Reaction of Some 1,2,4-Triazines with Acetobromoglucose

Mohga M. Eid, Sayed A. Abdel Hady, and Hosny A.W. Ali

Department of Chemistry, Faculty of Science, University of Cairo, Giza, A.R. Egypt

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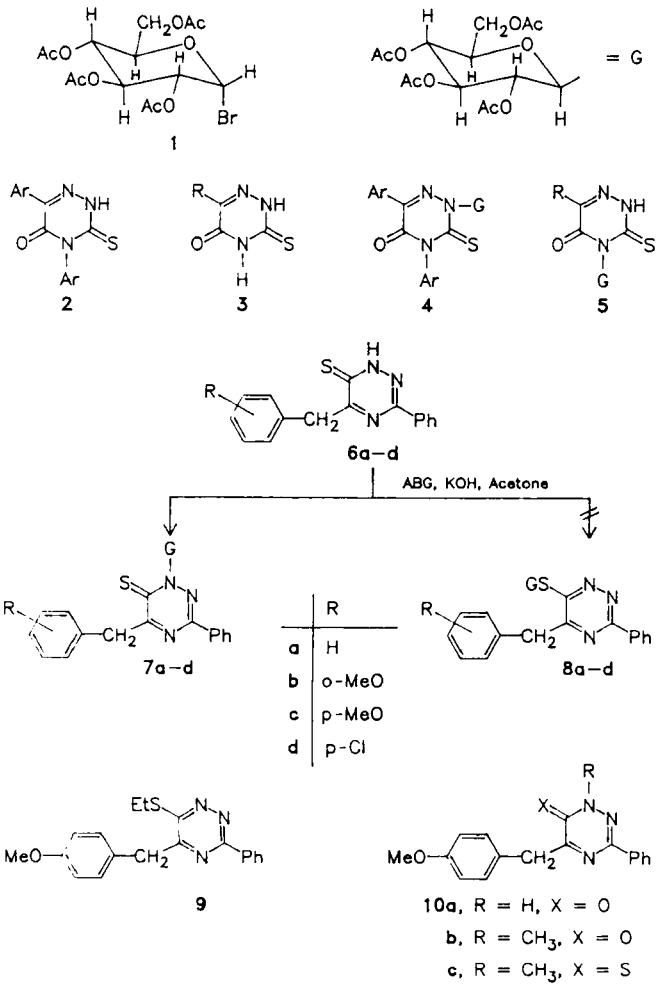
2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide (1) reacts with 5-benzyl-3-phenyl-1,2,4-triazin-6(1H)thiones **6a-d** and 4-aryl-6-benzyl-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-5-ones **11a-g** to give the corresponding N-glucosyl derivatives **7a-d** and **12a-g**, respectively. The structures of these glucosides were established by chemical and spectroscopic methods.

Reaktionen einiger 1,2,4-Triazine mit Acetobromglukose

2,3,4,6-Tetra-O-acetyl-α-D-glukopyranosylbromid (1) reagiert mit den 5-Benzyl-3-phenyl-1,2,4-triazin-6(1H)thionen **6a-d** und den 4-Aryl-6-benzyl-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-5-onen **11a-g** zu den entspr. N-Glukosylderivaten **7a-d** bzw. **12a-g**. Die Strukturen dieser Glukoside wurden auf chemischem und spektroskopischem Wege gesichert.

The biological importance of glycosides of 1,2,4-triazines is well known[1-4]. An efficient procedure for the selective synthesis of N-glycoside derivatives involves the reaction of persilylated 1,2,4-triazines with 1-halo-, 1-O-acetyl as well as 1-O-methyl acetylated sugars in the presence of *Friedel-Crafts* catalysts[1-3,5,6].

When 4,6-diaryl-3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines **2** and 6-substituted-3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines **3** were treated with acetobromoglucose (**1**) in alkaline medium, the corresponding N-glucosyl derivatives **4** and **5** were obtained[7,8].



