  Bull. Chem. Soc. Jpn., 62, 2701—2708 (1989)

The Synthesis of *C*-Nucleoside Precursors. II.[1] Synthesis and Conformational Analysis of 3-(Pentahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazines[2]

Mohammed A. E. SHABAN* and Mamdouh A. M. TAHA
Department of Chemistry, Faculty of Science, Alexandria University, Alexandria, Egypt
(Received November 14, 1988)

Reaction of 1-hydrazino-4-phenylphthalazine with aldohexoses (D-galactose, D-glucose, D-mannose, and D-talose) and 6-deoxyaldohexoses (L-fucose and L-rhamnose) gave the colored *aldehydo*-sugar (4-phenyl-1-phthalazinyl)hydrazones or the colorless 3-(pentahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazines. The former can be cyclized to the latter by catalytic dehydrogenation. Structure elucidation of the prepared compounds was made on the basis of their various spectral properties. The *C*-nucleoside precursors were further characterized as their *O*-acetyl derivatives and the configurational-conformational correlation of these acetates was studied. Some of the prepared compounds were screened for insectidicidal, nematicidal, and herbicidal activities and found to be inactive. They showed, however, good corrosion inhibition of aluminium in acid solutions.

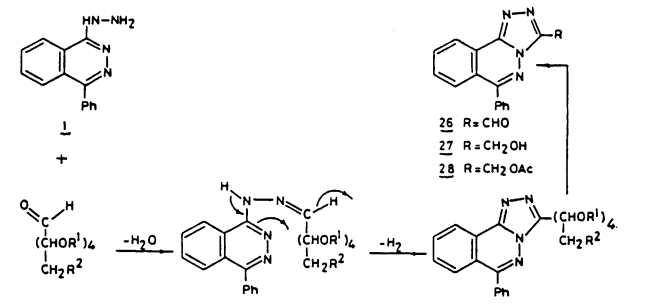
Since the isolation[3,4] of the first *C*-nucleoside pseudouridine in 1957 from yeast RNA, extensive research efforts have been aimed at the isolation and synthesis of newer members as well as of analogs.[5-8] Such efforts are rationalized in terms of the multifarious biological activities exhibited by these compounds mainly as a result of their close structural relationship to nucleosides. *C*-Nucleosides may be synthesized[9] by the approach involving carbon-to-carbon bond formation between the anomeric center of the sugar moiety and a preformed heterocycle or by stepwise construction of the heterocyclic system onto a properly functionalized glycosyl derivative with a fixed anomeric configuration.[10] Albeit yielding mixture of anomers, dehydrative cyclization of the polyhydroxyalkyl chains of heterocyclic compounds carrying polyhydroxyalkyl groups (acyclic *C*-nucleosides) offers a relatively simple approach for the synthesis of *C*-nucleosides.[11]

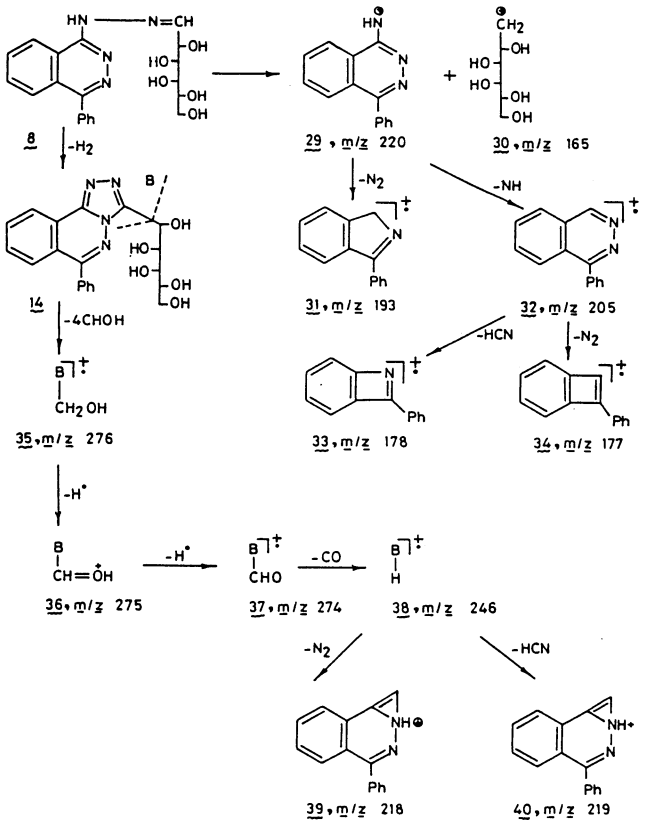
Continuing our work on the synthesis of polyhydroxyalkyl derivatives of heterocycles[12] and fused heterocycles[13,14] uesful as *C*-nucleoside precursors, we describe in this paper the synthesis of the title compounds. Hydrazinophthalazines are among the most medicinally useful hypotensive agents[15,16] which exert their effect as vasodilators by acting on the arteriolar smooth muscles. Studies have shown that Schiff bases[16] of hydrazinophthalazines as well as their cyclization products: 3-substituted 1,2,4-triazolo-[3,4-*a*]phthalazines,[17,18] also retain the hypotensive activity. Thus, 3-alkyl-1,2,4-triazolo[3,4-*a*]phthalazines were found[17] to be as potent as theophylline in inhibiting cyclic adenosine monophosphate phosphodiesterase and possess smooth muscle relaxant activity. Hydrazinophthalazines, however, are not without adverse effects[15] and search for less toxic derivatives thereof is highly desirable. We anticipated that *aldehydo*-sugar 1-phthalazinylhydrazones or their cyclized products 3-(pentahydroxypentyl)-1,2,4-triazolo[3,4-*a*]phthalazines may possess more potent hypotensive activity and less adverse effects since sugar moieties are expected to increase penetration of drugs into and secretion out of biological systems as a result of increasing their hydrophilicity.

