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On the Tautomerism of 2,4-Disubstituted 3,4,5,6-Tetrahydrobenzo[h]quinazolines

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Summary. The tautomerism of the title compounds was investigated by ^{1}H-, ^{13}C-NMR and UV spectroscopy. Compound **5** was compared with respect to its spectra with those of appropriate model compounds **1**,**3**,**4**, and **6**. This gave evidence that **5** predominates in the tautomeric form **5A**.

Keywords. Benzo[h]quinazolines; ^{13}C-NMR spectroscopy; Tautomerism.

Zur Tautomerie von 2,4-disubstituierten 3,4,5,6-Tetrahydrobenzo[h]chinazolinen

Zusammenfassung. Die Tautomerie von 2,4-disubstituierten 3,4,5,6-Tetrahydrobenzo[h]chinazolinen wurde durch ^{1}H-, ^{13}C-NMR- und UV-Spektroskopie untersucht. Der Vergleich der Spektren von **5** und der Modellverbindungen **1**,**3**,**4** und **6** legt nahe, daß für **5** das Tautomere **5A** dominiert.

Introduction

During our synthetic studies directed towards new bioactive compounds we reported the formation of 4-phenyl-3,4,5,6-tetrahydrobenzo[h]quinazoline-2(1*H*)-thione **(2)** and its 2-alkylmercapto derivatives. They were synthesized by direct alkylation of the parent thione. Accordingly, two tautomeric forms **5A** and **5B** [1] are to be considered. Because of the unstability of the latter compound (aromatization of the heterocyclic ring) its tautomeric structure was tentatively assigned to **5A** on the basis of our previous findings on methylation of 4-aryl-3,4,5,6,7,8-hexahydro-2(1*H*)-quinazolinethiones [2]. Since in a recent paper [3] the **5B** tautomer was found to predominate in 2,4-diaryl-benzo[h]quinazolines and the ^{1}H chemical shifts reported for the H-4 protons were rather different from those reported for the same protons of the same tautomeric from of 2-methyl-4-phenyl-benzo[h]quinazoline [4] we thought that it could be of interest to gain deeper insight into the problem of tautomerism in this class of compounds.

Results and Discussion

In order to obtain a suitable reference compound with fixed tautomeric structure the 3-methyl derivative of **2** was prepared from 2-benzylidene-1-tetralone and N-methyl-thiourea [4]. Although the ^{1}H-NMR spectrum of compound **4** contained

Table 1. Relevant ^{13}C-NMR data of compounds **1–6** measured in DMSO-d_6

Compound	C-1a	C-2	C-4	C-4a	C-5	C-6	C-6a	C-10	C-10a	Others
1	126.71[a]	176.01	44.58	108.29	23.76	27.14	135.43	121.08	127.80[a]	–
2	126.55[b]	174.44	58.72	111.44	23.78	27.52	135.60	121.84	128.01[b]	–
3	126.44[c]	174.12	58.02	111.54	23.73	27.47	135.49	121.73	127.69[c]	55.20 (OCH_3)
4	126.06[d]	175.74	65.82	111.33	23.51	27.41	135.43	121.84	127.80[d]	39.68[e] (NCH_3)
5·HI	–	163.17	58.18	116.42	23.46	26.81	135.49	121.95	–	14.30 (SCH_3)
5	133.86	155.53	58.62	112.57	24.59	27.30	135.16	122.49	126.12	12.46 (SCH_3)
6	133.76	157.32	66.63	112.41	24.32	27.24	135.11	122.65	126.88	13.36 (SCH_3) 35.54 (NCH_3)

[a, b, c, d] The assignments of the pairs may be interchanged

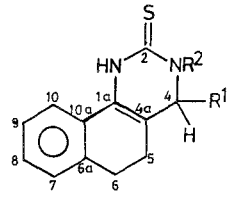
[e] In $CDCl_3$

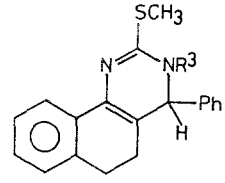
all resonances, their shifts from that of the parent compound **2** were not characteristic to allow structure assignment. To allow assignments of carbons in the ^{13}C-NMR spectra belonging to the partially saturated rings of the benzoquinazoline skeleton with peaks in the aromatic region (1 a, 4 a, 6 a, 10 a), derivatives **1** and **3** were synthesized. Preparation of **1** was effected by reacting 2-dimethylaminomethyl-1-tetralone (**7**) with ammonium thiocyanate via the reactive 2-methylene-1-tetralone intermediate [5]. The assignment of selected chemical shifts are listed in Table 1.

