SYNTHESIS AND REACTIONS OF TRIAZINE AZIDE TOWARDS NUCLEOPHILIC REAGENTS

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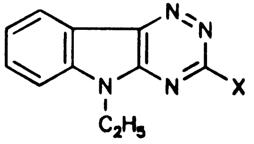
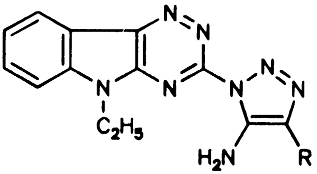
The hydrazinotriazine compound *I* was used for preparation of various fused heterocycles.



I, X = $NHNH_2$
II, X = N_3
IV, X = SCH_3
V, X = NH_2
X, X = $N{=}CHC_6H_5$
XIII, X = $NHCOC_6H_5$



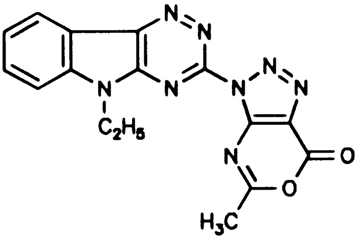
IIIa, R = CN
IIIb, R = $CO_2C_2H_5$
VI, R = COOH
VIII, R = $CONH_2$

EXPERIMENTAL

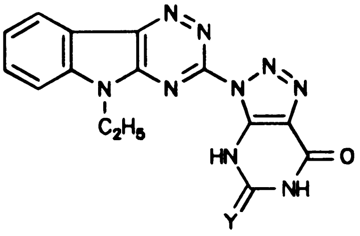
All melting points are uncorrected. The microanalysis were performed by the microanalysis unit at Assiut University. IR spectra were recorded in KBr pellets using a Pye–Unicam SP-1100 spectrophotometer. ^1H NMR spectra were measured in $(CD_3)_2SO$ with a Varian XL 100 spectrometer. The mass spectra were obtained using an AEF MS spectrometer operating at 70 eV. 5-Ethyl-3-hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indole (*I*) was prepared in a previous work[1]. Physical and spectral data of compounds *II* – *XVIII* are given in Table I.

Preparation of Azide *II* (Refs[2 – 5])

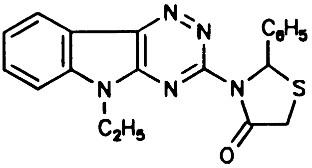
To a cooled solution of *I* (2.28 g, 0.01 mol) in concentrated phosphoric acid (15 ml), sodium nitrite (5 M, 12 ml) was added. The separated solid product was crystallized from absolute ethanol as yellow crystals to give the azide *II*. For $C_{11}H_9N_7$ (239.2) calculated: 55.23% C, 3.76% H, 41.00% N; found: 55.35% C, 3.92% H, 39.85% N.



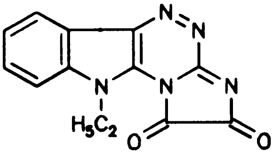
VII



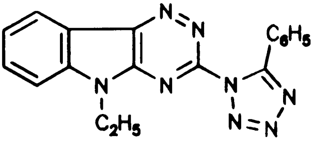
IX : a, Y = O
b, Y = S



XI



XII



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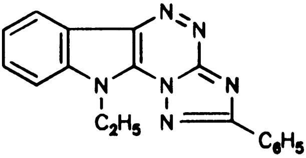
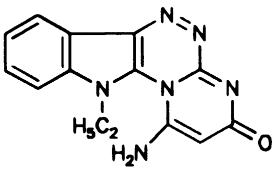
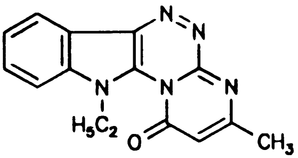


