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# Note

## Synthesis of *C*-nucleoside precursors: Alternative routes to 3-(polyhydroxyalkyl)-1,2,4-triazolo[3,4-*a*]phthalazines.

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1,2,4-Triazolo[3,4-*a*]phthalazines have been shown to possess antihypertensive[1–4], tuberculostatic[3], antiinflammatory[5], hypotensive[6,7], and cardiovascular[7] activities. We have previously described the synthesis[8–10], and conformational analysis[9,10], as well as some of the biological[9,10] activities and industrial[11,12] applications of 3-(polyhydroxyalkyl)-1,2,4-triazolo[3,4-*a*]phthalazines. In this paper we describe new routes for the synthesis of these compounds.

### RESULTS AND DISCUSSION

We have previously synthesized acyclic 1,2,4-triazolo[3,4-*a*]phthalazine *C*-nucleoside analogs by the dehydrogenative cyclization of hydrazones derived from monosaccharides and cyclic amidrazones, namely 1-hydrazinophtalazines[8–10]. Some monosaccharide hydrazones[13] derived from the other cyclic amidrazones such as 2-hydrazinoquinoline, 2-hydrazino-4-methylquinoline (2-hydrazinolepidine), 2-hydrazinobenzothiazole, and 2-hydrazinopyridine, however, were resistant to such a dehydrogenative cyclization even under catalytic conditions[13]. We decided, therefore, to direct our attention to derivatives other than hydrazones which possess better leaving entities than hydrogen. Hydrazides derived from aldonic acids and cyclic amidrazones seemed to us to fulfil this requirement since their dehydrative cyclization is expected to be much more facile than the dehydrogenative cyclization of the hydrazone congeners. In this paper we describe two routes for the synthesis of these hydrazides and their cyclization to the title compounds.

Reaction of 1-hydrazino-4-phenylphthalazine[4,14] (**2**) with D-glucono-1,5-lactone (**4**) or of 1-chloro-4-phenylphthalazine[14] (**6**) with D-gluconic acid hydrazide[14,15] (**8**) gave one and the same product. This product showed C=N and OH absorptions, its $^1$H-n.m.r. spectrum showed signals of nine aromatic protons in addition to the pentahydroxypentyl chain protons and hydroxyl protons, and it gave a satisfactory analysis

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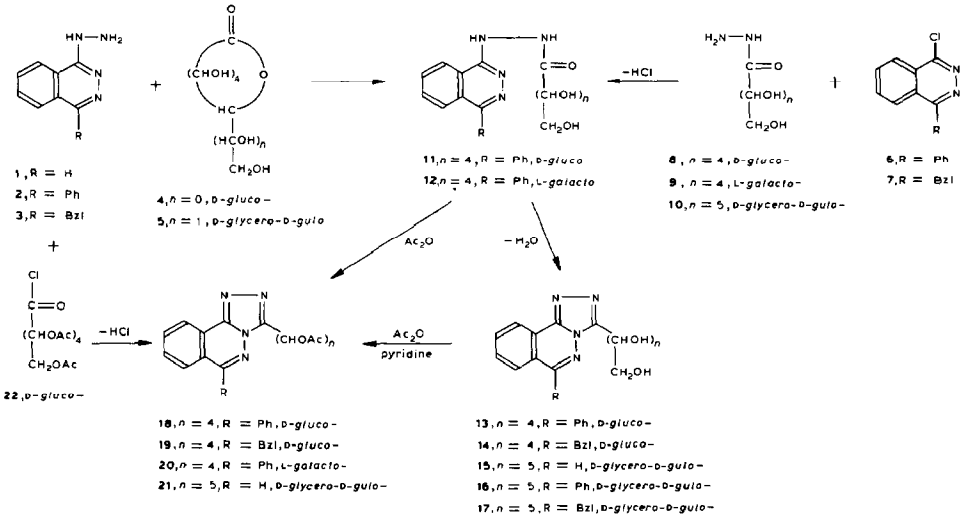
for the molecular formula $C_{20}H_{20}N_4O_5$. The product was identical with 3-(D-*gluco*-pentahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine (**13**) prepared in this laboratory by the autodehydrogenative cyclization of *aldehydo*-D-glucose (4-phenylphthalazin-1-yl)hydrazone[9]. It is evident, in both of these reactions, that **13** was readily formed through the dehydrative cyclization of the un-isolable hydrazide intermediate **11**. The acyclic *C*-nucleoside analogs **14**–**17** were similarly prepared by both of the two mentioned reactions without isolation of the intermediate hydrazides. Compound **14** was also identical with that previously prepared by the autodehydrogenative cyclization of *aldehydo*-D-glucose (4-benzylphthalazin-1-yl)hydrazone[16]. Compounds **15**, **16**, and **17**, bearing hexahydroxyhexyl chains, are described for the first time.




