Synthesis of 3-(Alditol-1-yl)triazolo[4′,3′ : 2,3]-1,2,4-triazino[5,6-*b*]indoles

Ahmed Mousaad, Hamida Abdel Hamid, Ahmed El Nemr, and El Sayed H. El Ashry*
Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt

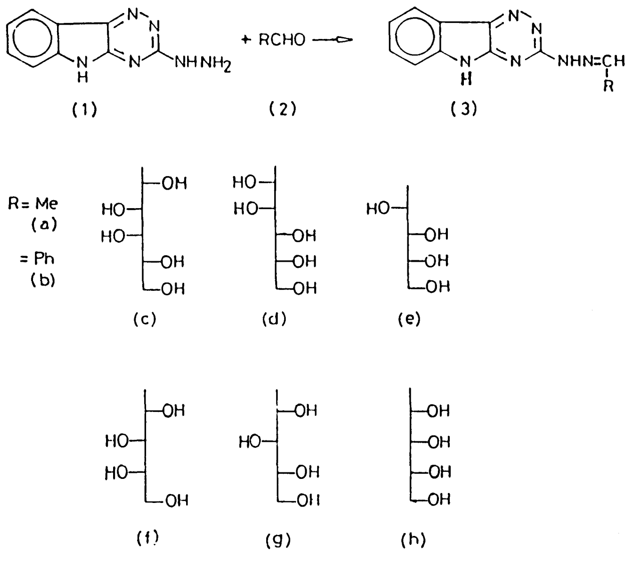
(Received May 7, 1991)

A series of the hydrazones were prepared by the reaction of 3-hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indole (**1**) with monosaccharides, and their acetylation was studied. Cyclodehydrogenation of the hydrazones gave 3-(substituted)-10*H*-1,2,4-triazolo[4′,3′ : 2,3][1,2,4]triazino[5,6-*b*]indole, whose acetylation and partial acetylation were carried out. The ring-chain tautomerism of the hydrazones promoted their heterocyclization. The linear structure, and not that of the angular isomer, has been selected for the products. This structure has been confirmed from a model study of the cyclization of the acetaldehyde derivative of **1**, which was found to be identical with that product obtained from the reaction of 4,5-diamino-3-methyl-1,2,4-triazole with isatin. Periodate oxidation of the hydrazones and their cyclized products was also studied.

The 5*H*-1,2,4-triazino[5,6-*b*]indoles[1–4] and triazolo-1,2,4-triazino[5,6-*b*]indoles[5] have demonstrated a broad spectra of antiviral and antibacterial activities. Furthermore, 5-substituted 3-hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indoles have antihypertensive activity.[6] Other members of such ring systems have been used as herbicides and dyes, as well as reagent in the determination of metal ions. Considerable attention has been drawn to the synthesis of several condensed heterocyclic systems derived from triazoles and triazines.[7–10] The annelation of a heterocycle to the 1,2,4-triazine ring via a functional group on position-3 may have two opportunities for cyclization to give two isomeric structures, depending on the nuclear nitrogen involved in the cyclization. The comparable nucleophilic character of N-2 and N-4 and/or the variation in electronic densities may play a role in the ring closure process.[11–22] These aspects, as well as the importance of C-nucleoside analogues and the interest in the synthesis of polyaza heterocycles, promoted the investigation of the synthesis of triazolo[1,2,4]triazino[5,6-*b*]indole ring systems linked to polyol residues whose degradation offers an avenue to a variety of heterocycles.