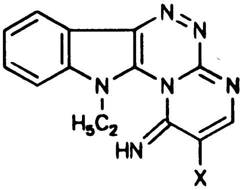
XV



XVI



XVII



XVIII : a, X = CN
b, X = $CO_2C_2H_5$

TABLE I
Characterization of some prepared compounds

Compound	M. p., °C Yield, %	Formula (M. w.)	IR, cm^{-1}	^1H NMR, δ ppm
II	231 75	$C_{11}H_9N_7$ (239.2)	2 150 (N_3)	
IIIa[a,b]	255 74	$C_{14}H_{11}N_9$ (305.3)	2 240 (C=N) 3 380, 4 380 (NH_2)	1.4 t, 3 H (CH_3); 4.3 q, 2 H (CH_2); 7.1 – 8.25 m, 4 H (arom. H); 9.8 s, 2 H (NH_2)
IIIb[a]	164 60	$C_{16}H_{16}N_8O_2$ (352.4)	1 725 (C=O) 3 380 (NH_2)	1.4 m, 6 H (2 CH_3); 4.3 m, 4 H (2 CH_3); 7.05 – 8.02 m, 6 H (arom. H + NH_2)
V[c]	273 66	$C_{11}H_{11}N_5$ (213.2)	3 380, 3 400 (NH_2)	1.45 t, 3 H (CH_3); 4.3 q, 2 H (CH_2); 7.1 – 8.25 m, 6 H (arom. H + NH_2)
VI[d]	285 71	$C_{14}H_{12}N_8O_2$ (324.3)	1 720 (C=O); 3 260 (NH_3^+)	1.5 t, 3 H (CH_3); 4.25 q, 2 H (CH_2); 7 – 8.15 m, 6 H (arom. H + NH_2); 10.9 s, 1 H (COOH)
VII	264 68	$C_{16}H_{12}N_8O_2$ (348.2)		1.6 t, 3 H (CH_3); 2.5 s, 3 H (CH_3); 4.6 q, 2 H (CH_2); 7 – 8.3 m, 4 H (arom. H)
VIII[e]	302 47	$C_{14}H_{13}N_9O$ (323.4)	1 680 (C=O) 3 300, 3 400 (NH_2)	
IXa	273 49	$C_{15}H_{11}N_9O$ (349.3)	3 300, 3 500 (NH) 1 670 (C=O)	1.35 t, 3 H (CH_3); 4.3 q, 2 H (CH_2); 7.1 – 8.25 m, 4 H (arom. H)
IXb[f]	309 75	$C_{15}H_{11}N_9OS$ (365.4)	3 340 (NH) 1 140 (C=S)	
X[g]	304 63	$C_{18}H_{15}N_5$ (301.3)	–	1.5 t, 3 H (CH_3); 4.2 q, 2 H (CH_2); 7.1 – 8.2 m, 9 H (arom. H); 10.0 s, 1 H (N=CH)
XI[h]	173 56	$C_{20}H_{16}N_5OS$ (374.4)	1 680 (C=O)	1.3 t, 3 H (CH_3); 4.2 q, 2 H (CH_2); 3.65 s, 2 H (CH_2); 7.2 – 8.15 m, 9 H (arom. H)
XII	201 64	$C_{13}H_9N_5O_2$ (267.2)	1 730 (C=O)	
XIII[i]	212 82	$C_{18}H_{15}N_5O$ (317.3)	3 150 (NH) 1 675 (C=O)	1.4 t, 3 H (CH_3); 4.2 q, 2 H (CH_2); 8.00 m, 10 H (arom.H + NH)

TABLE I
(*Continued*)

Compound	M. p., °C Yield, %	Formula (M. w.)	IR, cm^{-1}	^{1}H NMR, δ ppm
XIV	276 43	$C_{18}H_{14}N_8$ (342.3)	–	1.25 t, 3 H (CH_3); 4.2 q, 2 H (CH_2); 7.7 m, 9 H (arom. H)
XVI	286 75	$C_{14}H_{12}N_6O$ (281.2)	1 720 (C=O) 3 500 (NH_2)	
XVII^j	275 79	$C_{15}H_{13}N_5O$ (279.2)	1 715 (C=O)	1.3 t, 3 H (CH_3); 2.3 s, 3 H (CH_3); 4.2 q, 2 H (CH_2); 6.2 s, 1 H (CH arom.); 8 m, 4 H (arom. H)
XVIIIa	236 62	$C_{15}H_{11}N_7$ (289.2)	2 240 (C≡N) 3 300 (NH)	
XVIIIb^k	169 63	$C_{17}H_{15}N_6O_2$ (335.3)	1 710 (C=O) 3 250 (NH)	1.3 m, 6 H (2 CH_2); 3.7 s, 1 H (NH); 4.3 m, 4 H (2 CH_2); 7.8 m, 4 H (arom. H)

[a] ^{1}H NMR measured in $CDCl_3$; MS spectra (M^+): [b] 305, [c] 213, [d] 324, [e] 348, [f] 365, [g] 301, [h] 374, [i] 316, [j] 279, [k] 335.

