10-Carbethoxymethyl-3-phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-*b*]indole and Derivatives at its 10-Position

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Reaction of 3-phenyl-10*H*-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-*b*]indole (**4**) with ethyl chloroacetate gave 10-carbethoxymethyl-3-phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-*b*]indole (**3**). Condensation of **3** with hydrazine hydrate gave (3-phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-*b*]indol-10-yl)acetylhydrazine (**5**). Reactions of **5** with a number of aromatic aldehydes, acetophenone, cyclohexanone and D-galactose gave the corresponding hydrazones **6-12**. Condensation of **5** with acetylacetone gave the pyrazole **15**. Cyclization of **5** with CS_2 gave (3-phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-*b*]indol-10-yl)(2-thiol-1,3,4-oxadiazol-5-yl)methane (**16**). Reaction of **16** with ethyl chloroacetate gave the carbethoxy alkylated derivative (3-phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-*b*]indol-10-yl)[2-(thiocarbethoxymethyl)1,3,4-oxadiazol-5-yl]methane (**17**).

10-Carbethoxymethyl-3-phenyl-1,2,4-triazolo[3',4':2,3][1,2,4]triazino[5,6-*b*]indol und Derivate in Position 10

Die Reaktion von 3-Phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-*b*]indol (**4**) mit Ethylchloroacetat lieferte 10-Carbethoxymethyl-3-phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-*b*]indol (**3**). Kondensation von **3** mit Hydrazinhydrat gab (3-Phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-*b*]indol-10-yl)acetylhydrazin (**5**), das mit einigen aromatischen Aldehyden, Acetophenon, Cyclohexanon und Δ-Galactose zu den entspr. Hydrazonen **6-12** reagierte. Kondensation von **5** mit Acetylaceton gab das Pyrazol **15**. Cyclisierung von **5** mit CS_2 gab das (3-Phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-*b*]indol-10-yl)(2-thio-1,3,4-oxadiazol-5-yl)methan (**16**), dessen Reaktion mit Ethylchloroacetat gab das Carbethoxyalkyl-Derivat (3-Phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino-[5,6-*b*]indol-10-yl)-[2-(thiocarbethoxymethyl)1,3,4-oxadiazol-5-yl]methan (**17**).

The broad range of antiviral activity exhibited by 1,2,4-triazino[5,6-*b*]indoles prompted the synthesis of a great number of substituted derivatives[1,2]. The greatest antiviral activity[2,3] has been found with those having 3 and 5-substituents. They inhibited rhinovirus, herpes simplex, pseudorabies, vaccinia, semliki forest, and picorna virus. The activity may be due to a specific inhibition of viral RNA synthesis[4]. Moreover, triazinoindole as well as their 1,2,4-triazolo analogues had been tested as bacteriocids[5,6], fungicides[7], and analgesic[8] and antiinflammatory[9,10] agents. 3-Hydrazino-5-substituted 1,2,4-triazino[5,6-*b*]indole and its 1,2,4-triazolo derivative have antihypertensive properties[11,12]. These various biological aspects promoted the present investigation which deals with the functionalization of 3-phenyl-10*H*-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-*b*]indole.

Compound **1** was prepared by reacting 3-hydrazino[1,2,4]triazino[5,6-*b*]indole with benzaldehyde in EtOH. When the reaction was carried out in acetic acid, the product was formulated[13] as the *N*-acetyl derivative of **2**. Dehydrocyclisation of **1** to give the linear form **4** and not the isomeric angular structure **2** was carried out with $FeCl_3$. The linear structure **4** was also given[14] to a cyclized product resulting from the reaction of **1** with bromine in acetic acid.

Alkylation of **4** with ethyl chloroacetate/K_2CO_3 gave **3**. The IR-spectrum revealed the disappearance of the NH-band (3321 cm^{-1}) of **4** and showed absorption at 1735 cm^{-1} due to the carbonyl ester group. Its ^{1}H-NMR spectrum showed a triplet and a quartet at 1.26 and 4.18, respectively, ppm for the ethyl group, a singlet at 4.96 ppm for the methylene group.

