

SYNTHESIS AND SPECTROSCOPIC CHARACTERIZATION OF A SERIES OF NEW ANTHRALIN DERIVATIVES AND THEIR CORRESPONDING SPIRO-HETERO-CYCLES.

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ABSTRACT

Several 10-substituted anthralins were readily prepared. Their oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gave the corresponding novel heteroatomic systems.

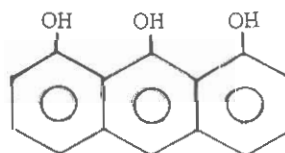
All derivatives were fully characterized by IR, Mass and  $^1\text{H}$ NMR Spectroscopy.

INTRODUCTION

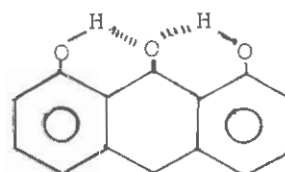
Since the first synthesis of anthralin, undertaken by Galewsky[1] in 1916, it was always believed that anthralin should be considered as 1,8,9-trihydroxy anthracene (1). However, only relatively recently the anthrone nature of the compound was elucidated, by Segal et al[2] who showed that anthralin existed in Keto form(2) in the crystalline state as well as in solution in chloroform or acetone.

The NMR data that Segal et al present leave no doubt about the structure: a two proton singlet at

$\delta$ 4.40 indicated the presence of two methylene protons and a low field two protons singlet at  $\delta$ 12.2 which disappears with  $\text{D}_2\text{O}$  is indicative of two internally hydrogenbonded hydroxyl groups.



(1)



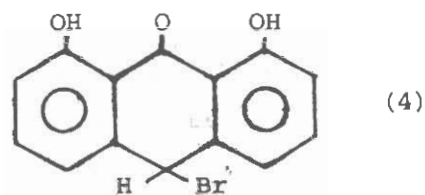
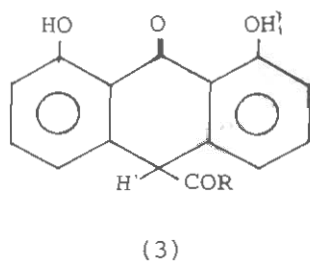
(2)

The anthrone system(2) is in tautomeric equilibrium with anthracene system(1) in solution, the position of this equilibrium depending on the polarity of the solvent. In relatively non-polar solvents, e.g. chloroform, the anthrone system is present exclusively, whereas in more polar solvents, e.g. DMF, there is a measurable contribution from the anthracene form[3].

On a laboratory scale anthralin is normally prepared by reduction of 1,8-dihydroxy-9,10-anthraquinone with dissolving metal-acid systems, typically tin and acetic acid[4] but on an industrial scale, catalytic hydrogenation is preferred[5].

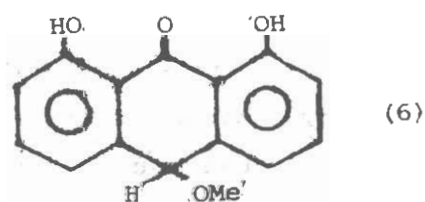
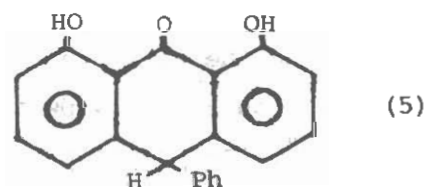
Mustakallio[6] has made a series of 10-acyl analogues(3; R=Et, n-Pr and n-Bu) by treating anthralin in benzene with a trace of pyridine followed the relevant acid chloride at 80 C, with yields of 20-45%.

The preparation of mono-halogenated species has been reported[7] using carbon disulphide, bromine and heat to give the C-10 monobromo derivative(4). Which can be taken to the C-10 dibromo compound by repeating the bromination under UV irradiation.

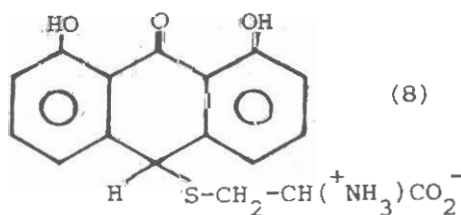
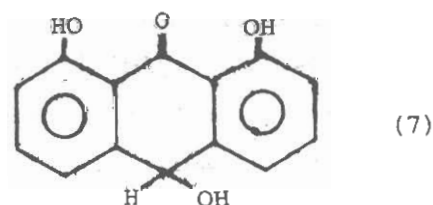


A number of reactions of 10-bromoanthralin(4) have been reported. It will undergo a Friedel-Crafts arylation with benzene in the presence of aluminium trichloride[7], giving 10-phenylanthralin(5) with a 15% yield.

