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Synthesis of the 1,2,4-Triazolo[4,3-*a*]quinazolin-5-ones and Related Compounds

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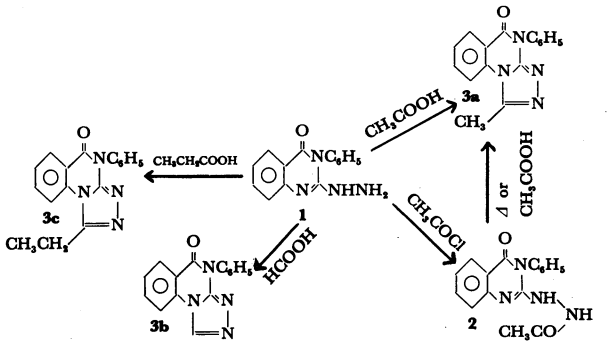
2-Hydrazino-3-phenyl-4(3*H*)-quinazolinone (**1**) underwent ring closure with aliphatic acid, aldehydes, and carbon disulfide to 1-alkyl-, 1-aryl-, and 1-mercapto-4-phenyl-1,2,4-triazolo[4,3-*a*]quinazolin-5(4*H*)-ones (**7**) for instance. The 1-alkylthio-3-phenyl-1,2,4-triazolo[4,3-*a*]quinazolin-5(4*H*)-ones were readily obtained from **7** and alkyl halides. Reaction of **1** with ethyl acetoacetate gave the corresponding hydrazone which was readily converted into 2-(3-methyl-5-oxo-2-pyrazolin-1-yl)-3-phenyl-4(3*H*)-quinazolinone.

The fusion of quinazoline ring with other biologically active nuclei has aroused considerable interest for synthetic organic chemists because many members of this family exhibit im potant biological activity.[1-3] Some tetrazolo[1,5-*a*]quinazolinones have been prepared,[4] as pesticides, from the corresponding 2-hydrazino-3-aryl-4(3*H*)-quinazolinones and nitrous acid. Tennant[5] first prepared 3-phenyl-1,2,3-triazolo[1,5-*a*]-quinazolin-5-one by condensation of *o*-azidobenzoic acid with phenylacetonitrile.

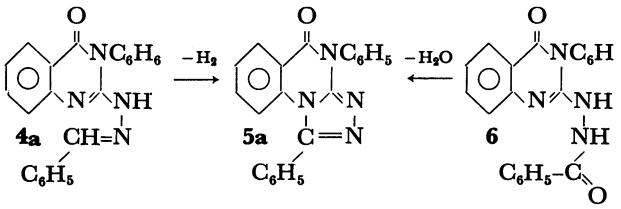
It has been observed in the present study that 2-hydrazino-3-phenyl-4(3*H*)-quinazolinone (**1**) reacted with acetyl chloride in the presence of potassium carbonate in dry chloroform gave 2-(2-acetylhydrazino)-3-phenyl-4(3*H*)-quinazolinone (**2**). Heating of **2** above its melting point for 10 min gave 1-methyl-4-phenyl-1,2,4-triazolo[4,3-*a*]quinazolin-5(4*H*)-one (**3a**), which also can be obtained *via* another route, by refluxing **1** or **2** in acetic acid. In a similar way, reaction of **1** with formic acid and propionic acid gave the corresponding 4-phenyl-1,2,4-triazolo[4,3-*a*]quinazolin-5(4*H*)-one (**3b**) and 1-ethyl-4-phenyl-1,2,4-triazolo-[4,3-*a*]quinazolin-5(4*H*)-one (**3c**) respectively as shown in the following scheme:



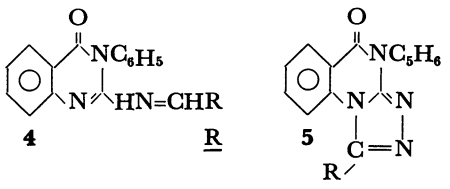
The NMR spectrum of **3a** (in $CDCl_3$) showed a singlet at 2.72 (3H, CH_3), a multiplet at 7.4—7.1 (5H, C_6H_5), and another multiplet at 8.2—7.8 (4H of quinazolinone ring), while the NMR spectrum of **3c** showed a triplet at 1.14 (3H, CH_3), a quartet at 3.23 (2H, CH_2), a multiplet at 7.4—7.0 (5H, C_6H_5) and a multiplet at 8.3—7.8 (4H of quinazolinone ring).