Only in one case was it possible to isolate the intermediate hydrazide, when the imidoyl chloride **6** reacted with L-galactonic acid hydrazide[14] (**9**) to give the 1-(L-galactonoyl)-2-(4-phenylphthalazin-1-yl)hydrazine (**12**). The isolability of **12** was possible on account of its low solubility. The hydrazide structure **12** was inferred for the product on the basis of its elemental analysis and the CON stretching vibration in the infrared. Cylclization and concomitant acetylation of the polyhydroxyalkyl chain of **12** took place upon heating with acetic anhydride, giving the acetylated *C*-nucleoside analog **20**. The i.r. spectrum of the latter showed only C=N and ester–carbonyl absorptions; the NH and CON absorptions present in the spectrum of the parent hydrazide were absent.

Compounds **13**–**17** were further characterized as their acetates. Compounds **13** and **14** gave the corresponding crystalline pentaacetates **18** and **19**; identical with those previously prepared[9,16]. Alternatively, the two pentaacetates **18** and **19** were also prepared in one step by the reaction of the corresponding cyclic amidrazone (**2** and **3**, respectively) with penta-*O*-acetyl-D-gluconoyl chloride[17] (**22**). Whereas compound **15**

also gave the crystalline hexaacetate derivative **21**, compounds **16** and **17** gave syrupy products.

## EXPERIMENTAL

*General methods.* — Melting points were determined with a Kofler block and are uncorrected. The i.r. spectra were recorded for potassium bromide discs on Unicam SP-1025 or Pye-Unicam SP-2000 spectrophotometers. Proton magnetic resonance spectra were carried out at 90 MHz with a Varian EM-390 spectrometer for solutions in $CDCl_3$ or $(CD_3)_2SO$. The homogeneity of nonpolar compounds was checked by t.l.c. on plates precoated with Silica Gel G (Merck; layer thickness 0.25 mm), used without pretreatment. The distance of solvent travel was 5 cm and the spots were detected by exposure to iodine vapour. Evaporations were performed in a rotary evaporator with the bath temperature being kept below 50°. Elemental microanalyses were performed in the Microanalysis Laboratory, Department of Chemistry, Faculty of Science, Alexandria University with a Perkin–Elmer PE-240 analyzer, or in the Microanalysis Unit, Cairo University, Cairo, Egypt.

*3-(Polyhydroxyalkyl)-1,2,4-triazolo[3,4-*a*]phthalazines* (**13–17**). — *Method A.* A solution of the cyclic amidrazone **1**, **2** (ref. 14) or **3** (ref. 14) (6 mmol) in MeOH (30 mL) was added to a solution of the aldonolactone **4** or **5** (6 mmol) in the minimum amount of water (~0.2 mL) and the mixture was heated for 15 min on a boiling-water bath. The product which separated after attaining ambient temperature was filtered off, washed with $CHCl_3$ and ether and crystallized from water–MeOH.

*Method B.* A solution of the imidoyl chloride **6** (ref. 14) or **7** (ref. 14) (6 mmol) in MeOH (30 mL) was added to a solution of the aldonic acid hydrazide **8** (refs. 14,15), **9** (ref. 14), or **10** (ref. 14) (6 mmol) in the minimum amount of water (~0.2 mL) and the mixture was heated for 15 min on a boiling-water bath. The product which separated after attaining ambient temperature was filtered off, washed with $CHCl_3$ and ether, and crystallized from water–MeOH. The following compounds were prepared:

*3-(*D-gluco-*Pentahydroxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a*]phthalazine* (**13**). — Yield: method *A*, 71%; method *B* 55%; m.p. 245–247°, lit.[9], m.p. 245–247°; t.l.c. in 1:1 $CHCl_3$–MeOH, $R_F$ 0.52; $\nu_{max}^{KBr}$ 3500, 3380 (OH) and 1550 $cm^{-1}$ (C=N); $^1$H-n.m.r. $(CD_3)_2SO$: $\delta$ 8.70–8.45 (*m*, 9 H, aromatic H), 5.58 (*d*, 1 H, exchangeable, O*H*), 5.30 (*m*, 1 H, alditol H), 4.60 (*m*, 2 H, one exchangeable H, alditol H + O*H*) and 4.28 (*m*, 3 H, exchangeable, 3 O*H*), the other protons were associated with the solvent to give a broad signal at $\delta$ 3.30.

*Anal.* Calc. 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.

*6-Benzyl-3-(*D-gluco-*penthahydroxypentyl)-1,2,4-triazolo[3,4-*a*]phthalazine* (**14**). — Yield: method *A*, 73%; method *B*, 56%; m.p. 210°, lit.[16], m.p. 210°; t.l.c. in 1:1 $CHCl_3$–MeOH, $R_F$ 0.55; $\nu_{max}^{KBr}$ 3350 (broad, OH) and 1640 $cm^{-1}$ (C=N); $^1$H-n.m.r. $(CD_3)_2SO$: $\delta$ 8.55–7.10 (*m*, 9 H, aromatic H), 5.35 (*d*, 1 H, alditol H) and 4.55 (*m*, 4 H, alditol $CH_2$ + Ph$CH_2$), the other protons were associated with the solvent to give a broad signal at $\delta$ 3.65.

*Anal.* Calc. for $C_{21}H_{22}N_4O_5 \cdot 0.5H_2O$: C, 60.14; H, 5.49; N, 13.37. Found: C, 60.49; H, 5.39; N, 13.55.

*3-(*D-glycero-D-gulo-*Hexahydroxyhexyl)-1,2,4-triazolo[3,4-*a]*phthalazine* (**15**). — Yield: method *A*, 51%; m.p. 210°; t.l.c. in 1:1 $CHCl_3$–MeOH, $R_F$ 0.52; $\nu_{max}^{KBr}$ 3500 (broad, OH) and 1630 $cm^{-1}$ (C=N); $^1$H-n.m.r. $(CD_3)_2SO$: $\delta$ 8.95 (*s*, 1 H, aromatic H), 8.55–7.67 (*m*, 4 H, aromatic H), 5.87 (*d*, 1 H, exchangeable, O*H*), 5.30 (*d*, 1 H, alditol H), and 4.90–4.00 (*m*, 6 H, alditol H), the other protons were associated with the solvent to give a broad signal at $\delta$ 3.65.

*Anal.* Calc. for $C_{15}H_{18}N_4O_6 \cdot 2H_2O$: C, 46.63; H, 5.70; N, 14.51. Found: C, 46.78; H, 5.41; N, 14.80.

*3-(*D-glycero-D-gulo-*Hexahydroxyhexyl)-6-phenyl-1,2,4.triazolo*[3,4-a]*phthalazine* (**16**). — Yield: method *A*, 51%; method *B*, 39%; m.p. 232–235°; t.l.c. in 1:1 $CHCl_3$–MeOH, $R_F$ 0.55; $\nu_{max}^{KBr}$ 3400 (broad, OH) and 1630 $cm^{-1}$ (C=N); $^1$H-n.m.r. $(CD_3)_2SO$: $\delta$ 8.83–7.55 (*m*, 9 H, aromatic H), 5.90 (*d*, 1 H, exchangeable, *OH*), 5.39 (*m*, 1 H, alditol H) and 4.90–4.05 (*m*, 8 H, alditol H and OH), the rest of the protons were associated with the solvent to give a broad signal at $\delta$ 3.55.

*Anal.* Calc. for $C_{21}H_{22}N_4O_6 \cdot 0.5H_2O$: C, 57.93; H, 5.29; N, 12.87. Found: C, 57.62; H, 5.33; N, 12.54.