5-Amino-1-(5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-triazole-4-carbonitrile (*IIIa*) (Ref.[6])

A mixture of *II* (2.39 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) in 25 ml of absolute ethanol containing 0.01 mol of sodium ethoxide was heated under reflux for 3 h. After cooling, the reaction mixture was poured into water and cooled overnight. The resulting semi-crystalline mass was removed, washed with water, dried in vacuo and crystallized from dioxane. For $C_{14}H_{11}N_9$ (305.3) calculated: 55.08% C, 3.60% H, 41.31% N; found: 55.32% C, 3.55% H, 41.15% N.

Ethyl-5-amino-1-(5-ethyl-5*H*-1,2,4-triazino[6,6-*b*]indol-3-yl)-1*H*-triazole-4-carboxylate (*IIIb*)

A mixture of *II* (2.39 g, 0.01 mol) and ethyl cyanoacetate (1.13 g, 0.01 mol) in 25 ml of absolute ethanol containing 0.01 mol of sodium ethoxide was heated under reflux for 4 h. After cooling the reaction mixture was poured into water and cooled overnight. The resulting precipitate was filtered and crystallized from chloroform–petroleum ether. For $C_{16}H_{16}N_8O_8$ (352.4) calculated: 54.54% C, 4.54% H, 31.81% N; found: 54.35% C, 4.85% H, 32.1% N.

5-Ethyl-3-amino-5*H*-1,2,4-triazino[5,6-*b*]indole *V*

Method A: A suspension of *II* (2.39 g, 0.01 mol) in 50 ml of absolute ethanol containing 0.01 mol sodium was heated under reflux for 1 h. After cooling the precipitate was collected and crystallized from methanol. For $C_{11}H_{11}N_5$ (213.2) calculated: 61.97% C, 5.16% H, 32.89% N; found: 62.25% C, 4.82% H, 32.75% N.

Method B: A mixture of *IV* prepared according to ref.[7] (2.44 g, 0.01 mol) and ammonium acetate (20 g) in acetic acid (20 ml) was heated under reflux for 3 h. Precipitate separated after cooling was filtered and crystallized from methanol. For $C_{11}H_{11}N_5$ (213.2) calculated: 61.97% C, 5.16% H, 32.86% N; found: 61.73% C, 4.81% H, 32.66% N.

5-Amino-1-(5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-triazole-4-carboxylic Acid (*VI*) (Ref.[8])

Method A: A mixture of *IIIa* (6.1 g, 0.02 mol) and 1 M sodium hydroxide (40 ml) was heated under reflux for 3 h. The mixture was filtered and the filtrate neutralized by 2 M hydrochloric acid (20 ml). The yellow precipitate was filtered, washed with water and crystallized from acetic acid.

Method B: A mixture of *IIIb* (3.52 g, 0.01 mol) and 2 M sodium hydroxide (300 ml) was heated under reflux for 5 h. The reaction mixture was filtered, the filtrate neutralized using 6 M hydrochloric acid (100 ml), and pale yellow precipitate separated, washed with water and crystallized from acetic acid. For $C_{14}H_{12}N_8O_2$ (324.3) calculated: 51.85% C, 3.70% H, 34.56% N; found: 52.05% C, 3.80% H, 34.32% N.

1-(5-Ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-6-methyl-1*H*-triazolo-[3,4-*d*]oxazin-4-one (*VII*)

Compound *VI* (3.24 g, 0.01 mol) was heated under reflux with excess acetic anhydride (20 ml) for 4 h. Acetic anhydride was removed by evaporation under reduced pressure to give deep yellow solid which was crystallized from benzene. For $C_{16}H_{12}N_8O_2$ (348.3) calculated: 55.17% C, 3.44% H, 32.18% N; found: 55.40% C, 3.55% H, 32.42% N.

