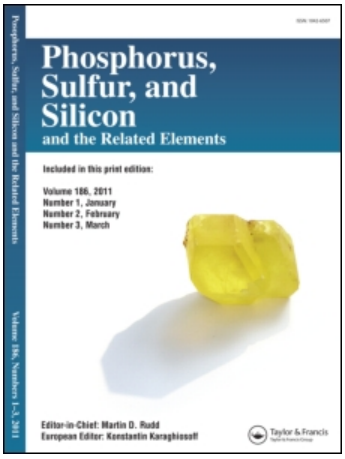

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SYNTHESIS AND REACTIONS OF 2-MERCAPTO-4-ARYL 4H-1,2,3,4,5,6-HEXAHYDRO-BENZO [h] QUINAZOLINES

Abou El-Fotooh G. Hammam[a]; S. M. Hussain[ab]; Iman R. Kotob[a]
[a] Applied Organic Chemistry Department, National Research Centre, Cairo, Egypt [b] Chemistry Department, Faculty of Science, Cairo University,

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SYNTHESIS AND REACTIONS OF 2-MERCAPTO-4-ARYL 4H-1,2,3,4,5,6-HEXAHYDRO-BENZO[h]QUINAZOLINES

ABOU EL-FOTOOH G. HAMMAM,† S. M. HUSSAIN[1] and IMAN R. KOTOB

National Research Centre, Applied Organic Chemistry Department, Dokki, Cairo, Egypt, and [1]Chemistry Department, Faculty of Science, Cairo University

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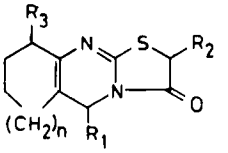
2-Mercapto-4-aryl-4H-1,2,3,4,5,6-hexahydrobenzo[h]quinazolines (**2**) have been synthesized. Compounds **2** reacted with chloroacetic acid, 2-bromopropanoic acid or 3-bromopropanoic acid in the presence of fused sodium acetate and acetic anhydride to give 5-aryl-5H-2,3,6,7-tetrahydrobenzo[h]thiazolo[2,3-b]quinazoline-3-ones (**3**), their 2-methyl derivatives (**5**) and 6-aryl-6H-2,3,7,8-tetrahydrobenzo[h]-1,3-thiazine-[2,3-b]quinazoline-4-ones (**6**), respectively. 2-(Arylmethylene)-5-aryl-5H-2,3,6,7-tetrahydrobenzo[h]thiazolo[2,3-b]quinazoline-3-ones (**4**) were prepared by the reaction of compounds **2** with chloroacetic acid, and aromatic aldehydes in presence of fused sodium acetate and acetic anhydride or by the reactions of compounds **3** with aromatic aldehydes in the presence of acetic anhydride.

Key words: Mercapto-benzoquinazolines; thiazolo-benzoquinazolines; thiazino-benzoquinazolines.

In our previous work,[1-5] we found that compounds such as [A], $n = 1$, possess high biological activity in the field of: plant health, animal health, insecticide, herbicides and rumen metabolism. Also compounds [B], $n = 2$, showed anti-cancer activity.[4]