Results and Discussion

The reaction of monosaccharides with 1-hydrazinophthalazine was first reported as early as 1954 by Menziani;[19,20] the products were erroneously ascribed 1-(1-phthalazinyl)-2-(glycosyl)hydrazine structures. In a previous publication[13] from this laboratory, this reaction was reinvestigated and the products were found to be either the colored (yellow to orange) *aldehydo*-sugar 1-phthalazinylhydrazones or the colorless 3-(polyhydroxyalkyl)-1,2,4-triazolo[3,4-*a*]-phthalazines. Rosenthal and Lee[21] synthesized the *C*-nucleoside 3-(β-D-ribofuranosyl)-1,2,4-triazolo[3,4-*a*]phthalazine by condensation of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid with 1-hydrazinophthalazine followed by removal of the *O*-benzoyl groups.

In the present investigation the aldohexoses D-galactose (**2**), D-glucose (**4**), D-mannose (**5**), and D-





Scheme 1.

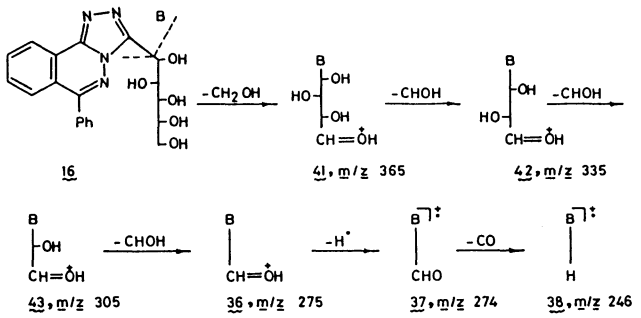
talose (**7**) as well as 6-deoxy-L-galactose (L-fucose, **3**) and 6-deoxy-L-mannose (L-rhamnose, **6**) were allowed to react with one molar equivalent of 1-hydrazino-4-phenylphthalazine[22,23] (**1**). The reaction products (**8** and **11**) of D-galactose and D-mannose were yellow and orange respectively while those (**16**, **19**, **15**, and **18**) of D-glucose, D-talose, L-fucose, and L-rhamnose were colorless.

The yellow product (**8**) of D-galactose had elemental analysis data agreeing with the monohydrate of the molecular formula $C_{20}H_{22}N_4O_5$. The IR spectrum of this product showed OH, NH, and C=N absorptions; its UV/visible spectrum revealed four maxima; and its ^{1}H NMR spectrum showed NH, CH=N, nine aromatic protons, and five OH signals. These data indicate that this product possesses the hydrazone structure: *aldehydo*-D-galactose (4-phenyl-1-phthalazinyl) hydrazone (**8**). The mass spectrum of **8** (see Scheme 1) did not show a molecular ion peak, yet revealed a fragmentation pattern consistent with the assigned structure. Cleavage of the hydrazono N-N bond gave the two fragments **29** (base peak, 100%) and **30** belonging to the phthalazine and sugar moieties respectively. Further cleavage of the heterocycle segment **29** gave fragments to which structures **31**—**34** were assigned on the basis of previous work[13,24-26] on similar systems.

The orange product obtained from the reaction of D-mannose (**5**) with 1-hydrazino-4-phenylphthalazine (**1**) gave analytical and spectral data similar to those obtained for hydrazone **8** and was, accordingly, assigned the structure of *aldehydo*-D-mannose (4-phenyl-1-phthalazinyl)hydrazone (**11**).

It was interesting to notice that repeated crystallization of the yellow hydrazone **8** gave a colorless product having different properties than those of the starting hydrazone. Thus, whereas **8** melted at 203—205 °C, the colorless product melted at 228—231 °C and the fingerprint region of their molecular spectra were substantially different. The UV/visible spectrum of the colorless product exhibited only two absorption maxima; the two other maxima which appeared in the spectrum of the hydrazone (**8**) were lacking. The ^{1}H NMR spectrum of the colorless product revealed the same number of aromatic and sugar chain protons as those of the parent hydrazone **8**, yet the azomethine and hydrazono protons (-CH=N-NH-) present in the spectrum of **8** were missing. In agreement with the ^{1}H NMR was the elemental analysis data which is compatible with the molecular formula $C_{20}H_{20}N_4O_5$; two hydrogens less than the starting hydrazone **8**. These data obviously indicated that repeated crystallization of **8** was accompanied by gradual thermal dehydrogenative cyclization until eventually transformed into the acyclic *C*-nucleoside 3-(D-*galacto*-pentahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]-phthalazine (**14**). This cyclization was carried out more efficiently under catalysis conditions by heating aqueous methanolic solutions of **8** with 10% palladium-on-charcoal whereupon **14** was obtained in high purity and excellent yield. Similarly, catalytic dehydrogenative cyclization of the orange *aldehydo*-D-mannose (4-phenyl-1-phthalazinyl)hydrozone (**11**) by heating its solution in aqueous methanol with 10% palladium-on-charcoal also gave the colorless 3-(D-*manno*-pentahydroxypentyl)-6-phenyl-1,2,4-triazolo-[3,4-*a*]phthalazine (**17**).

Reaction of D-glucose (**4**) with 1-hydrazino-4-phenylphthalazine (**1**) under the same conditions which were used for the reaction with D-galactose (**2**) and D-mannose (**5**) gave, unexpectedly, and a colorless product; the anticipated yellow hydrazone **10** has never been obtained. The ^{1}H NMR of this colorless product showed signals of the nine aromatic protons as well as the alditol chain protons; no azomethine or hydrazono proton signals (-CH=N-NH-) were present. The elemental analysis data agreed with the molecular formula $C_{20}H_{20}N_4O_5$ with two hydrogens less than the expected hydrazone **10**. These data would reconcile with the structure 3-(D-*gluco*-pentahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]-phthalazine (**16**). Thus, in contrast to D-galactose and D-mannose which gave the colored intermediate hydrazones, D-glucose directly gave the colorless cyclic triazolophthalazine. A plausible rationalization of this difference may be based upon the different solubilities of the intermediate hydrazones. The hydrazones (**8** and **11**) derived from D-galactose and D-



Scheme 2.

mannose were sparingly soluble enough to permit their separation while that (**10**) derived for D-glucose was soluble enough to remain in solution and, hence, undergoes thermal dehydrogenative cyclization to **16**. The mass spectrum of **16** did not reveal a molecular ion peak, yet showed the ($M-CH_2OH$) fragment (**41**, Scheme 2) which underwent sequential alditol chain fragmentation giving fragments **42**, **43**, and **36—38**. The B+30 fragment **36**, corresponding to the heterocyclic base carrying a protonated formyl group ($B-CHO^+H$), characteristic of [27] *C*-nucleosides appeared at *m/z* 275.