Although the isomerization of 1,2,4-triazolo[4,3-*c*]-quinazolines to 1,2,4-triazolo[1,5-*c*]quinazolines has been reported,[6] no such isomerization has been found in 4-phenyl-1,2,4-triazolo[4,3-*a*]quinazolin-5(4*H*)-one system. When **1** was treated with formic acid under milder conditions[7,8] than those used above, **3b** was obtained.

Fusion of **1** with benzaldehyde, for 3 min, gave benzaldehyde (4-oxo-3-phenyl-3,4-dihydro-2-quinazolinyl)hydrazone (**4a**), which was dehydrogenated to 1,4-diphenyl-1,2,4-triazolo[4,3-*a*]quinazolin-5(4*H*)-one (**5a**) when the reaction was continued for 2 h at 220—225 °C. The same result was also obtained by ring closure of 2-(2-benzoylhydrazino)-3-phenyl-4(3*H*)-quinazolinone (**6**) when heated over its melting point for 10 min. Similarly a series of the hydrazones (**4b—e**)



(Table 1) and 1-aryl-4-phenyl-1,2,4-triazolo[4,3-*a*]-quinazolin-5(4*H*)-ones (**5b—e**) (Table 2) were prepared from **1** and the appropriate aldehydes.

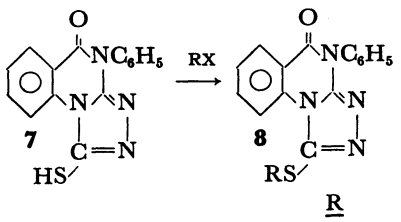


4 and **5a**; C_6H_5
b; C_6H_4Cl-*m*
c; C_6H_4Cl-*p*
d; $C_6H_4CH_3$-*p*
e; $C_6H_4OCH_3$-*p*

The IR spectra of **4a—e** showed bands at 1700—1685 and 3320—3260 cm^{-1} assignable to C=O and NH stretching frequencies, respectively. While the IR spectra of **5a—e** indicated the disappearance of the NH stretching frequency and revealed a characteristic band for C=O at 1690—1680 cm^{-1}.

Further, the reaction of **1** with one equivalent of carbon disulfide resulted in ring closure to 1-mercapto-4-phenyl-1,2,4-triazolo[4,3-*a*]quinazolin-5(4*H*)-one (**7**), which was readily converted into the corresponding alkylthio derivatives **8a—d** with alkyl halides in basic medium.

The NMR spectrum of **8b** (in $CDCl_3$) showed a triplet at 1.63 (3H, CH_3), a quartet at 3.5 (2H, S-CH_2) and a multiplet at 7.6—8.2 (9H, aromatic protons)



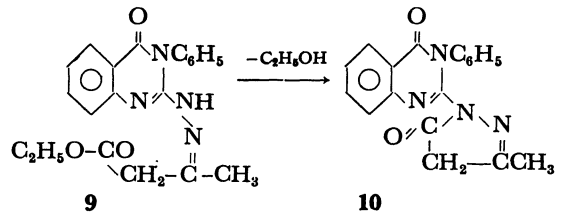
8a; CH_3
8b; C_2H_5
8c; CH_2CH
8d; $CH_2C_6H_5$
8e; $CH_2COOC_2H_5$
8f; CH_2COOH
8g; $CH_2CONHCH_2C_6H_5$

which is in agreement with its structure. Reaction of **7** with ethyl chloroacetate in dry acetone in the presence of potassium carbonate gave 1-ethoxycarbonylmethylthio-4-phenyl-1,2,4-triazolo[4,3-*a*]quinazolin-5(4*H*)-one (**8e**). The IR spectrum of **8e** showed two carbonyl bands one at 1690 cm^{-1} (due to quinazolinone nucleus) and the other at 1740 cm^{-1} (due to the ester group).