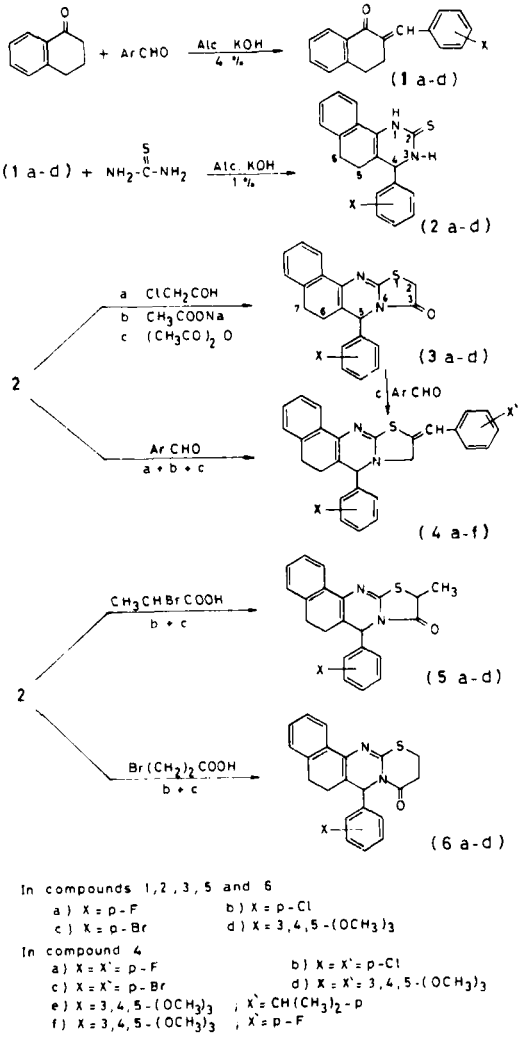
A) n = 1
B) n = 2

These facts led us to attempt the above reactions in order to obtain benzothiazoloquinazolines, a combination of ring system which might be expected to possess high biological activities.

The reactions of thiourea with 2-arylmethylene-1-tetralones have not been reported.[6-10] Now we have found that the newly synthesized 2-arylmethylene-1-tetralones **1** condense with thiourea in alcoholic potassium hydroxide (1%) to give 2-mercapto-4-aryl-4H-1,2,3,4,5,6-hexahydrobenzo[h]quinazolines **2**. The reaction can proceed by the addition to an arylidene double bond via a Michael

† To whom correspondence should be addressed at the National Research Centre.

type process[11] followed by cyclization to give **2**. For pertinent literature, see Reference 11. The structure of all new compounds were confirmed by physical and chemical methods.



The IR spectra of compounds **2** show absorption at 3285 cm^{-1} [NH] and at 1170 cm^{-1} assignable to [>C=S].[11] The ^{1}H-NMR of compound **2a** (DMSO) showed the two NH protons as two singlets at δ 9.0 ppm and at δ 9.8 ppm; the aromatic protons (8H) as multiplet in the δ 7.0–7.8 ppm region, the methine proton as a singlet (1H) at δ 5.0 ppm, and a multiplet in the δ 2.2–2.9 ppm region for the —CH_2—CH_2—group of the quinazoline ring. Compound **2** reacted with a chloro-acetic acid-acetic anhydride mixture in the presence of fused sodium acetate to give 5-aryl-5H-2,3,6,7-tetrahydrobenzo[h]thiazolo[2,3-b]-quinazoline-3-ones **3**. For pertinent literature, see Reference 12. The IR spectra of compounds **3** show bands at 1735 cm^{-1} (C=O) but there is no NH absorption. The ^{1}H-NMR

spectrum of compound **3d** ($CDCl_3$) showed signals at δ 7.30 (m, 4H, aromatic protons), δ 6.68 (s, 2H, aromatic protons), δ 5.50 (s, 1H, pyrimidine proton), δ 3.80 (s, 2H, thiazole protons), δ 3.90 (s, 9H, 3 OCH_3) and δ 2.20–2.90 ppm (m, 4H, 2 CH_2).

Compounds (**3**) contain an active methylene group, they condensed with the aromatic aldehydes in the presence of acetic anhydride to yield 2-(arylmethylene)-5-aryl-5H-2,3,6,7-tetrahydrobenzo[h]thiazolo-[2,3-b]quinazoline-3-ones **4**. However, the arylmethylene derivatives **4** were prepared directly from **2** by the action of chloroacetic acid, the aromatic aldehydes and fused sodium acetate in the presence of acetic acid-acetic anhydride mixtures. The IR spectra of compounds **4** showed an absorption band at 1715 cm^{-1}, this shift to lower frequency is due to conjugation with exocyclic double bond (it was 1735.cm^{-1} in compounds **3**). The ^{1}H-NMR spectrum of **4f** ($CDCl_3$) showed signals at δ 7.50–8.00 (m, 9H, aromatic protons and the benzylic proton), δ 6.70 (s, 2H, aromatic protons), δ 5.50 (s, 1H, pyrimidine proton), δ 3.90 (s, 9H, 3 OCH_3), and δ 2.20–2.90 ppm (m, 4H, 2CH_2).

Compounds **2** reacted with 2-bromopropanoic acid and 3-bromopropanoic acid (under the same condition used for the preparation of compounds **3** from **2** to yield 2-methyl-5-aryl-5H-2,3,6,7-tetrahydrobenzo[h]thiazolo[2,3-b]quinazoline-3-ones (**5**) and 6-aryl-6H-2,3,7,8-tetrahydrobenzo[h]-1,3-thiazine[2,3-b]quinazoline-4-ones (**6**), respectively.