Similar to D-glucose (**4**), 1-hydrazino-4-phenylphthalazine (**1**) reacted with L-fucose (**3**), L-rhamnose (**6**), and D-talose (**7**) to give the corresponding colorless 3-(polyhydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]-phthalazine **15**, **18**, and **19** respectively.

Oxidative cleavage of the alditol chains of **14—19** with sodium periodate at room temperature gave 4-formyl-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (**26**). Reduction of **26** with sodium borohydride gave 3-hydroxymethyl-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (**27**). Acetylation of **27** gave 3-acetoxymethyl-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (**28**). In their study on the pathogenesis of 1-hydrazinophthalazine-induced systemic lupus erythematosus, Zimmer et al.[28] synthesized 3-hydroxymethyl-1,2,4-triazolo[3,4-*a*]phthalazine and proved, by direct comparison, that it is a major metabolite found in the urine of hypertensive patients on treatment with this drug. 3-Hydroxymethyl-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (**27**) may, therefore, be used for a imilar study.

For further characterization of the 3-polyhydroxypentyl-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazines (**14—19**) and in order to study the configurational-conformational correlations of their alditol chains, their per-*O*-acetyl derivatives were prepared by acetylation with acetic anhydride in the presence of pyridine. Out of the six prepared acetates, only three could be obtained in a crystalline form namely: 3-(D-*galacto*-1,2,3,4,5-pentaacetoxypentyl)- (**20**), 3-(D-*gluco*-1,2,3,4,5-pentaacetoxypentyl)- (**22**), and 3-(L-*galacto*-1,2,3,4-tetraacetoxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (**21**). The three other per-*O*-acetyl derivatives **23—25** having the D-*manno*-, 5-deoxy-L-*manno*-, and D-*talo*-pentitol configurations respectively were obtained as syrupy products. The IR spectra of the crystalline acetates (**20—22**) showed ester carbonyl absorptions and their ^1HNMR spectra revealed nine aromatic protons followed by the alditol chain protons signals (see Table 1). Among the alditol chain protons, H-1 resonated at the highest field due to electronic deshielding by the adjacent heterocyclic system.[29] Alditol H-2 resonated at the next lower field followed by H-3, H-4, H-5, and H-5′. These assignments were made on the basis of signal multiplicities and compared very well with those of acetylated alditol derivatives of 1,2,3-triazoles,[30] tetrazoles,[31] 1,3,4-oxadiazoles,[32] thiazoles,[33] and benzothiazoles.[34] Knowing[33,35–38] that the magnitude of vicinal proton-proton coupling constants of < 4 Hz correspond to protons having gauche orientation (dihedral angle ca. 60°) and that values of >7 Hz correspond to antiparallel orientation (dihedral angle

Table 1. Chemical Shifts[a] (δ) of the Alditol-Chain Protons of 3-(Polyacetoxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazines in $CDCl_3$ at 90 MHz

Compound	Configuration	H-1	H2	H-3	H-4	H-5	H-5′	H-5″
20	D-*galacto*-	6.55 d	—	5.68[b] m	5.36m	4.28 dd	3.92 dd	—
21	5-deoxy-L-*galcto*-	6.58 d	5.73 dd	5.48 dd	5.13m	—	1.16[b] d	—
22	D-*gluco*-	6.63 d	6.20 dd	— 5.13[b] m	—	4.15 dd	3.87 dd	—

a) Multiplicity of signals: d=doublet, dd=doublet of doublet, and m=multiplet.
b) Overlapping signals.

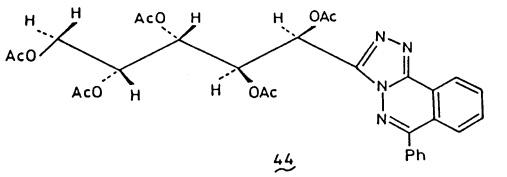
Table 2. Coupling Constants (Hz) of the Alditol-Chain Protons of 3-(Polyacetoxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazines

Compound	Configuration	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5''}$
20	D-*galacto*-	3	a)	a)	6	7.5	12
21	5-deoxy-L-*galacto*-	<3	9	4	7	—	—
22	D-*gluco*-	7.5	3	7.5	3	4.5	12

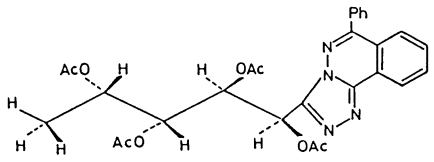
a) Unamenable to first order analysis due to overlapping of H-2 and H-3 signals.

ca. 180°), it is possible to predict the most favored conformations of compounds **20**, **21**, and **22** in terms of their observed coupling data (see Table 2).

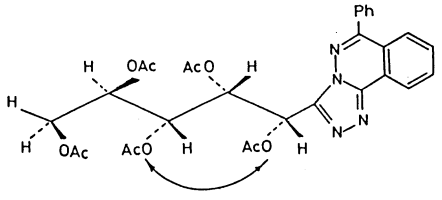
The small $J_{1,2}$ value (≤3 Hz) of the two *galacto*-pentitol derivatives: 3-(D-*galacto*-1,2,3,4,5-pentaacetoxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (**20**) and 3-(L-*galacto*-1,2,3,4-tetraacetoxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (**21**) indicates a gauche arrangement of H-1 and H-2. Like 2-methyl- and 2-phenyl-(D-*galacto*-1,2,3,4,5-pentaacetoxypentyl)-1,3,4-oxadiazoles[32] and penta-*O*-acetyl-D-galactitol,[39] the H-2 and H-3 signals of the D-*galacto*- derivative **20** were unamenable for analysis due to their overlapping. Fortunately, however, the H-2 and H-3 signals of the 5-deoxy-L-*galacto*- derivative **21** were not overlapping and the first-order analysis of the coupling constants was possible. The $J_{2,3}$ value of this derivative is large enough (9 Hz) to indicate exclusive antiparallel disposition of H-2 and H-3. On the other hand, the $J_{3,4}$ value of 4 Hz points out to the gauche relation of H-3 and H-4. These data are very compatible with the expected extended, planar, zigzag conformations **44** and **45** of **20** and **21** respectively in which the bulky heterocycle extends away from the acetylated alditol chain. These conformations are free of any unfavorable eclipsed 1,3-interactions and conform with those assigned[31–34] for other heterocyclic compounds with *galacto*-pentitol side chain.