10-Bromo-anthralin is converted quantitatively into 10-methoxy anthralin(6) by reaction with methanol[8].



Refluxing in 50% aqueous acetone resulted in 79% conversion to 10-hydroxy anthralin(7) which gave cysteinyl anthralin(8) with cysteine and hydrochloric acid[9].



Here we report synthesis of new 10-mono substituted anthralins by reaction of the bromo-compound with the appropriate nucleophiles, which will allow the cyclization of them to the corresponding new heteroatomic systems.

## EXPERIMENTAL

Improved preparation of 10-bromo-1,8-dihydroxy-9-anthrone(4)

1,8-dihydroxy-9-anthrone ( 17.3 g) was dissolved in  $CS_2$  (1.25 l ) by heating and the solution was treated dropwise with  $Br_2$  (18.4 g) with stirring at  $50^\circ C$ . The solution was left stirring at that temperature overnight, then cooled to room temperature and concentrated to 1/10 of its volume by removal of the solvent under reduced pressure. The yellow precipitate was filtered off, dried and then recrystallized from petroleum ether (b.p  $40-60^\circ C$ )/ $CHCl_3$  (1:1) to give 10-bromo-1,8-dihydroxy-9-anthrone (18.1 g, 77.5%). m.p= $149-151^\circ C$  (decomp.) lit[7]. m.p= $148-150^\circ C$  (decomp.), 52%.

10-(2'-Hydroxyethylthio)-1,8-dihydroxy-9-anthrone(9; R=OH; n=2).

10-Bromo-1,8-dihydroxy-9-anthrone (100 mg) was dissolved in dichloromethane (7 ml), and 2-mercaptoethanol (0.03 ml) was added. The solution was stirred at room temperature for 7 hrs, during which time the light brown solution became pale green. Removal of the solvent and recrystallization of

the residue from hexane / chloroform (5:1) gave the product (89 mg, 90%) as pale yellow needles, m.p= $146-147^\circ C$ . (Found C, 63.1; H, 4.75; S, 10.7%.  $C_{16}H_{14}O_4S$  requires C, 63.55; H, 4.7; S, 10.6%).

It had  $\delta$  ( $CDCl_3$ , 220 MHz) 1.68 (bs, 2'-OH), 2.42 (t,  $J=6$ ,  $1 \times CH_2$ ), 3.38 (t,  $J=6$ ,  $1 \times CH_2$ ), 5.26 (s, H-10), 6.95 (d,  $J=8.5$ , H-2+H-7), 7.14 (d,  $J=7.8$ , H-4+H-5) 7.53 (t,  $J=8$ , H-3+H-6), 12.11 (s, 1-OH+8-OH);  $\nu_{max}$  (film) 3364b, 1627s, 1598 vs, 1481s, 1448 s, 1365 m, 1334 m, 1272 vs, 1214 vs, 1155 s, 752 vs  $cm^{-1}$ ; and m/e EI 302 ( $M^+$ , 7.5), 227 (6.7), 226 (48), 225 (100%), 198 (9.2), 197 (35), 152 (6.5), 151 (11.7), 78 (6.9), 76 (6.5), 48 (11), 47 (15.6), 46 (4).

10-(2' Mercaptoethylthio)-1,8-dihydroxy-9-anthrone(9, R=SH; n=2).

10-Bromo-1,8-dihydroxy-9-anthrone (75 mg) was dissolved in dichloromethane (5 ml), and 1,2-ethanedithiol (0.05, 1.1 eq) was added. The solution was stirred at room temperature for 6 hours.

Removal of the solvent gave a pale green solid (80 mg), which was recrystallized from ethanol to give the product as pale yellow needles (67 mg, 86%) m.p= $133-134^\circ C$ . (Found C, 59.7; H, 4.4; S, 19.6%;  $M=318.0369$   $C_{16}H_{14}O_3S_2$  requires  $M=318.0384$ ; C, 60.3; H, 4.4; S, 20.1%).

