Cyclization Reactions of 3-Hydrazino[1,2,4]triazino[5,6-*b*]indole

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The reaction of 3-hydrazino[1,2,4]triazino[5,6-*b*]indole **I** with nitrous acid affords the azide **III** which could be cyclized with acetic anhydride to 10-acetyl-10*H*-tetrazolo[5',1':3,4][1,2,4]triazino[5,6-*b*]indole **IIb**. Cyclization reactions of **I** with acetic anhydride, ethyl chloroformate, carbon disulphide and aromatic aldehydes to the corresponding fused triazolo derivatives **V-VIII** are reported. On the other hand cyclization reactions of **I** with malononitrile, ethyl cyanoacetate, ethyl acetoacetate and acetylacetone to the corresponding condensed pyrazolino derivatives **IX-XI** are also reported. The reaction of **I** with α-dicarbonyl compounds to form mono and dihydrazones are reported. The structure of the compounds prepared and their cyclization mechanisms are reported.

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Joshi *et al.* [1] reported that the reaction of 3-hydrazino[1,2,4]triazino[5,6-*b*]indole **I** with nitrous acid (sodium nitrite/PAA) give 10*H*-tetrazolo[5',1':3,4][1,2,4]triazino[5,6-*b*]indole **II**, but in our laboratory we found that **I** reacted with nitrous acid (sodium nitrite/phosphoric acid) to give the azide **III** [2-5]. The structure of the azide **III** was confirmed by its analytical and spectral data. The ir spectrum of **III** shows a sharp band for azide group absorption at 2150 cm^{-1}. The azide **III** was cyclized to the tetrazolo compound **IIb** on treatment with acetic anhydride. Another proof for the azide formation is its cyclization to the corresponding 5-amino-4-carboxy[1,2,3]triazolyl[1,2,4]triazino[5,6-*b*]indole **IV** on treatment with ethyl cyanoacetate in the presence of sodium ethoxide [6]. On the other hand treatment of **I** with sodium nitrite/concentrated hydrochloric acid to give the corresponding tetrazolo compound **IIa** (*cf.* Chart I).

To continuation of our study on the reactivity of the hydrazino compound **I** toward different condensation cyclization reagents [7], we found that **I** when treated with