However, treatment of **8e** with aq potassium carbonate solution (5%) at 50 °C for 1 h gave 1-carboxymethylthio-4-phenyl-1,2,4-triazolo[4,3-*a*]quinazolin-5(4*H*)-one (**8f**), which was readily obtained by treatment of **7** with chloroacetic acid in the presence of potassium carbonate in dry acetone.

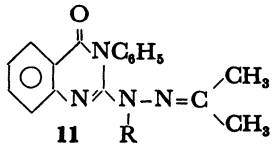
The IR spectrum of **8f** showed two carbonyl bands one at 1685 cm^{-1} (of quinazolinone nucleus) and the other at 1670 cm^{-1} (of the carboxyl group). Synthesis of 1-(benzylcarbamoylmethylthio)-4-phenyl-1,2,4-triazolo[4,3-*a*]quinazolin-5(4*H*)-one (**8g**) was achieved by reaction of **8e** with benzylamine in boiling ethanol. The IR spectrum of **8g** showed bands at 3180 cm^{-1} (NH), 1690 cm^{-1} (C=O of quinazolinone nucleus) and at 1665 cm^{-1} (C=O of amide).

On the other hand, treatment of **1** with ethyl acetoacetate in boiling ethanol produced the corresponding hydrazone **9**. Its IR spectrum exhibited two carbonyl bands one at 1685 cm^{-1} (due to quinazolinone ring) and the other at 1735 cm^{-1} (due to the ester group). When **9** was heated above its melting point for 5 min, the corresponding pyrazolinone **10** was obtained.



The IR spectrum of 2-(3-methyl-5-oxo-2-pyrazolin-1-yl)-3-phenyl-4(3*H*)-quinazolinone (**10**) showed in addition to the carbonyl band of quinazolinone nucleus at 1690 cm^{-1}, the amide band at 1665 cm^{-1}.

Refluxing of **1** with acetone gave the corresponding hydrazone **11a**. According to the literature,[9] attempted formation of **3a** by heating of **11a** at 220—225 °C for 2 h failed. However, **11a** was readily acetylated and sulfonylated using acetic anhydride and benzenesulfonyl chloride in pyridine to give the corresponding derivatives **11b** and **11c** respectively.



11a; H
b; $COCH_3$
c; $SO_2C_6H_5$

The IR spectrum of **11a** showed band at 1690 cm^{-1} (C=O of quinazolinone ring) and at 3320 cm^{-1} (NH group). While, the IR spectra of **11b** and **11c** revealed the disappearance of the NH stretching frequency.

Experimental

Melting points reported are uncorrected. IR spectra were recorded on a Beckman IR-20 spectrophotometer. ^1H NMR spectrum was recorded on a Varian EM-360 60 MHz using TMS as the internal standard.

2-(2-Acetylhydrazino)-3-phenyl-4(3H)-quinazolinone (2). To a solution of **1** (5 g, 0.02 mol) in dry chloroform (100 ml) containing anhyd potassium carbonate (0.5 g), acetyl chloride (0.01 mol) was added slowly. After the addition was complete, the reaction mixture was heated on a water bath for 1 h. The solvent was evaporated and the crude product was collected and crystallized from water as colorless needles, 2.3 g (80%), mp 142 °C. Found: C, 65.46; H, 4.91; N, 19.18%. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.76; N, 19.05%.

1-Methyl-4-phenyl-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-one (3a). **2** (1 g) was heated above its melting point for 5 min and after cooling, recrystallized from ethanol as colorless needles, 0.6 g (60%), mp 313 °C. The same compound was also obtained by refluxing **2** (1 g) with acetic acid (10 ml) for 20 min. The separated product was crystallized from ethanol 0.7 g (70%), no depression of melting point occurred on admixture with the sample prepared by the above procedure.

