664. *The Scope and Mechanism of Carbohydrate Osotriazole Formation. Part IX.*[1] *Fluorine Derivatives and the Insecticidal Action of the Formyltriazoles.*

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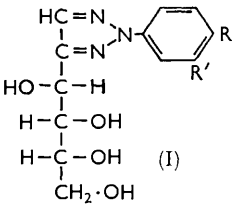
meta- and *para*-Substituted fluorophenylosotriazoles of some carbohydrates, and derived triazole-4-carboxylic acids, as well as corresponding 2-(halogenophenyl)-1,2,3-triazoles, have been prepared for screening as insecticides. Promising results were obtained for the last series. The properties of fluorophenyltriazoles differ from those of the other halogeno-derivatives only in the increased resistance of fluorine to catalytic hydrogenolysis.

The previous study of carbohydrate halogenophenylosotriazoles [2] has now been extended to the fluorine derivatives, with a view to their possible use as insecticides. The compounds prepared included a number of mono- and di-substituted phenylosotriazoles of the glucose series having fluorine in the *meta*- or *para*-position, as well as the *p*-fluorophenylosotriazoles of other monosaccharides. Also prepared for screening were some 2-(halogenophenyl)-1,2,3-triazole-4-carboxylic acids (III) and 4-formyl-2-(halogenophenyl)-1,2,3-triazoles (II). The latter gave promising results (see Table 6) on the larvæ of *Culex pipiens*; the most active compound was 2-(3,4-dibromophenyl)-4-formyl-1,2,3-triazole (II; R = R′ = Br) with LD_{50} 0·35 p.p.m., a value which compares favourably with that of existing insecticides. The halogenotriazole-4-carboxylic acids (III) are not appreciably toxic; the sugar halogenophenylosotriazoles (I) could not be included in this screening owing

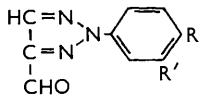
[1] Part VIII, preceding paper.

[2] El Khadem and El-Shafei, *J.*, 1958, 3117; 1959, 1655; El Khadem, El-Shafei, and Mohammed, *J.*, 1960, 3993; 1961, 2957.

to their sparing solubilities. More detailed tests are being carried out on *Culex* and other insects.



(I)



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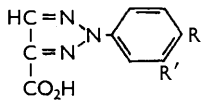

(III)

D-Glucose *p*-fluorophenylosotriazole (I; R = F, R′ = H) was prepared from the *p*-fluorophenylosazone by oxidation with copper sulphate or aqueous chlorine, bromine, or iodine, and, as with the previously investigated triazoles,[2] no halogenation took place since the 4-position was occupied. The *p*-fluoro-derivatives of D-galactose, L-sorbose, and D-xylose were prepared from the corresponding osazones and copper sulphate. This reagent also converted glucose *m*-fluorophenylosazone into the corresponding *m*-fluorophenylosotriazole (I; R = H, R′ = F). The *m*-fluorophenylosazone, when treated with chlorine, yielded glucose 4-chloro-3-fluorophenylosotriazole (I; R = Cl, R′ = F) and with bromine gave glucose 4-bromo-3-fluorophenylosotriazole (I; R = Br, R′ = F); halogenation in both cases took place in the 4-position as usual.

Fluorophenylosotriazoles are distinguished from the other halogenophenylosotriazoles by their resistance to hydrogenation with palladium on barium sulphate which readily removes the other halogens.

Sodium periodate was used to convert glucose halogenophenylosotriazoles (I) into the corresponding 4-formyl-2-halogenophenyl-1,2,3-triazoles (II). In this manner the *m*- and *p*-fluoro-, -chloro-, and -bromo-derivatives were prepared, as well as some disubstituted 4-halogeno-derivatives.

2-*m*- and 2-*p*-Fluorophenyl-1,2,3-triazole-4-carboxylic acid (III; R = H, R′ = F, and *vice versa*) and the 4-bromo-3-fluoro-derivative (III; R = Br, R′ = F) were prepared by the action of potassium permangante on the glucose fluorophenylosotriazoles.