Chart I

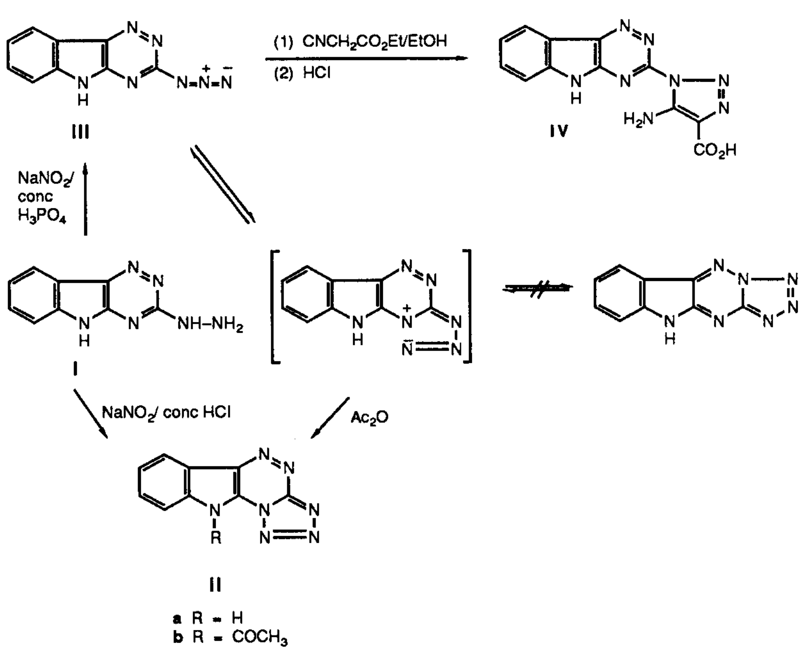
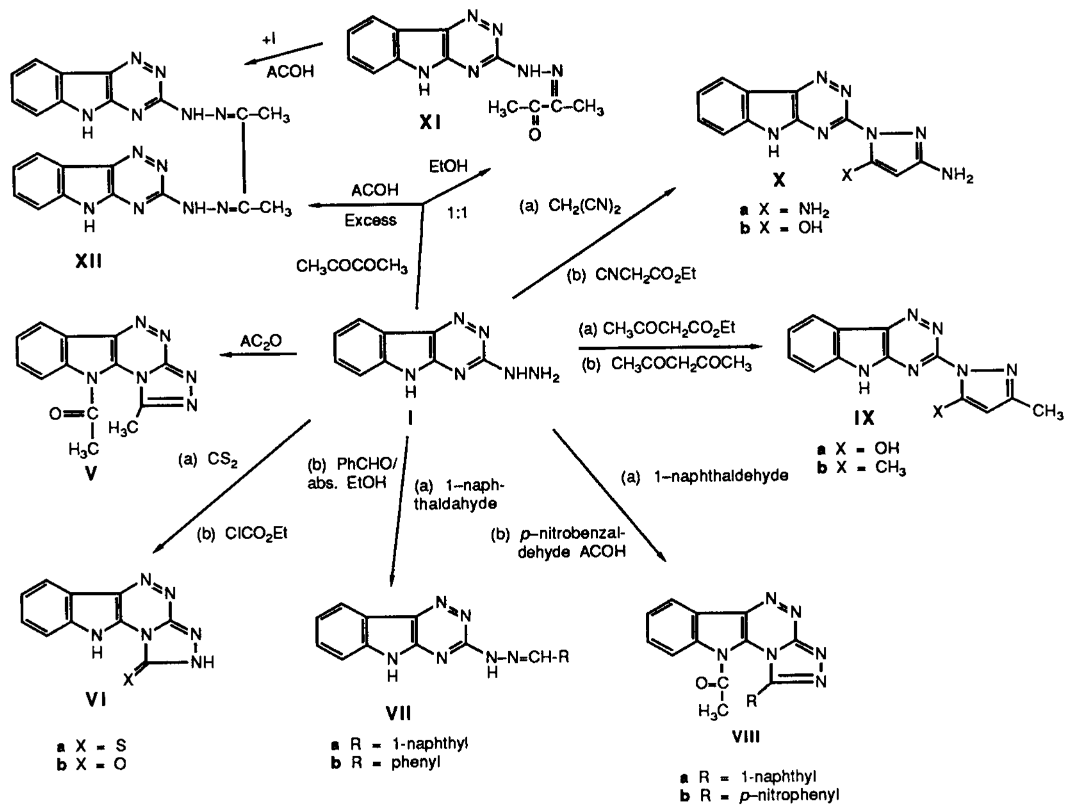


Chart II



acetic anhydride affords the fused triazolo compound namely 10-acetyl-1-methyl-10*H*-[1,2,4]triazolo[3',4':3,4][1,2,4]triazino[5,6-*b*]indole **V** (*cf.* Chart II). The ir spectrum showed a C=O band at 1720 cm^{-1} (for the acetyl group) and a C=N band at 1620 cm^{-1} and the absence of any absorption band in the amino region. The ^{1}H nmr spectrum in deuterated chloroform showed a singlet at δ 2.6 ppm (s, 3H, triazolo-CH_3), singlet at δ 2.8 ppm (s, 3H, acetyl group-CH_3), multiplet at δ 7.0 ppm (m, 4H, ArH).

Refluxing **I** with carbon disulphide produced 1,2-dihydro-10*H*-[1,2,4]triazolo[3',4':3,4][1,2,4]triazino[5,6-*b*]indole-1-thione **VIa** (*cf.* Chart II). The ir spectrum showed a C=S band at 1520 cm^{-1}, an NH broad band at 3400-3250 cm^{-1}, and a triazine C=N at 1620 cm^{-1}, as well as the absence of an SH band at 2600 cm^{-1}, which revealed its existance as the thione tautomer. The ^{1}H nmr spectrum in DMSO showed a broad resonance at δ 3.3 ppm (br, 2H, 2NH), multiplet at δ 7.2 ppm (m, 4H, ArH).

