Benzo[*b*]naphtho[2,1-*d*]thiophene (Thiachrysene) Derivatives as Potential Carcinostatic Molecules

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About twenty compounds of the benzo[*b*]naphtho[2,1-*d*]thiophene series have been synthesized, namely, 6-amino derivatives, with the aim of biological testing as possible carcinostatic molecules.

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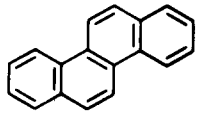
In 1953 Rudali, Buu-Hoï and Lacassagne reported the inhibitory effects of 6-aminochrysene (**1**) (Chrysenex, Continental Pharma) in mice on the growth of skin tumors induced by 20-methylcholanthrene as well as of spontaneously occurring mammary carcinomas (1). Later Huggins, *et al.*, found the same effect on mammary carcinomas induced by 7,12-dimethylbenz[*a*]anthracene in Sprague Dawley rats (2).

In a clinical trial this compound was found to produce objective regression of advanced mammary carinomas in several patients (3) whereas Gelzer and Loustalot confirmed the inhibitory activity of the compound in advanced experimental mammary cancer (4). Additionally 6-aminochrysene exhibited leucopenic activity (5) and this particular effect was used in the treatment of chronic myeloid leukaemia (6) and of splenomegaly (7). The mechansim of action of this compound is still not understood, however, it is possible, in the case of the effect on mammary cancer, to link the activity to the inhibitory effect of the drug against the estrogenic activity of triphenylethylene (8).

Although subcutaneous injection of 6-aminochrysene was found to induce both liver and lung tumors in male newborn Swiss mice (9), standard testing procedures in adult rats and mice, either by skin application or by subcutaneous unjection gave negative results and in addition, no chronic toxicity (1,10). Whereas chrysene is unable to induce tumors by subcutaneous injection in XVII nc/Z mice, benzo[*b*]naphtho[2,1-*d*]thiophene (**2**) (thiachrysene) shows a weak sarcomagenic activity in this strain (11). On the other hand, thiachrysene denotes a zoxazolamine hydroxylase inducing activity equal to that of the parent hydrocarbon (12). For these reasons we found it interesting to investigate a series of thiachrysene derivatives as possible antitumor agents.

Besides the preparation of the amino derivative **4** of **2**, easily obtained by reduction of the 6-nitrobenzo[*b*]naphtho[2,1-*d*]thiophene (**3**) with Raney nickel catalyst and hydrazine or through a Beckman rearrangement of the acetyl oxime derivative, this note deals with the synthesis of compounds bearing, at the 6 position of the thiachrysene nucleus various substituents previously shown to increase the antitumor activity of the parent 6-aminochrysene (13).

6-Acetylbenzo[*b*]naphtho[2,1-*d*]thiophene (**5**), obtained in good yield (*ca* 80%) by direct acetylation of **2** in benzene solution by means of acetyl chloride and stannic chloride, shows an nmr spectrum (60 MHz in deuteriochloroform with tetramethylsilane as the internal standard δ tms = 0) consistent with the proposed structure: δ 2.81 (singlet, 3H, CH_3) δ 7.5 (multiplet, 4H, H-2,3,8,9) δ 7.96 (multiplet, 3H, H-1,4,10) δ 8.43 (singlet, 1H, H-5 deshielded by the *ortho* effect of the carbonyl) δ 8.76 (multiplet, 1H, H-7 deshielded by the *peri* effect of the carbonyl). This



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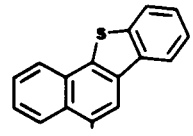
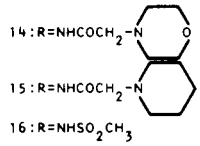


2: R=H
3: R=NO_2
4: R=NH_2
5: R=CO-CH_3
6: R= -C(=N-NH-CO-NH_2)-CH_3
7: R=NH-$COCH_3$
8: R=$NHCO_2C_2H_5$
9: R=$NHCO_2$(n)C_4H_9
10: R=$NHCO_2$(iso)C_4H_9
11: R=NH-$COCH_2Cl$
12: R=$NHCOCH_2$-NH-(n)C_8H_{13}
13: R=$NHCOCH_2$-N(C_2H_4OH)$_2$



16: R=$NHSO_2CH_3$
17: R=$NHSO_2$(α-NAPHTHYL)
18: R=$NHSO_2$(β-NAPHTHYL)