We report here the results of the reaction of acetobromoglucose (**1**) with the 5-benzyl-3-phenyl-1,2,4-triazin-6(1H)thiones **6a-d**[9]. Thus glucosidation of **6a-d** in aqueous acetone containing one equivalent of KOH gave a monoglucosyl derivative in each case. Among the different possible N-1 glucoside (**7a-d**) and S-glucoside (**8a-d**) derivatives the reaction leads to 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl) derivatives **7a-d** (Table 1). This structure assignment is based on spectroscopic evidence mainly uv, ^{13}C-nmr and ^{1}H-nmr. Thus comparing the uv-spectra of the S-ethyl derivative **9**[9], the N-methyl derivative **10c** and the glucosyl derivative **7b**, we found that **9** and **7b** had different absorption maxima (one maximum at 284 nm for **9** and two maxima at 312 and 318 nm for **7b**). On the other hand, **10c** had an absorption maximum at 320 nm similar to that of **7b** (318 nm). **10c** was prepared by first methylating **10a**[10] in methanolic $NaOCH_3$ with H_3CI to give **10b** followed by thiation of the latter with *Lawesson's* reagent.

The ^{13}C-nmr spectrum of **7d** in a mixture of acetone-d_6 and DMSO-d_6 revealed the following characteristic signals: 175.8 (s, $CH_3\underline{C}OO$), 20.4 (q, $\underline{C}H_3COO$), four doublets at 67.9, 69.4, 73.3, and 74.0 (4 CHOAc), three singlets at 168.9 (C=N); 164.3 (C=N) and 150.5 (C=S) of the 1,6-dihydro-1,2,4-triazine-6-thione; a doublet at 74.0 (N-$\underline{C}$HOR) and a triplet at 43.6 (-$\underline{C}H_2$Ar) ppm. The ^{13}C-nmr spectrum of **7c** in acetone-d_6 exhibits a similar pattern with an additional quartet at 56.6 ppm due to the ArO$\underline{C}H_3$ group. In both spectra the signals of the aryl carbon atoms appear in the region 127.2-133.2 ppm.

The chemical shifts of the C-atoms of the heterocyclic moiety together with that of the anomeric C-atom are in agreement with the N-glucoside structure rather than the S-glucoside isomer[11]. This, together with the appearance of the anomeric H-signal in the ^{1}H-nmr spectrum of **7a** at 6.80 ppm, with J = 9 Hz, similar to the values reported for N-glucosyl derivatives[7,8], gives additional support that glucosidation took place selectively at N-1 of the triazine ring and excludes S-glucosidation. This also suggests that the anomeric H acquires an axial conformation and consequently the glucosidic linkage has β-configuration. This reveals a S_N2-reaction between **1** and the triazines **6a-d** with inversion at the anomeric C. This is not surprising since the acetoxy group in position 2 of **1** is in a cis-configuration with respect to the

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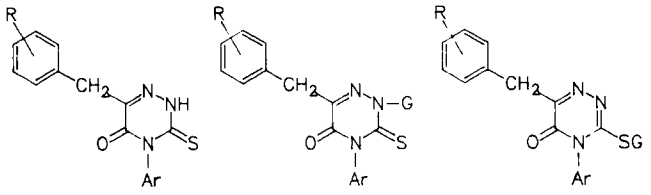
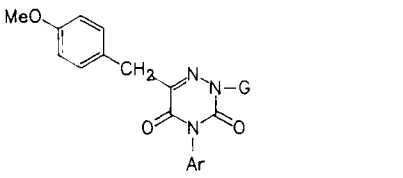
bromine atom, thus neighboring group participation which leads to retention of configuration at the anomeric C-atom is not favoured.



11a–g 12a–g 13a–g

	R	Ar
a	p-MeO	Ph
b	3,4-$(MeO)_2$	Ph
c	3,4-OCH_2O–	Ph
d	p-Cl	Ph
e	p-MeO	p-$MeOC_6H_4$
f	p-MeO	p-MeC_6H_4
g	p-Cl	p-$MeOC_6H_4$



14 Ar = p-$MeOC_6H_4$

Our next concern was to investigate the action of **1** on some 4-aryl-6-substituted benzyl-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-5-ones under the conditions described for **6a-d**. Some of the starting triazines **11a-d** were obtained as described[12]. The new triazines **11e-g** are synthesized using the same procedure starting with the appropriate azlactone and 4-arylthiosemicarbazide.

Treatment of an equimolar mixture of compounds **11a-g** and aqueous KOH with **1** in acetone at ambient temp. gave the 2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)triazines **12a-g** (Table 2) and not the S-glucosides **13a-g**.