It had  $\delta$  ( $CDCl_3$ , 220 MHz) 1.49 (t,  $J=8.2$ , SH), 2.30 (dt,  $J_1=8.2$ ,  $J_2=7.5$ ,  $CH_2SH$ ), 2.46 (t,  $J=7.5$ ,  $SCH_2$ ), 5.2 (s, H-10), 6.97 (d,  $J=8.5$ , H-2+H-7), 7.13 (d,  $J=7.8$ , H-4 + H-5), 7.54 (t,  $J=7.8$ , H-3+H-6), 12.12 (s,

1-OH + 8-OH);  $\nu_{\max}$  (film) 3031b, 2652b, 1628s, 1597vs, 1483s, 1447s, 1365m, 1274vs, 1205vs, 1158s, 761vs,  $\text{cm}^{-1}$ ; m/e EI 318 ( $\text{M}^+$ , 6), 256 (5.3), 227 (8.3), 226 (58.2), 225 (100%), 198 (11.4), 197 (39.8), 169 (5.3), 152 (8.3), 151 (15.2), 141 (8.4), 61 (12.7), 60 (10.8), 49 (19), 47 (14).

1,8-Dihydroxy-9,10-anthracene-1,8-dione-10-ethylenehemithioketal (11; X=O).

10-(2'-Hydroxyethylthio)-1,8-dihydroxy-9-anthrone (30.2 mg) was dissolved in dichloromethane (6 ml), and the solution was purged with nitrogen for 10 min., 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (22.7 mg) was then added. The solution was stirred at room temperature for 15 hours under nitrogen, during which time a white precipitate (2,3-dichloro-5,6-dicyano-1,4-hydroquinone) was formed. Filtration and removal of the solvent gave an orange brown solid, which was recrystallized from hexane to give the desired product (25 mg, 75%) as orange needles, m.p.=165-166°C. (Found C, 64.2; H, 4.05; S, 10.7  $\text{C}_{16}\text{H}_{12}\text{O}_4\text{S}$  requires C, 64; H, 4; S, 10.7%).

It had  $\delta$  ( $\text{CDCl}_3$ , 220 MHz) 3.37 (t,  $\underline{J}=5.7$ ,  $\text{OCH}_2$ ), 4.79 (t,  $\underline{J}=5.7$ ,  $\text{SCH}_2$ ), 6.96 (dd,  $\underline{J}_1=8.5$ ,  $\underline{J}_2=1.2$ , H-1 + H-7 or H-4+H-5), 7.16 (dd,  $\underline{J}_1=8$ ,  $\underline{J}_2=1.2$ , H-4+H-5 or H-2 + H-7), 7.52 (t,  $\underline{J}=8.2$ , H-3+H-6), 12.01 (s, 1-OH+8-OH);  $\nu_{\max}$  (film) 3072b, 1631s, 1608vs, 1601vs, 1573m, 1476s, 1265vs, 1215s, 1164s, 745m  $\text{cm}^{-1}$  and m/e EI 300 ( $\text{M}^+$ , 8.5), 241 (16.2), 240 (100%), 223 (5.2),

212 (16.5), 184 (13.8), 138 (6.4).

1,8-Dihydroxy-9,10-anthracene-dione-10-ethylenethioketal (11; X=S).

10-(2'-Mercaptoethylthio)-1,8-dihydroxy-9-anthrone (48.7 mg) was dissolved in dichloromethane (10 ml), and the solution was purged with nitrogen for 10 min., 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (34.05 mg) was then added. The solution was stirred at room temperature for 17 hrs under nitrogen, during which time a white precipitate of 2,3-dichloro-5,6-dicyano-1,4-hydroquinone was formed. Filtration and removal of solvent gave a dark green solid, which was extracted with hot hexane (20 ml).

Removal of the solvent gave a yellow solid (35 mg), which was recrystallized from hexane to give 1,8-dihydroxy-9,10-anthracenedione-10-ethylenethioketal (25 mg, 52%) as yellow needles, m.p.=197-199°C. (Found C, 60.65; H, 3.8; S, 20.5;  $\text{C}_{16}\text{H}_{12}\text{O}_3\text{S}_2$  requires C, 60.7; H, 3.8; S, 20.3%).