The downfield shifts observed for C-2 and especially for C-4 of compound **4** clearly indicated [6] that the attack of the N-methyl group of the thiourea took place at the β-carbon of the unsaturated ketone. By direct methylation of compound **4** and liberation of the base we got the N,S-dimethyl derivative **6** with fixed position of the C=N double bond [7]. In the ^{13}C-NMR spectrum of **6** the most important change was the large downfield shift of the C-1 a signal indicating the appearance of a new C=N bond. The spectrum of compound **5** synthesized via methylation of **2** and subsequent liberation of the base showed a close similarity in chemical shifts for the C-4 a and C-1 a carbons. This established the presence of an identical structure of the heterocyclic ring corroborating the formerly proposed [2] **5A** tautomeric structure of this type of compounds.

Further evidence could be drawn comparing the UV spectra of compounds **5** and **6**. Since they are in good agreement we can state that the two derivatives exist in the same tautomeric form.

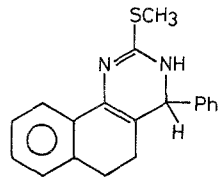
Neither in the ^{1}H- nor in the ^{13}C-spectra we found any indications of a tautomeric equilibrium between **5A** and **5B**.



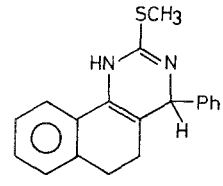


	R^1	R^2
1	H	H
2	Ph	H
3	4-CH_3O-C_6H_4	H
4	Ph	CH_3

	R^3
5·HI	H
5	H
6	CH_3



5A



5B

Experimental Part

Melting points were determined on a Boetius hot plate apparatus and are uncorrected. IR spectra were obtained with a SPECORD 75 IR type spectrophotometer (KBr). 60 MHz ^{1}H-NMR spectra were recorded on a Perkin-Elmer R 12 A spectrometer (temperature 35.0°C; tetramethylsilane as internal reference). 20 MHz ^{13}C-NMR measurements were recorded on a Bruker WP 80SY spectrometer (ambient temperature; *TMS* as internal standard). UV spectra (ethanol) were run on a Perkin-Elmer 402 spectrophotometer. The α,β-unsaturated ketones were prepared by aldol condensations [8]. The synthesis of **2** was published [1]. The preparation of **3** and **4** were effected analogously.

3,4,5,6-Tetrahydrobenzo[h]quinazoline-2(1H)-tione (**1**)

The mixture 5.99 g (25 mmol) of **7** and 3.80 g (50 mmol) of ammonium thiocyanate and 10 ml cyclohexanol was boiled in toluene (100 ml) by using a water separator for 6 h. The red oil formed was separated from the mother liquor, the latter was evaporated, and the residue was combined with the oily material. It was dissolved in chloroform and washed with water free of thiocyanate. The solution was dried over $MgSO_4$ and the solvent was removed. The residue was chromatographied on silica gel [Kieselgel 60, 0.063–0.2 mm, Reanal; 30 × 3.8 cm, benzene:ethyl acetate = 50:1 (*v*/*v*)] affording four fractions. According to TLC [Kieselgel 60 F_{254}, Merck; benzene:ethyl acetate = 1:1 (*v*/*v*)] the first three were impurities, the last one was compound **1** (R_f=0.58) 20%, m.p. 184°C (decomp. from methanol) (found C 66.70, H 5.71, N 13.00, S 15.04. $C_{12}H_{12}N_2S$ requires C 66.63, H 5.59, N 12.95, S 14.82%). ν_{max} (KBr) 3170 (NH), 1195 (thioamide I); δ_H (60 MHz, $CDCl_3$) 1.9–2.4 (2H, m, 5-H), 2.6–3.0 (2H, m, 6-H), 4.0–4.2 (2H, m, 4-H), 7.0–7.3 (4H, m, *Ar*), 6.90, 7.55 (2H, br, s, NH).