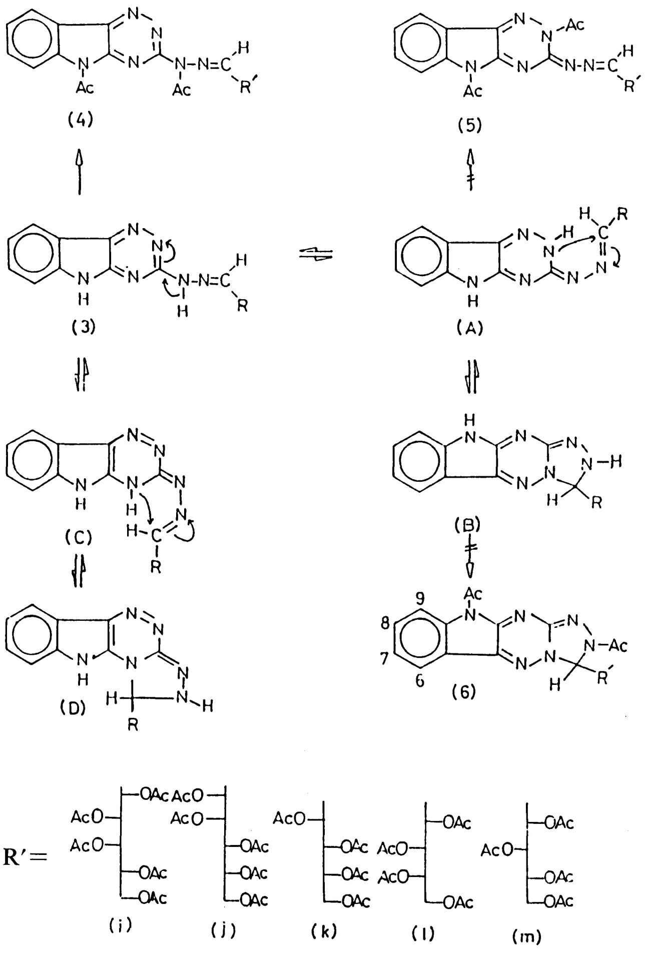
Results and Discussion

The reaction of 3-hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indole **1** with equimolar amounts of a number of monosaccharides was effected by heating the compounds for 0.5 h in an aqueous ethanolic solution and in the presence of a catalytic amount of acetic acid. The hydrazones **3** could be prepared, from the monosaccharides, D-galactose, D-mannose, D-arabinose, L-arabinose, D-xylose, and D-ribose. They are sparingly soluble in the solvents that are suitable for measuring ^{1}H NMR spectra. Consequently, it was not possible in this work to study the possibility of any structural changes of e.g. a hydrazone to a glycosylhydrazine structures.



Scheme 1.

The structure of the acetylated sugar hydrazones was found to be dependent on the type of the hydrazone residue as well as the acylating agent. Acetic anhydride in pyridine under mild conditions caused the acetylation of the hydroxyl groups without affecting the hydrazone residue of most types of hydrazones.[23] Boiling acetic anhydride caused further acetylation of the hydrazone residue to give O-,N-acetyl derivatives in the case of arylhydrazones, particularly those which are not involved in hydrogen bonding.[24,25] However, sugar aroylhydrazones and thiosemicarbazones undergo cyclization of the hydrazone residue into oxadiazoline and thiadiazoline rings.[26–29] Thus, treatment of compounds **3** with acetic anhydride in pyridine at room temperature gave colorless crystalline derivatives, whose combustion analysis indicated that peracetylation had taken place on both the polyol residue and on two NH groups. Furthermore, their IR spectra showed absorptions indicating the presence of OAc and NAc groups. The ^{1}H NMR spectrum of **4i** showed the presence of five OAc and two NAc groups. The two quartets at 3.83 and 4.42 ppm were assigned to H-6′ and H-6, respectively. The multiplets at 5.30 and 5.40 ppm were due to H-5, H-4, and H-3. The doublet of doublets at 5.55 ppm and the doublet at 6.50 ppm were due to H-2 and H-1, respectively. The four aromatic protons appeared in two sets, the first of which appeared as two triplets

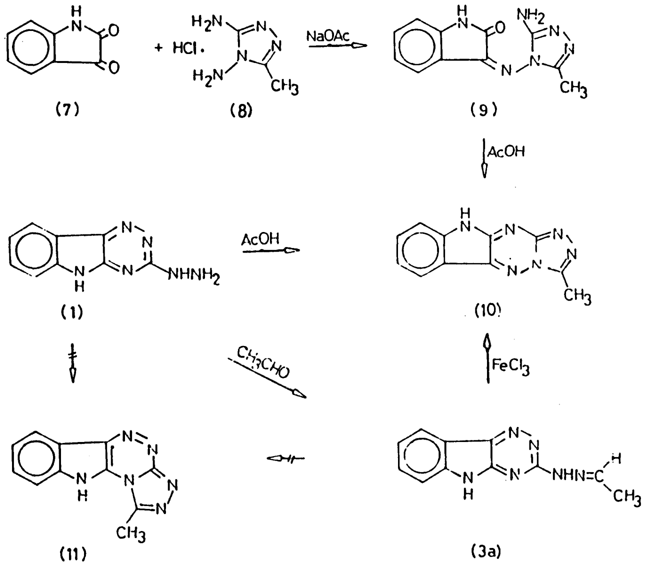


Scheme 2.

due to H-7 and H-8. The second set consisted of two doublets at lower field and were assigned due to H-6 and H-9 as consequence of their proximity to the nitrogen of the triazine ring and to the acetyl group respectively. Long range coupling with a value <1 Hz could be observed for each proton on the aromatic ring. Similarly, the ^{1}H NMR spectra of the other acetates showed a similar pattern (Table 1) to that discussed above. Considering the possible tautomeric forms of the starting hydrazones, two tautomers **A** and **C** may exist, whose ring-chain tautomerism might be represented by **B** and **D**, respectively. The relative preference of the tautomers with the angular **D** and linear **B** isomeric structures will be discussed later. As **A** and **B** might represent the most probable ones, the acetylation may give compounds **5** or **6**. However, these latter structures may be ruled out on the basis of the spectral data and the structure of the acetates may be proposed as **4**.

The derivatives of **1** with aromatic aldehydes could be readily cyclized by refluxing with thionyl chloride to give **12**.[20] However, thionyl chloride can not be selected for effecting the cyclization in the present work, but a 2 M (1 M=1 mol dm^{-3}) solution of iron(III) chloride in ethanol was found to be an effective reagent for the cyclodehydrogenation process. Thus when the hydrazones **3** were subjected to this reagent, yellow crystalline products were obtained. In order to deduce the site of annelation, a detailed study on the model compound **3a** was carried out. The product **10** resulting from the acetaldehyde derivative **3a** was found to be identical with that obtained from the reaction of **1** with boiling acetic acid. Although two isomeric structures could be assigned for this product, the product from the latter reaction was reported[22] to have the angular structure **11**. In the present study, the structure was found to be the linear **10** on the basis of its unambiguous synthesis by the condensation of 4,5-diamino-3-methyl-1,2,4-triazole **8** with isatin **7**. The relative reactivity of the two carbonyl groups of **7**, as well as the two amino groups in **8**, determines the regioselectivity of the reaction whereby **9** was expected to be formed as intermediate which undergoes cyclization to **10**≡**12a**. This type of regioselectivity agrees with that in the literature,[30] as the reaction of **8** with aryl glyoxal gave only one of the two possible positional isomers.

