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Studies on Coumarins, II[6)]

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4-(Bromomethyl)coumarins prepared by the reaction of phenols and 4-(bromoethyl)acetoacetate were reacted with various phenols and thiophenol to yield 4-(phenoxymethyl)- and 4-(thiophenoxymethyl)coumarins. The spectral properties and the antimicrobial activities against five micro-organisms are reported. Fragmentation of one of the ethers in the mass spectrometer is discussed.

Untersuchungen über Cumarine, 2. Mitt.[6)]

4-Bromomethylcumarine, hergestellt durch Umsetzung von Phenolen mit 4-Bromethylessigester, werden mit verschiedenen Phenolen und Thiophenol umgesetzt, um 4-Phenoxymethyl- und 4-Thiophenoxymethylcumarine zu erhalten. Über ihre spektralen Eigenschaften und über ihre antimikrobielle Aktivität gegen fünf Mikroorganismen wird berichtet. Die massenspektrometrische Fragmentierung wird am Beispiel eines der Ether diskutiert.

Many 4-substituted coumarin derivatives are known for their wide range of biological properties[1)]. The importance of arylether and arylthioether linkages is evidenced from their presence in many anti-mycobacterials,[2)] analgesics[3)] antibiotics[4)] and parasitic agents[5)]. It was of obvious interest to study the biological properties of the resulting compounds when these groups are linked to a coumarin ring.

In continuation of our studies[6)] on potential coumarin antimicrobials, during the present investigation, we report the synthesis of some new 4-bromomethyl, 4-phenoxymethyl and 4-thiophenoxymethylcoumarins. These coumpounds have been screened against five micro-organisms.

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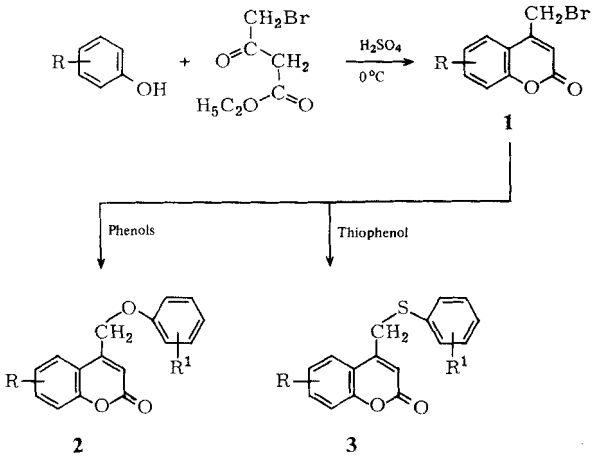
The required 4-bromomethylcoumarins[7] **1** were prepared from substituted phenols and 4-bromoethylacetoacetate[8]. The condensation of phenols was carried out by a slight modification of the earlier method[9]. The sulfides were synthesised by refluxing equimolar quantities of sodium thiophenolate and 4-bromomethylcoumarins in ethanol. The reactions are shown in scheme A.



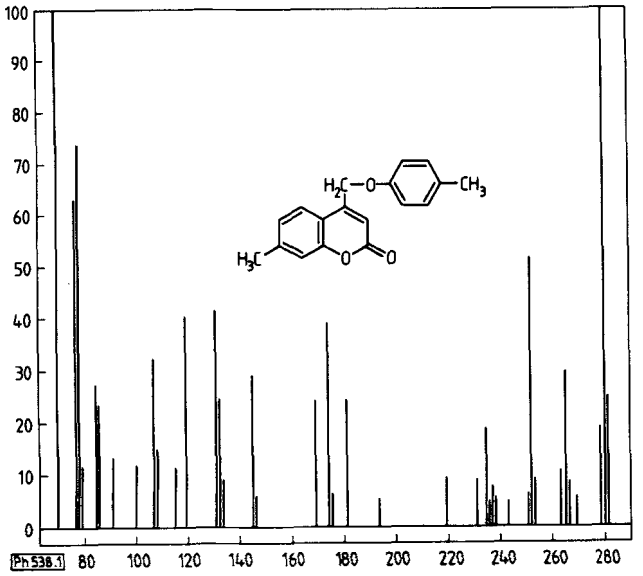
In the IR spectra the coumpounds **2** and **3** exhibited C=O stretching frequency around 1700 cm^{-1} and C=C in the region of 1400–1600 cm^{-1}. The vibrations due to the ether and the thioether linkages appeared from 1080–1250 cm^{-1}.