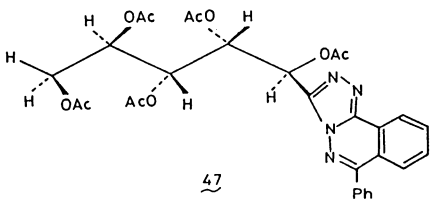
44



45



46



47

It would be expected that the extended, planar zigzag conformation **46** depicted for the 3-(D-*gluco*-1,2,3,4,5-pentaacetoxypentyl)-6-phenyl-1,2,4-triazolo-[3,4-*a*]phthalazine (**22**) represents a highly unfavorable situation owing to the dipolar eclipsed 1,3-interaction of the C-1 and C-3 acetoxyl groups. This expectation is, indeed, supported by the observed $J_{1,2}$ value (7.5 Hz); conformation **46** having H-1 and H-2 in a gauche arrangement would require a $J_{1,2}$ value of <4 Hz. Rotation about the C-1—heterocycle bond of **46** brings H-1 in the antiparallel orientation to H-2 and, therefore, mitigates the aforementioned 1,3-eclipsed interaction. This results in the formation of the "sickle" conformation **47** as a more favorable conformation of the D-*gluco*-derivative **22**. The observed $J_{2,3}$ and $J_{3,4}$ values (3 and 7.5 Hz respectively) are in congruence with the gauche and antiparallel dispositions of H-2–H-3 and H-3–H-4 respectively as depicted in the "sickle" conformation **47**.

Exploring some applications for the synthesized compounds, we have recently found[40,41] that 3-(D-*galacto*-pentahydroxypentyl)-6-phenyl-1,2,4-triazolo-[3,4-*a*]phthalazine (**16**) is a good inhibitor against the acid-corrosion of aluminium. Unfortunately however, compounds **8** and **11** showed no insecticidal activity when applied at the rate of 1000 ppm to the following insect species/host plant systems: mexican beet beetle (*Epilachna varivestis* Mulsant)/pinto bean (*Phaseolus vulgaris*); pea aphid (*Acyrthosiphon pisum* Harris)/fave bean (*Vicia faba*); southern armyworm (*Spodoptera eridania* Gramer)/pinto bean; and the two-spotted spider mite (*Tetranychus urticae*)/pinto bean.

Compounds **8** and **16** also showed no nematicidal activity at an application rate of 10 ppm against root-knot nematode (*Meloidogyne incognita*) hosted on cucumber (*Cucumis sativus*).

Compound **16** exhibited no herbicidal/plant growth regulation in the preemergence response and low activity (10—20%) in the post-emergence response screening when applied to the following test species: soybean (*Glycine max*, 20%); corn (*Zea mays*, 10%); wheat (*Triticum aestivum*, 10%); morningglory (*Ipomea spp*, 20%); velvetleaf (*Abutilon theophrasti*, 10%); barnyardgrass (*Echinochloa crus-galli*, 10%); and foxtail, green (*Setaria veridis*, 10%).

Experimental

General Methods. Melting points were determined with a Kofler block and are uncorrected. The infrared spectra (IR) were recorded for potassium bromide discs on a Unicam SP-1025 or Pye-Unicam SP-2000 spectrophotometers. Ultraviolet-visible spectra were recorded at ambient temper-

ature using a Unicam SP-1750 spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were carried out at ambient temperature (ca. 25 °C) and at 90 MHz with a Varian EM-390 spectrometer for solutions in $CDCl_3$ or $(CD_3)_2SO$. Mass spectra were performed on an analytical system consisting of a Du Pont 21-419 mass spectrometer interfaced with a Du Pont 492-094 data-acquisition system. Follow up of the reactions and checking the homogeneity of the prepared compounds were made by performing thin-layer chromatography (TLC) on Silica gel G (Merck) precoated plates (layer thickness 0.25 mm) used without pretreatment. All the ratios of the solvent systems used were volume-to-volume (v/v); the distance of solvent travel was 5 cm, and the spots were detected by exposition to iodine vapour for a few minutes. All solvent evaporations were performed in a Buchi rotary evaporator under diminished pressure, with an outside bath temperature kept below 50 °C. Elemental microanalyses were performed in the Microanalysis Laboratory, Chemistry Department, Faculty of Science, Alexandria University using Perkin-Elmer Model PE-240 analyzer and in the Microanalysis Unit, Chemistry Department, Faculty of Science, Cairo Universtity.

***aldehydo*-D-Galactose(4-phenyl-1-phthalazinyl)hydrazone (8).** A solution of 1-hydrazino-4-phenylphthalazine (**1**, 1 g) in methanol (20 ml) was filtered through a fritted-glass funnel and added to a filtered solution of D-galactose (**2**, 0.8 g) in water (0.5 ml). The mixture was heated for 10 minutes on a boiling water bath and then kept for 24 hours at room temperature. The crystalline yellow product which separated, was filtered, washed several times with filtered methanol to give 1 g (59%) of **8** as yellow needles, mp 203—205 °C. All attempts to crystallize this hydrazone led to its transformation into the cyclic triazolophthalazine **14**. TLC in 1 : 1 chloroform-methanol, R_f: 0.52; $\lambda_{max}^{50\%EtOH}$ 338, 280, 240, and 212 nm, ($\log\varepsilon$: 4.61, 4.96, and 5.10); ν_{max}^{KBr} 3400 (broad, OH), 3300 (NH) and 1640 cm^{-1} (C=N); ^{1}H NMR $(CD_3)_2SO$: δ=12.15 (s, 1H, deuteratable, NH), 8.80 (d, 1H, CH=N), 8.75—7.40 (m, 9H, aromatic H), 4.82 (d, 1H, deuteratable, OH), 4.60 (m, 1H, alditol H), 4.40 (m, 2H, deuteratable, 2 OH) and 4.15 (m, 2H, deuteratable, 2 OH), the other protons together with the solvent absorption were congregated in a broad signal at δ 3.35.