Theoretically, the two directions of ring closure towards the N-2 or N-4 atom may be assumed, in which case the linearly or angularly arranged triazolo-triazino-indole would form. The formation of the angular structure is favored in similar cases and on this basis,[16–19] the formation of **13** should be favored in comparison to the linear structure **12** because the 10-π-electron system (aromatic character) of the indole ring is preserved in the former. However, the formation of the linear isomer **12** is favored on electronic grounds, as the higher nucleophilicity[11–15] of N-2 than that of N-4, suggested that the cyclization is likely to take place at N-2. Moreover, the corresponding tautomer leading to the linear isomer is energetically more favored than that leading to the angular one. The structure with an azo group is not favored. Thus, the cyclization towards the linear isomer is the one of choice in the recent literature



Scheme 3.

Table 1. ^1H NMR Spectra of the Compounds in Solutions of $CDCl_3$. Chemical Shifts are Given on (δ) Scale and Coupling Constants in Hz

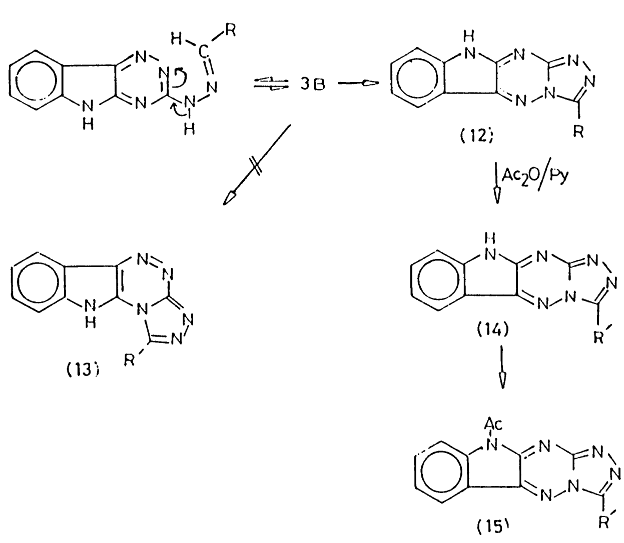
Assignment	Compd No.				Assignment	Compd No.					
	4i	**4j**	**4k**	**4l**		**14i**	**14m**	**15i**	**15j**	**15k**	**15l**
OAc(Xs)	2.00	1.93	2.01	2.00	OAc(Xs)	1.90	2.03	1.95	1.80	2.03	2.04
	2.07	1.99	2.07	2.05		1.94	2.13	2.05	1.97	2.14	2.17
	2.10	2.07	2.13	2.07		2.00	2.24	2.20	2.04	2.20	2.24
				2.11		2.22	—	—	2.08	—	—
						2.24	—	—	2.14	—	—
NAc(Xs)	2.49	2.49	2.55	2.54	NAc(Xs)	—	—	3.07	3.18	3.10	3.15
	3.00	2.98	3.07	3.05		—	—	—	—	—	—
H-6′	3.83(q)	↑			H-5′	3.93(q)	—	3.93(q)	4.20(q)	—	—
($J_{5,6'}$)	(7.5)				($J_{4,5'}$)	(6.3)		(7.5)	(5.2)		
($J_{6,6'}$)	(12.0)				($J_{5,5'}$)	(12.0)		(12.0)	(12.6)		
		4.10(m)									
H-6	4.22(q)	↓	—	—	H-5	4.33(q)	—	4.29(q)	4.50(q)	—	—
($J_{5,6}$)	(4.5)				($J_{4,5}$)	(4.5)		(6.0)	(3.0)		
H-5′	—	—	↑	4.12(q)	H-4′	—	↑	—	—	4.24(q)	4.27(q)
($J_{4,5'}$)				(6.0)	($J_{3,4'}$)					(5.0)	(5.0)
($J_{5,5'}$)				(10.5)	($J_{4,4'}$)					(12.0)	(12.5)
			4.23(m)								
			↓				4.42(m)				
H-5	↑	↑		4.30(q)	H-4	5.38(t)	↓	5.37(m)	5.20(m)	4.39(q)	4.40(q)
($J_{4,5}$)				(4.5)						(3.0)	(2.6)
		5.06(m)									
		↓									
	5.30,										
H-4	5.40(2m)		5.25(m)	5.23(m)	H-3	↑	5.55(m)	↑	5.77(dd)	5.45(m)	↑
						5.73(s)		5.67(m)			5.52(m)
									6.10(d)	5.79(dd)	
H-3	↓		5.50(dd)	5.47(dd)	H-2	↓	6.08(t)	↓	(1.0)		↓
($J_{3,4}$)		↑	(7.5)	(7.5)	($J_{2,3}$)						
		5.42(m)									
H-2	5.55(dd)	↓	5.70(t)	5.68(t)	H-1	6.63(s)	6.84(d)	6.57(d)	6.47(d)	6.70(d)	6.76(d)
($J_{2,3}$)	(2.5)				($J_{1,2}$)		(6.0)	(1.5)	(9.0)	(3.0)	(3.0)
H-1	6.50(d)	6.53(d)	6.60(d)	6.59(d)		—	—	—	—	—	—
($J_{1,2}$)	(4.5)	(4.5)	(4.5)	(4.5)							
Protons on the heterocyclic ring.											
H-9	8.47(d)	8.46(d)	8.52(d)	8.51(d)	H-6	8.11(d)	8.22(d)	8.21(d)	8.27(d)	8.22(d)	8.27(d)
($J_{8,9}$)	(9.0)	(8.4)	(8.5)	(9.0)	($J_{6,7}$)	(9.0)	(9.0)	(8.2)	(7.1)	(7.5)	(8.3)
H-8	7.57(t)	↑	↑	7.51(t)	H-7	7.23(t)	7.37(t)	↑	7.50(t)	7.56(t)	↑
($J_{7,8}$)	(9.0)				($J_{7,8}$)				(6.9)		
		7.66(m)	7.72(m)					7.62(m)			7.67(m)
H-7	7.77(t)	↓	↓	7.81(t)	H-8	7.77(t)	7.77(t)	↓	7.77(t)	7.76(t)	↓
H-6	8.67(d)	8.69(d)	8.74(d)	8.72(d)	H-9	7.82(d)	7.97(d)	8.64(d)	8.67(d)	8.65(d)	8.71(d)
($J_{6,7}$)	(9.0)	(9.0)	(8.4)	(9.0)	($J_{8,9}$)	(8.0)	(8.4)	(9.0)	(8.5)	(9.0)	(7.8)
	—	—	—	—	N–H	12.88(bs)	12.88(bs)	—	—	—	—