In the same manner, refluxing **I** with ethyl chloroformate produced 1,2-dihydro-10*H*-[1,2,4]triazolo[3',4':3,4][1,2,4]triazino[5,6-*b*]indol-1-one **VIb** (*cf.* Chart II). The ir spectrum showed the amide C=O band at 1700 cm^{-1}, NH broad band at 3300-3250 cm^{-1}, confirming the assumption that it exists as the keto tautomer and the C=N band at 1620 cm^{-1}.

On the other hand, refluxing **I** with 1-naphthaldehyde in absolute ethanol produced 1-naphthylidene(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-yl)hydrazone **VIIa** (*cf.* Chart II). The ir spectrum showed an NH broad band at 3300-3250 cm^{-1}, and a C=N band at 1620 cm^{-1}. Refluxing **I** with 1-naphthaldehyde in glacial acetic acid gave the corresponding triazolo compound, namely 10-acetyl-1-(1-naphthyl)10*H*-[1,2,4]triazolo[3',4':3,4][1,2,4]triazino[5,6-*b*]indole **VIIIa** (*cf.* Chart II). The ir spectrum showed a C=O band at 1680 cm^{-1} and a C=N band at 1620 cm^{-1}.

Refluxing **I** with benzaldehyde and/or *p*-nitrobenzaldehyde in ethanol and/or in glacial acetic acid behaved similarly to give both benzylidene(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-yl)hydrazone **VIIb** and 10-acetyl-1-(*p*-nitrophenyl)-10*H*-[1,2,4]triazolo[3',4':3,4][1,2,4]triazino[5,6-*b*]indole **VIIIb** respectively (*cf.* Chart II).

On the other hand, the cyclization reaction of **I** with ethyl acetoacetate afforded the condensed pyrazolino compound 3-(5'-hydroxy-3'-methyl-1*H*-pyrazol-1-yl)-5*H*-[1,2,4]triazino[5,6-*b*]indole **IXa** (*cf.* Chart II). The ir spectrum showed an NH broad band at 3200-3100 cm^{-1}, and the C=N band at 1620 cm^{-1} and the absence of any absorption band in the C=O region. The ^{1}H nmr spectrum in DMSO showed a singlet at δ 1.8 ppm (s, 3H, -CH_3), a broad band at δ 3.3 ppm (br, 2H, NH and OH), a singlet at δ 4.9 ppm (s, 1H, pyrazoline CH) and a multiplet at δ 7.0 ppm (m, 4H, ArH) and the absence of any signals due to the ethyl ester group.

In the same manner, refluxing **I** with acetylacetone produced 3-(3′,5′-dimethyl-1*H*-pyrazolo-1-yl)-5*H*-[1,2,4]triazino[5,6-*b*]indole **IXb** (*cf.* Chart II). The ir spectrum showed the NH band at 3250 cm^{-1} and the C=N band at 1620 cm^{-1} and the absence of any absorption band in the C=O region.

Refluxing **I** with malononitrile produced 3-(3′,5′-diamino-1*H*-pyrazol-1-yl)-5*H*-[1,2,4]triazino[5,6-*b*]indole **Xa** (*cf.* Chart II). The ir spectrum showed an NH_2 broad band at 3450-3300 cm^{-1} and the C=N band at 1620 cm^{-1} and the absence of any absorption band in the C≡N region showing that the two cyano groups of malononitrile were incorporated in ring formation.

Similarly, refluxing **I** with ethyl cyanoacetate produced 3-(3′-amino-5′-hydroxy-1*H*-pyrazol-1-yl)-5*H*-[1,2,4]triazino-[5,6-*b*]indole **Xb** (**cf.** Chart II).