It had  $\delta$  ( $\text{CDCl}_3$ , 220 MHz) 3.74 (s, 2XCH<sub>2</sub>), 6.94 (dd,  $\underline{J}_1=8.2$ ,  $\underline{J}_2=1.1$ , H-2+H-7 or H-4+H-5), 7.51 (t,  $\underline{J}=8.2$ , H-3+H-6), 7.72 (dd,  $\underline{J}_1=7.9$ ,  $\underline{J}_2=1.1$ , H-4+H-5 or H-2+H-7), 12.57 (s, 1-OH+8-OH);  $\nu_{\max}$  (film) 2850b, 1631vs, 1596vs, 1570m, 1478s, 1441s, 1296s, 1274s, 1256s, 1208s, 1156m, 849sh, 796sh, 750vs, 718s  $\text{cm}^{-1}$ ; and m/e EI 316 ( $\text{M}^+$ , 100%), 289 (15.7), 288 (64.9), 287 (65.6), 271 (21), 257 (16.9), 256 (78.1), 228 (17.1), 226 (8.3), 182 (5.3), 171 (7.9), 139 (6.3).

10-(Methoxycarbonylmethylthio)-1,8-dihydroxy-9-anthrone (10; R=Me, n=1).

10-Bromo-1,8-dihydroxy-9-anthrone (100 mg) was dissolved in dichloromethane (7 ml), and methylthioglycolate (0.03 ml) was added. The red-brown solution became yellow-green by addition of thiol. The solution was stirred at room temperature for 4 hrs. Removal of the solvent gave a pale green solid (110 mg), which was recrystallized from hexane to give 10-(methoxycarbonylmethylthio)-1,8-dihydroxy-9-anthrone (92 mg, 85%) as yellow needles, m.p.=120-122°C (decomp.) (Found C, 61.9; H, 4.3; S, 9.5.  $C_{17}H_{14}O_5S$  requires C, 61.8; H, 4.3; S, 9.7%).

It had  $\delta$  (CDCl<sub>3</sub>, 220 MHz) 2.99 (s, SCH<sub>2</sub>), 3.59 (s, OMe), 5.35 (s, H-10), 6.95 (d,  $\underline{J}$ =8.5, H-2+H-7), 7.09 (d,  $\underline{J}$ =7.5, H-4+H-5), 7.51 (t,  $\underline{J}$ =8, H-3+H-6), 12.08 (s, 1-OH+8-OH);  $\nu_{max}$  (film) 3040 b, 1736 s, 1612 vs, 1601 vs, 1484 s, 1448 vs, 1369 m, 1278 vs, 1222 s, 1166 m, 741 s cm<sup>-1</sup>; and m/e EI 330 (M<sup>+</sup>, 10.3), 256 (7.6), 226 (41.4), 225 (100%), 197 (30.5), 169 (3.7), 151 (10.7), 106 (12.3).

10-(Carboxymethylthio)-1,8-dihydroxy-9-anthrone (10; R=H; n=1).

(a) 10-Bromo-1,8-dihydroxy-9-anthrone (305 mg) was dissolved in dichloromethane (10 ml), and mercaptoacetic acid (0.07 ml) was added. The solution was stirred at room temperature for 3 days, during which time a yellow precipitate was formed, which

was filtered off, recrystallized from absolute ethanol to give the product (237 mg, 75%) as yellow needles, m.p.=151-152°C. (Found C, 60.9; H, 3.8; S, 10.1%;  $M=316.0410$   $C_{16}H_{12}O_5S$  requires C, 60.75; H, 3.8; S, 10.1%;  $M=316.0405$ ).

It had  $\delta$  (CDCl<sub>3</sub>, 220 MHz) 3.1 (s, SCH<sub>2</sub>), 5.42 (s, H-10), 7.01 (d,  $\underline{J}$ =8.5, H-2+H-7), 7.14 (d,  $\underline{J}$ =7.5, H-4+H-5); 7.57 (t,  $\underline{J}$ =8, H-3+H-6), 12.12 (s, 1-OH+8-OH);  $\nu_{max}$  (film) 2960 b, 1702 s, 1615 s, 1602 vs, 1446 s, 1274 vs, 1218 vs, 1185 s, 919 m, 728 vs cm<sup>-1</sup>; and m/e EI 316 (M<sup>+</sup>, 4.1), 256 (14), 241 (15), 240 (10.8), 238 (9.7), 227 (15.8), 226 (100%), 225 (82.2), 198 (16.5), 197 (47.4), 169 (6.6), 92 (28.2).