The ultraviolet absorption spectra of glucose fluorophenylosotriazoles (I), 2-fluorophenyl-4-formyl-1,2,3-triazoles (II) and 2-fluorophenyl-1,2,3-triazole-4-carboxylic acids (III) are characterised by a single peak between 257 and 277 mμ provided that no nitro-group is present. With the *para*-substituted phenylosotriazoles (I), formylhalogenophenyltriazoles (II) and halogenophenyltriazole-4-carboxylic acids (III), there is a gradual shift of the absorption maximum towards higher wavelength and a gradual increase in the extinction coefficient along the series fluoro-, chloro-, bromo-, iodo-. The *meta*-substituted derivatives, on the other hand, show little variation in the absorption maxima.

The dissociation constants of the acids (III) are in agreement with values of the other 2-(halogenophenyl)-1,2,3-triazole-4-carboxylic acids.[3,4]

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 previous procedure.[3]

Osazones were prepared by adding an aqueous solution of the monosaccharide (10 g. in 100 ml.), followed by a few drops of acetic acid, to the calculated amount of fluorophenylhydrazine hydrochloride and sodium acetate in water (400 ml.). The mixture was heated on the water-bath for the period shown and the *osazone* filtered off (see Table 1). Unless otherwise

[3] El Khadem, *J.*, 1961, 3146.
[4] Bishay, El Khadem, El-Shafei, and Meshreki, *J.*, 1962, 3154.

TABLE 1.

Substituted monosaccharide phenylosazones.

Sugar	Aryl subst.	Time of heating (hr.)	M. p. (decomp.)	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
D-Glucose ...	*m*-F	2	209—211°	65	55·2	5·4	14·1	$C_{18}H_{20}F_2N_4O_4$	54·8	5·1	14·2
D-Glucose ...	*p*-F *	1	204—206	88	54·9	5·3	14·0	$C_{18}H_{20}F_2N_4O_4$	54·8	5·1	14·2
D-Galactose	*p*-F	1	200—202	80	55·1	5·4	14·0	$C_{18}H_{20}F_2N_4O_4$	54·8	5·1	14·2
L-Sorbose ...	*p*-F	¼	Amorphous	—	—	—	—	—	—	—	—
D-Xylose ...	*p*-F	½	Amorphous	—	—	—	—	—	—	—	—

* Schiemann and Müller, *Ber.*, 1933, **66**, 727.

stated, the products crystallised from dilute ethanol and were soluble in boiling ethanol or methanol and insoluble in ether and water.

Monosaccharide Arylosotriazoles.—(A) *Oxidation with copper sulphate.* A solution of the osazone (5—10 g.) in hot dioxan or propan-2-ol (100—200 ml.) was refluxed with copper sulphate (5—10 g.) in water (100—200 ml.) for the period shown (see Table 2) and then filtered. To remove dioxan or propan-2-ol, the filtrate was distilled until 100—200 ml. of distillate had collected and the residue was allowed to cool. The glucose *derivatives* then separated and were crystallised from dilute ethanol; they were soluble in hot ethanol or methanol and sparingly soluble in hot water. To obtain the other osotriazoles, the solution was first freed from copper sulphate by passage of hydrogen sulphide and neutralisation of the filtrate with barium carbonate, and then evaporated to dryness. The *products* crystallised from water and were soluble in cold ethanol or methanol and sparingly soluble in cold water.

(B) *Oxidation with chlorine.* Chlorine was bubbled into a suspension of the osazone (5 g.) in water (200 ml.) for 2 hr., and the mixture kept overnight. The osotriazole obtained was filtered off, washed, and crystallised from dilute ethanol (see Table 2).

(C) *Oxidation with bromine.* The osazone (5 g.), suspended in cold water (250 ml.), was treated with bromine (8 ml.) and left overnight at room temperature with occasional shaking. The osotriazole was filtered off, washed, and crystallised from dilute ethanol (see Table 2).

(D) *Oxidation with iodine.* The osazone (2 g.) was suspended in a solution of iodine (20 g.) in 10% aqueous potassium iodide (200 ml.) and left at room temperature for 3 weeks with occasional shaking. The osotriazole was filtered off, washed, and crystallised from dilute ethanol (see Table 2).

