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Synthesis of 2-Aryl-6,6-dimethyl-8-oxo-5,6,7,8-tetrahydro-1,2,4-4*H*-triazolo [3,2-*b*]benzothiazoles and their 3-Aryl-[3,4-*b*] Isomers

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Summary. Condensation of 3-aryl-5-thio-1,2,4-4*H*-trizoles (**2a–i**) and 2-bromodimedone (**3**) in *THF*/benzene gave 2-aryl-6,6-dimethyl-8-oxo-5a-hydroxy-5,5a,6,7,8,8a-hexahydro-1,2,4-4*H*-triazolo [3,2-*b*]benzothiazoles (**5a–i**). These were also obtained by a one step synthesis on heating a mixture of dimedone, *NBS*, and **2a–i** in benzene containing a trace of benzoyl peroxide. Thermal dehydration of **5a–i** in *PPA*/anhydrous ethanol yielded the corresponding 2-aryl-6,6-dimethyl-8-oxo-5,6,7,8-tetrahydro-1,2,4-4*H*-triazolo[3,2-*b*]benzothiazoles (**6a–i**). The formation of [3,4-*b*] fused isomers (**4a–i**) during the reaction of **2** with **3** was ruled out by an unambiguous synthesis of **8a–i**. Antibacterial screening of selected compounds against *Escherichia coli* and *Staphylococcus aureus* was not encouraging.

Keywords. 3-Aryl-5-thio-1,2,4-4*H*-triazoles; Dimedone; 2-Bromodimedone; Cyclic hydroxy intermediates; Isomeric [3,2-*b*] and [3,4-*b*] benzothiazoles.

Synthese von 2-Aryl-6,6-dimethyl-8-oxo-5,6,7,8-tetrahydro-1,2,4-4*H*-triazolo[3,2-*b*]benzothiazolen und ihrer 3-Aryl-[3,4-*b*]-Isomeren

Zusammenfassung. Die Kondensation von 3-Aryl-5-thio-1,2,4-4*H*-triazolen (**2a–i**) mit 2-Bromdimedon (**3**) in *THF*/Benzol ergab 2-Aryl-6,6-dimethyl-8-oxo-5a-hydroxy-5,5a,6,7,8,8a-hexahydro-1,2,4-4*H*-triazolo[3,2-*b*]benzothiazole (**5a–i**). Dasselbe Ergebnis wurde durch Erhitzen einer Mischung von Dimedon, *NBS* und **2a–i** in Benzol unter Zusatz einer Spur Benzoylperoxid in einer einstufigen Synthese erreicht. Thermische Dehydrierung von **5a–i** in *PPA*/Ethanol(abs.) ergab die entsprechenden 2-Aryl-6,6-dimethyl-8-oxo-5,6,7,8-tetrahydro-1,2,4-4*H*-triazolo[3,2-*b*]benzothiazole (**6a–i**). Die Bildung [3,4-*b*]-kondensierter Isomere (**4a–i**) während der Reaktion von **2** mit **3** konnte durch eine eindeutige Synthese von **8a–i** ausgeschlossen werden. Antibakterielles Screening ausgewählter Verbindungen gegenüber *Escherichia coli* und *Staphylococcus aureus* brachte keine ermutigenden Resultate.

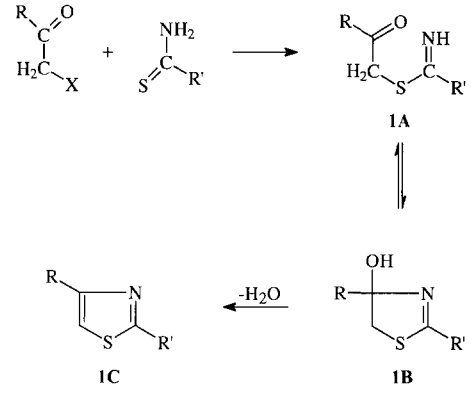
Introduction

In continuation of our interest in condensed tetrahydrobenzothiazoles of pharmacological interest [1–4], we now report the synthesis and antibacterial activity of