5-Amino-1-(5-ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-triazole-4-carboxamide (*VIII*)

A mixture of *IIIa* (6.1 g, 0.02 mol) and sulfuric acid (80%, 25 ml) was heated on a steam bath for 1 h. The reaction mixture was cooled, poured onto ice-water mixture to give a precipitate which was filtered, washed with water and crystallized from acetic acid. For $C_{14}H_{13}N_9O$ (323.3) calculated: 52.01% C, 4.02% H, 39.00% N; found: 52.15% C, 4.00% H, 38.78% N.

1-(5-Ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-1*H*-triazolo[3,4-*d*]pyrimidine-4,6-(5*H*,7*H*)-dione (*IXa*) (Refs[9,10])

Compound *IIIb* (0.704 g, 0.002 mol) and urea (0.3 g, 0.005 mol) were fused at 170 °C in an oil bath for 2 h. After cooling, the solid product was washed several times with benzene and crystallized from ethanol. For $C_{15}H_{11}N_9O_2$ (349.3) calculated: 51.57% C, 3.15% H, 36.10% N; found: 51.37% C, 3.25% H, 36.22% N.

1-(5-Ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol-3-yl)-6-mercapto-1*H*-triazolo[3,4-*d*]-pyrimidin-4-ol (*IXb*) (Refs[9,10])

Compound *IIIb* (0.704 g, 0.002 mol) and thiourea (0.38 g, 0.005 mol) were fused at 170 °C in an oil bath for 3 h. The solid product evolved after cooling, was washed several times with benzene and crystallized from methanol. For $C_{15}H_{11}N_9SO$ (365.4) calculated: 49.31% C, 3.01% H, 34.52% N; found: 49.15% C, 3.20% H, 34.35% N.

5-Ethyl-3-[(phenylmethylene)amino]-5*H*-1,2,4-triazino[5,6-*b*]indole (*X*)

A mixture of *V* (2.13 g, 0.01 mol) and benzaldehyde (1.52 ml, 0.015 mol) was heated at 200 °C in an oil bath for 4 h. The formed solid product was washed with benzene and crystallized from ethanol. For $C_{18}H_{15}N_5$ (301.3) calculated: 71.76% C, 4.98% H, 23.25% N; found: 71.62% C, 4.82% H, 22.95% N.

Synthesis of 5-Ethyl-3-(4-oxo-2-phenyl-3-thiazolinyl)-5*H*-1,2,4-triazino[5,6-*b*]indole (*XI*)

A mixture of *X* (3.01 g, 0.01 mol) and thioglycolic acid (1.38 g, 0.015 mol) in dry benzene (50 ml) was heated under reflux using water separator until no more water distilled (4 h). The reaction mixture was concentrated under reduced pressure to give green precipitate. It was filtered, washed with diethyl ether and crystallized from benzene. For $C_{20}H_{16}N_5OS$ (374.4) calculated: 64.17% C, 4.27% H, 18.71% N, 8.55% S; found: 64.32% C, 4.61% H, 18.42% N, 8.33% S.

10-Ethyl-10-*H*-imidazolo[3,4 : 3,4][1,2,4]triazino[5,6-*b*]indol-1,2-dione (*XII*) (Ref.[11])

A mixture of *V* (2.13 g, 0.01 mol) and oxalyl chloride (1 ml, 0.012 mol) in dry pyridine was heated under reflux for 3 h. After cooling the precipitate was collected and crystallized from methanol. For $C_{143}H_9N_5O_2$ (267.2) calculated: 58.42% C, 3.37% H, 26.21% N; found: 58.62% C, 3.15% H, 26.35% N.

5-Ethyl-3-benzamido-5*H*-1,2,4-triazino[5,6-*b*]indole (*XIII*) (Ref.[12])

To a solution of *V* (2.13 g, 0.01 mol) in dry pyridine (1.2 ml, 0.01 mol) benzoyl chloride was added dropwise with stirring. The reaction mixture was kept at room temperature for about 3 h and then poured into ice-cold water. The precipitate of *VI* was filtered off, washed with water, 10% aqueous sodium bicarbonate and water and crystallized from ethanol. For $C_{18}H_{15}N_5O$ (317.3) calculated: 68.13% C, 4.73% H, 22.08% N; found: 68.33% C, 4.62% H, 21.98% N.

