NOVEL HETEROCYCLES FROM 3-BROMO-4-BROMOMETHYLCOUMARINS

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Abstract - Whereas 3-bromo-4-bromomethyl-7-methoxycoumarin reacted very reluctantly with phenoxides, it was rapidly converted into pyridinium salts by simply substituted pyridines. The novel tetracyclic salt (11) was formed from the reaction with 2-aminopyridine. Some of the pyridinium salts show interesting pharmacological activities.

We have reported the preparation of the ether (1), from the reaction of 3-bromo-4-bromomethylcoumarin (2) with 1-naphthoxide and its rearrangement to the benzopyran (3)[1]. The sensitivity of the compound (2) to hydroxide, by which it was rapidly converted into (4), precluded any attempts to prepare (1) in homogeneous protic, basic media. The use of 1-naphthoxide in anhydrous dimethylformamide (DMF) afforded a lower yield of (1) than did the phase transfer method reported, and so the efficient preparation of ethers of the type (1) remained a problem. We attempted to prepare (1) by adding pyridine to a solution of (2) and 1-naphthol in chloroform, at room temperature (about 30°C) but observed the immediate and almost quantitative precipitation of the pyridinium salt (5).

This affinity of (2) for pyridine [2] prompted us to prepare a series of simple pyridinium salts using 2-methylpyridine, 3-methylpyridine, 3,5-dimethylpyridine, nicotinamide and quinoline as the nitrogen heterocycles, so providing the products (6) - (10) respectively. These reaction could be accomplished in very high yield (greater than 70%) by the general process of refluxing the dibromide (2) in acetone, or chloroform, with the nitrogen heterocycle for about 20 hours. The spectroscopic data and melting points of these and other compounds are shown in the table 1.

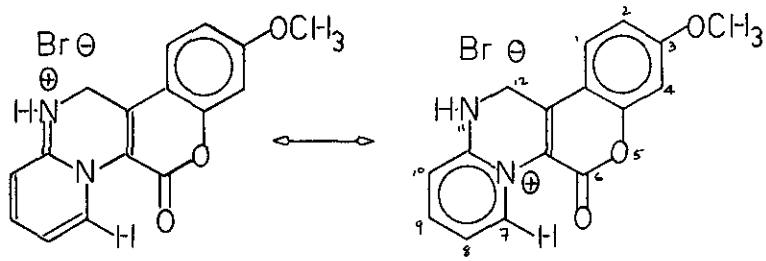
In order to explore the ability of other nucleophilic sites to attack the dibromide (2), the reaction with 2-aminopyridine was performed in refluxing dioxane. Here there was the possibility of attack by either the ring nitrogen or the amino group, but we only obtained the product (11), in 45% yield[3]. The spectroscopic data (see table 1) and analytical data were consistent with the structure given.

The other possible isomeric structure, (11'), for the product from the 2-aminopyridine reaction was eliminated by a possible consideration of the NMR spectra of the previously described compounds (5), (7), (8) and (3).

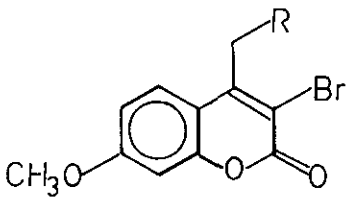
The NMR spectra of (5), (7) and (8) showed the resonances of the protons attached to the carbons 2' and/or 6' of the pyridinium ring in the range δ8.48-8.97. Thus H-6' of compound (5) resonated at δ8.97, H-2' and H-6' of compound (7) resonated at δ8.75 and H-2' and H-6' of compound (8) resonated at δ8.48. The NMR spectrum of compound (3) demonstrated the deshielding of the proton H-7, which was coplanar with, and six atoms removed from, the carbonyl oxygen at C-6. H-7 of the compound (3) resonated at δ8.52.