The reaction of **I** with α dicarbonyl compounds was assumed to involve one or both of the carbonyl groups in the condensation. Thus, heating equimolar amounts of **I** and diacetyl in ethanol gave only the corresponding monohydrazone namely 2-(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-yl)-hydrazono-3-oxobutane **XI**, which showed ir absorption bands characteristic of C=O at 1670 cm^{-1} and NH broad band at 3400-3250 cm^{-1}. However in the presence of excess **I** the corresponding 2,3-bis(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-yl)hydrazonobutane **XII** was produced (*cf.* Chart II), whose structure was confirmed by elemental analysis and the ir absorption spectrum which reveals the absence of absorption bands due to C=O in contrast to the monohydrazone derivative **XI**. The same result is also obtained if the monohydrazone **XI** is heated with an excess of compound **I**.

Biological Activity of the Synthesised Compounds.

Some of the prepared compounds were tested for antibacterial activity. Two different microbial groups were used for this purpose: (a) Gram negative bacteria (*Bacillus cereus* G–ve); (b) gram positive bacteria (*E-coli* G+ve). The biological assay was determined according to the filter paper disc method a. Assay plates were incubated at 25° one day for the bacteria used [9]. The test results are shown in Table I.

Table I

Antibacterial Activity [a] [b]

Compound	*Bacillus Cereus* G−Ve	*E-Coli* G+Ve
V	+ Ve	− Ve
VIa	++ Ve	− Ve
VIb	+ Ve	− Ve
VIIa	− Ve	− Ve
VIIIb	− Ve	− Ve
IXa	+ Ve	− Ve
IXb	+ Ve	− Ve
XI	+ Ve	− Ve
XII	+++ Ve	− Ve

[a] Diameter of the zone of inhibition: − 1 cm; + = 1 to 1.5 cm; ++ = 1.5 to 2 cm; +++ 2 cm. [b] The solvent was DMSO.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded (potassium bromide) on a Shimadzo 200-91506 spectrophotometer. The ^{1}H nmr spectra were recorded on a Varian A-60 spectrometer and chemical shifts are expressed in δ ppm using TMS as the internal indicator. Analytical data were obtained from the microanalytical unit at Cairo University.

3-Hydrazino[1,2,4]triazino[5,6-*b*]indole **I** was prepared according to the literature method [8].

Reaction of **I** with Nitrous Acid (Sodium Nitrite/Phosphoric Acid).

To a cooled solution of **I** (0.01 mole) in concentrated phosphoric acid (15 ml) sodium nitrite solution (5*N*, 12 ml) was added. The separated solid product was recrystallized from dimethylformamide as yellow crystals to give the azide **III** with mp >300° and in a yield of *ca.* 70%; ir: NH 3300 cm^{-1}, azide 2150 cm^{-1}, C=N 1620 cm^{-1}.

Anal. Calcd. for $C_9H_5N_7$: C, 51.18; H, 2.37; N, 46.44. Found: C, 51.1; H, 2.3; N, 46.4.

10-Acetyl-10*H*-tetrazolo[5′,1′:3,4][1,2,4]triazino[5,6-*b*]indole (**IIb**).

Refluxing **III** (0.01 mole) in excess of acetic anhydride (10 ml) for one hour a solid was obtained which was recrystallized from dimethylformamide as yellow crystals with mp >300° and in a yield of *ca.* 65%; ir: C=O 1720 cm^{-1}, C=N 1620 cm^{-1}.

Anal. Calcd. for $C_{11}H_7N_7O$: C, 52.17; H, 2.76; N, 38.73. Found: C, 52.1; H, 2.5; N, 38.6.

General Procedure for the Reaction of **I** with Acetic Anhydride, Carbon Disulphide, Ethyl Chloroformate and/or Aromatic Aldehydes.

Refluxing **I** (0.01 mole) with acetic anhydride and/or carbon disulphide, ethyl chloroformate and/or 1-naphthaldehyde and *p*-nitrobenzaldehyde for three hours. The solid which separated was recrystallized from the appropriate solvent.

10-Acetyl-1-methyl-10*H*-[1,2,4]triazolo[3′,4′:3,4][1,2,4]triazino-[5,6-*b*]indole (**V**).