The structures assigned to **12a-g** are based on chemical and spectroscopic evidence. Thus, as a typical example, when **12e** was treated with H_2O_2 in acetic acid desulfurization to the corresponding 3,5-dioxo derivative **14** was obtained. The structure of the latter was evidenced from elemental analysis and the IR-spectrum which shows two carbonyl bands at 1750 (acetate C=O) and 1670 cm^{-1} (amide C=O). The ^{1}H-nmr spectrum of **12a** showed the anomeric proton signal at δ = 6.75 ppm with J = 9 Hz. This is consistent with the proposed N-glucosidation as well as β-configuration of the anomeric C.

Experimental Part

Melting points are uncorrected.- IR spectra (KBr pellets): Unicam SP 1200.- UV spectra (dioxane): Unicam SP 1750.- ^{1}H-nmr spectra ($CDCl_3$): Varian EM 390 (90 MHz). Chemical shifts in ppm (δ) relative to tetramethylsilane.- Temp. in °C.

5-Benzyl and substituted benzyl-3-phenyl-1,2,4-triazin-6(1H)thiones **6a-d**

Compounds **6a-d** were prepared as described by thiation of the corresponding 5-benzyl and substituted benzyl-3-phenyl-1,2,4-triazin-6(1H)ones[9].

5-p-Methoxybenzyl-1-methyl-3-phenyl-1,2,4-triazin-6(1H)one (**10b**)

A solution of **10a** (2.9 g, 0.01 mole) in methanolic $NaOCH_3$ (from 0.3 g (0.013 g atom) Na^o in 20 ml methanol) was left with H_3CI (0.62 ml, 0.01 mole) at room temp. overnight. The precipitate was recrystallized from acetic acid to give colorless crystals of **10b**: 75%; m.p. 305°.- $C_{18}H_{17}N_3O_2$ (307.4) Calc. C 70.4 H 5.6 N 13.7 Found C 70.3 H 5.7 N 13.5.- IR: 1655 (amide C=O).

5-p-Methoxybenzyl-1-methyl-3-phenyl-1,2,4-triazin-6(1H)thione (**10c**)

To a suspension of **10b** (0.2 g, 0.0007 mole) in dry toluene (5 ml) was added *Lawesson's* reagent (0.3 g). The mixture was heated under reflux for 12 h and the orange solid was collected by filtration while hot. Recrystallization form DMF afforded **10c**: 96%; m.p. 320°.- $C_{18}H_{17}N_3OS$ (323.4) Calc. C 66.9 H 5.3 N 13.0 S 9.9 Found C 67.2 H 5.3 N 12.9 S 9.7.- λ max (dioxane) 320 nm.

Table 1

Compound	Mp °C	Yield %	Solvent	Formula M.W.	Analysis % Calcd./Found C	H	N	S	Cl
7a [a]	205	64	AcOH	$C_{30}H_{31}N_3O_9S$	59.1	5.1	6.9	5.3	–
				(609.7)	59.4	5.0	7.0	5.4	–
7b [b]	160	87	EtOH	$C_{31}H_{33}N_3O_{10}S$	58.2	5.2	6.6	5.0	–
				(639.7)	58.3	5.2	6.3	4.9	–
7c	174	73	EtOH	$C_{31}H_{33}N_3O_{10}S$	58.2	5.2	6.6	5.0	–
				(639.6)	57.9	5.1	6.4	5.0	–
7d	209	70	EtOH	$C_{30}H_{30}ClN_3O_9S$	55.9	4.7	6.5	5.0	5.50
				(644.1)	55.9	4.5	6.4	5.2	5.40

[a] **7a**: ir: 1750 cm^{-1} (acetate C=O).- ^{1}H-nmr: δ 1.85-2.10 overlaping s, 12H, 4 $OCOCH_3$), 4.20 (d, 2H, CH_2OAc), 4.25 (d, 2H, CH_2-Ar), 5.10-6.10 (br m, 4H, H2'-,3'-,4'-5'-H (glucose)), 6.8 (d, 1H, anomeric H) and 7.23-8.30 ppm (m, 10H, arom. H).

[b] **7b**: uv: λ max (dioxane) (log ε): 312 (3.18), 318 nm (3.14).