TABLE 2.

Formation of fluorophenylosotriazoles.

No.	Monosaccharide phenylosazone	Subst. in product	Method	Time	M. p.	Yield (%)
1	D-Glucose *m*-F	*m*-F	A	4 hr.	198°	52
2	D-Glucose *m*-F	4-Cl-3-F	B	2 hr.	218	20
3	D-Glucose *m*-F	4-Br-3-F	C	1 day	232	35
4	D-Glucose *p*-F	*p*-F	A	2 hr.	214	42
5	D-Glucose *p*-F	*p*-F	B	2 hr.	214	30
6	D-Glucose *p*-F	*p*-F	C	1 day	214	40
7	D-Glucose *p*-F	*p*-F	D	21 days	214	45
8	D-Galactose *p*-F	*p*-F	A	1 hr.	123	38
9	L-Sorbose *p*-F	*p*-F	A	½ hr.	131	40
10	D-Xylose	*p*-F	A	1 hr.	108	32

No.	Found (%) C	H	F	N	Formula	Required (%) C	H	F	N
1	51·0	5·3	6·6	15·0	$C_{12}H_{14}FN_3O_4$	50·9	4·9	6·7	14·8
2	46·0	4·4	—	12·9	$C_{12}H_{13}FClN_3O_4$	45·7	4·1	—	13·2
3	40·1	3·6	—	11·4	$C_{12}H_{13}FBrN_3O_4$	39·8	3·6	—	11·6
4	51·0	5·0	6·9	15·0	$C_{12}H_{14}FN_3O_4$	50·9	4·9	6·7	14·8
5	50·7	5·1	6·9	15·2	$C_{12}H_{14}FN_3O_4$	50·9	4·9	6·7	14·8
6	50·8	5·2	7·0	15·2	$C_{12}H_{14}FN_3O_4$	50·9	4·9	6·7	14·8
7	51·0	5·2	6·9	15·1	$C_{12}H_{14}FN_3O_4$	50·9	4·9	6·7	14·8
8	50·7	5·1	—	19·4	$C_{12}H_{14}FN_3O_4$	50·9	4·9	—	14·8
9	50·9	5·1	6·9	14·9	$C_{12}H_{14}FN_3O_4$	50·9	4·9	6·7	14·8
10	52·3	5·1	—	16·3	$C_{11}H_{12}FN_3O_3$	52·2	4·7	—	16·6

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 the whole was extracted with ether. The ether layer was washed, dried, and evaporated. The products crystallised from dilute ethanol and were soluble in ethanol, methanol, and ether and insoluble in water. Thus were obtained D-*glucose* p-, m. p. 98° (80%) (Found: C, 53·3; H, 5·0; N, 9·3. $C_{20}H_{22}FN_3O_8$ requires C, 53·2; H, 4·9; N, 9·3%), and m-*fluorophenylosotriazole tetra-acetate*, m. p. 83° (82%) (Found: C, 53·3; H, 4·9; N, 9·1%).

2-*Aryl*-4-*formyl*-1,2,3-*triazoles.*—The osotriazole (200—400 mg.) was shaken at room temperature with aqueous sodium metaperiodate (755 mg. in 10 ml.) for 24 hr. The crystalline shape of the solid quickly changed and the product obtained by filtration (see Table 3) was crystallised from dilute ethanol. It was souble in ethanol or methanol and insoluble in water.

TABLE 3.

Substituted 4-formyl-2-phenyl-1,2,3-triazoles.