Reaction of **3** with hydrazine hydrate gave the hydrazide **5**. Its IR-spectrum showed an absorption at 1685 cm^{-1} (urethan). Condensation of **5** with benzaldehyde, *p*-hydroxy- and *p*-nitrobenzaldehydes, cinnamaldehyde, acetophenone, and cyclohexanone gave the corresponding hydrazones **6-11**. - Reaction of **5** with D-galactose gave the hydrazone **12**.

The reaction of hydrazine **5** with acetylacetone in presence of acetic acid afforded **15**. On the other hand, when the reaction was carried out in presence of a catalytic amount of piperidine, the ^{1}H-NMR spectrum of the isolated mixture showed the presence of **15** in addition to the presumably formed intermediate **13**.

The later showed two singlets for the two methyl groups at 1.77 and 2.13 ppm, whereas those of **15** appeared at 2.26 and 2.41 ppm. This suggests that the reaction proceeds *via* the open-chain hydrazone **13**. Cyclization of **13** may take place *via* the 5-hydroxy pyrazoline **14**, which readily dehydrated under the reaction conditions to give **15**. Structure **15** was also confirmed by the disappearance of the characteristic IR bands due to NH and NH_2 groups of **5** and the appearance of an amide absorption band at 1736 cm^{-1}.

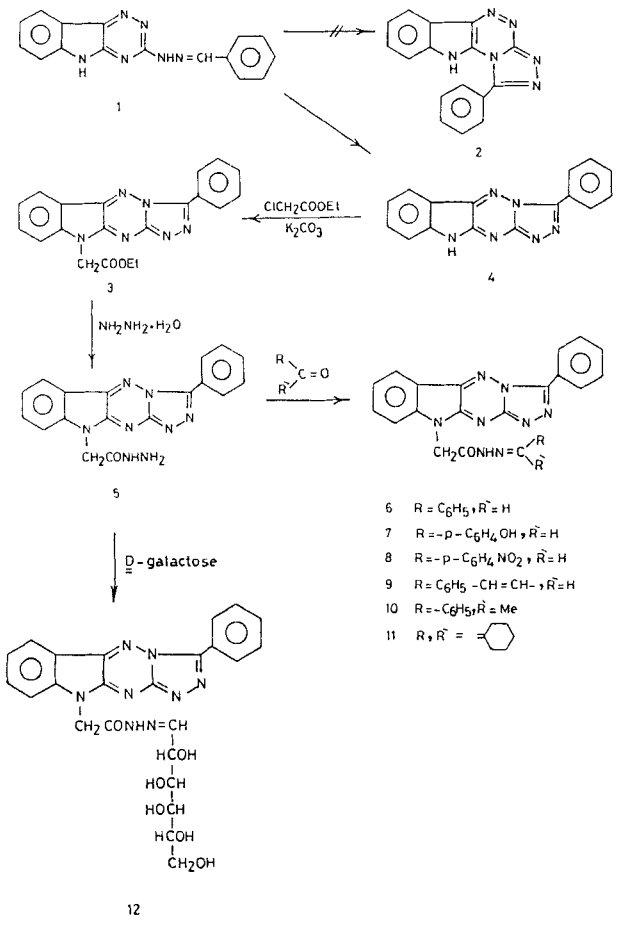
Reaction of **5** with CS_2 in a solution of KOH followed by acidification gave (3-phenyl-1,2,4-triazolo[4',3':2,3]-[1,2,4]triazino[5,6-*b*]indol-10-yl)(2-thiol-1,3,4-oxadiazol-5-yl)methane (**16**). Its IR-spectrum showed no carbonyl absorption, so confirming cyclization. Reaction of **16** with ethyl chloroacetate gave **17**, whose IR-spectrum showed an ester group at 1735 cm^{-1}.

Appreciation is expressed to Prof. *Z.M. El Shafei* for his valuable discussions.