Table 2

Compound	Mp °C	Yield %	$[\alpha]_D^{27}$	Formula M.W.	Analysis % Calcd./Found C	H	N	S	Cl
12a	217	82	-86.95	$C_{31}H_{33}N_3O_{11}S$	56.8	5.1	6.4	4.9	–
				(656.1)	57.0	5.2	6.4	4.6	–
12b	162	67	+84.45	$C_{32}H_{35}N_3O_{12}S$	56.1	5.1	6.1	4.7	–
				(685.7)	56.1	5.4	6.1	4.7	–
12c	184	65	-75.72	$C_{31}H_{31}N_3O_{12}S$	55.6	4.7	6.3	4.8	–
				(699.7)	55.8	4.3	6.3	4.6	–
12d	205	68	-118.9	$C_{30}H_{30}ClN_3O_{10}S$	54.6	4.6	6.4	4.9	5.3
				(660.1)	54.7	4.5	6.4	4.9	5.6
12e	150	57	+ 5.42	$C_{32}H_{35}N_3O_{12}S$	56.1	5.1	6.1	4.7	–
				(685.7)	55.8	5.0	6.3	4.5	–
12f	154	78	-14.83	$C_{32}H_{35}N_3O_{11}S$	57.4	5.3	6.3	4.8	–
				(669.7)	57.4	5.1	6.4	5.0	–
12g	189	90	-36.28	$C_{31}H_{32}ClN_3O_{11}S$	54.0	4.7	6.1	4.6	5.1
				(690.1)	53.7	4.3	6.1	4.5	5.3

12a,b were recrystallized from butanol.
12c-g were crystallized from ethanol.
12a: ir: 1755 (acetate C=O) and 1710 cm^{-1} (amide C=O).- ^{1}H-nmr: δ 1.95-2.10 (overlaping s, 12H, 4 $OCOCH_3$), 3.70 (s, 3H, OCH_3), 3.90 (br s, 2H, CH_2-Ar), 4.20 (d, 2H, CH_2OAc), 5.10-5.90 (m, 4H, 2'-,3'-,4'-,5'-H (glucose), 6.75 (d, 1H, anomeric H), and 6.75-7.50 ppm (m, 9H, arom. H).

4-Aryl-6-substituted benzyl-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-5-ones **11e-g**

11e-g were prepared as described by *Mansour* et al.[12] for the synthesis of **10a-d** using the appropriate azlactone and 4-arylthiosemicarbazide[13]. The triazines were recrystallized from ethanol. Yield ca. 90%.

11e: mp. 192°.- $C_{18}H_{17}N_3O_3S$ (355.4) Calc. C 61.0 H 4.8 N 11.8 S 9.0 Found C 61.0 H 4.7 N 11.9 S 8.9.

11f: mp. 164°.- $C_{18}H_{17}N_3O_2S$ (339.4) Calc. C 63.7 H 5.0 N 12.4 S 9.5 Found C 63.8 H 4.9 N 12.1 S 9.2.

11g: mp. 168°.- $C_{17}H_{14}ClN_3O_2S$ (359.8) Calc. C 56.7 H 3.9 N 11.7 S 9.2 Cl 9.7 Found C 56.4 H 3.6 N 12.1 S 9.5 Cl 10.0.

Reaction of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide **1** *with compounds* **6a-d** *and* **11a-g**

6a-g[9] and **11a-g** (0.01 mole) were dissolved in aqueous KOH (0.01 mole in 10 ml water), then **1** (0.011 mole) dissolved in acetone (10 ml) was added. The mixture was stirred for 30 min and left overnight at room temp. The precipitate was filtered, washed with water, alcohol and recrystallized from the proper solvent to yield **7a-d** and **12a-g**, respectively (Table 1 and Table 2).

Action of H_2O_2 on compound **12e**

12e (0.5 g) was dissolved in acetic acid (5 ml), then H_2O_2 (30%) (1.0 ml) was added. The mixture was boiled for 5 min, left to cool, and diluted with water. The precipitate was recrystallized from ethanol as colorless crystals of compound **14**, mp. 168°. Yield 77%.- $C_{32}H_{35}N_3O_{13}$ (669.3) Calc. C 57.4 H 5.3 N 6.3 Found C 57.6 H 5.5 N 6.5. The ir-spectrum shows bands at 1670 (amide C=O) and 1750 cm^{-1} (acetate C=O).

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