*6-Benzyl-3-(*D-glycero-D-gulo-*hexahydroxyhexyl)-1,2,4-triazolo[3,4-*a]*phthalazine* (**17**). — Yield: method *A*, 51% method *B*, 40%; m.p. 170–171°; t.l.c. in 1:1 $CHCl_3$-MeOH, $R_F$ 0.54; $\nu_{max}^{KBr}$ 3300 (broad, OH) 1630 $cm^{-1}$ (C=N); $^1$H-n.m.r. $(CD_3)_2SO$: $\delta$ 8.55–7.00 (*m*, 9 H, aromatic H), 5.83 (*d*, 1 H exchangeable, O*H*), 5.32 (*m*, 1 H, alditol H) and 4.40 (*m*, 9 H, alditol H and OH + Ph$CH_2$), the other protons were associated with the solvent to give a broad signal at $\delta$ 3.50.

*Anal.* Calc. for $C_{22}H_{24}N_4O_6 \cdot H_2O$: C, 57.64; H, 5.68; N, 12.23. Found: C, 57.51; H; H, 5.93; N, 12.10.

*3-(Polyacetoxyalkyl)-1,2,4-triazolo[3,4-*a]*phthalazines* (**18**, **19**, and **21**). — *Method A*. A solution of the 3-(polyhydroxyalkyl)-1,2,4-triazolo[3,4-*a*]phthalazine **13**, **14**, **15**, **16**, or **17** (4 mmol) in pyridine (5 mL) was treated with $Ac_2O$ (5 mL) and the mixture was kept for 24 h at ambient temperature. The mixture was poured onto crushed ice and the product that separated was filtered off, washed with water, and crystallized from MeOH.

*Method B*. A solution of 1-hydrazino-4-phenylphthalazine (**2**) or 4-benzyl-1-hydrazinophthalazine (**3**) (6 mmol) in $CHCl_3$ (20 mL) was added to a solution of penta-*O*-acetyl-D-gluconoyl chloride[17] (**22**, 6 mmol) in $CHCl_3$ (30 mL) and the mixture was heated for 20 min on a boiling-water bath. The product obtained after evaporation of most of the solvent was filtered and crystallized from MeOH. The following compounds wepe prepared:

*3-(*D-gluco-*1,2,3,4,5-Pentaacetoxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a]*phthalazine* (**18**). — Yield: method *A* ,59%; method *B*, 46%; m.p. 140–142°, lit.[9], m.p. 140–142°; t.l.c. in 9:1 $CHl_3$–MeOH, $R_F$ 0.52; $\nu_{max}^{KBr}$ 1760 and 1745 $cm^{-1}$ (ester-carbonyl, *O*-acetyl groups); $^1$H-n.m.r. ($CDCl_3$): $\delta$ 8.80–7.48 (*m*, 9 H, aromatic H), 6.63 (*d*, 1 H, alditol H-1), 6.20 (*dd*, 1 H, alditol H-2), 5.13 (*m*, 2 H, alditol H-3 + H-4), 4.15 (*dd*, 1 H, alditol H-5),

3.87 (*dd*, 1 H, alditol H-5), 2.07 (*s*, 6 H, 2 acetyl groups), 2.02, 1.88 and 1.75 (*s*, 3 H each, 3 acetyl groups).

*Anal.* Calc. 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.

*6-Benzyl-3-(*D-gluco-*1,2,3,4,5-pentaactoxypentyl)-1,2,4-triazolo[3,4-*a]*phthalazine* (**19**). — Yield: method *A*, 60%; method *B*, 47%; m.p. 80°, lit.[6], m.p. 80°; t.l.c. in 9:1 $CHCl_3$–MeOH, $R_F$ 0.51; $\nu_{max}^{KBr}$ 1760 $cm^{-1}$ (ester–carbonyl, *O*-acetyl groups); $^1$H-n.m.r. ($CDCl_3$): $\delta$ 8.68–7.10 (*m*, 9 H, aromatic H), 6.65 (*d*, 1 H, alditol H-1), 6.25 (*dd*, 1 H, alditol H-2), 5.33 (*dd*, 1 H, alditol H-3), 5.05 (*m*, 1 H, alditol H-4), 4.51 (*s*, 2 H, ph$CH_2$), 4.22 (*dd*, 1 H, alditol H-5), 4.00 (*dd*, 1 H, alditol H-5), 2.10 (*s*, 9 H, 3 acetyl groups), and 1.93 (*s*, 6 H, 2 acetyl groups).