If the product from the 2-aminopyridine reaction possessed the structure (II'), its the NMR spectrum would be expected to show the resonances of <u>two</u> protons at very low field; namely, H-11 which would be attached to the partially positively changed N-11 and H-7. The proton H-7 of compound (11') would be expected to resonate considerably below δ9.00, as not only would it bear a spatial relationship to the C-6 carbonyl group which was identical to that found with H-7 of compound (3) and so be very deshielded, but <u>in addition</u>, H-7 of compound (11') would be analogous to H-2'of the simple pyridinium salts and would be expected to experience similar deshielding influences as felt by H-2' of these pyridinium salts.

In fact the NMR spectrum of the aminopyridine product showed only <u>one</u> proton below δ8.33, this proton being the N-<u>H</u> of (11). This fact unequivocally eliminated (11') as the possible structure of the product of the 2-aminopyridine reaction.



11'



1 R = 1-Naphthoxyl

2 R = Br

5 R = Pyridinium Bromide

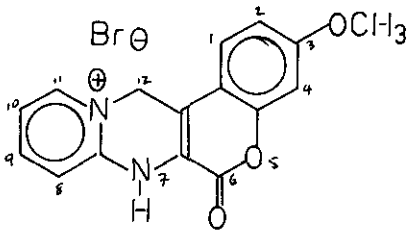
6 R = 2-Methylpyridinium Bromide

7 R = 3-Methylpyridinium Bromide

8 R = 3,5-Dimethylpyridinium Bromide

9 R = 3-Aminocarbonylpyridinium Bromide

10 R = Quinolinium Bromide



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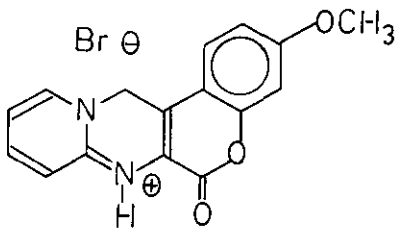

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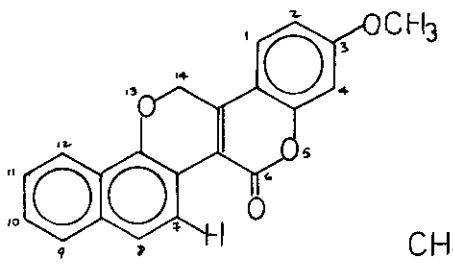

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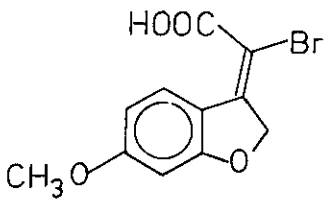