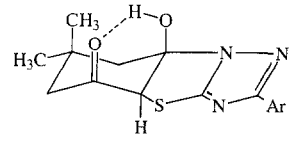
2-aryl-6,6-dimethyl-8-oxo-5,6,7,8-tetrahydro-1,2,4-4*H*-triazolo[3,2-*b*]benzothiazoles (**6a–i**) and of the isomeric 3-aryl-6,6-dimethyl-8-oxo-5,6,7,8-tetrahydro-1,2,4-4*H*-triazolo[3,4-*b*]benzothiazoles (**8a–i**). The formation of cyclic hydroxy intermediates (**5a–i**) during the reaction of 2-bromodimedone (**3**) and 3-aryl-5-thio-1,2,4-4*H*-triazoles (**2a–i**) is explained. **5a–i** were also obtained in excellent yields by a one pot synthesis from dimedone, *NBS*, and **2**. Structure assignment of **6a–i** was confirmed by unambiguous syntheses of **8a–i** and comparison of their UV, IR, NMR, and Mass spectra.

Results and Discussion

It is well known that during *Hantzsch*'s thiazole synthesis an intermediate isothiouronium compound is formed which exists in an open chain keto form and/or in a ring hydroxy form (**1A⇌1B**).



The stability of an intermediate depends upon the nature of the reactants and kinetics of the reaction. It has been shown that the final thiazole (**1C**) is obtained by dehydration of the hydroxy intermediate [9], whereas the formation of stable hydroxy intermediates (**1B**, $R = CF_3$ and $R' = Ph$) during the reaction of CF_3COCH_2Br and thiobenzamide has been reported [10]. Now we wish to report the exclusive formation of ring hydroxy intermediates (**5a–i**) during the reaction of a cyclic α-bromoketone (**3**) and a cyclic thioamide (**2a–i**) (see Scheme 1). The polarity of different solvents did not affect the course of this reaction at room temperature. Even heating the reactants in *THF*/benzene did not affect the reaction; only **5a–i** were obtained in both cases. The stability of **5a–i** is explained on the basis of chelate bonding (see below).



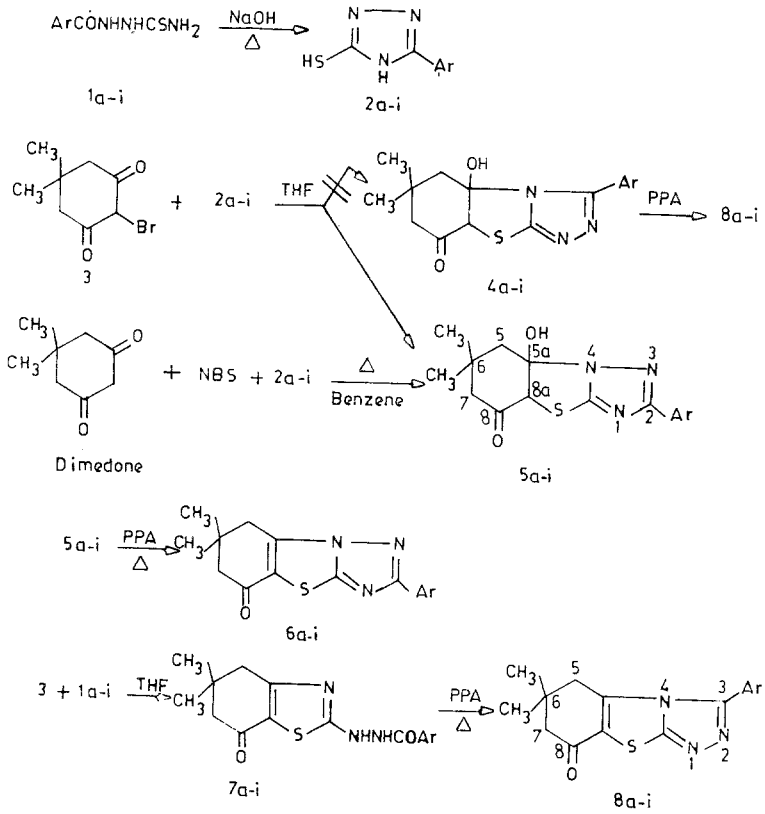
IR and ^1H NMR spectra agreed with the proposed structure. For example, the IR spectrum of **5a** (KBr) show a broad absorption at 3150 cm^{-1} (bonded OH), a valley at 2500 and 1900 cm^{-1} (OH) and a weak band at 1660 cm^{-1} (C=O), characteristic of chelation between OH and C=O groups. The same chemical shift of 2.55 ppm for 5-CH_2 and 7-CH_2 in the ^1H NMR spectrum of **5a** suggests their