*Anal.* Calc. for $C_{31}H_{32}N_4O_{10}$: C, 60.00; H, 5.16; N, 9.03. Found: C, 59.80; H, 5.46; N, 8.81

*3-(*D-glycero-D-gulo-*1,2,3,4,5,6-Hexaacetoxyhexyl)-1,2,4-triazolo[3,4-*a]*phthalazine* (**21**). — Yield: method *A*, 67%; m.p. 170°; t.l.c. in 9:1 $CHCl_3$–MeOH, $R_F$ 0.54; $\nu_{max}^{KBr}$ 1770 $cm^{-1}$ (ester–carbonyl, *O*-acetyl groups); $^1$H-n.m.r. ($CDCl_3$): $\delta$ 8.67–8.45 (*m*, 2 H, aromatic H), 8.00–7.67 (*m*, 3 H, aromatic H), 6.45 (*d*, 1 H, alditol H-1), 5.92 (*dd*, 1 H, alditol H-2), 5.67 (*dd*, 1 H, alditol H-3), 5.34 (*dd*, 1 H, alditol H-4), 4.95 (*m*, 1 H, alditol H-5), 4.18 (*m*, 2 H, alditol H-6), 2.17 (*s*, 3 H, acetyl group), 2.07 (*s*, 9 H, 3 acetyl groups), 1.95 and 1.90 (*s*, 3 H each, 2 acetyl groups).

*Anal.* Calc. for $C_{27}H_{30}N_4O_{12} \cdot H_2O$: C, 52.26; H, 5.16; N, 9.03. Found: C, 52.52; H, 5.18; N, 8.90.

*1-(*L-*Galactonoyl)-2-(4-phenylphthalazin-1-yl)hydrazine* (**12**). — A solution of 1-chloro-4-phenylphthalazine (**6**, 1 g) in MeOH (30 mL) was added to a solution *L*-galactonic acid hydrazide[14] (**9**, 0.9 g) in the minimum amount of water (~0.2 mL) and the mixture was heated for 20 min on a boiling water bath. The product that separated after cooling was filtered off, washed with $CHCl_3$ and ether and crystallized from water–MeOH to give 1 g (58%), m.p. 210°; t.l.c. in 1:1 $CHCl_3$–MeOH, $R_F$ 0.43; $\nu_{max}^{KBr}$ 3350 (broad, OH + NH) and 1680 $cm^{-1}$(CON).

*Anal.* Calc. for $C_{20}H_{22}N_4O_6$: C, 57,97; H, 5.31; N, 13.53. Found: C, 57.77; H, 5.10; N, 13.79.

*3-(*L-galacto-*1,2,3,4,5-Pentaacetoxypentyl)-6-phenyl-1,2,4-triazolo[3,4-*a]*phthalazine* (**20**). — A solution of **12** (1 g) in pyridine (5 mL) was treated with $Ac_2O$ (5 mL) and kept for 24 h at room temperature. The mixture was poured onto crushed ice and the product that separated was filtered off, washed with water, and crystallized from MeOH to give 0.8 g (55%) of **20**; m.p. 200°; t.l.c. in 9:1 $CHCl_3$–MeOH, $R_F$ 0.52; $\nu_{max}^{KBr}$ 1760 $cm^{-1}$ (ester-carbonyl, *O*-acetyl groups); $^1$H-n.m.r. ($CDCl_3$) $\delta$ 8.80–7.46 (*m*, 9 H, aromatic H), 6.55 (*d*, 1 H, alditol H-1), 5.68 (*m*, 2 H, alditol H-2+ H-3), 5.38 (*m*, 1 H, alditol H-4), 4.30 (*dd*, 1 H, alditol H-5), 3.92 (*dd*, 1 H, alditol H-5), 2.25, 2.15, 2.05, 2.00 and 1.95 (*s*, 3 H each, 5 acetyl groups).

*Anal.* Calc. for $C_{30}H_{30}N_4O_{10} \cdot H_2O$: C, 57.69; H, 5.13; N, 8.97. Found: C, 57.31; H, 4.84; N, 9.06.

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