Experimental Part

Mps: Meltemp apparatus with a 76-mm immersion thermometer, uncorrected.- TLC: Bakerflex silica gel IB-F (2.5-7.5 cm) plates.- IR spectra:

  0365-6233/93/0303-0153 $ 5.00 + .25/0



Scheme 1

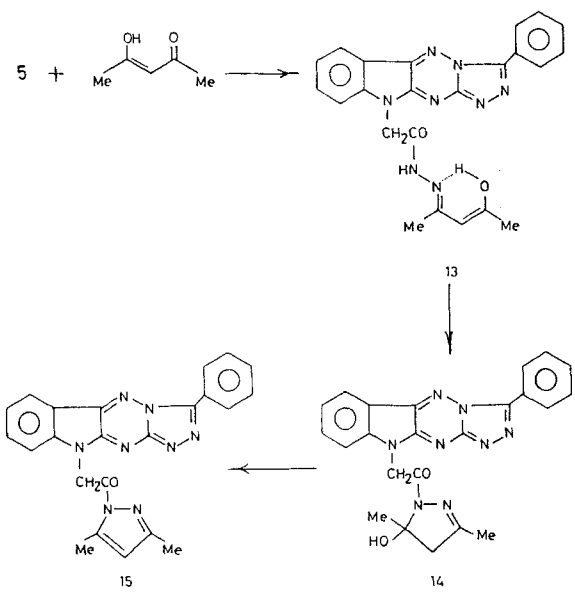
Unicam SP 1025.- ^{1}H-NMR spectra: Varian EM-390, in $CDCl_3$ or $(CD_3)_2SO$, Me_4Si as internal or external reference. Chemical shifts (δ) downfield from Me_4Si.- Microanalyses: Unit of Microanalysis, Faculty of Science, Cairo and Assiut Universities.

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

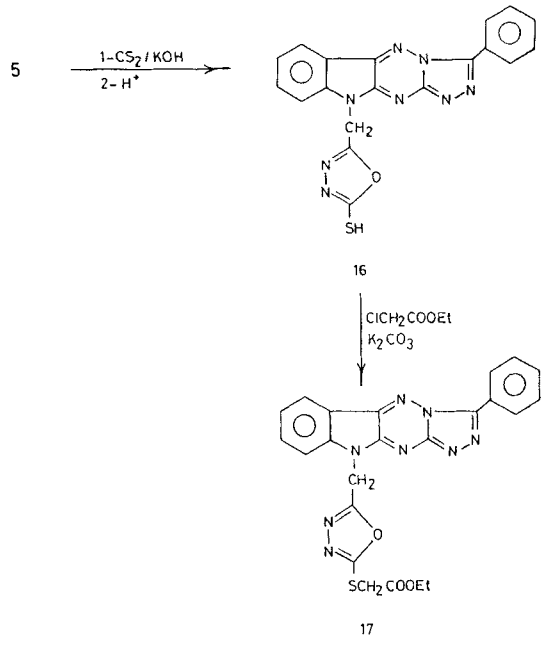
A 2M solution of $FeCl_3$ in EtOH (1.0 ml) was added dropwise to a boiling solution of **1** (0.73 g, 2.50 mmol) in EtOH (50 mL). Heating was continued for 10 min, then the mixture was kept overnight at room temp. The solvent was removed *in vacuo* and the residue was washed repeatedly with water. The yellow product was crystallized from *N,N*-dimethylformamide, mp. > 300° (Lit.[14] mp. > 300°).

10-Carbethoxymethyl-10H-3-phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-b]indole (**3**)

The mixture of **4** (0.70 g, 2.44 mmol) in dry acetone (50 mL) and *N,N*-dimethylformamide (10 mL), anhydrous K_2CO_3 (2.0 g, 14.47 mmol) and ethyl chloroacetate (0.4 g, 3.26 mmol) was heated under reflux for 6 h. It was filtered and the filtrate was concentrated. The solid mass which separated out on cooling, was filtered off, washed with EtOH and recrystallized from *N,N*-dimethylformamide in yellow needles, yield 0.82 g (90%); mp. 225°.- $C_{20}H_{16}N_6O_2$ Calcd. C 64.5 H 4.33 N 22.6 Found C 64.5 H 4.36 N 22.6.- IR: ν = 1735 cm^{-1} (ester).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.26 (t, 3H, CH_3CH_2), 4.18 (q, 2H, CH_3CH_2), 4.96 (s, 2H, CH_2COO), 7.38 and 8.41 (2m, 6H, 2H aromatic), 8.14 (d, 1H, J 7.5 Hz, H-9).