3a was also obtained by refluxing **1** (2.5 g; 0.01 mol) with acetic acid for 2 h, as described above in 65% yield. Found: C, 69.67; H, 4.46; N, 20.31%. Calcd for $C_{16}H_{12}N_4O$: C, 69.57; H, 4.35; N, 20.29%.

4-Phenyl-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-one (3b). A mixture of **1** (0.01 mol), 2.5 g and formic (20 ml) was refluxed for 2 h, then the excess acid was evaporated under reduced pressure and the residue was crystallized from ethanol to give colorless needles, 2.1 g (80%), mp 332—334 °C. Found: C, 68.74; H, 3.66; N, 21.45%. Calcd for $C_{15}H_{10}N_4O$: C, 68.70; H, 3.82; N, 21.37%.

The same product was obtained by heating the above mixture at 55 °C for 45 min. The excess acid was evaporated under reduced pressure at 50 °C and the crude product was crystallized from ethanol to give **3b**. There is no melting point depression and the infrared was superimposable with that of **3b** prepared according to above procedure.

1-Ethyl-4-phenyl-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-one (3c). It was prepared by refluxing a mixture of **1** (2.5 g; 0.01 mol) and propionic acid (20 ml) as previously described in **3b**. The crude product was crystallized from ethanol–benzene mixture as colorless needles, 2 g (70%), mp 285—287 °C. Found: C, 70.46; H, 4.70; N, 19.61%. Calcd for $C_{17}H_{14}N_4O$: C, 70.34; H, 4.83; N, 19.31%.

Table 1. Physical data of hydrazones **4a—e**

Compd No.	Mp θ_m/°C	Formula	Calcd(Found) (%) C	H	N
4a	232	$C_{21}H_{16}N_4O$	74.12	4.71	16.47
			(74.36	4.65	16.61)
b	223	$C_{21}H_{15}N_4OCl$	67.37	4.01	14.97
			(67.28	4.26	14.66)
c	287	$C_{21}H_{15}N_4OCl$	67.37	4.01	14.97
			(67.35	4.16	14.85)
d	242	$C_{22}H_{18}N_4O$	74.57	5.08	15.82
			(74.36	5.18	15.63)
e	238	$C_{22}H_{18}N_4O_2$	71.35	4.86	15.14
			(71.58	4.78	15.41)

Table 2. 1-Aryl-4-phenyl-1,2,4-triazolo [4,3-*a*] quinazolin-5(4*H*)-ones (**5a—e**)

Compd No	Mp θ_m/°C	Formula	Calcd(Found) (%) C	H	N
5a	238	$C_{21}H_{14}N_4O$	74.56	4.14	16.57
			(74.46	4.08	16.28)
b	225	$C_{21}H_{13}N_4OCl$	67.74	3.49	15.05
			(67.65	3.51	15.14)
c	261	$C_{21}H_{13}N_4OCl$	67.74	3.49	15.05
			(67.65	3.31	15.21)
d	299	$C_{22}H_{16}N_4O$	75.00	4.55	15.91
			(75.21	4.46	15.81)
e	282	$C_{22}H_{16}N_4O_2$	71.74	4.35	15.22
			(71.65	4.52	15.41)

Table 3. 1-Alkylthio-4-phenyl-1,2,4-triazolo [4,3-*a*]quinazolin-5(4*H*)-ones (**8a—d**)

Compd No.	Mp θ_m/°C	Formula	Calcd(Found) (%) C	H	N	S
8a	213—215	$C_{16}H_{12}N_4OS$	62.33	3.89	18.18	10.39
			(62.46	3.71	18.09	10.56)
b	183	$C_{17}H_{14}N_4OS$	63.35	4.34	17.39	9.94
			(63.48	4.46	17.21	9.76)
c	186—187	$C_{18}H_{14}N_4OS$	64.67	4.19	16.76	9.58
			(64.92	4.36	16.81	9.77)
d	195	$C_{22}H_{16}N_4OS$	68.75	4.16	14.58	8.33
			(68.71	4.35	14.33	8.18)