Calcd for $C_{20}H_{22}N_4O_5 \cdot H_2O$: C, 57.69; H, 5.77; N, 13.46%. Found: C, 58.10; H, 5.60; N, 13.10%.

3-(D-*galacto*-Pentahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (14). Method (A): Attempted crystallization of *aldehydo*-D-galactose (4-phenyl-1-phthalazinyl)hydrazone (**8**) from water-methanol gave a gelatinous product which showed two spots on TLC (1 : 1 chloroform-methanol). One spot migrated at a rate similar to that of the parent hydrazone **8** (R_f: 0.52) and the other was slightly less polar (R_f: 0.55) and corresponds to that of **14**. Repeated crystallization from the same solvent caused the gradual transformation of **8** into **14** which crystallized from water-methanol as colorless needles, mp 228—231 °C; TLC in 1 : 1 chloroform-methanol, R_f: 0.55; $\lambda_{max}^{50\%EtOH}$ 244 and 212 nm ($\log\varepsilon$: 4.81 and 4.63); ν_{max}^{KBr} 3420 (broad, OH) and 1630 cm^{-1} (broad C=N); ^{1}H NMR $(CD_3)_2SO$: δ=8.75—7.37 (m, 9H, aromatic H), 5.37 (m, 2H, alditol H), 4.75 (d, 1H, deuteratable, OH), 4.40 (m, 1H, deuteratable, OH), 4.22 (d, 3H, deuteratable, 3 OH), and 3.75 (m, 2H, alditol H), the other protons together with the solvent absorption were gathered in a broad signal at δ=3.53.

Calcd for $C_{20}H_{20}N_4O_5$: C, 60.60; H, 5.09; N, 14.13%. Found: C, 60.10; H, 5.05; N, 14.74%.

Method (B): A solution of *aldehydo*-D-galactose (4-phenyl-1-phthalazinyl)hydrazone (**8**, 1 g) in a mixture of water (5 ml) and methanol (20 ml) was treated with 10% palladium-on-charcoal (0.5 g) and refluxed for 4 hours. The catalyst was filtered off on a layer of Celite and the filtrate was evaporated to dryness. Crystallization of the residue from water-methanol gave 0.7 g (70%) of **14**, mp and mixed mp 228—231 °C, having the same spectral properties as that obtained according to method (A).

3-(D-*galacto*-1,2,3,4,5-Pentaacetoxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (20). 3-(D-*galacto*-Pentahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (**14**, 1 g) was treated with pyridine (5 ml) and acetic anhydride (5 ml) for 24 hours at room temperature. The mixture was poured onto crushed ice and the product which separated was filtered, washed with water, and crystallized from methanol to give 0.9 g (59%) of **20**, mp 195—198 °C; TLC in 9 : 1 chloroform-methanol, R_f: 0.65; ν_{max}^{KBr} 1760 cm^{-1} (ester-carbonyl, *O*-acetyl groups); ^{1}H NMR ($CDCl_3$): δ=8.80—7.46 (m, 9H, aromatic H), 6.55 (d, 1H, alditol H-1), 5.68 (s, 2H, alditol H-2+H-3), 5.36 (m, 1H, alditol H-4), 4.28 (dd, 1H, alditol H-5), 3.92 (dd, 1H, alditol H-5′), 2.24, 2.13, 2.03 (3s, 3H each, 3 acetyl groups), and 1.98 (s, 6H, 2 acetyl groups).

Calcd for $C_{30}H_{30}N_4O_{10}$: C, 59.40, H, 4.99; N, 9.24%. Found: C, 59.85; H, 4.64; N, 9.67%.

3-(L-*galacto*-1,2,3,4-Tetrahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (15). A solution of 1-hydrazino-4-phenylphthalazine (**1**, 1 g) in methanol (20 ml) was added to a solution of 6-*deoxy*-L-galactose (L-fucose, **3**, 0.69 g) in the least amount of water (ca. 0.2 ml), and the mixture was heated for 20 minutes on a boiling water bath. The product, which separated after cooling was filtered, washed with chloroform and ether, and crystallized from water-methanol to give 0.9 g (56%) of **15**, mp 243—245 °C, TLC in 1 : 1 chloroform-methanol, R_f: 0.52; ν_{max}^{KBr} 3400 (boroad, OH) and 1625 cm^{-1} (C=N); ^{1}H NMR $(CD_3)_2SO$: δ=8.60—7.35 (m, 9H, aromatic H), 5.35 (m, 2H, alditol H), 4.68 (s, 1H, deuteratable, OH) and 1.06 (d, 3H, pentitol CH$_3$), the other protons and hydroxyl protons together with the solvent absorption were congregated in a broad signal at δ=3.45.

Calcd for $C_{20}H_{20}N_4O_4$: C, 63.16; H, 5.26; N, 14.74%. Found: C, 63.51; H, 5.30; N, 14.79%.

3-(L-*galacto*-1,2,3,4-Tetraacetoxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (21). A solution of 3-(L-*galacto*-1,2,3,4-tetrahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]-phthalazine (**15**, 1 g) in pyridine (4 ml) was treated with acetic anhydride (4 ml) and kept at room temperature for 24 hours. The mixture was poured onto crushed ice and the product which separated was filtered, washed with water, and crystallized from methanol to give 0.6 g (42%) of **21**, mp 252—255 °C; TLC in 9 : 1 chloroform-methanol, R_f: 0.62; ν_{max}^{KBr} 1760 and 1745 cm^{-1} (ester-carbonyl, *O*-acetyl groups); ^{1}H NMR ($CDCl_3$): δ=8.80—7.47 (m, 9H, aromatic H), 6.58 (d, 1H, alditol H-1), 5.73 (dd, 1H, alditol H-2), 5.48 (dd, 1H, alditol H-3), 5.13 (m, 1H, alditol H-4), 2.20, 2.11, 1.92, 1.88 (4s, 3H each, 4 acetyl groups), and 1.16 (d, 3H, pentitol CH$_3$).