Scheme 2



Scheme 3

(3-Phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-b]indol-10-yl)acetylhydrazine (**5**)

A mixture of **3** (0.2 g, 5.37 mmol) and 99% hydrazine hydrate (0.25 g, 8.0 mmol) in *N,N*-dimethylformamide (60 mL) was heated under reflux for 30 min. The mixture was cooled and the product was filtered off, washed with $CHCl_3$ and recrystallized from *N,N*-dimethylformamide in yellow needles, yield 1.71 g (90%); mp. 69°.- $C_{18}H_{14}N_8O$ Calcd. C 60.3 H 3.94 N 31.3 Found C 60.5 H 4.00 N 31.5.- IR: ν = 3375 and 3100 (NH_2 and NH), 1685 cm^{-1} (OCN).

Benzaldehyde (3-Phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-b]-indol-10-yl)acetylhydrazone (**6**)

The mixture of **5** (0.50 g, 1.40 mmol) in *N,N*-dimethylformamide (60 mL) benzaldehyde (0.15 g, 1.4 mmol), and piperidine (0.1 mL) was heated under reflux for 2 h. The product which separated out on cooling, was filtered off, washed with EtOH, dried, and recrystallized from *N,N*-dimethylformamide in yellow plates, yield 0.45 g (73%); mp. 340-342°.- $C_{25}H_{18}N_8O$ Calcd. C 67.3 H 4.06 N 25.1 Found C 66.6 H 4.10 N 25.3.- IR: ν = 3220 (NH), 1690 cm^{-1} (OCN).

p-Hydroxybenzaldehyde (3-phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino-[5,6-b]indol-10-yl)acetylhydrazone (**7**)

For procedure see **6**. **7** was recrystallized from *N,N*-dimethylformamide in yellow needles, yield 0.38 g (60%); mp. 318-320°.- $C_{25}H_{18}N_8O_2$ Calcd. C 64.9 H 3.92 N 24.2 Found C 64.5 H 3.89 N 24.2.- IR: ν = 3480 (OH), 3160 (NH), 1690 cm^{-1} (OCN).- ^{1}H-NMR (DMSO-d_6): δ (ppm) = 5.44 (s, 2H, CH_2), 6.71 (m, 2H, CH and OH), 7.33-8.38 (m, 14 H, aromatic H and NH).

p-Nitrobenzaldehyde (3-phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino-[5,6-b]indol-10-yl)acetylhydrazone (**8**)

For procedure see **6**. **8** was recrystallized from *N,N*-dimethylformamide in yellow plates, yield 0.55 g (80%); mp. 348-350°.- $C_{25}H_{17}N_9O_3$ Calcd. C 61.1 H 3.49 N 25.6 Found C 61.0 H 3.32 N 25.6.- IR: ν = 1685 cm^{-1} (OCN).

Cinnamaldehyde (3-phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-b]-indol-10-yl)acetylhydrazone (**9**)

The mixture of **5** (0.50 g, 1.4 mmol) in *N,N*-dimethylformamide (60 mL), cinnamaldehyde (0.19 g, 1.4 mmol), and piperidine (0.1 mL) was heated under reflux for 4 h and processed as above. **9** crystallized from *N,N*-dimethylformamide in yellow needles, yield 0.48 g (73%); mp. 285-286°.- $C_{27}H_{20}N_8O$ Calcd. C 68.6 H 4.26 N 23.7 Found C 68.6 H 4.11 N 23.6.- IR: ν = 3270 and 3200 (NH), 1690 cm^{-1} (OCN).- ^{1}H-NMR (DMSO-d_6): δ (ppm) = 5.40 (s, 2H, CH_2), 6.93 (m, 3H, 3 CH), 7.17-8.39 (m, 14 H, aromatic H) and 11.66 (bs, 1H, NH).

Acetophenone (3-phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-b]-indol-10-yl)acetylhydrazone (**10**)

For procedure see **6**. **10** crystallized from *N,N*-dimethylformamide in yellow needles, yield 0.40 g (62%); mp. 206-207°.- $C_{26}H_{20}N_8O$ Calcd. C 67.8 H 4.38 N 24.3 Found C 67.6 H 4.57 N 24.4.- IR: ν = 3280 (NH), 1700 cm^{-1} (OCN).