^{1}H-NMR spectra: In the case of compounds **2** and **3** the triplet doublet pattern for C-3-H and 4-CH_2R was observed (J ~ 2 Hz) as a result of the allylic coupling. However in 4-bromomethylcoumarins both C-3-H and 4-CH_2 protons appeared as singlets since electronegativity and inductive effect of the groups linked are known to influence the mode of such long range couplings[10,11]. The methylene protons resonated around 4–5 ppm and the C-3-H between 6.3 to 6.7 ppm. The resonance signals due to methyl, methoxy and aromatic protons appeared around 2.4, 3.8 and 7.0–7.7 ppm resp. (Tab. 3).

Mass spectra: The principle fragmentation in the case of compound **2** g was elucidated as follows: From the bar graph it can be seen that the molecular ion ($M^{+\cdot}$) itself constitutes the base peak at m/e 280. The peaks due to (M+1), (M-H), (M-CH_3), (M-CO_2), [M-(H+CO_2)], (M-CO), [M-(H+CO)], and [M-(CO+CH_3)] are observed at m/e values 281, 279, 265, 236, 235, 252, 251, and 237 resp. (Fig. 1).

The main fragmentation occurs by the loss of carbon monoxide from the coumarin nucleus by the ring contraction to give the ion **I** with the benzofuran ring[12]. The further fission of ion **I** may occur by the homolytic cleavage of the C-O bond of the ether linkage to give two daughter ions **II** and **III** which compete for the positive charge. The ion **III**, after ring expansion, is likely to lose an acetylene molecule by the well-known Retro*Diels-Alder* reaction to give the ion **IV** to form a major peak of high intensity 42 % at m/e 119 (Fig. 2).

Another possible route for the odd-electron ion **I** is the expulsion of a toluene molecule by a hydride ion transfer to give another odd-electron ion **V**, which may further expel a molecule of carbon monoxide to give the 7-methyl benzofuran ion **VI**. This ion **VI** in turn may expel a molecule of carbon monoxide or a hydrogen radical and a carbon monoxide to give even electron ions which is well documented[12].


100
90
80
70
60
50
40
30
20
10
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Ph538.1
80
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120
140
160
180
200
220
240
260
280

Fig. 1: MS of **2g**

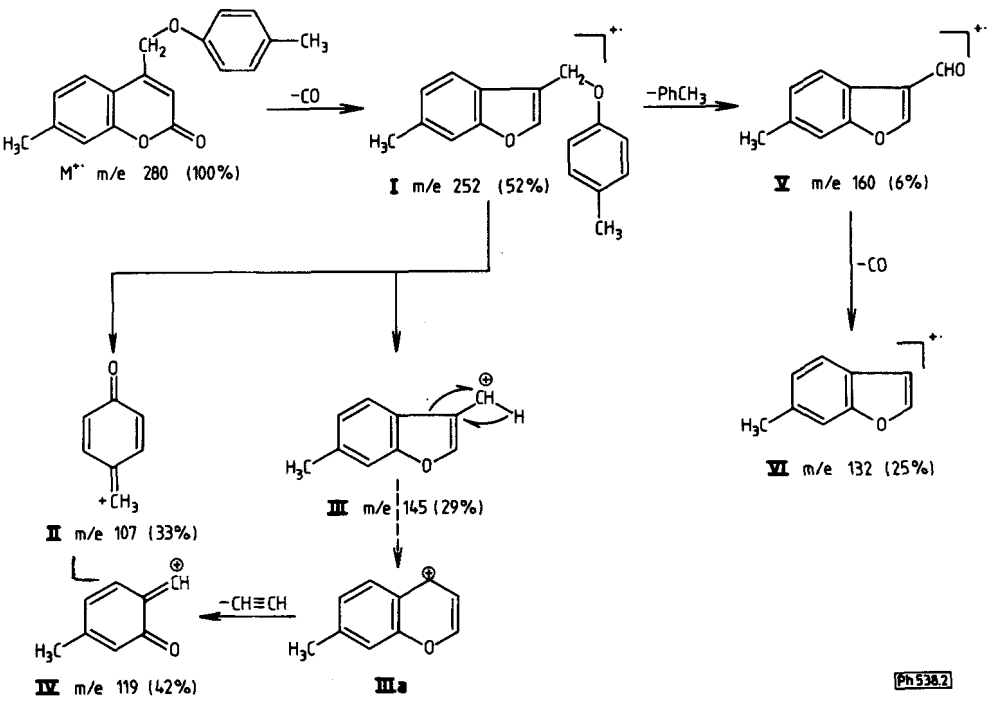
-CO
-PhCH3
-CO
-CH≡CH
M+· m/e 280 (100%)
I m/e 252 (52%)
V m/e 160 (6%)
VI m/e 132 (25%)
II m/e 107 (33%)
III m/e 145 (29%)
IV m/e 119 (42%)
IIIa
Ph538.2

