_2–O		H	230	3·64	246	2·34	—
			285—286	3·76	290	3·72	—
			300—310	3·80	—	—	—
Osotriazole tetra-acetate							
NH_2	H	H	300	4·27	240	2·63	—
2-*Aryl*-1,2,3-*triazole*-4-*carboxylic acids*							
NO_2	H	H	310	4·27	256	2·82	4·54
NO_2	Cl	H	286	4·23	250	3·84	4·44
NO_2	Me	H	—	—	—	—	4·57
Cl	NO_2	H	242	4·27	—	—	—
NH_2	H	H	—	—	—	—	5·28
NH_2	Me	H	—	—	—	—	5·37
NHAc	H	H	282	4·85	245	4·27	—
H	H	Me	—	—	—	—	5·10
Cl	Cl	H	276—278	4·46	234—238	3·58	4·68
Br	Cl	H	276	4·57	238	3·27	4·63
Br	H	Me	258	4·06	—	—	4·95
Br	Br	H	280	4·49	240	3·42	4·67
Br	CO_2H	H	260—264	4·39	226—228	3·92	5·04

filtered and concentrated; *glucose* p-*aminophenylosotriazole tetra-acetate* separated. Crystallised from methanol, it had m. p. 120°, the solubility being as for the other acetates (Found: C, 53·3; H, 5·4; N, 12·6. $C_{20}H_{24}N_4O_8$ requires C, 53·6; H, 5·4; N, 12·5%).

(b) Glucose 3-chloro-4-nitrophenylosotriazole tetra-acetate (2 g.) was catalytically hydrogenated as above, yielding the preceding acetate, m. p. and mixed m. p. 120°.

2-*Phenyl*-1,2,3-*triazole*-4-*carboxylic Acid*.—A solution of 2-*m*-chlorophenyl-1,2,3-triazole-4-carboxylic acid (0·3 g.) in ethanol was catalytically hydrogenated as above and yielded 2-phenyl-1,2,3-triazole-4-carboxylic acid (0·2 g.), m. p. and mixed m. p. 191° [10] (Found: C, 57·1; H, 3·6; N, 22·2; Cl, 0·0. Calc. for $C_9H_7N_3O_2$: C, 57·1; H, 3·7; N, 22·2%).

Various 2-*Aryl*-1,2,3-*triazole*-4-*carboxylic Acids*.—A boiling suspension of the osotriazole (1—2 g.), in water (100—200 ml.), was treated with potassium permanganate (3—6 g.) until a pink colour persisted. The hot mixture was filtered, treated with sodium hydrogen sulphite, and acidified. The *acid* which separated recrystallised from water–ethanol; it was soluble in ethanol or methanol and insoluble in water (see Table 4).

2-p-*Aminophenyl*-1,2,3-*triazole*-4-*carboxylic Acid*.—2-*p*-Nitrophenyl-1,2,3-triazole-4-carboxylic acid (1 g.) in methanol (50 ml.) was heated with 1·5% aqueous sodium dithionite (200 ml.) for 1 hr. The solution was poured in water (100 ml.) containing a little ammonia, concentrated, and extracted with ether. The ether layer was washed, dried, and concentrated, whereby 2-p-*aminophenyl*-1,2,3-*triazole*-4-*carboxylic acid* separated (0·3 g.). Crystallised from water–ethanol, it had m. p. 265° (decomp.) and was soluble in ethanol, methanol, and ether and insoluble in water (preliminary experiments showed that it possessed bacteriostatic activity against pneumococcus *in vitro*) (Found: C, 53·1; H, 4·0; N, 27·4. $C_9H_8N_4O_2$ requires C, 52·9; H, 3·9; N, 27·4%).

2-(4-*Amino*-3-*methylphenyl*)-1,2,3-*triazole*-4-*carboxylic Acid*.—2-(3-Methyl-4-nitrophenyl)-1,2,3-triazole-4-carboxylic acid (0·6 g.), when catalytically hydrogenated, yielded 2-(4-*amino*-3-*methylphenyl*)-1,2,3-*triazole*-4-*carboxylic acid* (0·3 g.), m. p. 215—217°, solubility as for the other acids (Found: N, 25·6. $C_{10}H_{10}N_4O_2$ requires N, 25·7%).

Spectra and Dissociation Constants.—These are recorded in Table 5.

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[10] El Khadem, Diss., Zürich, 1950, p. 80; Hardegger and Schreier, *Helv. Chim. Acta*, 1952, **35**, 232.