Subst. in Ph	M. p.	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
m-F	65—66°	58	57·0	3·3	—	$C_9H_6FN_3O$	56·5	3·1	—
p-F	89—90	62	56·4	3·1	22·0	$C_9H_6FN_3O$	56·5	3·1	22·0
m-Cl.....	90	56	52·4	2·5	19·6	$C_9H_6ClN_3O$	52·5	2·9	20·2
p-Cl	121	68	52·0	3·1	20·0	$C_9H_6ClN_3O$	52·5	2·9	20·3
4-Cl-3-Me...	105	52	53·9	3·8	19·1	$C_{10}H_8ClN_3O$	54·2	3·6	19·0
4-Cl-3-NO_2	113—114	48	43·3	2·3	21·8	$C_9H_5ClN_4O_3$	42·8	2·0	22·2
m-Br	96	54	42·8	2·0	16·4	$C_9H_6BrN_3O$	42·9	2·4	16·7
p-Br.....	114	60	42·8	2·1	16·5	$C_9H_6BrN_3O$	42·9	2·4	16·7
3,4-Br_2.....	149	73	32·7	1·9	12·6	$C_9H_5Br_2N_3O$	32·6	1·5	12·7
4-Br-2-Me	99	44	44·9	3·4	15·7	$C_{10}H_8BrN_3O$	45·1	3·0	15·8
4-Br-3-Me	106	46	45·6	2·9	16·1	$C_{10}H_8BrN_3O$	45·1	3·0	15·8

TABLE 4.

Substituted 2-phenyl-1,2,3-triazole-4-carboxylic acids.

Subst. in Ph	M. p.	Yield (%)	Found (%) C	H	F	N	Equiv.	Formula	Required (%) C	H	F	N	Equiv.
m-F	195°	36	52·7	3·0	9·1	20·4	198	$C_9H_6FN_3O_2$	52·2	2·9	9·2	20·3	207
p-F	218	35	52·1	3·1	9·4	20·3	203	$C_9H_6FN_3O_2$	52·2	2·9	9·2	20·3	207
4-Br-3-F	242	28	37·9	1·8	—	14·5	282	$C_9H_5FBrN_3O_2$	37·8	1·7	—	14·7	286

TABLE 5.

Ultraviolet absorption data and dissociation constants.

R	R′	*o*-Subst.	$\lambda_{max.}$ (mμ)	log ε	$\lambda_{min.}$ (mμ)	log ε	pK_a
Osotriazoles (I)							
F	H	H	268	4·29	222	2·30	—
H	F	H	270—272	4·33	224	3·19	—
Cl	F	H	275	4·43	226—228	3·40	—
Br	F	H	272	4·42	228	3·44	—
NO_2	F	H	230	3·96	262	3·96	—
			310	4·34	—	—	—
2-*Aryl*-4-*formyl*-1,2,3-*triazoles* (II)							
F	H	H	265—267	4·31	220—222	3·55	—
Cl	H	H	272	4·52	228	2·82	—
Cl	Me	H	274—276	4·33	230—232	3·25	—
Br	H	H	274	4·44	228	3·54	—
Br	H	Me	257	4·20	224	3·80	—
Br	Me	H	275	4·39	234	3·30	—
Br	Br	H	275—277	4·44	240	3·60	—
2-*Aryl*-1,2,3-*triazole*-4-*carboxylic acids* (III)							
F	H	H	272	4·24	227	3·05	4·84
H	F	H	272	4·28	226—228	3·05	4·76
Br	F	H	277	4·37	230	2·99	4·63

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, decolorised by sulphur dioxide, then acidified. The acid which separated recrystallised from dilute ethanol; it was soluble in hot ethanol or methanol and insoluble in water (see Table 4).

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

Toxicity —Screening tests were carried out on fourth-instar larvæ of *Culex pipiens*. For each test 50—60 larvæ were used per concentration in 2—3 replicates, with a control. The concentration ranged from 0·02 to 1·6 p.p.m. and kills were recorded after 24 and 48 hr. Solvents used were alcohol for the triazoles, and acetone for D.D.T. used for comparison. Results are shown in Table 6.

TABLE 6.

Toxicity * of 4-formyl-2-phenyl-1,2,3-triazoles (II).

R	R′	*o*-Subst.	LD_{50} † (p.p.m.)
Br	Br	H	0·35
Cl	H	H	0·58
Br	H	H	0·74
Br	Me	H	0·88
Br	H	Me	1·00
F	H	H	>2

* Calculated as LD_{50} after 24 hr., on log-probit paper. † D.D.T. used for comparison, gave a value of 0·03 p.p.m.

This work was supported by a grant from the Supreme Council for Science, U.A.R.

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[*Received, December 28th,* 1962.]