4-(4-Methoxyphenyl)-3,4,5,6-tetrahydrobenzo[h]quinazoline-2(1H)-thione (**3**)

87%, m.p. 200°C (decomp., from methanol) (found C 70.91, H 5.80, N 8.73, S 9.80. $C_{19}H_{18}N_2OS$ requires C 70.78, H 5.63, N 8.69, S 9.94%). ν_{max} (KBr) 3180 and 3260 (NH), 1195 (thioamide I); δ_H (60 MHz, $CDCl_3$) 1.7–2.3 (2H, m, 5-H), 2.5–3.0 (2H, m, 6-H), 3.78 (3H, s, OCH_3), 5.03 (1H, s, 4-H), 6.7–7.7 (8H, m, *Ar*), 7.80 (2H, br, s, NH).

3-Methyl-4-phenyl-3,4,5,6-tetrahydrobenzo[h]quinazoline-2(1H)-thione (**4**)

82%, m.p. 185°C (decomp., from methanol) (found C 74.40, H 6.03, N 9.23, S 10.42. $C_{19}H_{18}N_2S$ requires C 74.47, H 5.92, N 9.14, S 10.46%). ν_{max} (KBr) 3100–3350 (NH), 1275 (thioamide I). δ_H (60 MHz, $CDCl_3$) 1.7–2.2 (2H, m, 5-H), 2.5–2.9 (2H, m, 6-H), 3.25 (3H, s, NCH_3), 4.88 (1H, s, 4-H), 7.0–7.4 (9H, m, *Ar*), 7.85 (1H, br, s, NH).

2-Methylmercapto-4-phenyl-3,4,5,6-tetrahydrobenzo[h]quinazoline (**5**)

It was obtained according to [1]. The crude product was *immediately* recrystallized and investigated, because at room temperature, especially in solution, it turned into an aromatic compound [1]. Because of the instability of the compound it could not be analyzed. 92%, m.p. 63°C (decomp., from methanol). ν_{max} (KBr) 3135 and 3355 (NH); δ_H (60 MHz, $CDCl_3$) 1.8–2.2 (2H, m, 5-H), 2.5–2.9 (2H, m, 6-H), 2.52 (3H, s, SCH_3), 3.7 (1H, br, s, NH), 4.95 (1H, s, 4-H), 6.9–7.4 (8H, m, *Ar*), 7.8–8.0 (1H, m, 10-H). λ_{max}[nm] 210, 241 and 342.

2-Methylmercapto-4-phenyl-3,4,5,6-tetrahydrobenzo[h]quinazoline Hydroiodide (**5** · **HI**)

Its preparation was described earlier [1].

3-Methyl-2-methylmercapto-4-phenyl-3,4,5,6-tetrahydrobenzo[h]quinazoline (**6**)

It was prepared from **3** analogously to the preparation of **4** in two steps (alkylation and liberation of the free base [1]). 31%, m.p. 116–117°C (from methanol) (found C 74.93, H 6.30, N 8.71, S 9.88. $C_{20}H_{20}N_2S$ requires C 74.96, H 6.29, N 8.74, S 10.00%). ν_{max} (KBr) no characteristic bands. δ_H (60 MHz, $CDCl_3$) 1.8–2.2 (2H, m, 5-H), 2.5–2.9 (2H, m, 6-H), 2.55 (3H, s, SCH_3), 2.82 (3H, s, NCH_3), 4.73 (1H, s, 4-H), 6.9–7.4 (8H, m, *Ar*), 7.8–8.1 (1H, m, 10-H), λ_{max}[nm] (ε) 211 (14125), 243 (15850), 346 (1700).

2-Dimethylaminomethyl-1-tetralone Hydrochloride (**7**)

A mixture of 9.72 g (80 mmol) 1-tetralone, 6.52 g (80 mmol) dimethylammonium chloride, 4.80 g (160 mmol) paraformaldehyde and 0.60 ml concentrated hydrochloric acid was refluxed in ethanol (160 ml) for 3 h. The hot solution was filtered, the solvent was evaporated and the residue was triturated with acetone. The colorless precipitate was filtered off and rinsed with acetone, it was recrystallized from the mixture of acetone and methanol. 43%, m.p. 152–153°C (from acetone and methanol) (found C 65.16, H 7.70, Cl 14.60, N 6.09, $C_{13}H_{18}ClNO$ requires C 65.13, H 7.57, Cl 14.79, N 5.84%). ν_{max} (KBr) 1680 (C=O). δ_H (60 MHz, *DMSO-d_6*) 2.5–3.9 (7H, m, 2-, 3-, 4-H, NCH_2), 2.80 (6H, s, NCH_3), 7.1–8.0 (4H, m, *Ar*), 10.7 (1H, br, s, NH^+).

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