*Reaction of 2-Hydrazino-3-phenyl-4(3H)-quinazolinone (**1**) with Aldehydes.* A mixture of appropriate aldehyde (0.011 mol) and **1** (0.01 mol) was heated for 3 min, and after cooling to room temperature, crystallized from ethanol–benzene mixture as colorless needles. The yield was about 85—90%.

*2-(2-Benzoylhydrazino)-3-phenyl-4(3H)-quinazolinone (**6**).* It was prepared from **1** (0.02 mol) and benzoyl chloride (0.02 mol) in chloroform solution containing potassium carbonate as previously described in **2**. The crude product was crystallized from ethanol as colorless needles, 2.4 g (69%), mp 149—151 °C. IR (KBr), 3340 (NH), 3230 (NH), 1665 (amide CO) cm^{-1}. Found: C, 70.56; H, 4.31; N, 15.62%. Calcd for $C_{21}H_{16}N_4O$: C, 70.79; H, 4.49; N, 15.73%.

*1-Aryl-4-phenyl-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-ones (**5a—e**).* A mixture of appropriate aldehyde (0.015 mol) and **1** (0.01 mol) was heated at 210—225 °C for 2 h. The pyrolysis residue was cooled and triturated with ethanol. The crude product was crystallized from ethanol (charcoal) forming colorless needles of **5a—e**. The yield was about 55—65%. **5a** was also obtained by heating benzaldehyde (4-oxo-3-phenyl-3,4-dihydro-2-quinazolinyl)hydrazone (**4a**) for 1 h at 220—225 °C. The pyrolysis residue, treated as described above gave **5a** in yield 45%.

The same product **5a**, was also obtained in 70% yield by heating **6** (1 g) over its melting point for 10 min as described in **3a**.

*1-Mercapto-4-phenyl-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-one (**7**).* **1** (2 g), methanol (100 ml), potassium hydroxide (0.7 g), and carbon disulfide (6 ml) were refluxed for 4 h. After removal of the methanol, dilute potassium hydroxide was added and the alkaline solution was filtered. After precipitation with dilute hydrochloric acid, the crude product was filtered and recrystallized from ethanol as colorless needles, 1.8 g (77%), mp 342—344 °C. Found: C, 61.41; H, 3.26; N, 19.18; S, 10.76%. Calcd for $C_{15}H_9N_4OS$: C, 61.22; H, 3.40; N, 19.05; S, 10.88%.

*Reaction of **7** with Alkyl Halides.* A solution of **7** (0.5 g; 0.002 mol) and sodium hydroxide (0.1 g) in water (10 ml) was stirred while the appropriate alkyl halide (0.004 mol) was added dropwise. The reaction mixture was stirred for 2 h, then the excess alkyl halide was evaporated and the residue recrystallized from benzene–pet. ether (60—80 °C) mixture, forming colorless needles of the products **8a—d**. The yield was about 65—70%.

*1-Ethoxycarbonylmethylthio-4-phenyl-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-one (**8e**).* To a solution of **7** (1 g) in dry acetone (30 ml) containing anhyd potassium carbonate (0.5 g), ethyl chloroacetate (0.5 ml) was added slowly. The reaction mixture was refluxed on a steam bath for 30 min, then filtered, evaporated and the crude product was collected and crystallized from pet. ether (60—80°C) as colorless needles, 0.9 g (70%), mp 116 °C. Found: C, 60.15; H, 4.32; N, 14.95; S, 8.71%. Calcd for $C_{19}H_{16}N_4O_3S$: C, 60.00; H, 4.21; N, 14.73; S, 8.42%.