The IR spectra of compounds **5** show an absorption band at 1735 cm^{-1}, (C=O). The ^{1}H NMR spectrum of **5d** ($CDCl_3$) showed signals at δ 7.50–8.80 (m, 4H, aromatic protons), δ 6.70 (s, 2H, aromatic protons), δ 5.60 (s, 1H, pyrimidine proton), δ 4.15 (q, 1H, methine proton of the thiazole ring), δ 1.80 (d, 3H, CH_3 of thiazole ring), δ 3.95 (s, 9H, 3 OCH_3) and 2.45–3.00 ppm (m, 4H, 2 CH_2).

The IR spectra of compounds **6** show an absorption band at 1700 cm^{-1} (C=O). The ^{1}H NMR spectrum of **6d** ($CDCl_3$) showed signals at δ 7.30–7.90 (m, 4H, aromatic protons), δ 6.70 (s, 2H, aromatic protons), δ 5.60 (s, 1H, pyrimidine proton), δ 3.90 (s, 9H, 3 OCH_3) and δ 2.40–3.00 (m, −8H, for the 2CH_2 of the quinazoline ring and 2CH_2 of the thiazine ring).

EXPERIMENTAL

2-Arylmethylene-1-tetralones **1**.[13] This method is a modification of the method reported by A. Hassner.[13] 0.05 Mole of the appropriate aromatic aldehydes were dissolved in 7.4 g (0.05 mole) of 1-tetralone with stirring at 40°C, where upon a homogenous liquid is formed. After cooling to the room temperature the liquid was treated with 5 ml of 4% ethanolic KOH (slow addition with stirring). The dark violet hot precipitate was stirred for 5 min, where the violet colour disappear. The precipitate was filtered off, washed with dilute ethanol to give 14 g (89%) of **1** which were crystallized from ethanol (see Table I).

2-Mercapto-4-aryl-4H-1,2,3,4,5,6-hexahydrobenzo[h]-quinazoline (**2**). A mixture of thiourea (1.52 g, 0.02 mol), equimolecular amounts of compounds **1**, ethanol (200 ml) and potassium hydroxide solution (1 g in 2 ml of water) was refluxed for 15 minutes whereas colourless crystals were separated. Heating was continued for further 15 minutes and the reaction mixture was allowed to cool. The crystalline material was collected and recrystallised from the proper solvent, (See Table I).

Synthesis of compounds (**3**, **5** *and* **6**). A mixture of 0.01 mole of compounds **2** with 0.01 mole of chloroacetic acid, 0.01 mole of 2-bromopropanoic acid or 0.01 mole of 3-bromopropanoic acid and 6 g