magnetic equivalence which is due to the intramolecular hydrogen bonding of the OH group with the 8-oxo group. The open chain keto structure of **5a** cannot justify the magnetic equivalence, since one of the oxo groups is always under the influence of the N_1–N_2 part of the triazole ring at any moment.

Considering the cumbersome and time consuming preparation of 2-bromo-dimedone from dimedone [5], a one pot synthesis of **5a–i** was achieved in excellent yields (80–90%) by heating a mixture of dimedone, *NBS*, and **2** in benzene containing a trace of benzoyl peroxide. **3** was formed *in situ* and consumed by 2 during the reaction.

Dehydration of **5a–i** to **6a–i** was affected in better yields by heating in *PPA* at 150 °C, whereas simultaneous condensation and dehydrocyclization took place when a mixture of **2** and **3** was refluxed in anhydrous ethanol for 12 h.

The ^{1}H NMR spectra of **6a–i** showed peaks at 2.60 (5-CH_2) and 3.10 (7-CH_2) ppm, indicating the cleavage of chelate bonding in **5a–i** after dehydration. In fact, a strong C=O band appeared at 1680 cm^{-1} in the IR spectra of **6a–i**.



Where,

Ar	Ar
a, Ph	e, o-chloro-Ph
b, p-tolyl	f, p-methoxy-Ph
c, m-tolyl	g, p-nitro-Ph
d, p-chloro-Ph	h, m-nitro-Ph
	i, benzyl

Scheme 1

A reaction of **3** and **2a–i** could theoretically afford cyclic intermediates **5a–i** or **4a–i** (Scheme 1) which undergo a subsequent dehydration to **6a–i** or **8a–i**, respectively. IR, ^{1}H NMR and Mass spectra could not distinguish isomeric **6a–i** and **8a–i**. An independent and unambiguous synthesis of the [3,4-*b*] isomers (**8a–i**) established the correct structure of the [3,2-*b*] isomers (**6a–i**).

Antibacterial Screening

Compounds **6a**, **6b**, **6d**, **6f**, **6g**, **8a**, **8b**, **8d**, **8f**, and **8g** were screened against *Escherichia coli* and *Staphylococcus aureus* by the cup-plate method [11] at a dose of 100 µg using norfloxacin as a standard drug. Only **6b**, **6g**, **8b**, **8c**, and **8g** were comparable to the standard drug.

Experimental

Melting points were measured in uniform open capillaries and are uncorrected. All solvents were distilled prior to use. TLC: silica gel G plates (3 × 8 cm); column chromatography: neutral alumina (2 × 30 cm); UV (ethanol): Hitachi 150–20 UV/Vis spectrophotometer as λ_{max} (log ε) nm; IR (KBr/nujol, cm^{-1}): Perkin-Elmer 783 and 881 spectrometers; ^{1}H NMR ($CDCl_3$/*DMSO*-d_6, δ (ppm)): Varian 300 MHz and Perkin-Elmer 90 MHz spectrometers, *TMS* as an internal reference; Mass spectra: Finning-Mat 8230 spectrometer, direct insertion technique. Dimedone was purchased from Ubichem Ltd., England. 2-Bromodimedone (**3**), m.p. 178 °C, was prepared by the cupric bromide method [5]. 1-Aroylthiosemicarbazides (**1a–i**) from aroylhydrazines [6, 7] and 3-aryl-5-thio-1,2,4-4*H*-triazoles (**2a–i**) from **1a–i** [2,6,8] were prepared according to literature methods and agreed with the reported melting points.