for the formation of fused rings. Consequently, the cyclization in the present study may have taken place at N-2 and the obtained compounds may be identified as 3-substituted-10*H*-1,2,4-triazolo[4′,3′: 2,3][1,2,4]triazino-[5,6-*b*]indole.

Acetylation of **12** with acetic anhydride in pyridine at room temperature afforded yellow crystalline derivatives **15** whose combustion analysis indicated that six and five acetyl groups were introduced in the corresponding hexose and pentose derivatives, respectively. Their IR spectra showed bands at 1780—1755 (OAc) and 1740—1710 (NAc) cm^{-1}. The ^1H NMR spectrum of **15j** confirmed the presence of the five OAc groups in addition to the NAc group, whereas no CH=N signal can be found confirming that the heterocyclization had taken place. The four aromatic protons appeared in a pattern similar to that of **4**.

Partial acetylation of **12** afforded the yellow crystalline derivatives, **14** whose IR spectra showed bands at 3320 (NH), and 1765 (OAc) cm^{-1}. The ^1H NMR spectrum of **14** did not show signals that could be attributed to the N-acetyl groups, but the rest of the spectrum has almost the same pattern as that of **15**.

Periodate oxidation of **3c** afforded a pale yellow crystalline product **16** whose combustion analysis was consistent with the molecular formula $C_{11}H_8N_6O$. Its infrared spectrum showed absorption bands at 3221 (NH) and 1692 (CHO) cm^{-1}. To confirm that glyoxal

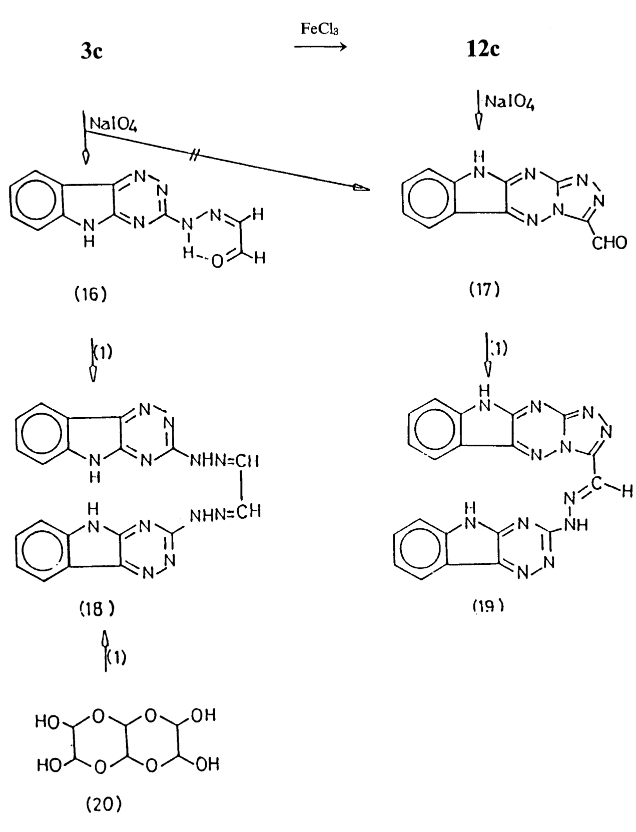


R and R′ as in Schemes 1 and 2 respectively.