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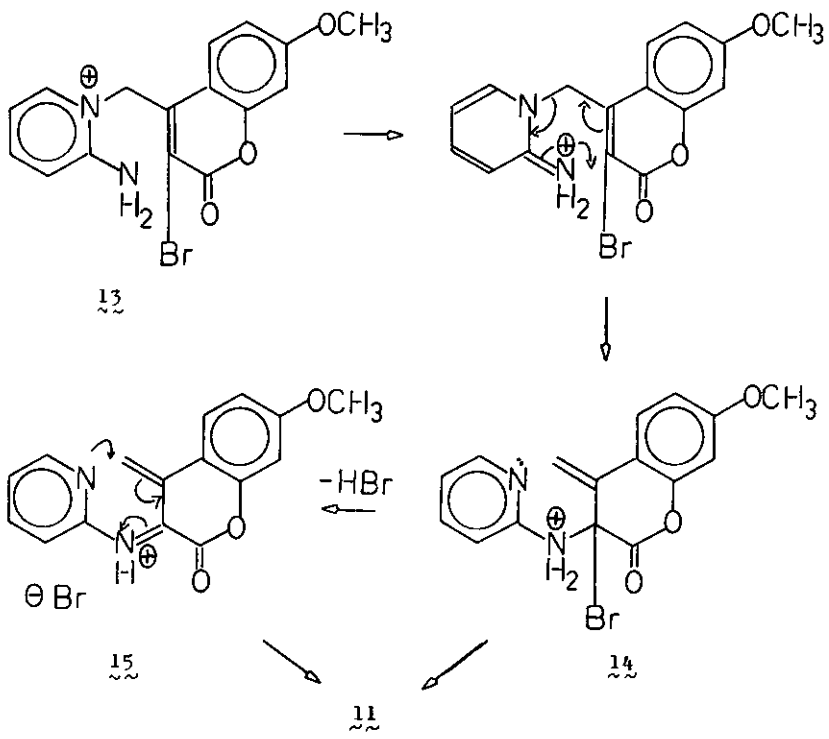
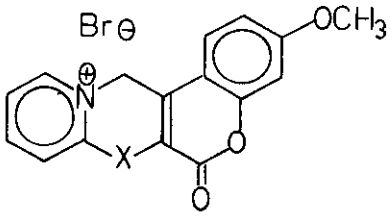
COMPOUND (m.p.)	NMR (δ)						ν_{max} (cm^{-1})
	CH_2	H-5	H-6	H-8	O-CH_3	OTHER RESONANCES	
1 (171-3°)[a]	5.53	7.78, d J=9.5	6.83, dd J=9.5, 1.0	6.83	3.83	6.67 - 8.20 (10 H, m)	1731, 1625, 1604
2 (182-4°)[a]	4.76	7.72, d J=9.5	6.93, dd J=8.5, 1.0	6.87	3.90		1724, 1621, 1601
5 (243-5°)[b]	6.38	7.85, d J=9.0	7.12, dd J=9.0, 1.5	7.03	3.97	H-2', H-6': 8.97, d, J=6.0; H-4': 8.62 t, J=6.0; H-3', H-5': 8.13, t, J=6.0	1725, 1610, 1595
6 (228-30°)[b]	6.12	7.72, d J=9.0	7.07	7.00	3.95	C-CH_3: 3.20; 7.72-8.60 (4H, m)	1725, 1620, 1600
7 (197-9°)[b]	6.35	7.88, d J=9.0	7.15, dd J=9.0, 1.5	7.07	4.00	C-CH_3: 2.65; H-2', H-6': 8.75; H-4': 8.43, d, J=8.0; H-5': 8.00, t, J=8.0	1710, 1611, 1591
8 (191-3°)[b]	6.25	7.82, d J=9.0	7.13, dd J=9.0, 1.5	7.00	3.97	2 x C-CH_3: 2.58; H-2', H-6': 8.48; H-4': 8.13	1725, 1617, 1585
9 (248-50°)[b]	6.43	7.90, d J=9.0	7.13, dd J=9.0, 1.0	7.03	3.97	H-2': 9.67; H-4', H-6': 9.03; H-5', NH_2: 7.58-8.42, m.	1720, 1676, 1618, 1595
10 (232-3°)[b]	6.62	7.65, d J=9.5	7.08, dd J=9.0, 1.0	7.08	3.97	7.82-8.92 (7H, m)	1712, 1615, 1594
17 (188-9°)[a]	5.60	7.73, d J=9.0	6.83, dd J=9.0, 1.5	6.75	3.85	H-3': 6.60, d, J=10.0; H-4', H-6': 7.30, m; H-5': 6.15, t, J=7.0	1719, 1661, 1621, 1601
	CH_2	H-1	H-2	H-4	O-CH_3	OTHER RESONANCES	
11 [250°(d)][b]	6.00		7.17	7.08	4.00	7.33-8.33 (5H, m); H-7: 9.67	1722, 1647, 1612, 1593
3 (212-5°)[a]	5.30	7.68, d J=9.0	6.78, dd J=9.0, 1.0	6.73	3.80	H-7: 8.52, d, J=8.5; H-12: 8.12, m; 7.17-7.87 (5H, m)	1724, 1620

a: $CDCl_3$ used as solvent; b: $CDCl_3$/Trifluroacetic acid (1:1) used as solvent;