2-Aryl-6,6-dimethyl-8-oxo-5a-hydroxy-5a,5,6,7,8,8a-hexahydro-1,2,4,-4H-triazolo [3,2-b]benzothiazoles (**5a–i**)

A: From 2-Bromodimedone (**3**) *and* **2a–i**

A mixture of **3** (4.38 g, 20 mmol) and **2a** (3.54 g, 20 mmol) in *THF* (100 ml) was stirred at room temperature. A solid hydrobromide separated within 8 h. Stirring continued for 48 h in order to complete the reaction. The mixture was filtered and the solid was washed with *THF* (5 ml), and dried. Solution of the product in aqueous Na_2CO_3 solution and reprecipitation by acidification with acetic acid afforded the free base **5a** which was further purified by column chromatography using a benzene-chloroform-petroleum ether mixture (50:10:40 v/v/v) as eluent. Yield 3.47 g (55%); m.p. 211–12 °C; IR (KBr): 3150 (OH), broad valley at 2500 and 1900 (OH), 1660 (w, C=O); ^{1}H NMR ($CDCl_3$): 8.00–7.30 (m, 5 H, Ph), 7.70 (s, 1 H, 8a-H), 3.99 (s, 1 H, OH exchangeable with D_2O), 2.55 (s, 4 H, 5-CH_2 and 7-CH_2), 1.20 (s, 6 H, 6-Me_2); $C_{16}H_{17}N_3O_2S$ (315); calcd.: C 60.95, H 5.39, N 13.33; found: C 61.25, H 5.21, N 13.21. **5b–i** were prepared and identified similarly (see Table 1 for analytical data).

A reaction of **2a** (20 mmol) and **3** (20 mmol) in different solvents like ethanol, benzene, or *DMF* at room temperature gave **5a** only in 40–50% yields. The same reaction at higher temperature (boiling *THF*/benzene) for 8 h did not improve the yield of **5a** (52%).

B: One pot synthesis of **5a–i** *starting from dimedone*

A mixture of dimedone (2.8 g, 20 mmol), *NBS* (3.56 g, 20 mmol) and **2a** (3.54 g, 20 mmol) in benzene (100 ml) containing a trace of benzoyl peroxide was heated to reflux for 6 h. The solvent was removed

Table 1. Analytical data of **5a–i**

Compound	Method A Yield (%)	m.p. (°C)	Method B Yield (%)	m.p. (°C)	Mol. Formula[a]	IR(KBr) O–H (cm^{-1})	C=O (cm^{-1})	^1H NMR ($CDCl_3$) 5a-OH (ppm)	8a-H (ppm)
5a	55	210–12	84	211–12	$C_{16}H_{17}N_3O_2S$	3150, 2500, 1900	1660	3.99	7.70
5b	51	225–26	82	226–27	$C_{17}H_{19}N_3O_2S$	3150, 2460, 1890	1645	4.10	7.65
5c	53	194–95	80	196–97	$C_{17}H_{19}N_3O_2S$	3160, 2500, 1900	1650	4.25	7.66
5d	54	214–15	87	216–17	$C_{16}H_{16}ClN_3O_2S$	3168, 2480, 1880	1660	3.95	7.64
5e	48	198–99	80	198–99	$C_{16}H_{16}ClN_3O_2S$	3155, 2560, 1900	1640	3.98	–
5f	55	216–18	85	218–19	$C_{17}H_{19}N_3O_3S$	3165, 2500, 1895	1655	4.50	7.70
5g	58	168–69	88	168–69	$C_{16}H_{16}N_4O_4S$	3160, 2500, 1890	1650	4.20	–
5h	50	207–08	82	209–10	$C_{16}H_{16}N_4O_4S$	3150, 2490, 1900	1645	4.50	–
5i	49	214–15	78	215–16	$C_{17}H_{19}N_3O_2S$	3150, 2460, 1890	1655	4.30	7.70

[a] All compounds gave satisfactory elemental analyses

under diminished pressure, and the crude hydrobromide salt separating on cooling was filtered and air-dried. It was dissolved in aqueous Na_2CO_3 solution and acidified with acetic acid to get the free base **5a**. Purification of **5a** by column chromatography (cf. method A) gave 5.39 g (84%) **5a**, m.p. 212 °C. Samples from both methods gave identical IR and ^1H NMR spectra and identical elemental analyses. Similarly, the remaining compounds **5b–i** were obtained in excellent yields (for analytical data, see Table 1).

