BENZOPYRANO[3,4-b]INDOLES AND QUINOLINES

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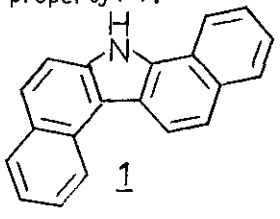
Various benzopyranoindoles and benzopyranoquinolines derived from chroman-3-one have been synthesized with the aim of including them in structure activity studies of the carcinogenic potency in the carbazole and acridine series. From a physicochemical point of view, the structure of the isolated compounds is discussed in regard to some of their NMR properties.

The most recent studies on chemical carcinogenesis have demonstrated the importance of the "non-K-region"(1) in the mechanism of hydrocarbon induced carcinogenesis(2-4). However, our studies on a great number of carbazole and acridine derivatives(5-8) appear to show that the "K-region" is a very important site for the appearance of carcinogenicity.

It is well-known that both dibenzo-carbazoles 1 and 2 are powerful carcinogens, particularly 7H-dibenzo[c,g]carbazole 2(9,10), whereas, in the benzacridine series, only the benz[c]acridine derivatives 3 have such activity, provided that R=CH_3. Very few compounds of the benz[a]acridine series 4 have such property(8).



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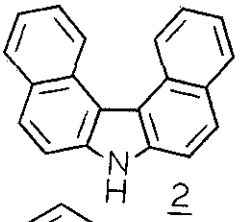

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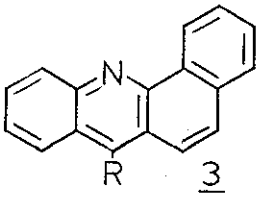
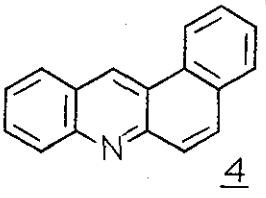


R 3



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During the past few years we have studied the variation of carcinogenic potency of some compounds related to benzo and dibenzocarbazoles and to benzacridines in which we have replaced the "K-region" by a second heteroatom such as $-S-CH_2-$ or $-O-CH_2-$[5,6,11]. In the benzo and dibenzo carbazoles series, such modifications strongly enhance the carcinogenic potency, as in the case of 6,13-dihydro[1]benzothiopyrano (or benzopyrano) [4,3-b]benzo[e]indoles 5 (X=S or O)[5,12], except for 6,7 dihydro[1]benzothiopyrano[3,4-b]benzo[e] - indole 6[11], a new sulphur analogue of the very potent 7H-dibenzo[c,g]carbazole 2, which has only weak activity by subcutaneous route[12].

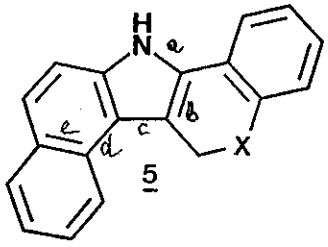
By contrast, in benz[c]acridine family, this modification decreased the carcinogenic potency (7 is less active than 3; $R=CH_3$) but fluorination of such molecules on the 4 position (7, $R_2=F$) strongly enhanced this property even when $R_1=H$ (8 and 9 are stronger carcinogens than 7)[6].

We now describe some benzopyranoindoles and benzopyranoquinolines obtained from chroman-3-one 11[13] and needed for further biological experiments.

The Fisher indole synthesis (A) of some arylhydrazones of 11 has led us to the benzopyranoindoles 12-18 whereas the Friendländer-Kempter reaction (B) has furnished the benz[a]acridine analogues 19 and 20 - Scheme 1 -.

Indoles were readily obtained from chroman-3-one (0.02 moles) by boiling 5 minutes with 0.02 moles of the appropriate arylhydrazine and a few drops of acetic acid. The brownish mixture was then heated 5 min. in boiling acetic acid saturated with hydrogen chloride. After cooling and dilution with water, the precipitate was chromatographed on silica gel (elution with cyclohexane/benzene 1:1). The yields were about 80%.

Quinolines were synthesized by heating (140°, 30 min.) a mixture of 11 (0.015 moles) and o-aminoacetophenone hydrochloride or o-aminobenzaldehyde



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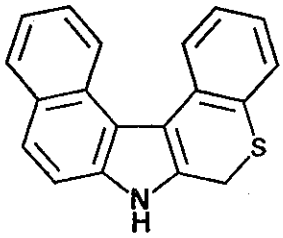

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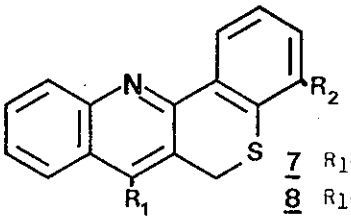
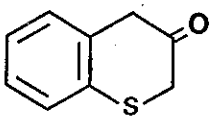