Scheme 4.

mono(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazone (**16**) was not oxidatively cyclized to **17** during the periodate oxidation process, the latter compound **17** was synthesized by the periodate oxidation of **12c** and it was found to be different from **16**. The infrared spectrum of **17** showed bands at 3380 (NH) and 1697 (CHO) cm^{-1}. Its ^{1}H NMR spectrum showed, in addition to the aromatic protons the carbaldehyde and the NH groups as singlets at 10.27 and 15.27 ppm respectively.

Further confirmation for the identity of the aldehyde **16** was achieved via its reaction with the hydrazine **1** to give glyoxal bis[(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazone] (**18**). This latter product was found to be identical with an authentic sample obtained by the reaction of glyoxal with two molar equivalents of **1**. Furthermore, the bishydrazone **18** was found to be different from compound **19** that was obtained by the reaction of **17** with **1**.



Scheme 5.

Experimental

Melting points were determined on a Meltemp apparatus and are uncorrected. IR spectra were recorded with a Unicam SP 1025 spectrophotometer. ^{1}H NMR spectra were determined with an EM-390 spectrometer using tetramethylsilane(TMS) as the standard and chemical shifts are given on the δ scale. TLC was performed on Bakerflex silica gel 1B-F

Table 2. Elemental Analysis and IR Spectral Data of Sugar (5*H*-1,2,4-Triazino[5,6-*b*]indol-3-yl)hydrazones (3)

Compound	Yield	Mp	Molecular formula		Analysis/%			ν_{max}(KBr)/cm^{-1}		
	%	°C			C	H	N	OH	NH	C=N, C=C
3a	70	260—262	$C_{11}H_{10}N_6$	Calcd	58.40	4.46	37.15		3211	1617
				Found	58.55	4.47	36.99			
3b	70	>350$^{a)}$	$C_{16}H_{12}N_6$	Calcd	66.65	4.19	29.15		3212, 3123	1614
				Found	66.42	4.32	29.45			
3c	70	195—197	$C_{15}H_{18}N_6O_5$	Calcd	49.72	5.01	23.20	3351	3211	1615
				Found	49.41	5.07	23.23			
3d	65	235—236	$C_{15}H_{18}N_6O_5$	Calcd	49.72	5.01	23.20	3368	3281, 3209	1610
				Found	49.97	5.30	22.99			
3e	60	232—234	$C_{14}H_{16}N_6O_4$	Calcd	50.60	4.85	25.29	3238	3180	1614
				Found	50.29	4.86	25.05			
3f	64	235—237	$C_{14}H_{16}N_6O_4$	Calcd	50.60	4.85	25.29	3238	3191	1615
				Found	50.39	4.80	25.41			
3g	63	208—210	$C_{14}H_{16}N_6O_4$	Calcd	50.60	4.85	25.29	3410	3225	1614
				Found	50.42	4.82	25.21			
3h	56	184—186	$C_{14}H_{16}N_6O_4$	Calcd	50.60	4.85	25.29	3378	3238	1615
				Found	50.64	5.02	25.20			

a) Lit,[22] mp>350 °C.

(2.5—7.5 cm) plates. Microanalyses were performed in the Unit of Microanalysis at the Universities of Cairo and Assuit.

Sugar(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazones (3). To a solution of **1** (15 mmol) in ethanol (200 ml) was added the respective sugar **2** (15 mmol) and acetic acid (0.1 ml). The mixture was heated under reflux on a water-bath for 30 min. The solid, which separated on cooling, was collected by filtration, washed with ethanol and dried. The yellow product was crystallized from *N,N*-dimethylformamide (Table 2).

Peracetylated Sugar-1-acetyl-1-(5-acetyl-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazones (4). A cold solution of **3** (1.38 mmol) in dry pyridine (5.0 ml) was treated with acetic anhydride (5.0 ml). The mixture was kept for 3 d at room temperature with occasional shaking. It was poured onto crushed ice and the product was collected by filtration, washed repeatedly with water, dried and recrystallized from ethanol as colorless needles (Table 3).

3-Methyl-10*H*-1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole (10). (a) A 2 M solution of iron(III) chloride in ethanol (1.0 ml) was added dropwise to a boiling solution of **3a** (0.50 g, 2.9 mmol) in ethanol (50 ml). Heating was continued for 10 min and the mixture was then kept overnight at room temperature. The solvent was removed under reduced pressure and the residue was washed repeatedly with water. The yellow product crystallized from *N,N*-dimethylformamide (60%), mp>300 °C, ν_{max} (KBr): 3440 (broad, NH) and 1615 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=2.69 (s, 3H, CH$_3$), 7.27 (d, 1H, $J_{7,8}$=7.5 Hz, H-7), 7.43 (d, 1H, H-8), 7.68 (d, 1H, $J_{6,7}$=7.5 Hz, H-6), 8.12 (d, 1H, $J_{8,9}$=7.5 Hz, H-9).

Found: C, 58.92; H, 3.44; N, 37.32%. Calcd for $C_{11}H_8N_6$: C, 58.92; H, 3.60; N, 37.48%.