2-Aryl-6,6-dimethyl-8-oxo-5,6,7,8-tetrahydro-1,2,4-4H-triazolo[3,2-b]benzothiazoles (**6a–i**)

A: From the reaction of **3** *and* **2** *in anhydrous ethanol*

A mixture of **3** (4.38 g, 20 mmol) and **2a** (3.54 g, 20 mmol) in anhydrous ethanol (150 ml) was refluxed for 12 h. Condensation and dehydrocyclization took place simultaneously. Removal of the solvent and basification of the residue with aqueous Na_2CO_3 solution resulted in a solid product which was filtered and washed with cold water (5 ml). **6a** was chromatographed on neutral alumina by eluting with a benzene-petroleum ether mixture (40:60 v/v). Recrystallisation from ethanol yielded 3.14 g (53%) **6a** M.p. 202–203 °C; IR (KBr): 1680 (C=O), 1580 (C=N); no bands in the region of 3500–3150, 2500, and 1900, suggesting the absence of OH group; ^1H NMR ($CDCl_3$): 8.15–7.40 (m, 5 H, Ph), 3.10 (s, 2 H, 7-CH_2), 2.60 (s, 2 H, 5-CH_2), 1.20 (s, 6 H, 6-Me_2); MS (*m/z*): 297 (100%), $C_{16}H_{15}N_3OS$ (297); calcd.: C 64.64, H 5.05, N 14.14; found: C 64.27, H 4.71, N 13.88.

In veiw of the cumbersome preparation of **3** and the poor yield of **6a**, the remaining **6a–i** were not prepared by this method.

Table 2. Analytical data of **6a–i** and **8a–i**

Compound	Yield (%)	m.p. (°C)	Mol. Formula[a]	IR (KBr) C=O (cm^{-1})	^1H NMR ($CDCl_3$) Ar-H (ppm)
6a	76	202–03	$C_{16}H_{15}N_3OS$	1680	8.15–7.40 (m)
6b	74	207–08	$C_{17}H_{17}N_3OS$	1675	8.00–7.50 (dd)
6c	75	164–65	$C_{17}H_{17}N_3OS$	1670	8.10–7.30 (m)
6d	78	232–33	$C_{16}H_{14}ClN_3OS$	1675	7.96–7.28 (dd)
6e	75	155–56	$C_{16}H_{14}ClN_3OS$	1678	8.65–7.30 (m)
6f	72	191–92	$C_{17}H_{17}N_3O_2S$	1670	8.00–7.32 (dd)
6g	78	268–69	$C_{16}H_{14}N_4O_3S$	1680	8.30–7.42 (dd)
6h	74	170–71	$C_{16}H_{14}N_4O_3S$	1675	8.23–7.40 (m)
6i	75	109–10	$C_{17}H_{17}N_3OS$	1675	7.40–7.15 (m)
8a	78	211–12	$C_{16}H_{15}N_3OS$	1680	8.20–7.40 (m)
8b	70	182–83	$C_{17}H_{17}N_3OS$	1675	8.05–7.30 (dd)
8c	75	167–68	$C_{17}H_{17}N_3OS$	1685	8.00–7.25 (m)
8d	74	182–83	$C_{16}H_{14}ClN_3OS$	1685	8.05–7.32 (dd)
8e	78	144–45	$C_{16}H_{14}ClN_3OS$	1680	8.15–7.36 (m)
8f	79	158–59	$C_{17}H_{17}N_3O_2S$	1680	8.10–7.30 (dd)
8g	80	264–65	$C_{16}H_{14}N_4O_3S$	1675	8.28–7.40 (dd)
8h	82	183–84	$C_{16}H_{14}N_4O_3S$	1680	8.20–7.45 (m)
8i	74	104–05	$C_{17}H_{17}N_3OS$	1685	7.50–7.22 (m)

