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Studies on Potential Antiviral Compounds, XI**

Thiosemicarbazones of Hydroaromatic Ketones***

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Some thiosemicarbazones of hydroaromatic ketones with linear and angular tricyclic structures were prepared and tested for in vitro antiviral activities against vaccinia virus, IHD stock, and parainfluenza type 3 virus, HA-I/CR-8 stock. The thiosemicarbazone of 2,3-dihydro-4(1H)-phenanthrenone **(10)** was the most active compound.

Untersuchungen über potentiell antivirale Verbindungen, 11. Mitt.: Thiosemicarbazone hydroaromatischer Ketone

Einige Thiosemicarbazone von hydroaromatischen Ketonen mit linearer und angularer Struktur wurden hergestellt und auf ihre antivirale *in vitro*-Aktivität gegen Vaccinia Virus, IHD Stock und Parainfluenza Typ 3 Virus, HA-I/CR-8 Stock, untersucht. Das 2,3-Dihydro-4(1H)-phenanthrenon-thiosemicarbazon **(10)** war die wirksamste Verbindung.

The significance of α-(N)-heterocyclic carboxaldehyde thiosemicarbazones as antineoplastic agents is well known[1]. Moreover, thiosemicarbazones of heterocyclic aldehydes and ketones are still of a great interest as antiviral agents[2,3] also in the field of viral molecular biology. Antivaccinia activity was recently found in a series of naphtho[2,1-b]furan-1(2*H*)-one **(1)**, 2,3-dihydro-1*H*-benz[e]indene-1-one **(2)**, naphtho[1,2-b]furan-3(2*H*)-one **(3)** and 1,2-dihydro-3*H*-benz[e]indene-3-one **(4)** thiosemicarbazones[4,5], (**3** and **4** are isomers, resp., of **1** and **2**). Methisazone, used as a reference standard possesses a similar activity, but unlike methisazone, some of the tested compounds revealed an inhibitory action against parainfluenza replication[5]. Antivaccinia activity in this series of hydroaromatic ketone thiosemicarbazones was influenced by moving the site of substitution in the hydrazone side chain to the 3-position[5]. As an attempt to complete the preliminary investigations on the structure-activity relationships, it was of interest to observe the influence of geometry of the tricyclic system on antiviral activity, by examining linear and angular structures, as well as the enlargement of the pentatomic ring (thiosemicarbazones of compounds **5–15**). The results of these experiments are here reported after a check-up of the previous data since some of them had been obtained at concentrations showing some kind of cell toxicity[5].

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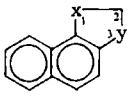
Discussion

Table 1 shows a quite interesting *in vitro* antivaccinia activity for some compounds (thiosemicarbazones of **5, 6, 7, 9, 10**). On the contrary, parainfluenza growth inhibition activities are of little significance. The thiosemicarbazone of the 2,3-dihydro-4(1H)-phenanthrenone **(10)** shows an *in vitro* antivaccinia activity comparable to that of methisazone, taken as a reference standard, associated with parainfluenza growth inhibition activity.

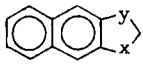
Regarding structure-activity relationships, a certain correspondence is observed among isosteric derivatives (thiosemicarbazones of **1** and **2, 3** and **4, 5** and **6, 9** and **10**) with the exception of thiosemicarbazones of **7** and **8**.

Linear structures appear to enhance the antivaccinia activity of tricyclic systems with a pentatomic ring (thiosemicarbazones of **5** and **6**); on the other hand, angular structures are more active when they are associated with a six-membered ring (thiosemicarbazones of **7, 9** and **10**.)

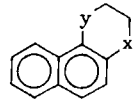
It should be noticed that only thiosemicarbazones of angular and type **14** structures show some parainfluenza growth inhibition activity.