(b) A 5% sodium hydroxide solution (6 ml) was purged with nitrogen for 10 min., 10-(methoxycarbonylmethylthio)-1,8-dihydroxy-9-anthrone (60 mg) was then added. The solution was stirred at room temperature for 10 min., under nitrogen. The red-brown solution was then diluted with water (10 ml) and neutralized with 10% HCl to form the product as a pale brown precipitate, which was extracted with chloroform (15 ml). The organic layer was then washed with water, and dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of the solvent and recrystallization of the residue from ethanol gave 10-(carboxymethylthio)-1,8-dihydroxy-9-anthrone (41.3 mg, 72%) as yellow needles, m.p.=150-152°C.

The NMR, IR and Mass spectra was similar to those obtained by first method.

Cyclization of 10-(carboxymethylthio)-1,8-dihydroxy-9-anthrone (12).

10-(Carboxymethylthio)-1,8-dihydroxy-9-anthrone (55 mg) was dissolved in dichloromethane (8 ml), and the solution was purged with nitrogen for 10 min. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (39.5 mg) was then added, and the solution was stirred at room temperature overnight under nitrogen, during which time a white precipitate of 2,3-dichloro-5,6-dicyano-1,4-hydroquinone was formed. The solution was filtered and the solvent was removed from the filtrate to give a brown solid, which was extracted with chloroform (3 ml). Filtration and removal of the solvent was followed by extraction of the solid with hot hexane (3 x 2 ml) portions. Removal of the solvent and recrystallization from hexane gave the cyclized product (49 mg, 83%) as pale brown crystals mp = 140-155°C (decomp.). (Found  $M = 314.0276$   $C_{16}H_{10}O_5S$  requires  $M = 314.0249$ ).

It had  $\delta$  (CDCl<sub>3</sub>, 220 MHz) 4.05 (s, CH<sub>2</sub>), 7.02 (dd,  $J_1 = 8.5$ ,  $J_2 = 1$ , H-2 + H-7), 7.10 (dd,  $J_1 = 7.5$ ,  $J_2 = 1$ , H-4 + H-5), 7.57 (t,  $J = 8$ , H-3 + H-6), 11.98 (s, 1-OH + 8-OH);  $\nu_{max}$  (film) 3583 b, 2250 b, 1766 s, 1630 s, 1599 vs, 1573 s, 1445 vs, 1413 s, 1275 vs, 1190 vs, 1168 vs, 966 vs, 723 vs cm<sup>-1</sup>, and m/e EI 314 (M<sup>+</sup>, 14.3), 268 (11.1), 256 (10.8), 242 (14.4), 241 (100%), 240 (65.8), 238 (23.9), 228 (12.2), 212 (8.7), 184 (8.2).

## RESULTS AND DISCUSSION

The preparation of 10-bromo-1,8-dihydroxy-9-anthrone (4) has been reported [7] by refluxing the CS<sub>2</sub> solution of 1,8-dihydroxy-9-anthrone (2) with bromine in 52% yield. In an attempt to increase the yield, we noticed that there are appreciable amounts of bromo compounds arising from substitution of bromine on aromatic rings of 1,8-dihydroxy-9-anthrone (2). Therefore we chose a mild condition in order to decrease the chance of aromatic substitution reactions by bromine. We succeeded in increasing the yield to 77.5%.

Treatment of 10-bromo-1,8-dihydroxy-9-anthrone (4) with mercapto-alkanols and bismercapto-alkanes in dichloromethane at room temperature yields the corresponding 10-(hydroxyalkylthio) and 10-(mercapto-alkylthio)-anthralins (9; R=OH, SH respectively; n=1,2,3,...).