TABLE I

Compd.	M.P. solvent	Yield %	(X/X_1)	Formula M.W.	Analysis % Calcd./Found C	H	N	S
1a	115	90	F-4	$C_{17}H_{13}FO$	80.08	5.19		
	E		—	(2523)	80.10	5.10		
1c	150	92	Br-4	$C_{17}H_{13}BrO$	65.17	4.18		
	E		—	(313.3)	65.20	4.13		
1d	125	89	Y	$C_{20}H_{19}O_4$	74.27	5.92		
	E		—	(323.4)	74.33	5.89		
2a	241	83	F-4	$C_{18}H_{15}FN_2S$	69.65	4.87	9.02	10.33
	D			(310.4)	69.63	4.90	9.00	10.10
2b	256	86	Cl-4	$C_{18}H_{15}ClN_2S$	66.15	4.63	8.57	9.81
	A		—	(326.8)	66.10	4.58	8.6	9.7
2c	248	90	Br-4	$C_{18}H_{15}BrN_2S$	58.21	4.07	7.54	8.63
	D		—	(371.4)	57.96	3.98	7.5	8.6
2d	226	89	Y	$C_{21}H_{21}N_2O_3S$	66.11	5.55	7.34	8.40
	D		—	(381.5)	66.00	5.36	7.2	8.3
3a	204	78	F-4	$C_{20}H_{15}FN_2OS$	68.54	4.32	7.99	9.15
	D		—	(350.5)	68.48	4.23	7.8	9.0
3b	208	80	Cl-4	$C_{20}H_{15}ClN_2OS$	65.48	4.12	7.64	8.74
	D		—	(3.66.8)	65.51	3.98	7.5	8.7
3c	180	79	Br-4	$C_{20}H_{15}BrN_2OS$	58.38	3.68	6.81	7.79
	D		—	(411.4)	58.27	3.62	6.7	7.8
3d	185	83	Y	$C_{23}H_{22}N_2O_4S$	65.53	5.02	6.65	7.61
	D		—	(422.5)	65.48	4.96	6.6	7.5
4a	203	93	F-4	$C_{27}H_{18}F_2N_2OS$	71.84	3.97	6.14	7.02
	D		F-4	(456.5)	71.78	3.88	6.0	6.9
4b	215	94	Cl-4	$C_{27}H_{18}Cl_2N_2OS$	66.26	3.70	5.72	6.55
	D		Cl-4	(489.4)	66.10	3.65	5.6	6.6
4c	185	93	Br-4	$C_{27}H_{18}Br_2N_2OS$	56.06	3.14	4.84	5.54
	D		Br-4	(578.5)	56.00	2.96	4.7	5.5
4d	222	93	Y	$C_{33}H_{32}N_2O_7S$	65.98	5.37	4.66	5.33
	D		Y	(600.6)	65.80	5.41	4.5	5.3
4e	205	94	Y	$C_{33}H_{32}N_2O_4S$	71.71	5.83	5.07	5.80
	D		$CH(CH_3)_2$-4	(552.7)	71.68	5.78	5.00	5.7
4f	216	93	Y	$C_{30}H_{25}FN_2O_4S$	68.16	3.39	5.30	6.06
	D		—F-4	(528.6)	68.20	3.28	5.1	5.9
5a	160	80	F-4	$C_{21}H_{17}FN_2OS$	69.21	4.70	7.69	8.80
	E		—	(364.40)	69.18	4.68	7.7	8.8
5b	154	83	Cl-4	$C_{21}H_{17}ClN_2OS$	66.23	4.50	7.36	8.42
	E		—	(380.9)	66.10	4.48	7.3	8.4
5c	150	79	Br-4	$C_{21}H_{17}BrN_2OS$	59.29	4.03	6.58	7.54
	E		—	(425.4)	59.22	4.00	6.6	7.4
5d	183	80	Y	$C_{24}H_{24}N_2O_4S$	66.18	5.32	6.43	7.36
	D		—	(436.5)	66.10	5.26	6.2	7.4
6a	250	73	F-4	$C_{21}H_{17}FN_2OS$	69.21	4.70	7.69	8.80
	D		—	(364.4)	68.98	4.58	7.6	8.7
6b	142	85	Cl-4	$C_{21}H_{17}ClN_2OS$	66.23	4.50	7.36	8.42
	E		—	(380.9)	66.30	4.40	7.4	8.2
6c	148	78	Br-4	$C_{21}H_{17}BrN_2OS$	59.29	4.03	6.58	7.54
	E		—	(425.4)	59.33	4.10	6.4	7.3
6d	176	84	Y	$C_{24}H_{24}N_2O_4S$	66.18	5.32	6.43	7.36
	E		—	(436.5)	66.22	5.29	6.3	7.4

Note: In all Compounds Y = 3,4,5-(OCH_3)-

Keys of Solvents: A = Acetic acid; E = Ethyl alcohol; D = Dioxane.

of fused sodium acetate in 30 ml of glacial acetic acid and 15 ml of acetic anhydride was refluxed for 2 h, left to cool then poured gradually into cold water, the solid obtained was filtered off, washed with water and crystallized from the proper solvent (See Table I).

2-(Arylmethylene)-5-aryl-5H-2,3,6,7-tetrahydrobenzo[h]thiazolo[2,3-b]-quinazoline-3-ones (**4**). a. A mixture 1 g of **3** an equimolecular amount of the appropriate aldehyde and 3 ml of acetic anhydride was refluxed for 1 h, left to cool, then poured into cold water. The solid formed was collected and crystallized from the proper solvent. (see Table I).

b. A mixture of 0.05 mol of **2** 1 g of chloroacetic acid, 2 g of fused sodium acetate, 20 ml of acetic acid, 10 ml of acetic anhydride and an equimolecular amount of appropriate aldehyde was refluxed for 3 h. The reaction mixture was cooled and poured into cold water. The precipitate formed was collected and crystallized from the proper solvent (See Table I).

All the newly synthesized compounds are under biological, tests, after completion will be published separately.

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