7 R_1=CH_3; R_2=H
8 R_1=CH_3; R_2=F
9 R_1=H ; R_2=F



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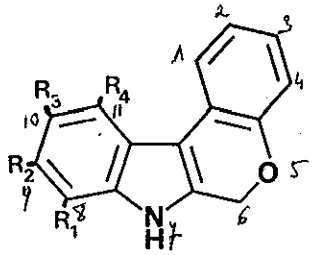
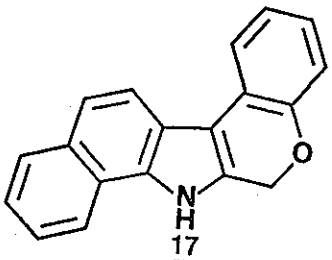


12 R_1=R_2=R_3=R_4=H
13 R_1=CH_3; R_2=R_3=R_4=H
14 R_2=CH_3; R_1=R_3=R_4=H
15 R_3=CH_3; R_1=R_2=R_4=H
16 R_4=CH_3; R_1=R_2=R_3=H



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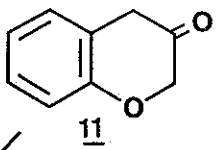
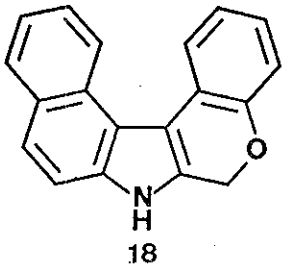


11



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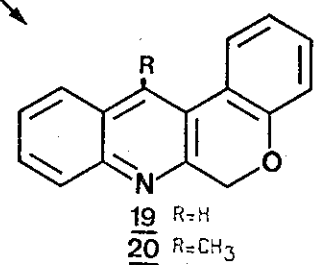


19 R=H
20 R=CH_3

Scheme 1

hydrochloride (0,01 mole). After treatment with aqueous ammonia, the mixture was extracted with chloroform (3x50ml) and the organic phase was washed three times with dilute aqueous sodium hydroxide, dried over Na_2SO_4 and evaporated under vacuum. The yellowish solid was then chromatographed on silica gel (elution with benzene) to yield the quinolines with a recovery of 65% (19) to 75% (20).

The 6,7-dihydrobenzopyrano[3,4-b]indole system has been already described, first by King et al.[14], as an oxo hydroxy derivative and secondly as 12 by Chatterjea et al.[15], also starting from chroman-3-one but as an ambiguous darkish product of m.p. 206-208° (m.p. of 12 is 156° in the present study). This heterocyclic system is of interest not only as a complement to our studies on chemical carcinogenesis but also as a possible natural substance since various benzypyranoindoles (i.e. lycorenan) are minor but common constituents of some amaryllidaceae. To our knowledge, the 6H-benzopyrano[3,4-b]quinoline nucleus has not yet been reported.

The cyclization of the m-tolylhydrazone of 11 give a 1:1 mixture of indoles 14 and 16 (measured by NMR) which could not be separated since all these methylated indoles 13-16 are very sensitive to light and air, darkening rapidly, giving numerous spots on thin layer chromatograms. For the same reasons, compounds 13 and 15 have not given microanalytical results consistent with the calculated values.

The NMR spectra (60 MHz) of these compounds are very similar to those of the sulphur analogues[11] and are consistent with the above structures (table 1). The deshielding of the methylene protons is also in good agreement with structures 12-20. In effect, if the cyclization occurs at the α position of the heteroatom to furnish structures such as 21, these two protons should have a low chemical shift as for 4H-[1]benzopyran 22 ($\delta_{3,24}$)[16], whereas for our molecules this value is closer to that found for 2H-[1]benzopyrano 23 ($\delta_{4,53}$)[17].