[a] All compounds gave satisfactory elemental analyses

Table 3. Analytical data of **7a–i**

Compound	Yield (%)	m.p. (°C)	Mol. Formula[a]	IR (KBr) NHNH (cm^{-1})
7a	65	201–02	$C_{16}H_{17}N_3O_2S$	3300–3180
7b	69	197–98	$C_{17}H_{19}N_3O_2S$	3280–3150
7c	66	188–89	$C_{17}H_{19}N_3O_2S$	3300–3160
7d	71	196–98	$C_{16}H_{16}ClN_3O_2S$	3280–3150
7e	67	174–75	$C_{16}H_{16}ClN_3O_2S$	3300–3160
7f	64	191–92	$C_{17}H_{19}N_3O_3S$	3280–3150
7g	69	186–87	$C_{16}H_{16}N_4O_4S$	3300–3150
7h	67	172–73	$C_{16}H_{16}N_4O_4S$	3280–3160
7i	60	174–75	$C_{17}H_{19}N_3O_2S$	3260–3180

[a] All compounds gave satisfactory elemental analyses

B: By dehydration of **5a–i** *in PPA*

A mixture of 5 g of **5a** and freshly prepared *PPA* (from 20 g of P_2O_5 and 15 g of H_3PO_4) was heated in an oil bath maintained at 150 °C for 6 h. The thick syrupy mass obtained on cooling was poured onto crushed ice (200 g) and left overnight. The separated solid was filtered, washed with Na_2CO_3 solution and water, dried (P_2O_5), and purified by chromatography on a neutral alumina column (cf. method A). Recrystallisation of the product from ethanol yielded 4.51 g (76%) **6a**. M.p. 202–03 °C, mixed m.p. with the sample from method A 200 °C. The remaining **6b–i** were similarly prepared and identified for analytical data, see Table 2.

2-Aroylhydrazino-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrobenezo-thiazoles (**7a–i**)

To a solution of **3** (4.38 g, 20 mmol) in *THF* (100 ml), 1-benzoylthiosemicarbazide (**1a**, 3.90 g, 20 mmol) was added and the mixture was stirred for 48 h at room temperature. The separating solid hydrobromide was filtered, washed with *THF* (5 ml), and air-dried. It was neutralized (Na_2CO_3 solution), and the free base **7a** was then filtered, washed, and dried (P_2O_5). Purification by column chromatography using benzene-petroleum ether (50:50 v/v) as eluent afforded 4.10 g (65%) **7a**. M.p. 201–02 °C; IR (KBr): 3300–3180 (NHNH), 1680 (C=O); $C_{16}H_{17}N_3O_2S$ (315); calcd.: C 60.95, H 5.40, N 13.33; found: C 61.21, H 5.69, N 13.56.

Compounds **7b–i** were prepared and identified similarly; for analytical data, see Table 3.

3-Aryl-6,6-dimethyl-8-oxo-5,6,7,8-tetrahydro-1,2,4-4H-triazolo[3,4-b]benzothiazoles (**8a–i**)

A mixture of 5 g of **7a** and freshly prepared *PPA* (from 20 g of P_2O_5 and 15 g of H_3PO_4) was heated in an oil bath at 160 °C for 4 h. The reaction mixture was treated as in the case of the *PPA* dehydration of **5a**. The solid product was collected and purified by crystallization from ethanol. Yield 3.01 g (78%). M.p. 211–12 °C, mixed m.p. with **6a** 192–95 °C indicating **6a** and **8a** to be different compounds; IR (KBr): 1690 (C=O), 1580 (C=N); ^1H NMR ($CDCl_3$): 8.20–7.40 (m, 5 H, Ph), 3.12 (s, 2 H, 7-CH_2), 2.60 (s, 2 H, 5-CH_2), 1.25 (s, 6 H, 6-Me_2); MS (*m/z*): 297 (100%); $C_{16}H_{15}N_3OS$ (297); calcd.: C 64.64, H 5.05, N 14.14; found: C 64.38, H 4.96, N 14.12.

Compounds **8b–i** were prepared similarly; for analytical data, cf. Table 2.

Acknowledgements

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