Calcd for $C_{28}H_{28}N_4O_8$: C, 61.31; H, 5.11; N, 10.22%. Found: C, 61.35; H, 5.29; N, 10.16%.

3-(D-*gluco*-Pentaacetoxypentyl)-6-phenyl-1,2,4-triazolo-[3,4-*a*]phthalazine (16). A solution of 1-hydrazino-4-phenylphthalazine (**1**, 1 g) in methanol (30 ml) was treated with a solution of D-glucose (**4**, 0.8 g) in the least amount of water (ca. 0.3 ml) and the mixture was heated for 15 minutes on a boiling water bath. The mixture was left to attain ambient temperature and the product which separated was filtered, washed with chloroform and ether, and crystallized from water-methanol to give 1 g (59.5%) of **16**, mp 245—247 °C; TLC in 1:1 chloroform-methanol R_f: 0.52; ν_{max}^{KBr} 3500, 3380 (OH) and 1550 cm^{-1} (C=N); ^1H NMR $(CD_3)_2SO$: δ=8.70—8.45 (m, 9H, aromatic H), 5.58 (d, 1H, deuteratable, O<u>H</u>), 5.30 (m, 1H, alditol H), 4.60 (m, 2H, deuteratable proton, O<u>H</u>+ undeuteratable proton, alditol H), and 4.28 (m, 3H, deuteratable, 3O<u>H</u>), the other protons together with the solvent absorption were congregated in a broad signal at δ=3.30.

Calcd for $C_{20}H_{20}N_4O_5$: C, 60.60; H, 5.09; N, 14.13%. Found: C, 60.68; H, 5.24; N, 13.99%.

3-(D-*gluco*-1,2,3,4,5-Pentaacetoxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (22). 3-(D-*gluco*-Pentahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (**16**, 1 g) was treated with pyridine (5 ml) and acetic anhydride (5 ml) and kept at room temperature for 24 hours. The mixture was poured onto crushed ice (150 ml) and the product which separated was filtered, washed with water, and crystallized from methanol to give 0.9 g (59%) of **22**, mp 140—142 °C. TLC in 9:1 chloroform-methanol; R_f: 0.52, ν_{max}^{KBr} 1760 and 1745 cm^{-1} (ester-carbonyl, *O*-acetyl groups); ^1H NMR ($CDCl_3$): δ=8.80—7.48 (m, 9H, aromatic H), 6.63 (d, 1H, alditol H-1), 6.20 (dd, 1H, alditol H-2), 5.13 (m, 1H, alditol H-3+H-4), 4.15 (dd, 1H, alditol H-5), 3.87 (dd, 1H, alditol H-5'), 2.07 (s, 6H, 2 acetyl groups), 2.02, 1.88, and 1.75 (3s, 3H each, 3 acetyl groups).

Calcd for $C_{30}H_{30}N_4O_{10}$: C, 59.40; H, 4.99; N, 9.24%. Found: C, 59.30; H, 5.09; N, 9.40%.

***aldehydo*-D-Mannose (4-Phenyl-1-phthalazinyl)hydrazone (11).** A solution of 1-hydrazino-4-phenylphthalazine (**1**, 1 g) in methanol (30 ml) was added to a solution of D-mannose (**5**, 0.8 g) in the least amount of water (ca. 0.2 ml) and the mixture was heated for 15 minutes on a boiling water bath. The mixture was kept at ambient temperature for an overnight and the orange crystalline product which separated was filtered, washed with chloroform and ether. Crystallization from water-methanol gave 1 g (59%) of **11**, as orange plates, mp 195—198 °C; TLC in 1:1 chloroform-methanol, R_f: 0.43; $\lambda_{max}^{50\%EtOH}$ 350 and 284 nm (log ε: 2.39 and 2.70); ν_{max}^{KBr} 3430, 3350 (OH), 3280 (NH), 1640, 1610, and 1595 cm^{-1} (C=N); ^1H NMR $(CD_3)_2SO$: δ=12.15 (s, 1H, deuteratable, N<u>H</u>), 8.37 (m, 1H, aromatic H), 5.05 (d, 1H, deuteratable, O<u>H</u>), and 4.60—4.10 (m, 5H, 4 deuteratable protons, 4O<u>H</u>+undeuteratable proton, alditol H), the other protons together with the solvent absorption were gathered in a broad signal at δ=3.35.

Calcd for $C_{20}H_{22}N_4O_5 \cdot H_2O$: C, 57.69; H, 5.77; N, 13.46%. Found: C, 58.01; H, 5.52; N, 13.20%.

3-(D-*manno*-Pentahydroxypentyl)-6-phenyl-1,2,4-triazolo-[3,4-*a*]phthalazine (17). To solution of *aldehydo*-D-mannose (4-phenyl-1-phthalazinyl)hydrazone (**11**, 1 g) in a mixture of water (10 ml) and methanol (30 ml) 10% palladium-on-charcoal (0.5 g) was added and the mixture was refluxed for 3 hours. The catalyst was filtered off on a bed of Celite and the filtrate was evaporated to dryness. Crystallization of the residue from water-methanol gave 0.8 g (81%) of **17**, mp 198—202 °C; TLC in 1:1 chloroform-methanol, R_f: 0.60; $\lambda_{max}^{50\%EtOH}$ 246 nm (log ε: 3.51); ν_{max}^{KBr} 3350 (broad, OH) and 1650 cm^{-1} (broad, C=N); ^1H NMR $(CD_3)_2SO$: δ=8.68—7.42 (m, 9H, aromatic H), 5.70 (d, 1H, deuteratable, O<u>H</u>), 5.27 (m, 1H, alditol H), 4.40 (m, 5H, 4 deuteratable protons, 4O<u>H</u>+undeuteratable proton, alditol H), and 3.75 (m, 4H, alditol H).

Calcd for: $C_{20}H_{20}N_4O_5 \cdot 0.5H_2O$: C, 59.26; H, 5.19; N, 13.83%. Found: C, 59.66; H, 5.16; N, 13.51%.