Table 1: *Compounds* **2**

2	R	R^1	M.P.°C	Yield %	Formula	Analysis Requ. C	Requ. H	Found C	Found H
a	6-CH_3	-H	145–146[a]	80	$C_{17}H_{14}O_3$	76,7	5.26	76.4	5.04
b	6-CH_3	-4'-CH_3	184–185[a]	82	$C_{18}H_{16}O_3$	77.1	5.71	77.0	5.52
c	6-CH_3	-2'-CH_3	207–209[a]	88	$C_{18}H_{16}O_3$	77.1	5.71	76.9	5.49
d	6-CH_3	2'-Cl	225–226[a]	90	$C_{17}H_{13}O_3Cl$	67.8	4.32	67.7	4.02
e	6-CH_3	4'-Cl	217–218[a]	87	$C_{17}H_{13}O_3Cl$	67.8	4.32	67.5	4.14
f	7-CH_3	-H	130–131[a]	80	$C_{17}H_{14}O_3$	76.7	5.26	76.4	5.02
g	7-CH_3	4'-CH_3	137–138[a]	87	$C_{18}H_{16}O_3$	77.1	5.71	77.4	5.48
h	7-CH_3	2'-CH_3	139–140[c]	86	$C_{18}H_{16}O_3$	77.1	5.71	77.2	5.51
i	7-CH_3	2'-Cl	163–164[a]	83	$C_{17}H_{13}O_3Cl$	67.8	4.32	67.5	4.20
j	7-CH_3	4'-Cl	175–176[a]	85	$C_{17}H_{13}O_3Cl$	67.8	4.32	67.6	4.10
k	7-OCH_3	-H	112–114[a]	81	$C_{17}H_{14}O_4$	72.3	4.96	72.1	4.74
l	7-OCH_3	-4'-CH_3	119–120[a]	87	$C_{18}H_{16}O_4$	72.9	5.40	72.7	5.18
m	7-OCH_3	2'-CH_3	164–165[a]	75	$C_{18}H_{16}O_4$	72.9	5.40	72.7	5.21
n	7-OCH_3	2'-Cl	180–181[a]	90	$C_{17}H_{13}O_4Cl$	64.4	4.10	64.2	3.90
o	7-OCH_3	4'-Cl	162–163[a]	80	$C_{17}H_{13}O_4Cl$	64.4	4.10	64.3	3.92
p	6-OCH_3	-H	161–162[b]	81	$C_{17}H_{14}O_4$	72.3	4.96	72.1	4.69
q	6-OCH_3	4'-CH_3	141[d]	82	$C_{18}H_{16}O_4$	72.9	5.40	72.7	5.19
r	6-OCH_3	2'-CH_3	156–157[d]	80	$C_{18}H_{16}O_4$	72.9	5.40	72.6	5.21
s	6-OCH_3	2'-Cl	183–184[c]	88	$C_{17}H_{13}O_4Cl$	64.4	4.10	64.3	3.84
t	6-OCH_3	4'-Cl	188–189[b]	79	$C_{17}H_{13}O_4Cl$	64.4	4.10	64.2	3.88
u	6-Cl	-H	162–163[b]	75	$C_{16}H_{11}O_3Cl$	67.1	3.84	67.3	3.59
v	6-Cl	4'-CH_3	184–185[b]	80	$C_{17}H_{13}O_3Cl$	67.8	4.32	67.7	4.00
w	6-Cl	2'-CH_3	195[b]	79	$C_{17}H_{13}O_3Cl$	67.8	4.32	67.5	4.10
x	6-Cl	2'-Cl	231–232[b]	85	$C_{16}H_{10}O_3Cl_2$	59.8	3.11	59.6	2.89
y	6-Cl	4'-Cl	220[b]	80	$C_{16}H_{10}O_3Cl_2$	59.8	3.11	59.5	3.34
z	7-Cl	-H	158–159[e]	80	$C_{16}H_{11}O_3Cl$	67.1	3.84	67.4	3.61
a'	7-Cl	4'-CH_3	162–163[a]	82	$C_{17}H_{13}O_3Cl$	67.8	4.32	67.6	4.08
b'	7-Cl	2'-CH_3	179–180[b]	87	$C_{17}H_{13}O_3Cl$	67.8	4.32	67.6	4.19
c'	7-Cl	2'-Cl	213–214[a]	90	$C_{16}H_{10}O_3Cl_2$	59.8	3.11	59.6	2.90
d'	7-Cl	4'-Cl	209–210[e]	84	$C_{16}H_{10}O_3Cl_2$	59.8	3.11	59.5	3.29