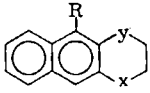
1: y = O; x = CO
2: y = CH_2 x = CO
3: y = CO x = O
4: y = CO x = CH_2



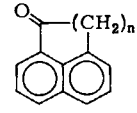
5: y = O x = CO
6: y = CH_2 x = CO



7: y = O x = CO
8: y = CH_2 x = CO
9: y = CO x = O
10: y = CO x = CH_2



11: R = Br y = O x = CO
12: R = CH_3 y = O x = CO
13: R = H y = CH_2 x = CO



14: n = 2
15: n = 1

Experimental Part

Elemental analyses: Laboratory for Microanalysis of the Faculty of Pharmacy of the University of Pisa, Italy. *Mp's*: not corr. (Electrothermal Melting Point Apparatus). *IR spectra*: Perkin Elmer 177 spectrophotometer (nujol mull technique). They agreed with the proposed structures. *Thin layer chromatography*: used to check sample homogeneity (Baker-Flex Silica Gel IB-F, acetone-petroleum ether 3:7 v/v).

Microbiology. – The antiviral activities of thiosemicarbazones of Table 1 against the IHD strain of vaccinia virus and the Ha-I/CR-8 strain of type 3 parainfluenza virus were evaluated by means of plaque inhibition tests, using the cell system of human KB tumor cells according to a reported procedure[6,7]. All the compounds were tested as 26 μM aqueous solutions.

Thiosemicarbazones. – Thiosemicarbazones listed in Table 1 with their antiviral characteristics were prepared according to a standard method[4].

Ketones. – Commercially unavailable ketones were prepared according to reported procedures unless otherwise indicated.

Naphtho[2,3-b]furan-3(2H)-one(**5**). Obtained according to[8].

Table 1: *Thiosemicarbazones*

Precursor Ketones	Recryst. Solv. [a]	MP°	Formula	Calc.	Found	Conc. μM	Conc. γ/ml	Growth Inhibition (log_{10} units) Virus Vaccinia	Virus Type 3 Parainfluenza
5	A and B	214–216	$C_{13}H_{11}N_3OS$	C 60,7 H 4,31 N 16,9	60,5 4,24 16,5	26	6,7	3,16	–
6	B	234–238[b]	$C_{14}H_{13}N_3S$	C 65,9 H 5,13 N 16,5	66,1 5,25 16,5	26	6,6	3,22	–
7	B	212–214	$C_{14}H_{13}N_3OS$	C 62,0 H 4,83 N 15,5	61,9 4,79 15,2	26	7	3,15	–
8	C	204–206	$C_{15}H_{15}N_3S$	C 66,9 H 5,61 N 15,6	66,7 5,69 15,5	26	7	1,17	0,71
9	B	228–229	$C_{14}H_{13}N_3OS$	C 62,0 H 4,83 N 15,5	61,8 4,84 15,9	26	7	3,27	0,50
10	C–D	193–195	$C_{15}H_{15}N_3S$	C 66,9 H 5,61 N 15,6	66,8 5,93 15,4	26	7	4,11	1,40
11	B	235–237	$C_{14}H_{12}BrN_3OS$	C 48,0 H 3,45 N 12,0	48,5 3,73 12,2	26	9,1	–	–
12	B	242–243	$C_{15}H_{15}N_3OS$	C 63,1 H 5,30 N 14,7	62,8 5,78 14,3	26	7,4	1,29	–
13	B	232–235[b]	$C_{15}H_{15}N_3S$	C 66,9 H 5,61 N 15,6	67,0 5,83 15,4	26	7	–	–
14	C	206–208[b]	$C_{14}H_{13}N_3S$	C 65,9 H 5,13 N 16,5	66,3 5,50 16,3	26	6,6	–	1,24
15	C	235–240[d]	$C_{13}H_{11}N_3S$	C 64,7 H 4,59 N 17,4	64,3 4,46 17,6	26	6,3	1,73	–
Metisazone[e]						26	6,1	4,43	–
1[f]						26	6,7	0,60	0,54
2[f]						26	6,6	0,53	< 0,50
3[g]						26	6,7	0,98	0,66
4[g]						26	6,6	–	0,74

a: A = Methyl Cellosolve-water; B = 100 % ethanol; C = 95 % ethanol; D = water. b: With decomposition. c: Lit.[17]: reported 247°. d: Lit.[18]: reported 227–228°. e: Commercial product. f: Reference[4]. g: Reference[5].