Attempted Preparation of 23. Acetylation of 3-(D-*manno*-(pentahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]-phthalazine (**17**) with acetic anhydride in the presence of pyridine and processing of the reaction mixture as given for the preparation of **20** gave an uncrystallizable syrupy product.

3-(L-*manno*-1,2,3,4-Tetrahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (18). A solution of 1-hydrazino-4-phenylphthalazine (**1**, 1 g) in methanol (20 ml) was added to a solution of 6-deoxy-L-mannose (L-rhamnose **6**, 0.69 g) in the least amount of water (ca. 0.2 ml) and the mixture was heated for 15 minutes on a boiling water bath. The mixture was kept for an overnight at room temperature and the product which separated was filtered, washed with chloroform and ether, and crystallized from water-methanol to give 0.8 g (50%) of **18**, mp 150—154 °C; TLC in chloroform-methanol, R_f: 0.70; ν_{max}^{KBr} 3300 (broad, OH) and 1640 cm^{-1} (broad, C=N); ^1H NMR $(CD_3)_2SO$: δ=8.68—7.41 (m, 9H, aromatic H), 5.66 (s, 1H, deuteratable, O<u>H</u>), 5.25 (m, 1H, alditol H), and 1.18 (d, 3H, pentitol C<u>H</u>$_3$), the other protons and hydroxyl protons together with the solvent absorption were gathered in a broad signal at δ=3.80.

Calcd for $C_{20}H_{20}N_4O_4 \cdot H_2O$: C, 60.30; H, 5.50; N, 14.07%. Found: C, 60.87; H, 5.51; N, 13.71%.

Attempted Preparation of 24. Acetylation of **18** with acetic anhydride and pyridine yielded uncystallizable syrupy product.

3-(D-*talo*-Pentahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (19). A solution of 1-hydrazino-4-phenylphthalazine (**1**, 1 g) in methanol (20 ml) was treated with a solution of D-talose (**7**, 0.8 g) in the least amount of water (ca. 0.2 ml) and the mixture was heated for 15 minutes on a boiling water bath. The mixture was left to attain ambient temperature and the product which separated was filtered and washed with chloroform and ether. Crystallization from water-methanol gave 0.9 g (54%) of **19**, mp 238—240 °C; TLC in 1:1 chloroform-methanol, R_f: 0.54; ν_{max}^{KBr} 3580, 3260 (broad, OH), and 1620 cm^{-1} (C=N); ^1H NMR $(CD_3)_2SO$: δ=8.80—7.58 (m, 9H, aromatic H), 5.92 (m, 1H, deuteratable, O<u>H</u>), 5.45 (d, 1H, alditol H), 4.89 (d, 1H, deuteratable, O<u>H</u>), and 4.45 (m, 3H, 2 deuteratable protons, 2O<u>H</u>+undeuteratable proton, alditol H), the other protons and hydroxyl protons together with the solvent absorption were gathered in a broad siganl at δ=3.58

Calcd for $C_{20}H_{20}N_4O_5$: C, 60.60; H, 5.09; N, 14.13%. Found: C, 60. 32; H, 5.13; N, 14.01%.

Attempted Preparation of 25. Acetylation of **19** gave an uncrystallizable syrupy product.

3-Formyl-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (26). A suspension of any of the 3-(pentahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (**14—19**, 1 g) in distilled water (15 ml) was treated with a solution of sodium periodate (2.4 g) in distilled water (15 ml) and stirred for one

hour at room temperature. The product was filtered, washed with water, 10% sodium thiosulfate solution and water, and crystallized from methanol to give 0.4 g (57%) of **26**, mp 223—225 °C; TLC in 1 : 1 chloroform-methanol, R_f: 0.76; ν_{max}^{KBr} 1740 (CHO) and 1620 cm^{-1} (C=N); ^1H NMR $(CD_3)_2SO$: δ=10.37 (s, 1H, CHO), and 8.85—7.50 (m, 9H, aromatic H).

Calcd for $C_{16}H_{10}N_4O \cdot 0.5H_2O$: C, 67.85; H, 3.89%. Found: C, 67.64; H, 4.31%.

3-Hydroxymethyl-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (27). A solution of sodium borohydride (0.1 g) in water (5 ml) was dropwisely added to a suspension of 3-formyl-6-phenyl-1,2,4-triazolo[3,4,-*a*]phthalazine (**26**, 1 g) in water (10 ml) while stirring. The mixture was kept at room temperature for an overnight and then treated with a few drops of acetic acid. The product which separated was filtered, washed with water and crystallized from methanol to give 0.7 g (70%) of **27**, mp 248—250 °C; TLC in 1 : 1 chloroform-methanol, R_f: 0.78; ν_{max}^{KBr} 3300 (broad, OH) and 1620 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ=8.85—7.50 (m, 9H, aromatic H), 5.25 (s, 2H, CH_2), and 2.48 (s, 1H, deuteratable, OH).

Calcd for $C_{16}H_{12}N_4O$: C, 69.57; H, 4.35%. Found: C, 69.40; H, 4.49%.

3-Acetoxymethyl-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (28). 3-Hydroxymethyl-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (**27**, 1 g) was treated with pyridine (2 ml) and acetic anhydride (2 ml) at room temperature for 24 hours. The mixture was poured onto crushed ice and then extracted with chloroform. The extract was successively washed with aqueous solutions of potassium hydrogensulfate (10%), saturated sodium hydrogencarbonate and water, and dried (Na_2SO_4). Evaporation of the solvent gave a syrup which crystallized from methanol to give 0.7 g (61%) of **28**, mp 195 °C; TLC in 9 : 1 chloroform-methanol, R_f: 0.52; ν_{max}^{KBr} 1760 cm^{-1} (ester-carbonyl, *O*-acetyl group); ^1H NMR ($CDCl_3$): δ=8.85—7.52 (m, 9H, aromatic H), 5.74 (s, 2H, CH_2) and 2.18 (s, 3H, acetyl group).

Calcd for $C_{18}H_{14}N_4O_2 \cdot 0.5H_2O$: C, 66.06; H, 4.59; N, 17.13%. Found: C, 66.46; H, 4.60; N, 16.90%.

