TABLE I

ACID DISSOCIATION CONSTANTS

Compound	K_1	K_2	Melting point, °C. Lit.	Found
3-Nitrocatechol	2.2×10^{-7}	....	86	84
4-Nitrocatechol	1.3×10^{-7}	....	174	176
3,4-Dinitrocatechol	4.1×10^{-5}	5.4×10^{-9}	.....	147–148
Protocatechualdehyde[13]	4.4×10^{-8}	....	153–154	152
Protocatechualdoxime[14]	2.1×10^{-9}	....	157	156
Protocatechunitrile[14]	1.9×10^{-8}	....	156	156
3,4-Dihydroxybenzophenone	1.8×10^{-8}	....	145[6]	147–148
3-Methoxycatechol[15]	5.3×10^{-10}	....	.....	.....
3-Methylcatechol	5.3×10^{-10}	....	45, 47, 68	58–62

3,4-Dihydroxybenzophenone.[7]—Sixty-five grams of catechol dibenzoate, 185 ml. of nitrobenzene and 56 g. of anhydrous aluminum chloride were heated on the steam-bath for six hours. Ice and hydrochloric acid were then added, and, after the decomposition was complete, the nitrobenzene was steam distilled. The remaining solution was chilled and the solid material collected, dried and dissolved in 400 ml. of methanol. The resulting solution was saturated with anhydrous hydrogen chloride, and refluxed for 3.5 hours. Methanol was removed on the steam-bath, water was added to the residue, and the mixture was steam distilled to remove methyl benzoate. The residual mixture was boiled, enough water was introduced to effect solution, and decolorizing charcoal was added. After being boiled for several minutes, the solution was filtered and chilled. The product was collected and recrystallized four times from hot water. The resulting colorless crystalline material melted at 147–148°, and showed no melting point depression when mixed with an authentic specimen.[7] The substance appeared to contain a small amount of water of crystallization, which was not determined exactly.

3-Methylcatechol.—Orthovanillin was reduced[9] to 2-hydroxy-3-methoxytoluene in 45% yield. The latter was converted to 3-methylcatechol by the de Vries[10] demethylation procedure. The viscous oil obtained by distillation (130–139° (20 mm.)) of the crude product solidified on standing in the refrigerator. Vacuum sublimation at 0.8 mm. gave a white substance melting at 58–62°. The melting point has been reported[11] as 45, 47 and 68°. The compound gave a negative test for aldehydes with 2,4-dinitrophenylhydrazine.

Dissociation constants were obtained by potentiometric titration[12] of 10^{-3} *M* solutions of the substances in question with 0.02 *N* NaOH at 25° against a Beckman Model G *p*H meter. In each case the dissociation constant was an average of values calculated from data near the mid-point of the titration (Table I). The figures for the last three compounds are only approximate, since the titration curves were poor.

Spectrophotometric data were determined on the Beckman Model DU spectrophotometer at 2×10^{-4} *M* concentrations. From some of these data it was possible to calculate[16] dissociation constants in confirmation of the potentiometrically derived values. Thus, 4-nitrocatechol in 1.25 *M* HCl and in 0.04 *M* phosphate buffers, had extinction coefficients at 430 mμ of 200, 1.0×10^4 and 1.375×10^4 at *p*H's 0.11, 7.1 and 8.0, which yield a value of 1.8×10^{-7} for the apparent dissociation constant. The constant for 3-nitrocatechol has been derived similarly.[16]

Discussion

The dissociation constants of several of the present group of compounds have been determined in 40% dioxane–water by Corse and Ingraham[17] and show excellent qualitative agreement with the present results, especially when the difference in the dielectric constants of the media is considered. The present values for 3- and 4-nitrocatechol are significantly lower than those found by Gilbert, Laxton and Prideaux[1]; no evident reason can be shown for this discrepancy. The value found for protocatechualdehyde is of the same order of magnitude as that of Pauly, *et al.*[2]

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Substitution Reactions of 2- and 3-Methylthianaphthene

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The nitration of 2-methylthianaphthene gave a mononitro derivative in 48% yield. This was shown to be the 2-methyl-3-nitrothianaphthene by reduction and acetylation to 2-methyl-3-acetaminothianaphthene which was desulfurized by the useful technique of Mozingo[2] with Raney nickel catalyst to form 1-acetamino-1-phenylpropane. This last compound was identical with an authentic sample.