Crystallisation from: a = benzene, b = dioxan + ethanol + water; c = ethanol; d = toluene + petrol ether; e = xylene + petrol ether.

The substituents in the phenoxy moiety are denoted by prime numbers.

Antimicrobial studies: All the compounds were tested against E. coli, S. aureus, P. vulgaris, B. subtilis and A. aerogenes. Among the various compounds **1** the 6-chloro and 7-chloro substitution favoured the growth inhibition of E. coli, B. subtilis and S. aureus, but were less active against P. vulgaris and A. aerogenes. In the case of the compounds **2** activity was increased due to 6-methoxy and 7-methoxy substituents in the coumarin ring and was further enhanced by chloro substitution in the phenoxy moiety, leading to complete inhibition of the growth of E. coli and partial inhibition in the cases of P. vulgaris

Table 2: *Compounds* **3**

3	R	m.p.°C	Formula	Yield %	Analysis Required C	H	Found C	H
a	6-CH_3	85[a]	$C_{17}H_{14}O_2S$	59	72.3	4.96	72.1	4.62
b	7-CH_3	86[b]	$C_{17}H_{14}O_2S$	62	72.3	4.96	72.0	4.71
c	6-OCH_3	65[b]	$C_{17}H_{14}O_3S$	70	68.4	4.69	68.1	4.50
d	7-OCH_3	108–109[c]	$C_{17}H_{14}O_3S$	74	68.4	4.69	68.2	4.42

Crystallisation from: a = aqueous methanol; b = petrol ether; c = aqueous ethanol

Table 3: *Proton chemical shifts* (δ) ppm of **2**

2	R	R^1	C-3-H(t)	4-CH_2-O-R′(d)	R	R^1	Ar-H(m)
g	7-CH_3	4′-CH_3	6.63	5.20	2.46	2.33	6.8–7.3
i	7-CH_3	2′-Cl	6.70	5.30	2.48	–	7.0–7.6
l	7-OCH_3	4′-CH_3	6.38	5.06	3.78	2.22	6.8–7.2
s	6-OCH_3	2′-Cl	6.75	5.28	3.88	–	7.0–7.5
v	6-Cl	4′-CH_3	6.70	5.16	–	2.35	6.9–7.6
b′	7′-Cl	2′-OCH_3	6.75	5.26	–	2.38	7.0–7.7

The substituents in the phenoxy moiety are indicated by prime numbers.

and S. aureus. No impact was observed on the growth of B. subtilis and A. aerogenes. All the sulfides **3** showed consistent inhibition of the growth of both S. aureus and E. coli and were inactive against other strains.

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Experimental

M.P.: Open capillaries (uncorr.); *IR spectra:* Carl-Zeiss UR-10; *NMR Spectra:* Varian A-60, Chemical shift: (δ) ppm downfield from TMS. *Mass spectrum:* CEC-21-110.

6-Chloro-4-bromomethylcoumarin

A mixture of 100 mmoles of p-chlorophenol and 100 mmoles of 4-bromoethylacetoacetate was added portionwise to 30 ml conc. sulfuric acid below 5° with constant stirring. After the addition was complete (45 min) the reaction flask was left overnight at room temp. The deep brown viscous oil was slowly decomposed in 1000 ml ice water, when a brown semisolid slowly separated which soon solidified. The residue was washed with water and finally with ethanol and was crystallised from acetic acid as silky needles, m.p. 168–169 °C. Yield 4 g (15 %). $C_{10}H_6O_2ClBr$ Requ.: C 43.8 H 2.19 Found: C 43.6 H 2.23.

IR spectrum (Nujol): 1725 (C=O), 1560, 1600 (skeletal) and 1180, 1220 cm^{-1} (C-O-C).