This compound was obtained as yellow crystals (ethyl alcohol), mp >300°; ir: C=O 1720 cm^{-1}, C=N 1620 cm^{-1}; ^{1}H nmr: δ 2.6 (s, 3H, triazolo-CH_3), 2.8 (s, 3H, acetyl group-CH_3), 7.0 (m, 4H, ArH).

Anal. Calcd. for $C_{13}H_{10}N_6O$: C, 58.64; H, 3.75; N, 31.57. Found: C, 58.4; H, 3.5; N, 31.3.

1,2-Dihydro-10*H*-[1,2,4]triazolo[3′,4′:3,4][1,2,4]triazino[5,6-*b*]indole-1-thione (**VIa**).

This compound was obtained as red crystals (DMF) mp >300°; ir: NH 3400-3250 cm^{-1}, C=N 1620 cm^{-1}, C=S 1520 cm^{-1}; ^{1}H nmr: δ 3.3 (br, 2H, 2NH), 7.2 (m, 4H, ArH).

Anal. Calcd. for $C_{10}H_6N_6S$: C, 49.58; H, 2.47; N, 34.71; S, 13.22. Found: C, 49.5; H, 2.4; N, 34.6; S, 13.2.

1,2-Dihydro-10*H*-[1,2,4]triazolo[3′,4′:3,4][1,2,4]triazino[5,6-*b*]-indol-1-one (**VIb**).

This compound was obtained as yellow crystals (ethyl alcohol), mp >300°; ir: NH 3300-3250 cm^{-1}, C=O 1700 cm^{-1}, C=N 1620 cm^{-1}.

Anal. Calcd. for $C_{10}H_6N_6O$: C, 53.09; H, 2.65; N, 37.16. Found: C, 52.9; H, 2.6; N, 36.8.

10-Acetyl-1-(1-naphthyl)-10*H*-[1,2,4]triazolo[3',4':3,4][1,2,4]triazino[5,6-*b*]indole (**VIIIa**).

This compound was obtained as yellow crystals (DMF), mp >300°; ir: C=O 1680 cm^{-1}, C=N 1620 cm^{-1}.

Anal. Calcd. for $C_{22}H_{14}N_6O$: C, 69.84; H, 3.70; N, 22.22. Found: C, 69.8; H, 3.5; N, 21.9.

10-Acetyl-1-(*p*-nitrophenyl)-10*H*-[1,2,4]triazolo[3',4':3,4][1,2,4]-triazino[5,6-*b*]indole (**VIIIb**).

This compound was obtained as orange crystals (DMF) mp >300°; ir: C=O 1680 cm^{-1}, C=N 1620 cm^{-1}.

Anal. Calcd. for $C_{18}H_{11}N_7O_3$: C, 57.9; H, 2.94; N, 26.27. Found: C, 57.7; H, 2.7; N, 25.9.

Condensation of I with 1-Naphthaldehyde and/or Benzaldehyde.

Compound **I** (0.01 mole) and 1-naphthaldehyde and/or benzaldehyde was heated in absolute ethanol. The solid which separated on cooling was filtered and recrystallized from the proper solvent.

3-(1-Naphthylidenehydrazono)-3,4-dihydro-5*H*-[1,2,4]triazino-[5,6-*b*]indole (**VIIa**).

This compound was obtained as yellow crystals (DMF) mp >300°; ir: NH 3300-3250 cm^{-1}, C=N 1620 cm^{-1}.

Anal. Calcd. for $C_{20}H_{14}N_6$: C, 71.00; H, 4.14; N, 24.85. Found: C, 70.8; H, 4.1; N, 24.6.

3-(Benzylidenehydrazono)-3,4-dihydro-5*H*-[1,2,4]triazino[5,6-*b*]-indole (**VIIb**).

This compound was obtained as yellow crystals (DMF) mp >300°; ir: NH 3300-3250, C=N 1620 cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}N_6$: C, 66.66; H, 4.16; N, 29.16. Found: C, 66.6; H, 4.1; N, 28.9.

General Procedure for the Reaction of I with Ethyl Acetoacetate, Acetylacetone, Malononitrile and/or Ethyl Cyanoacetate.