(b) A solution of **1** (10 mmol) in glacial acetic acid (20 ml) was boiled for 8 h. The solvent was evaporated under reduced pressure to give a yellow residue (70%) that was crystallized from *N,N*-dimethylformamide. The product was identical with that obtained by method (a).

(c) A mixture of isatin **7** (0.2 g, 1.4 mmol) and **8** (0.204 g, 1.36 mmol), sodium acetate (0.11 g, 1.36 mmol) in a mixture of ethanol (100 ml) and water (20 ml) was refluxed for 1 h. Acetic acid (0.2 ml) was added, and the reflux was continued for 4 h. The mixture was cooled and the product (68%) was collected by filtration, washed with ethanol and recrystallized from *N,N*-dimethylformamide. It was identical with that of (a).

3-(Alditol-1-yl)-10*H*-1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino-[5,6-*b*]indole (12). A 2 M solution of Iron(III) chloride in ethanol (1.0 ml) was added dropwise to a boiling solution of **3** (2.5 mmol) in ethanol (150 ml). Heating was continued for 10 min and the mixture was then kept for overnight at room temperature. The solvent was removed under reduced pressure and the residue was washed repeatedly with water. The yellow product crystallized from *N,N*-dimethylformamide (Table 4).

3-(Penta(tetra)-*O*-acetyl-pentitol(tetritol)-1-yl)-10*H*-1,2,4-triazolo[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole (14). A cold solution of **12** (1.1 mmol) in dry pyridine (5 ml) was treated

Table 3. Elemental Analysis and IR Spectral Data of Peracetylated Sugar-1-acetyl-1-(5-acetyl-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazones (**4**)

Compound	Yield	Mp	Molecular formula		Analysis/%			ν_{max}(KBr)/cm^{-1}		
	%	°C			C	H	N	OCO	NCO	C=N, C=C
4i	82	206—207	$C_{29}H_{32}N_6O_{12}$	Calcd	53.04	4.91	12.80	1750	1700	1620
				Found	52.90	4.77	12.60			
4j	60	198—200	$C_{29}H_{32}N_6O_{12}$	Calcd	53.04	4.91	12.80	1754	1714	1629
				Found	52.83	4.65	12.59			
4k	65	165—167	$C_{26}H_{28}N_6O_{10}$	Calcd	53.42	4.83	14.38	1753	1701	1619
				Found	53.70	4.97	14.48			
4l	70	160—162	$C_{26}H_{28}N_6O_{10}$	Calcd	53.42	4.83	14.38	1751	1701	1620
				Found	53.23	4.84	14.65			
4m	67	170—172	$C_{26}H_{28}N_6O_{10}$	Calcd	53.42	4.83	14.38	1750	1720	1604
				Found	53.60	4.81	14.30			

Table 4. Elemental Analysis and IR Spectral Data of 3-(Alditol-1-yl)-10*H*-1,2,4-triazolo-[4′,3′:2,3][1,2,4]triazino[5,6-*b*]indole (**12**)

Compound	Yield	Mp	Molecular formula		Analysis/%			ν_{max}(KBr)/cm^{-1}	
	%	°C			C	H	N	NH & OH	C=N, C=C
12b	85	>300	$C_{16}H_{10}N_6$	Calcd	67.12	3.52	29.36	3321	1619
				Found	66.90	3.32	29.21		
12c	50	273—275	$C_{15}H_{16}N_6O_5$	Calcd	50.00	4.48	23.23	3414, 3208	1620
				Found	49.76	4.37	23.27		
12d	46	258—260	$C_{15}H_{16}N_6O_5$	Calcd	50.00	4.48	23.23	3383, 3259	1618
				Found	49.72	4.27	23.11		
12e	51	247—249	$C_{14}H_{14}N_6O_4$	Calcd	50.91	4.27	25.45	3349, 3249	1619
				Found	51.11	4.31	25.70		
12f	51	250—252	$C_{14}H_{14}N_6O_4$	Calcd	50.91	4.27	25.45	3342, 3248	1619
				Found	50.70	4.40	25.62		
12h	52	258—259	$C_{14}H_{14}N_6O_4$	Calcd	50.91	4.27	25.45	3356, 3269	1618
				Found	50.71	4.39	25.51		

Table 5. Elemental Analysis and IR Spectral Data of 3-(Penta(tetra)-*O*-acetylpentitol(tetritol)-1-yl)-10*H*-1,2,4-triazolo[4′,3′: 2,3][1,2,4]triazino[5,6-*b*]indole (**14**) and 10-Acetyl-3-(penta(tetra)-*O*-acetylpentitol(tetritol)-1-yl)-1,2,4-triazolo[4′,3′: 2,3][1,2,4]triazino[5,6-*b*]indole (**15**)