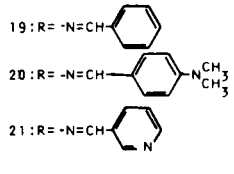


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Table 1

Compounds	molecular formula	found C%	found H%	found N%	required C%	required H%	required N%	m.p. (Crystallization solvent.)
6-Nitro BNT (a) **3**	$C_{16}H_9NO_2S$	68.42	3.27	4.90	68.80	3.25	5.01	202° (ethanol)
6-Amino BNT **4**	$C_{16}H_{11}NS$	76.79	4.45	5.35	77.07	4.45	5.62	172° (benzene)
6-Acetyl BNT **5**	$C_{18}H_{12}OS$	77.89	4.39	(S% 11.50)	78.25	4.38	(S% 11.61)	165° (cyclohexane)
Semicarbazone of **5** **6**	$C_{19}H_{15}N_3OS$	68.65	4.63	12.32	68.44	4.53	12.60	250° (butyl alcohol)
6-Acetamido BNT **7**	$C_{18}H_{13}NOS$	73.94	4.57	4.60	74.20	4.50	4.81	303° (toluene)
N-[6-BNt] (b) carbamic acid ethyl ester **8**	$C_{19}H_{15}NO_2S$	71.11	4.64	4.30	71.00	4.70	4.36	203° (benzene)
n-butyl ester **9**	$C_{21}H_{19}NO_2S$	72.38	5.54	3.85	72.21	5.44	4.00	173° (cyclohexane)
isobutyl ester **10**	$C_{21}H_{19}NO_2S$	72.56	5.92	3.66	72.21	5.44	4.00	178° (cyclohexane)
6-Chloracetamido BNT **11**	$C_{18}H_{11}ClNOS$	65.91	3.85	4.37	66.37	3.71	4.30	268° (xylene)
6-[*N*,*n*-octylamino]acetamido BNT **12**	$C_{26}H_{30}N_2OS$	74.80	7.32	6.52	74.60	7.22	6.69	103° (hexane)
6-[*N*-*bis*(β-hydroxyethyl)amino]acetamido BNT **13**	$C_{22}H_{22}N_2O_3S$	66.74	5.70	7.02	66.98	5.62	7.10	152° (xylene)
6-[*N*-morpholino]acetamido BNT **14**	$C_{22}H_{20}N_2O_2S$	69.84	5.36	7.47	70.18	5.35	7.44	165° (benzene)
6-[*N*-piperidinyl]acetamido BNT **15**	$C_{23}H_{22}N_2OS$	73.70	6.01	7.12	73.76	5.92	7.48	156° (hexane)
N-6-BNt methylsulfonamide **16**	$C_{17}H_{13}NO_2S$	62.43	4.15	4.34	62.38	3.97	4.27	279° (xylene)
N-6-BNt-1-naphthylsulfonamide **17**	$C_{26}H_{17}NO_2S_2$	71.19	4.03	3.16	71.05	3.87	3.19	256° (xylene)
N-6-BNt-2-naphthylsulfonamide **18**	$C_{26}H_{17}NO_2S_2$	71.06	4.05	2.95	71.05	3.87	3.19	273° (xylene)
N-benzylidene-6-amino BNT **19**	$C_{23}H_{15}NS$	81.98	4.46	4.10	81.86	4.48	4.15	154° (ethanol)
N-(4-dimethylamino benzylidene)-6-amino BNT **20**	$C_{25}H_{20}N_2S$	78.71	5.26	7.25	78.91	5.30	7.36	235° (xylene)
N-(3-pyridylmethylene)-6-amino BNT **21**	$C_{22}H_{14}N_2S$	78.10	4.17	7.75	78.10	4.13	8.27	216° (ethanol)

(a) BNT = benzo[*b*]naphtho[2,1-*d*]thiophene. (b) BNt = (6-benzo[*b*]naphtho[2,1-*d*]thienyl)-.

compound forms the semicarbazone (**6**) quantitatively as well as the oxime derivative. The latter is easily converted to the 6-acetamidothiachrysene (**7**) by a Beckman rearrangement using acetic acid saturated in dry hydrochloric acid. Reaction of the amine **4** with chloroformates in dry pyridine following the procedure described by Buu-Hoï, *et al.* (14) affords compounds **8-10** in almost quantitative yield. Condensation of chloracetyl chloride with aminothiochrysene in refluxing xylene leads to 6-chloracetamidobenzo[*b*]naphtho[2,1-*d*]thiophene (**11**) which can be reacted with amines to form compounds **12-15**.