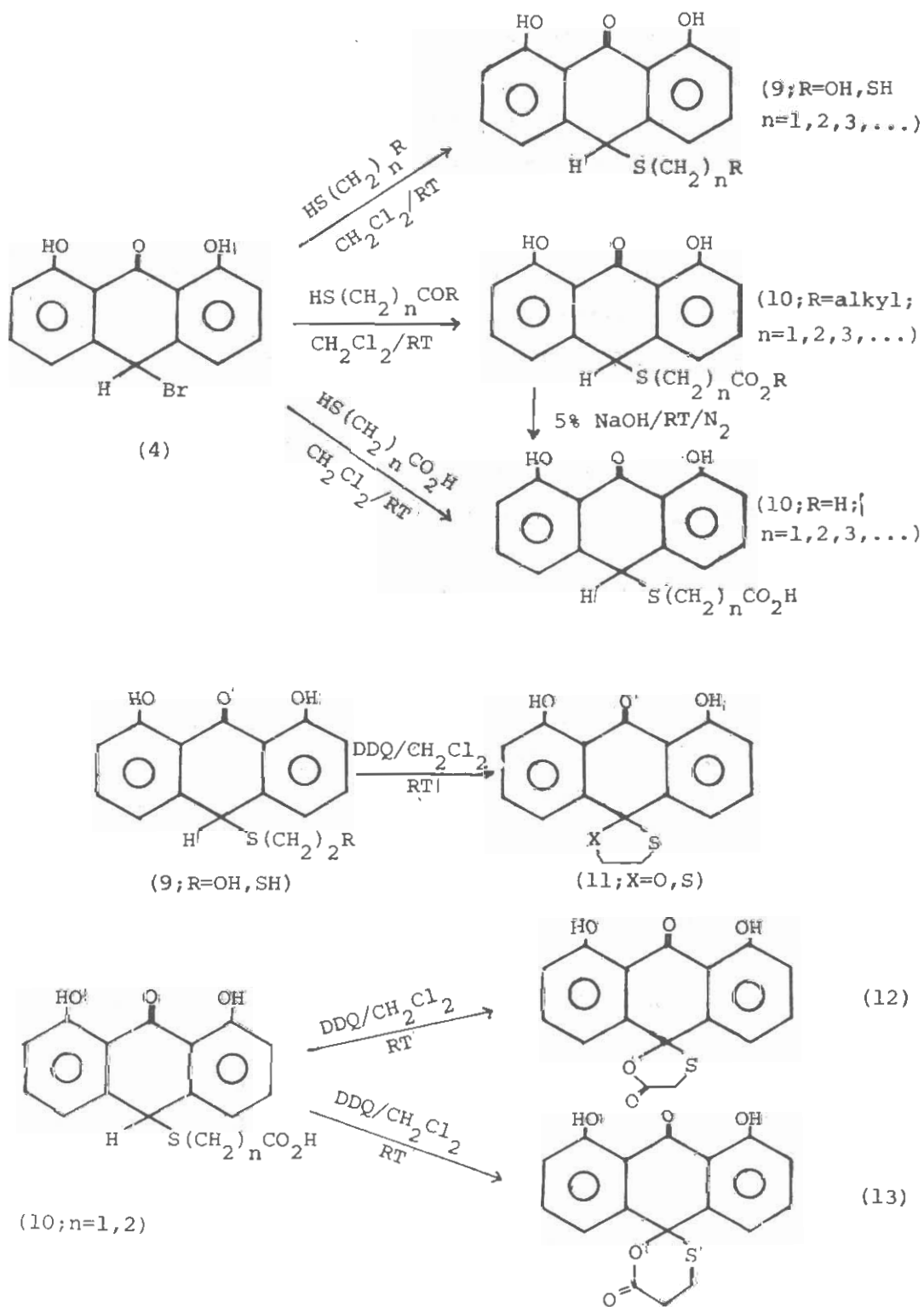
Analogously, when mercapto-alkanoic acids and their esters are employed in the reaction with 10-bromoanthralin (4), the corresponding 10-substituted anthralins (10; R=H, Alkyl; n=1,2,3,...) are obtained. The hydrolysis of the esters (10; R=Alkyl) provides an alternative route to the synthesis of acids (10; R=H).

Oxidation of the alcohols and thiols (9; R=OH, SH; n=2) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gave the corresponding ethylene hemi-

thioetal (11; X=O) and ethylenethioetal (11; X=S) respectively.

Similarly, oxidation of the carboxylic acids (10; R=H; n=1, 2) with

2,3-dichloro-5,6-dicyano-1,4-benzoquinone afforded the corresponding spiro-heterocycles (12; n=1) and (13; n=2) respectively.



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