Compound	Yield	Mp	Molecular formula		Analysis/%			$\nu_{\max}$(KBr)/cm^{-1}			
	%	°C			C	H	N	NH & OH	OCO	NCO	C=N
14i	77	200—201	$C_{25}H_{26}N_6O_{10}$	Calcd	52.63	4.59	14.73	3129	1746	—	1606
				Found	52.33	4.64	14.99				
14m	70	199—201	$C_{22}H_{22}N_6O_8$	Calcd	53.01	4.45	16.86	3258	1749	—	1618
				Found	52.99	4.25	16.75				
15a	85	>335$^{b)}$	$C_{13}H_{10}N_6O$	Calcd	58.64	3.79	31.57	—	—	1716	1605
				Found	58.92	3.59	31.40				
15b	60	298—300	$C_{18}H_{12}N_6O$	Calcd	65.84	3.68	25.60	—	—	1721	1618
				Found	65.83	3.68	25.60				
15i	74	220—221	$C_{27}H_{28}N_6O_{11}$	Calcd	52.94	4.61	13.72	—	1749	1710	1607
				Found	52.76	4.44	13.62				
15j	75	208—210	$C_{27}H_{28}N_6O_{11}$	Calcd	52.94	4.61	13.72	—	1745	—	1607
				Found	52.92	4.53	13.57				
15k	84	202—204	$C_{24}H_{24}N_6O_9$	Calcd	53.33	4.48	15.55	—	1745	1719	1606
				Found	53.15	4.55	15.26				
15l	84	205—207	$C_{24}H_{24}N_6O_9$	Calcd	53.33	4.48	15.55	—	1746	1710	1606
				Found	53.11	4.42	15.46				
15m	75	204—205	$C_{24}H_{24}N_6O_9$	Calcd	53.33	4.48	15.55	—	1743	—	1618
				Found	52.21	4.41	15.71				

b) Lit,[22] mp>300 °C.

with acetic anhydride (5.0 ml) and the mixture was kept overnight at room temperature with occasional shaking. It was poured onto crushed ice and the product was collected by filtration, washed with water and dried. It was crystallized from ethanol as yellow needles (Table 5).

10-Acetyl-3-(penta(tetra)-*O*-acetylpentitol(tetritol)-1-yl)-1,2,4-triazolo[4′,3′: 2,3][1,2,4]triazino[5,6-*b*]indole (15). A cold solution of **12** (1.1 mmol) in dry pyridine (5 ml) was treated with acetic anhydride (5.0 ml) and the mixture was kept 3 d at room temperature with occasional shaking. It was poured onto crushed ice the product was collected by filtrtion, washed with water and dried. It was crystallized from ethanol as yellow needles (Table 5).

Glyoxal Mono(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazone (16). A suspension of **3c** (2.0 g, 5.5 mmol) in water (200 ml) was treated with a solution of sodium metaperiodate (4.71 g, 22 mmol) in water (100 ml). The mixture was stirred for 12 h, and then kept for overnight at room temperature. The product was filtered, washed with water and dried. It was crystallized from ethanol as pale yellow plates (60%), mp >300 °C; $\nu_{\max}$ (KBr): 3221 (NH), 1692 (CHO), and 1615 cm^{-1}.

Found: C, 54.94; H, 3.29; N, 34.84%. Calcd for $C_{11}H_8N_6O$: C, 54.99; H, 3.36; N, 34.99%.

10*H*-1,2,4-Triazolo[4′,3′: 2,3][1,2,4]triazino[5,6-*b*]indole-3-carbaldehyde (17). A suspension of **12a** (0.54 g, 1.5 mmol) in water (100 ml) was treated with a solution of sodium metaperiodate (1.28 g, 6 mmol) in water (50 ml). The mixture was treated as above and the product was crystallized from *N*,*N*-dimethylformamide as yellow plates (85%), mp>300 °C; $\nu_{\max}$ (KBr): 3380 (NH), 1697 (CHO) and 1613 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=7.43 (m, 2H, H-7,8), 7.70 (d, 1H, $J_{6,7}$=7.5 Hz, H-6), 8.20 (d, 1H, $J_{8,9}$=7.5 Hz, H-9), 10.27 (s, 1H, CHO), 15.27 (bs, 1H, NH).

Found: C, 55.12; H, 2.31; N, 35.24%. Calcd for $C_{11}H_6N_6O$: C, 55.46; H, 2.54; N, 35.28%.

Glyoxal Bis[(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazone] (18). (a) To a solution of **16** (0.20 g, 0.83 mmol) in ethanol (50 ml) was added an ethanolic solution of **1** (0.17 g, 0.85 mmol) and piperidine (0.1 ml) and the mixture was heated under reflux for 1 h. The solid which separated out on cooling was collected by filtration, washed with ethanol and dried. It was crystallized from *N*,*N*-dimethylformamide as yellow plates (70%), mp >300 °C; $\nu_{\max}$ (KBr): 3211, 3157 (NH), and 1609 cm^{-1}.

Found: C, 57.12; H, 3.56; N, 40.01%. Calcd for $C_{20}H_{14}N_{12}$: C, 56.87; H, 3.34; N, 39.79%.

(b) To a solution of **1** (3.34 g, 16.68 mmol) in ethanol was added glyoxal (0.48 g, 8.27 mmol) and piperidne (0.1 ml) and the mixture was boiled for 1 h. It was processed as above to give the title compound as yellow plates (60%) identical with that obtained by method (a).