Substituted sulfonyl chlorides also react with **4** affording the sulfonamides **16-18** whereas condensation of various aldehydes leads to the imines **19-21**.

The physical properties of these compounds are summarized in Table 1. All these molecules gave nmr spectra consistent with the proposed structures and are presently being tested for carcinostatic activity.

EXPERIMENTAL

All melting points were measured with a capillary tube apparatus and are not corrected. The nmr spectra were recorded on a Varian EM 360 at 60 MHz.

Benzo[*b*]naphtho[2,1-*d*]thiophene was prepared following the procedure of Rabindran and Tilak (15).

6-Nitrobenzo[*b*]naphtho[2,1-*d*]thiophene (**3**).

To a refluxing solution of 0.01 mole of thiachrysene (2.34 g.) in 50 ml. of acetic acid, nitric acid (d, 1.49, 0.5 ml., 0.012 mole) was added dropwise. After addition, reflux was maintained for 10 minutes and the solution was diluted with water (200 ml.). The precipitate was collected and recrystallized from ethyl alcohol leading to **3** in 90% yield.

6-Aminobenzo[*b*]naphtho[2,1-*d*]thiophene (**4**).

6-Nitrothiachrysene (1.1 g., 4×10^{-3} mole) was dissolved in 100 ml. of ethyl alcohol and refluxed with 8 ml. of hydrazine hydrate and 1 g. of Nickel catalyst for 3 hours. The solution was then diluted with water and the precipitate purified by chromatography on silicic acid (Merck 60) eluting with benzene. The amine crystallizes as long colorless needles from benzene, yield 78%.

6-Acetylbenzo[*b*]naphtho[2,1-*d*]thiophene (**5**).

To 100 ml. of a benzene solution of 0.01 mole of thiachrysene (2.34 g.) and 0.01 mole of stannic chloride (2.6 g.), 0.012 mole (1 g.) of acetyl chloride was added dropwise and the mixture refluxed for 2 hours. After decomposition with ice the benzene solution was washed with water, dried over sodium sulfate and evaporated to dryness. Ketone **5** was purified by chromatography on silicic acid eluting with a mixture benzene:cyclohexane (1:1), yield 80%.

The semicarbazone **6** and the oxime were obtained by refluxing 0.01 mole of the acetyl derivative **5** with 0.01 mole of semicarbazide hydrochloride or hydroxylamine hydrochloride, respectively, in 50 ml. of ethyl alcohol in the presence of 0.01 mole of sodium acetate for 30 minutes. These substances were isolated, after cooling of the solution, as colorless needles in almost quantitative yields.

6-Acetamidobenzo[*b*]naphtho[2,1-*d*]thiophene (**7**).

The oxime (0.005 mole) was directly converted into 6-acetamidobenzo-[*b*]naphtho[2,1-*d*]thiophene (**7**) by refluxing for 15 minutes in 30 ml. of a 1:1 mixture of acetic anhydride and acetic acid saturated with dry hydrogen chloride. The acetamido derivative crystallized as long colorless needles (yield 90%).

6-Chloracetamidobenzo[*b*]naphtho[2,1-*d*]thiophene (**11**).

The amine **4** was (0.01 mole) treated with 0.01 mole of chloroacetyl chloride in 300 ml. of refluxing xylene for 1 hour. After cooling, **11** crystallizes as long colorless needles, yield 90%.

Aminoacetamidobenzo[*b*]naphtho[2,1-*d*]thiophenes (**12-15**).

Condensation of the chloracetamido derivative with the appropriate amines either in refluxing xylene or isopropyl alcohol affords compounds **12-15**.

(6-Benzo[*b*]naphto[2,1-*b*]thienyl)sulfonamides (**16-18**).

These compounds were prepared according to the standard procedure described by Do Cao Thang *et al.*, (16) by treatment of the amine **4** with one equivalent of the appropriate sulfonyl chloride in dry pyridine, with yields of 80-90%.

Schiff Bases (**19-21**).

These compounds were easily obtained by condensation of the appropriate aldehyde with 6-aminothiachrysene in refluxing ethyl alcohol (benzaldehyde) or acetic acid (4-dimethylamino benzaldehyde, pyridine-3-aldehyde) in yields of 70 to 80%.

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