NMR ($CDCl_3$): δ (ppm) = C-3-H s, 6.60; 4-CH_2Br, s, 4.53; Ar-H, m, 7.4–7.7. Similarly 7-chloro-4-bromomethylcoumarin was prepared from m-chlorophenol and 4-bromoethyl-acetoacetate, m.p. 215–216 °C. Yield, 3.8 g (14 %).

$C_{10}H_6O_2ClBr$, Requ.: C 43.8 H 2.19 Found: C 43.9 H 2.04.

IR spectrum (Nujol): 1735 (C=O), 1560, 1610 (skeletal) and 1250, 1180 cm^{-1} (C-O-C).

NMR ($CDCl_3$): δ (ppm) = C-3-H, s, 6.66; 4-CH_2Br, s, 4.53; Ar-H, m,7.4–7.7.

4-Phenoxymethylcoumarins **2**, *General method*

A mixture of 1.8 g anhydrous potassium carbonate, 20 mmoles of phenol and 50 ml of dry acetone was stirred for about 30 min. To this were added 4.0 mmoles of substituted 4-bromomethylcoumarins and the stirring continued for 24 h. The reaction mixture was worked up in the following two ways:

A) The mixture was filtered and the filtrate was concentrated to a quarter of the original vol. and diluted with water. The separated solid was washed with 100 ml 10 % ethanol to remove excess of phenol. Then the residue was recrystallised from a suitable solvent. This method was employed for phenol and cresols.

B) In the case of chlorophenols the filtrate did not afford any thing after the dilution. The residue was neutralised with 50 ml (1:1) hydrochloric acid and the solid was recrystallised from a suitable solvent (Table 1).

4-Thiophenoxymethylcoumarins **3**. *General method*

In a dry round bottom flask fitted with a reflux condenser and a calcium chloride guard tube a solution of sodium ethoxide was prepared from 4 mmol sodium in 25 ml absol. ethanol. To this was added 4.0 mmoles of thiophenol with shaking followed by the addition of 4.0 mmoles of a substituted 4-bromomethylcoumarin. The reaction mixture was refluxed on a water bath for 2 h. The solution was concentrated and diluted with 100 ml water. The cooled, turbid solution was extracted with 3x50 ml ether. The ether layer was washed with 100 ml 1 % sodium hydroxide and finally with 100 ml water. The ether layer was dried over calcium chloride. The oil obtained after removal of the ether was pourred over a column containing neutral alumina and eluted with benzene or 80:20 (v/v) benzene ethylacetate. The solvent was removed under reduced pressure, and the residual solid was recrystallised from a suitable solvent (Table 2).

Antimicrobial studies

The test compounds were dissolved in purified DMF at a concentration of 2000 μg/ml. Each agar plate was treated with 0.1 ml of the test solution and the zone of inhibition was measured after 24 h. Phenol was employed as a standard.

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Reaktionen von N-Alkoxycycliminiumsalzen, 11. Mitt.[1)]

Reaktionen von 2-Chlor-N-methoxy-3-(-4)-nitropyridinium-(perchlorat) mit Aminen

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Eingegangen am 18. Dezember 1981

Vergleichende Untersuchungen zum Reaktionsverhalten 3-, 4- und 5-nitrosubstituierter 2-Chlor-N-methoxypyridiniumsalze gegenüber aromatischen und aliphatischen Aminen ergaben eine deutliche Abhängigkeit der Reaktivität sowie der Reaktionswege von der Stellung der Nitrogruppe im Pyridinring.
Während Umsetzungen des 3-Nitroderivates **1a** durch Angriff an C-6 und anschließende Ringöffnung zu 1-Methoxyimino-2,4-pentadienderivaten gekennzeichnet sind, ist das 4-Nitroderivat **1b** charakterisiert durch eine deutlich geringere Reaktivität sowie ein komplexeres Reaktionsverhalten und ein zusätzliches reaktives Zentrum an der 4-Position des Pyridinringes.

Reactions of *N*-Alkoxycycliminium Salts, XI: Reactions of 2-Chloro-*N*-methoxy-3-or-4-nitropyridinium Perchlorate with Amines

Reactions of 3-, 4- and 5-nitro-2-chloro-*N*-methoxypyridinium salts with aromatic and aliphatic amines show a remarkable dependence with regard to reactivity and pathway on the position of the nitro group. While reactions of the 3-nitro derivative **1a** are characterized by attack at position 6 of the pyridine ring followed by ring cleavage yielding stable 1-methoxyimino-2,4-pentadiene derivatives, reactions of the 4-nitro compound **1b** are more complex and the reactivity is remarkably decreased.

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