*1-Carboxymethylthio-4-phenyl-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-one (**8f**).* A mixture of **8e** (0.5 g) and 20 ml sodium carbonate solution (5%) was stirred for 2 h at 50 °C. The reaction mixture was cooled and acidified, the solid separated was filtered off and crystallized from ethanol as colorless needles to give **8f**, mp 208 °C, 0.3 g (75%). Found: C, 57.81; H, 3.51; N, 15.71; S, 9.26%. Calcd for $C_{17}H_{12}N_4O_3S$: C, 57.95; H, 3.41; N, 15.91; S, 9.09%.

The same product was also obtained by reaction of **7** (0.5 g) and chloroacetic acid in the presence of potassium carbonate in acetone as described before in **8e**. Evaporation of the solvent after acidification gave **8f** in 45% yield.

*1-(Benzylcarbamoylmethylthio)-4-phenyl-1,2,4-triazolo[4,3-a]-quinazolin-5(4H)-one (**8g**).* A mixture of **8e** (0.5 g) and benzylamine (0.3 g) in ethanol (15 ml) was refluxed for 2 h. The reaction mixture was reduced to its half volume and cooled. The separated product was collected and recrystallized from the same solvent as colorless needles, mp 254 °C, (0.3 g; 50%). Found: C, 65.41; H, 4.51; N, 15.90; S, 7.51%. Calcd for $C_{24}H_{19}N_5O_2S$: C, 65.30; H, 4.30; N, 15.87; S, 7.26%.

*2-(3-Methyl-5-oxo-2-pyrazolin-1-yl)-3-phenyl-4(3H)-quinazolinone (**10**). a)*: A mixture of **1** (0.002 mol) and ethyl acetoacetate (0.0025 mol) in ethanol (30 ml) was refluxed for 3 h. The reaction mixture was concentrated and cooled. The separated colorless product was crystallized from the same solvent to give the corresponding hydrazone (**9**) mp 142 °C, 5.9 g (82%). Found: C, 65.71; H, 5.58; N, 15.61%. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.93; H, 5.49; N, 15.38%.

b): The hydrazone **9** (0.5 g) was heated over its melting

point for 10 min, the residue was cooled and crystallized from pyridine–methanol mixture as colorless needles (**10**), mp 360 °C, 0.3 g (75%). Found: C, 67.86; H, 4.52; N, 17.81%. Calcd for $C_{18}H_{14}NO_2$: C, 67.79; H, 4.40; N, 17.61%.

*Acetone (4-Oxo-3-phenyl-3,4-dihydro-2-quinazolinyl) hydrazone (**11a**).* A mixture of **1** (1 g) and acetone (15 ml) was refluxed for 2 h. The solvent was evaporated the residue was crystallized from ethanol as colorless needles, mp 185 °C, 0.9 g (81%). Found: C, 69.76; H, 5.58; N, 19.36%. Calcd for $C_{17}H_{16}N_4O$: C, 69.86; H, 5.47; N, 19.17%.

*Acetylation of **11a**.* A mixture of **11a** (0.2 g), acetic anhydride (1 ml) and pyridine (1 ml) was heated on a steam bath for 30 min. The yellow crystalline product was separated, collected and crystallized from ethanol to give **11b**, mp 278 °C, 0.2 g (93%). Found: C, 71.78; H, 5.76; N, 17.80%. Calcd for $C_{19}H_{18}N_4O$: C, 71.69; H, 5.66; N, 17.61%.

*Sulfonylation of **11a**.* A mixture of **11a** (0.2 g), benzenesulfonyl chloride (0.2 ml) and pyridine (2 ml) was heated on a steam bath for 30 min. The reaction mixture was cooled and poured into cold water. The brown solid product was collected and crystallized from methanol to give **11c** as brown crystals, mp 194—195 °C, 0.1 g (45%). Found: C, 63.76; H, 4.51; N, 12.80; S, 7.42%. Calcd for $C_{23}H_{20}N_4O_3S$: C, 63.88; H, 4.62; N, 12.96; S, 7.40%.

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