References

1) Reactions of Sugars with Amidrazones and Hydrazidines. Part II; for Part I, see Ref. 13.

2) In the preliminary reports on this work: M. A. E. Shaban, M. A. M. Nassr, and M. A. M. Taha, *Carbohydr. Res.*, **113**, C16 (1983); M. A. E. Shaban and M. A. M. Nassr, Am. Chem. Soc. 186th National Meeting, Washigton, D. C., (1983) CARB-23, the phenyl group position was erroneosly numbered 5.

3) W. E. Cohn, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **16**, 166 (1957).

4) F. F. Davis and F. W. Allen, *J. Biol. Chem.*, **227**, 907 (1957).

5) R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y. (1970) pp. 354—404.

6) G. D. Daves, Jr., and C. C. Cheng, *Progr. Med. Chem.*, **13**, 303 (1976).

7) S. Hanessian and A. G. Pernet, *Adv. Carbohydr. Chem. Biochem.*, **33**, 111 (1976).

8) M. Slavik, "Antitumor Antibiotics," ed by S. K. Carter, H. Umezawa, J. Douros, and Y. Sukurai, Springer-Verlag, Berlin (1978).

9) See for example: M. P. Mertes, J. Zielinski, and C. Pillar, *J. Med. Chem.*, **10**, 320 (1967).

10) See for example: C. K. Chu, *Heterocycles*, **22**, 345 (1984); M. C. Clingerman and J. A. Secrist, III, *J. Org. Chem.*, **48**, 3141 (1983); W. J. Hennen, B. C. Hinshaw, T. A. Riley, S. G. Wood, and R. K. Robins, *J. Org. Chem.*, **50**, 1741 (1985).

11) See for example: J. G. Buchanan, S. J. Moorhouse, and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, **1981**, 2258; M. A. E. Sallam and S. M. E. Abdel Megid, *Carbohydr. Res.*, **125**, 85 (1984).

12) M. Shaban and M. Nassr, *Org. Prep. Proced. Int.*, **8**, 107 (1976), and previous references cited therein.

13) M. A. E. Shaban, R. S. Ali, and S. M. El-Badry, *Carbohydr. Res.*, **95**, 51 (1981).

14) M. A. E. Shaban, M. A. M. Taha, and A. Z. Nasr, Am. Chem. Soc. 190th National Metting, Chicago, Ill., CARB-28 (1985).

15) W. T. Comer and A. W. Gomoll, "Medicinal Chemistry," ed by A. Burger, Wiley-Interscience, New York (1970), pp. 1027—1064.

16) "Handbook of Experimental Pharmacology XXXIX: Antihypertensive Agents," ed by F. Gross, Springer-Verlag, Berlin (1977), p. 39.

17) A. Ishii, K. Kubo, T. Deguchi, and M. Tanaka, *Yakugaku Zasshi*, **99**, 533 (1979); *Chem. Abstr.*, **91**, 133826z (1979).

18) H. M. Faid Allah and R. Soliman, *J. Heterocycl. Chem.*, **24**, 667 (1987).

19) E. Menziani, *Bol. Sci. Fac. Chim. Ind. (Bologna)*, **12**, 162 (1954); *Chem. Abstr.*, **50**, 355i (1956).

20) E. Menziani, *Med. Sper.*, **25**, 277 (1954); *Chem. Abstr.*, **50**, 828g (1956).

21) A. Rosenthal and H. H. Lee, *J. Carbohydr. Nucleosides, Nucleotides*, **5**, 559 (1978).

22) J. Druey and B. H. Ringier, *Helv. Chim. Acta*, **34**, 195 (1951).

23) M. A. E. Shaban, unpublished results.

24) M. A. M. Nassr, S. M. El-Badry, and M. A. E. Shaban, *J. Chinese Chem. Soc.*, **32**, 65 (1985).

25) J. H. Bouri, R. G. Cooks, P. F. Donaghue, J. A. Halleday, and H. J. Rodda, *Aust. J. Chem.*, **20**, 2677 (1967).

26) Q. N. Porter and J. Baldas, "Mass Spectrometery of Heterocyclic Compounds," Wiley-Interscience, New York, N. Y. (1971), p. 463.

27) L. B. Townsend and R. K. Robins, *J. Heterocycl. Chem.*, **6**, 459 (1969).

28) H. Zimmer, R. Glaser, J. Kokosa, D. A. Garteiz, E. V. Hess, and A. Litwin, *J. Med. Chem.*, **18**, 1031 (1975).

29) H. S. El-Khadem, D. Horton, and T. F. Page, Jr., *J. Org. Chem.*, **33**, 347 (1968).

30) H. El-Khadem, D. Horton, and J. D. Wander, *J. Org. Chem.*, **37**, 1630 (1972).

31) A. M. Seldes, I. M. E. Thiel, and J. O. Deferrari, *Carbohydr. Res.*, **39**, 11 (1975).

32) A. M. Seldes, E. G. Gros, I. M. E. Thiel, and J. O. Deferrari, *Carbohydr. Res.*, **49**, 49 (1976).

33) J. B. Lee and B. F. Scanlon, *Tetrahedron*, **25**, 3413 (1969).

34) L. Szilagyi, R. Bognar, and I. Farkas, *Carbohydr. Res.*, **26**, 305 (1973).

35) L. D. Hall, *Advan. Carbohydr. Chem.*, **19**, 51 (1964).

36) R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **43**,

2059 (1965).
37) B. Coxon, *Tetrahedron*, **21**, 3481 (1965).
38) J. M. Williams, *Carbohydr. Res.*, **11**, 347 (1969).
39) S. J. Angyal, R. Le Fur, and D. Gagnaire, *Carbohydr. Res.*, **23**, 121 (1972).
40) B. A. Abdel-Nabey, M. Shaban, and M. Essa, Proceedings, 6th Eur. Symp. on Corrosion Inhibitors, Ferrara, Italy, 1985, p. 295.
41) B. A. Abdel-Nabey, M. M. Essa, and M. A. E. Shaban, *Surface Technol.*, **26**, 165 (1985).