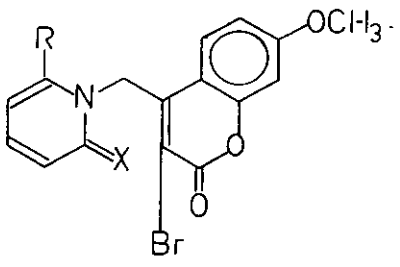


13 15 14 11

SCHEME I



16 X = O or CRR'



17 X = O, R = H

18 X = CH_2, R = H

whereas all the simple pyridinium salts showed λ_{max} 347 (log ε 4.19)in their UV spectra, (12) showed λ_{max} 329, 340, 392, 402 (inflex.), 449 (inflex.) and 470 (inflex.) (log ε 3.98, 3.98, 4.23, 4.21, 3.79, 3.50,respectively) which indicated that the resonance contribution of the canonical form (12) was considerable. Indeed, the signal for the methylene protons in the NMR spectrum of (12) appeared at δ 6.00, considerably upfield from that shown by the simple pyridinium salts, so indicating that the N-Me did not bear as large a partial positive charge as in the simple pyridinium salts.

Because of the low temperature at which the reaction proceeded (a 25% yield of the compound can be obtained by refluxing the reagents in CH_2Cl_2 for 70 hr) and the striking absence of an isolable (detectable) intermediate in the reaction mixture, the mechanism of formation of (11) was of interest. If (13) is regarded as an obligatory intermediate in this reaction the cyclisation must proceed, not by nucleophilic attack at the electron rich C-3 of the coumarin, but by a Claisen rearrangement process. The Claisen rearrangement of neutral (uncharged) aromatic compounds, and the amino-Claisen rearrangements, usually require a high temperature,~200°C, in order to proceed at a reasonable rate[4]. Acid catalysis is known to greatly accelerate these reactions however and to permit them to proceed at reasonably low temperatures[5]. This consideration prompted the proposal of the mechanism shown in scheme 1. Whether the intermediate (14) is transformed directly into (11), or first to (15), is not known, but (15) is a plausible intermediate and must be considered.

This success prompted us to attempt to prepare a series of compounds like (16). The reaction of the dibromide (2), with the sodium salt of 2-hydroxypyridine, in DMF at -10°C for 15 min , produced (17) in 40% yield. The compound (17) did not cyclise in refluxing p-xylene, and was recovered, but was transformed to a complex mixture in refluxing N,N-diethylaniline.

The salt (6) is potentially convertible to the compound (18) by base[3] and this might be expected to cyclise in the desired fashion. In fact, (6) was stable in refluxing 2-methylpyridine, but gave a complex mixture of products on refluxing in N,N-diethylaniline.

It might well be that the high electron density on the atom (group) X of (17) and (18) prohibited the molecule assuming the desired conformation shown in (17) and (18), because of repulsion with the electron rich C-3 (or-Br).

These pyridinium salts are extremely sensitive to aqueous base and are reduced by zinc in acetic acid quantitatively to 3-bromo-4-methyl-7-methoxycoumarin.

We intend to introduce a group R into the molecules (17) and (18) in order to force these molecules into the desired conformation for cyclisation. Our results will be reported in a forthcoming full paper.

The compounds (5) and (10) have stimulated much interest in a pharmacological screening programme[6], because, in addition to their anticoagulant properties, they can also precipitatean excitement in rats, before causing their deaths. The quinolinium (10) salt is more toxic than the pyridinium salt (5), while the salt (9) is completely inactive.

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6. This programme is being conducted along with Dr. R. Bourne and Dr. M. West, Department of Pharmacology, University of the West Indies, Kingston 7, Jamaica.

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