By heating **I** (0.01 mole) with ethyl acetoacetate, and/or acetylacetone, and/or malononitrile, and/or ethyl cyanoacetate, the solid on cooling was filtered and recrystallized from the appropriate solvent.

3-(5'-Hydroxy-3'-methyl-1*H*-pyrazol-1-yl)-5*H*-[1,2,4]triazino[5,6-*b*]-indole (**IXa**).

This compound was obtained as grey crystals (DMF) mp >300°; ir: NH 3300-3100 cm^{-1}, C=N 1620 cm^{1}; ^1H nmr: δ 1.8 (s, 3H, $-CH_2$), 3.3 (br, 2H, NH and OH), 4.9 (m, 4H, ArH).

Anal. Calcd. for $C_{13}H_{10}N_6O$: C, 58.64; H, 3.75; N, 31.57. Found: C, 58.4; H, 3.4; N, 31.4.

3-(3',5'-Dimethyl-1*H*-pyrazol-1-yl)-5*H*-[1,2,4]triazino[5,6-*b*]indole (**IXb**).

This compound was obtained as grey crystals (DMF) mp >300°; ir: NH 3250 cm^{-1}, C=N 1620 cm^{-1}.

Anal. Calcd. for $C_{14}H_{12}N_6$: C, 63.63; H, 4.54; N, 31.81. Found: C, 63.4; H, 4.3; N, 31.5.

3-(3',5'-Diamino-1*H*-pyrazol-1-yl)-5*H*-[1,2,4]triazino[5,6-*b*]indole (**Xa**).

This compound was obtained as yellow crystals (ethyl alcohol), mp >300°; ir: NH_2 3450-3300 cm^{-1}, C=N 1620 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}N_8$: C, 54.13; H, 3.75; N, 42.10. Found: C, 54.1; H, 3.5; N, 41.9.

3-(3'-Amino-5'-hydroxy-1*H*-pyrazol-1-yl)-5*H*-[1,2,4]triazino[5,6-*b*]-indole (**Xb**).

This compound was obtained as yellow crystals (ethyl alcohol, mp >300°; ir: NH_2 3400-3300 cm^{-1}, C=N 1620 cm^{-1}.

Anal. Calcd. for $C_{12}H_9N_7O$: C, 53.93; H, 3.37; N, 36.70, Found: C, 53.7; H, 3.3; N, 36.4.

Reaction of I with Diacetyl.

1- Formation of **XI**.

A mixture of **I** (0.01 mole) and diacetyl (0.01 mole) in absolute ethanol was refluxed for 3 hours. The reaction mixture was allowed to cool and the solid product which precipitated was collected and recrystallized from the appropriate solvent.

2-(5*H*-[1,3,4]triazino[5,6-*b*]indol-3-yl)hydrazono-3-oxobutane (**XI**).

This compound was obtained as orange crystals (DMF) mp >300°; ir: NH 3400-3250 cm^{-1}, C=O 1670 cm^{-1}, C=N 1620 cm^{-1}.

Anal. Calcd. for $C_{13}H_{12}N_6O$: C, 58.20; H, 4.47; N, 31.34. Found: C, 57.9; H, 4.4; N, 31.3.

2- Formation of **XII**.

Method (A).

By refluxing **I** (0.02 mole) and diacetyl (0.01 mole) in glacial acetic acid for 3 hours, the reaction mixture was allowed to cool and the solid product was recrystallized from the appropriate solvent.

Method (B).

By refluxing **XI** (0.01 mole) and **I** (excess) in glacial acetic acid, the reaction mixture was allowed to cool and the solid product was recrystallized from the appropriate solvent.

2,3-Bis(5*H*-[1,2,4]triazino[5,6-*b*]indol-3-yl)hydrazonobutane (**XII**).

This compound was obtained as orange crystals (DMF) mp >300°; ir: NH 3400-3250, C=N 1620 cm^{-1}.

Anal. Calcd. for $C_{22}H_{18}N_{12}$: C, 58.66; H, 4.00; N, 37.33. Found: C, 58.6; H, 3.7; N, 37.1.

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