10*H*-1,2,4-Triazolo[4′,3′: 2,3][1,2,4]triazino[5,6-*b*]indole-3-carbaldehyde(5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)hydrazone (19). To a solution of **17** (0.30 g, 1.26 mmol) in ethanol (50 ml) was added a solution of **1** (0.25 g, 1.26 mmol) in ethanol (50 ml) and piperidine (0.1 ml). The mixture was heated under reflux on a water-bath for 30 min. The solid which separated on cooling was collected by filtration, washed with ethanol and dried. It was recrystallized from *N*,*N*-dimethylformamide as red plates (70%), mp>350 °C; $\nu_{\max}$ (KBr): 3221, 3114 (NH), and 1616 cm^{-1}.

Found: C, 56.91; H, 2.68; N, 39.75%. Calcd for $C_{20}H_{12}N_{12}$: C, 57.14; H, 2.88; N, 39.98%.

We thank Professor Z. M. El-Shafei for his valuable discussions.

References

1) J. M. Gwaltney, *Proc. Soc. Exp. Biol. Med.*, **133**, 1148 (1970).

2) J. M. Z. Gladych, R. Hornby, J. Hunt, D. Jack, J. J. Boyle, R. J. Ferlauto, R. Haff, C. Kormendy, F. Stanfield, and R. Stewart, *J. Med. Chem.*, **15**, 277 (1972).

3) R. F. Haff, J. J. Boyle, R. Stewart, R. Ferlauto, J. M. Z. Gladych, J. Hunt, and D. Jack, *Nature,* **221**, 286 (1969).

4) Allen and Hanburys Ltd., Netherlands Patent 6410823 (1965); *Chem. Abstr.,* **63**, 13295 (1965).

5) Allen and Hanburys Ltd., Netherlands Patent 6410715 (1965); *Chem. Abstr.,* **63**, 13294 (1965).

6) D. Kaminsky, U. S. Patent 3752891 (1971); *Chem. Abstr.,* **79**, 149326 (1973).

7) R. Madronero and S. Vega, *J. Heterocycl. Chem.,* **15**, 1127 (1978).

8) S. W. Schneller and D. G. Barthdomew, *J. Heterocycl. Chem.,* **15**, 439 (1978).

9) E. J. Gray and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1,* **1977**, 1492.

10) M. Robba, D. Maume, and J. Ch. Lancelot, *J. Heterocycl. Chem.,* **15**, 1209 (1978).

11) S. Castillon, E. Melendez, and J. Vilarrasa, *J. Heterocycl. Chem.,* **19**, 61 (1982).

12) J. Daunis, H. Lopes, and G. Maury, *J. Org. Chem.,* **42**, 1018 (1977).

13) J. Daunis and M. Follet, *Bull. Soc. Chim. Fr.,* **1975**, 857.

14) M. M. Goodman, J. L. Atwood, R. Carlin, W. Hunter, and W. W. Paudler, *J. Org. Chem.,* **41**, 2860 (1976).

15) A. Monge Vega, I. Aldama, M. M. Robbani, and E. Frenandez-Alvarez, *J. Heterocycl. Chem.,* **17**, 77 (1980).

16) K. C. Joshi and P. Chand, *J. Heterocycl. Chem.,* **17**, 1783 (1980).

17) T. Sasaki, K. Minamoto, and S. Fukuda, *Chem. Ber.,* **101**, 2747 (1968).

18) S. Rossi and R. Trave, *Chem. Ind. (Milan),* **40**, 827 (1958); *Chem. Abstr.,* **53**, 7194 (1959).

19) A. Messmer, G. Hajos, J. Tamas, and A. Neszmelyi, *J. Org. Chem.,* **44**, 1823 (1979).

20) M. I. Younes, A. M. Abdel-Alim, H. H. Abbas, and S. A. Metwally, *Arch. Pharm. (Weinheim, Ger.),* **320**, 1196 (1987).

21) M. I. Younes, H. H. Abbas, and S. A. Metwally, *Arch. Pharm. (Weinheim, Ger.),* **320**, 1191 (1987).

22) F. F. Abdel-Latif, R. M. Shaker, S. A. Mahgoub, and M. Z. A. Badr, *J. Heterocycl. Chem.,* **26**, 769 (1989).

23) M. L. Wolfrom, G. Fraenkel, D. R. Lineback, and F. Komitsky, Jr., *J. Org. Chem.,* **29**, 457 (1964).

24) Z. M. El Shafei and E. S. H. El Ashry, *Carbohydr. Res.,* **3**, 184 (1966).

25) H. El Khadem, Z. M. El Shafei, and M. M. Mohammed Ali, *J. Org. Chem.,* **29**, 1565 (1964).

26) L. Somogyi, *Carbohydr. Res.,* **75**, 325 (1979).

27) L. Somogyi, *Carbohydr. Res.,* **64**, 289 (1978).

28) E. S. H. El Ashry, Y. El Kilany, A. A. Abdallah, and K. Mackawy, *Carbohydr. Res.,* **113**, 273 (1983).

29) E. S. H. El Ashry, M. A. Nassr, Y. El Kilany, and A. Mousaad, *Bull. Chem. Soc. Jpn.,* **60**, 3405 (1987).

30) R. I. Trust, J. D. Albright, F. M. Lovell, and N. A. Perkinson, *J. Heterocycl. Chem.,* **16**, 1393 (1979).