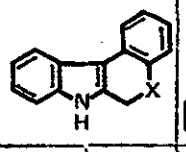
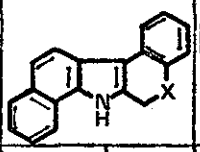
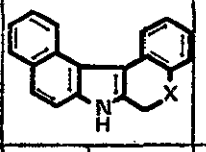
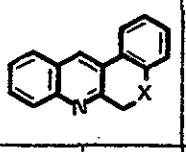
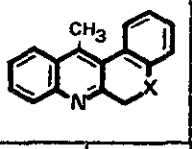
											13	14 + 16	15
X=	S	O	S	O*	S	O	S	O	S	O			
CH_2	4.07	5.23	4.18	5.48	3.94	5.06	4.21	5.33	4.08	5.1	5.3	5 5.21	5.2
CH_3	-	-	-	-	-	-	-	-	2.87	2.77	2.38	2.40 2.80	2.46
H_1	7.93	7.8	8.0	7.95	8.14	8.05	7.89	7.96	7.61	-	7.7	-	7.63
H_2	-	-	7.30	-	7.31	-	7.30	-	7.30	-	-	-	-
H_3	7.08	-	7.12	-	7.16	-	7.30	-	7.30	-	-	-	-
H_4	-	-	8.0	7.95	7.57	-	7.50	-	7.61	-	-	-	-
H_8	-	-	-	-	7.46	-	8.06	-	8.05	7.9	-	-	-
H_9	-	-	-	-	7.63	-	7.71	-	7.73	-	-	-	-
H_{10}	-	-	-	-	7.92	7.88(?)	7.53	-	7.57	-	-	-	-
H_{11}	8.02	7.8	8.0	8.11	7.42	-	7.91	-	8.10	7.9	7.7	-	7.65
H_{12}	-	-	7.63	-	7.45	-	8.39	8.26	-	-	-	-	-
H_{13}	-	-	8.12	8.04	8.71	8.76	-	-	-	-	-	-	-
NH	-	7.8	8.72 11.36*	10.96	8.34	8.05	-	-	-	-	7.7	7.5	7.63
Other Aromatics	7.18-7.48	6.88-7.36	7.36-7.64	7.03-7.86	-	6.96-7.7	-	6.86-8	-	6.83-7.7	6.8-7.16	6.83-7.93	6.8 7.2

Table 1

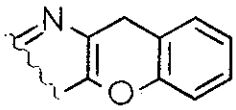
The NMR values(ppM, δ_{tms}=0)of sulphur compounds are reported in ref.11(100MHz,Varian XL 100) Spectra of compounds 12 - 20 have been recorded on a Varian T 60 spectrometer at 60MHz.Spectra have been measured in deuteriochloroform or in deuterioacetone(*).

The physical characteristics of compounds 12-20 are reported in table 2. Except for 13 and 15 (for which C% is about - 1% of the theoretical value) all this molecules have given consistent microanalytical results (±0,3%) for C, H and N.

Table 2

Physical constants of compounds 12-20

Compounds	Crystalline shape color(solvent)	m.p.
6,7-dihydro[1]benzopyrano[3,4-b]indole 12	colorless needles (C_6H_{12})	156°
8-methyl-6,7-dihydro[1]benzopyrano[3,4-b]-indole 13	colorless needles (CH_3OH/H_2O)	152°
9-methyl-6,7-dihydro[1]benzopyrano[3,4-b]-indole 14 and	light yellow	137° to
11-methyl-6,7-dihydro[1]benzopyrano[3,4-b)-indole 16	crystals(CH_3OH/H_2O)	140°
10-methyl-6,7-dihydro[1]benzopyrano[3,4-b]-indole 15	light yellow needles (C_6H_{12})	141°
6,7-dihydro[1]benzopyrano[3,4-b]benzo[g]-indole 17	colorless prismatic needles($CH_3C_6H_5$)	238°
6,7-dihydro[1]benzopyrano[3,4-b]benzo[e]-indole 18	light yellow microcrystals (C_6H_6/C_6H_{12})	159°
6H[1]benzopyrano[3,4-b]quinoline 19	thin colorless needles (CH_3OH/H_2O)	109°
12-methyl-6H[1]benzopyrano[3,4-b]quinoline 20	short colorless needles (CH_3OH)	92°



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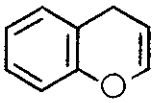

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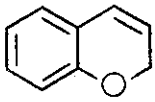

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The carcinogenic potency by subcutaneous injection in mice (strain XVII nc/Z of the Radium Institute, Dr. F. E. Zajdela) is now under investigation. Results are at present only preliminary since such tests normally require at least 1 year for completion, but it now appears that such modifications of the K-region enhanced carcinogenicity in the 13H-dibenzocarbazole series and could have the same property in the benz[c]acridine family (i.e. the fluorinated derivatives of 7). Nevertheless benzothiopyranoindole 6 derived from 7H-dibenzo-[c,g]carbazole 2 is only a weak carcinogen(12) and it would be interesting to see, for example, if benzopyrano[3,4-b]benzo[e]indole 18 has a weaker or a stronger potency than the parent dibenzocarbazole 2.

A more complete discussion of the structure-activity relationship for both benzopyrano and benzothiopyrano quinoline and indole series will be published with all biological results obtained with these compounds(6a), in the light of the more recent studies (i.e. metabolic activation, DNA interaction, carcinogenic potencies) presently in progess in our laboratory with the parents benzo and dibenzocarbazoles and benzacridines.

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