2,3-dihydro-1H-benz[f]inden-1-one(**6**).

Obtained according to *Horner* and al.[9] by oxidation of 2,3-dihydro-1*H*-benz[f]indene. The desired product was accompanied by 2,3-dihydro-1*H*-benz[f]indene-4,9-dione from which it was separated by absorption chromatography (silica gel, benzene-ethyl acetate 9/1 v/v).

2,3-Dihydro-1H-benz[f]indene

Obtained, in turn, by *Clemmensen* reduction (56,5 % yield) of 2,3-dihydro-1*H*-benz[f]indene-1,3-dione[10].

2,3-dihydro-4H-naphtho[1,2-b]pyran-4-one(**7**) and *2,3-dihydro-1H-naphtho[2,1-b]pyran-1-one*(**9**).

Obtained by the method of *Bachman* and *Levine*[11] modified by *Colonge* and *Guyot*[12].

3,4-Dihydro-1(2H)-phenanthrenone (**8**) and *2,3-dihydro-4(1H)-phenanthrenone* (**10**).

Obtained according to[13].

2,3-Dihydro-9-bromo-4H-naphtho[2,3-b]pyran-4-one(**11**) and
2,3-dihydro-9-methyl-4H-naphtho[2,3-b]pyran-4-one(**12**).

Obtained according to[14].

3,4-Dihydro-1(2H)-anthracenone(**13**).

Obtained according to *Agranat* and *Shih*[15] by cyclisation of 4-(2-naphthalenyl)-butanoic acid with polyphosphoric acid; to improve the yield, the desired compound was separated from the reaction mixture by repeated petroleum ether extractions at ca. 70° instead of preparative t.l.c..

2,3-Dihydro-1H-phenalen-1-one(**14**).

Synthesized according to *Fieser* and *Gates*[16] by cyclisation of 3-(1-naphthalenyl)-propanoic acid with anhydrous hydrogen fluoride. The latter was obtained, in turn, by *Willgerodt* reaction from 1-(1-naphthalenyl)-1-propanone.

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[Ph 292]

Kurzmitteilungen

„Inverse" Diels-Alder-Additionen, 12. Mitt.[1]

Croton- und Zimtaldehyd-N,N-dimethylhydrazone als bifunktionelle Dienophile

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Elektronenreiche C=C-[2] bzw. C=N-Doppelbindungen[3] zeigen eine ausgeprägte Reaktivität als Dienophile in der „inversen" Diels-Alder-Addition. Für einen Reaktivitätsvergleich beider dienophiler Komponenten erschien es aufschlußreich, das im Tetrazin **1** s-cis-fixierte Azinsystem mit Verbindungen umzusetzen, die sowohl eine reaktive C=C- als auch eine aktivierte C=N-Bindung in sich vereinigen. Hier bieten sich die N,N-Dimethylhydrazone α,β-ungesättigter Aldehyde **2** als Edukte an, die auf Grund unterschiedlicher elektronischer, aber auch sterischer Einflüsse des Restes R verschiedenartig reagieren sollten.

Für Crotonaldehyd-N,N-dimethylhydrazon **(2a)** ($R = CH_3$) erweist sich unter den angewendeten Reaktionsbedingungen die C=C-Doppelbindung als das reaktivere Dienophil. Als einziges Reaktionsprodukt aus der Umsetzung mit **1** erhält man in 75 proz. Ausbeute das chirale Dihydropyridazin **3** als Racemform. Hinweise auf die Anwesenheit anderer Cycloadditionsprodukte im Reaktionsgemisch konnten nicht erhalten werden. Zimtaldehyddimethylhydrazon **(2b)** ($R = C_6H_5$) verhält sich anders. Hier lassen sich in einer Gesamtausbeute von etwa 95 % zwei Reaktionsprodukte isolieren. Dominierend

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