Cyclohexanone (3-phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-b]-indol-10-yl)acetylhydrazone (**11**)

For procedure see **6**. **11** crystallized from *N,N*-dimethylformamide in yellow needles, yield 0.44 g (72%); mp. 269-271°.- $C_{24}H_{22}N_8O$ Calcd. C 65.7 H 5.06 N 25.6 Found C 66.0 H 4.88 N 25.8.- IR: ν = 3220 (NH), 1690 cm^{-1} (OCN).

D-Galactose (3-phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-b]-indol-10-yl)acetylhydrazone (**12**)

The mixture of **5** (1.0 g, 2.79 mmol) in *N,N*-dimethylformamide (100 mL), of D-galactose (0.50 g, 2.79 mmol) in water (10 mL), and acetic acid (0.2 mL) was heated under reflux for 2 h. The solid mass, which separated on cooling, was filtered off, washed with EtOH, dried and crystallized from *N,N*-dimethylformamide (yellow plates), yield 0.9 g (62%); mp. > 350°.- $C_{24}H_{24}N_8O_6$ Calcd. C 55.4 H 4.65 N 21.5 Found C 55.0 H 4.90 N 21.1.- IR: ν = 3436 (OH), 3263 (NH), 1692 cm^{-1} (OCN).

3,5-Dimethyl-1-(3-phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-b]indol-10-yl)acetyl pyrazole (**15**)

The solution of **5** (0.50 g, 1.40 mmol) in EtOH (150 mL), acetylacetone (0.14 g, 1.40 mmol), and acetic acid (0.1 mL) was heated under reflux for 2 h. The product which separated on cooling, was filtered off, washed with EtOH and dried. **15** crystallized from EtOH in yellow needles, yield 0.36 g (61%); mp. 257-259°.- $C_{23}H_{18}N_8O$ Calcd. C 65.4 H 4.29 N 26.5 Found C 65.4 H 4.32 N 26.6.- IR: ν = 1736 cm^{-1} (OCN), 1607 (C=N).- ^{1}H-NMR (DMSO-d_6): δ (ppm) = 2.26 and 2.41 (2s, 6H, 2 CH_3), 5.80 (d, J = 1·5 Hz, 2H, CH_2), 6.21 (s, 1H, CH) and 7.24-8.34 (2m, 9H, aromatic H).

(3-Phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-b]indol-10-yl)(2-thiol-1,3,4-oxadiazol-5-yl)methane (**16**)

A solution of **5** (1.0 g, 2.80 mmol), KOH (0.16 g, 2.80 mmol) and CS_2 (4.0 mL) in *N,N*-dimethylformamide (50 mL) was heated under reflux for 8 h. The mixture was concentrated, poured onto crushed ice and acidified with dil. HCl. The precipitate was washed with water and crystallized from *N,N*-dimethylformamide in yellow plates, yield 0.77 g (69%); mp. 313-315°.- $C_{19}H_{12}N_8OS$ Calcd. C 57.0 H 3.02 N 28.0 Found C 56.7 H 3.36 N 28.0.- IR: ν = 2920 cm^{-1} (SH).

(3-Phenyl-1,2,4-triazolo[4',3':2,3][1,2,4]triazino[5,6-b]indol-10-yl)[2-(thiocarbethoxymethyl)-1,3,4-oxadiazol-5-yl]methane (**17**)

The solution of **16** (0.20 g, 0.50 mmol), and NaOH (0.02 g, 0.50 mmol) in *N,N*-dimethylformamide (50 mL) was added $ClCH_2$-CO-OEt (0.06 g, 0.50 mmol). The mixture was heated under reflux for 1 h, and the solid mass which separated on cooling, was filtered off, washed with EtOH, dried, and crystallized from *N,N*-dimethylformamide (yellow needles), yield 0.15 g (60%); mp. 215-216°.- $C_{23}H_{18}N_8O_3S$ Calcd. C 56.8 H 3.73 N 23.0 Found C 56.9 H 3.71 N 22.6.- IR: ν = 1735 cm^{-1} (COO).

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[Ph29]