1-(5-Ethyl-5*H*-1,2,4-triazino[5,6-*b*]indol)-5-phenyltetrazole (*XIV*) (Ref.[12])

A mixture of *XIII* (3.17 g, 0.01 mol) and PCl_5 (2 ml) is heated at 120 °C for 1.5 h. The resulting solution was distilled under reduced pressure to remove the traces of $POCl_3$, residue stirred for 12 h with a cold solution of sodium azide in aqueous acetone containing sodium acetate. Acetone was removed by distillation under reduced pressure and the aqueous layer extracted with chloroform, concentrated and white precipitate crystallized from benzene. For $C_{18}H_{14}N_8$ (342.3) calculated: 63.15% C, 4.09% H, 32.74% N; found: 63.35% C, 4.15% H, 32.95% N.

10-Ethyl-2-phenyl-10*H*-[1,2,4]triazolo[5,1 : 3,4][1,2,4]triazino[5,6-*b*]indole (*XV*) (Ref.[13])

Compound *XIV* (3.42 g, 0.01 mol) was heated at 280 °C in a sand bath for 1 h. After cooling, the solid product was washed with diethyl ether and crystallized from ethanol. For $C_{18}H_{14}N_6$ (314.3) calculated: 68.78% C, 4.45% H, 27.07 N; found: 68.45% C, 4.63% H, 27.24% N.

11-Ethyl-1-amino-11*H*-pyrimido[3,4 : 3,4]-1,2,4-triazino[5, 6-*b*]indol-3-one (*XVI*) (Ref.[14])

A mixture of *V* (2.13 g, 0.01 mol) and ethyl cyanoacetate (5 ml) was heated under reflux for 3 h. After cooling a brown precipitate separated, which was filtered and crystallized. For $C_{14}H_{12}N_6O$ (281.2) calculated: 59.78% C, 4.27% H, 29.89% N; found: 59.62% C, 3.92% H, 30.10% N.

11-Ethyl-3-methyl-11*H*-pyrimido[3,4 : 3,4]-1,2,4-triazino[5,6-*b*]indol-1-one (*XVII*) (Ref.[14])

A mixture of *V* (2.13 g, 0.01 mol) and ethyl acetoacetate (5 ml) was heated under reflux for 5 h. After cooling a deep red precipitate separated, which was filtered and crystallized from benzene–ethanol (1 : 1). For $C_{15}H_{13}N_5O$ (279.2) calculated: 64.51% C, 4.65% H, 25.08% N; found: 64.35% C, 4.80% H, 25.16% N.

11-Ethyl-1-iminopyridino[3,4 : 3,4]-1,2,4-triazino[5,6-*b*]indol-2-carbonitrile (*XVIIIa*) (Refs[15,16])

A mixture of *V* (2.13 g, 0.01 mol) and ethoxymethylenemalononitrile (1.22 g, 0.01 mol) in absolute ethanol (100 ml) was heated under reflux for 3 h. After cooling yellow precipitate separated, which was filtered and crystallized from methanol. For $C_{15}H_{11}N_7$ (289.2) calculated: 62.28% C, 3.8% H, 33.91% N; found: 62.32% C, 4.15% H, 33.61% N.

11-Ethyl-1-iminopyrimido[3,4 : 3,4]-1,2,4-triazino[5,6-*b*]indol-2-carboxylate (*XVIIIb*) (Refs[15,16])

A mixture of *II* (2.13 g, 0.01 mol) and ethoxymethylene cyanoacetate (1.7 g, 0.01 mol) in absolute ethanol (100 ml) was heated under reflux for 2 h. After cooling a white precipitate separated, which was filtered and crystallized from ethanol. For $C_{17}H_{15}N_6O_2$ (335.3) calculated: 60.69% C, 4.47% H, 25.07% N; found: 60.75% C, 4.65% H, 25.20% N.

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