Bromination of 2-methylthianaphthene gave 2-methyl-3-bromothianaphthene in 88% yield. The structure of the product was proved by conversion through the Grignard reagent to 2-methyl-3-thianaphthenecarboxylic acid which was desulfurized as above to the known α-phenylbutyric acid. The 2-methyl-3-thianaphthenecarboxylic acid was identical in melting point with an acid obtained by Gaertner[3] and shown to be 2-methyl-3-thianaphthenecarboxylic acid by oxidation to 2,3-thianaphthenedicarboxylic acid.

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[2] R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, THIS JOURNAL, **65**, 1013 (1943).

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Metalation of 3-methylthianaphthene with *n*-butyllithium gave, subsequent to carbonation, 3-methyl-2-thianaphthenecarboxylic acid which was again proved by desulfurization to the known β-phenylbutyric acid. The same desulfurization product would have been obtained from metalation in the methyl group giving thianaphthene-3-acetic acid. However, this product has been prepared several times by different workers[4] and there is general agreement on its melting point of 109°, whereas our acid melts at 244.5–245°. Desulfurization therefore constitutes rigorous structure proof. 3-Methyl-2-thianaphthenecarboxylic acid is mentioned by Gaertner[5] as the product from the action of carbon dioxide on the Grignard reagent from 3-chloromethylthianaphthene.

Nitration of 3-methylthianaphthene gave 2-nitro-3-methylthianaphthene in 25% yield. The structure of this compound was indicated as above by reduction, acetylation, desulfurization and hydrolysis giving the known 2-phenyl-1-aminopropane. Here again the desulfurization technique does not distinguish nitration in the 2-position from substitution in the methyl group. This latter type of substitution is however highly unlikely under the conditions employed.

Acknowledgment.—The authors wish to express appreciation to the Research Corporation for financial aid in this work.

Experimental[6]

2-Methyl-3-bromothianaphthene.—A solution of 5 g. (0.034 mole) of 2-methylthianaphthene[7] in 30 ml. of chloroform was cooled in an ice-bath and a dilute solution of bromine in chloroform added dropwise with stirring until a permanent bromine color was obtained in the reaction mixture. Evaporation of the solvent gave a solid which was pressed between filter paper to produce 7.0 g. (88%) of 2-methyl-3-bromothianaphthene, m.p. 42–42.5°. Recrystallization from 95% ethanol did not change the melting point.

Anal. Calcd. for C_9H_7BrS: S, 14.11. Found: S, 14.19, 14.08.

The above bromo compound was converted to the Grignard reagent and carbonated in normal fashion except that formation of the Grignard reagent was initiated by use of considerable methyl iodide. There was obtained a 50% yield of 2-methyl-3-thianaphthenecarboxylic acid, m.p. 194–195°. Gaertner[3] reports m.p. 196°. Since this work had been completed before the appearance of Gaertner's work,[3] the acid was desulfurized to α-phenylbutyric acid, m.p. 33.5–35°, identical in melting point and mixed melting point with a commercial sample. The amide derivatives, m.p. 85–86°, were prepared from both samples and were also identical.

2-Methyl-3-nitrothianaphthene.—Ten grams (0.067 mole) of 2-methylthianaphthene dissolved in 65 ml. of acetic acid was cooled in an ice-bath while 30 ml. of concentrated nitric acid was added over a five-minute period. The reaction mixture was allowed to stand 30 minutes in the ice-bath and the precipitated solid removed by filtration, washed and dried to give 5.75 g. (48%) of nitro compound, m.p. 96–98°. Recrystallization from ethanol raised the melting point to 98–98.5°.

Anal. Calcd. for $C_9H_7NO_2S$: N, 7.25. Found: N, 7.25, 7.06.

2-Methyl-3-acetaminothianaphthene.—The nitro compound (5 g. or 0.028 mole) was reduced in acetic acid–acetic anhydride solvent with Raney nickel catalyst at 50 p.s.i. hydrogen pressure in the normal fashion. There was obtained 2.73 g. (51%) of 2-methyl-3-acetaminothianaphthene, m.p. 186–186.5°.

Anal. Calcd. for $C_{11}H_{11}NOS$: N, 6.82. Found: N, 6.89.

The acetamino compound was desulfurized[2] to N-acetyl-1-phenylpropylamine m.p. 77–78°, identical in melting point and mixed melting point with a sample prepared from the Leuckart reaction with propiophenone according to the method of Crossley and Moore.[8]

Metalation of 3-Methylthianaphthene.—To a solution of 6.6 g. (0.044 mole) of 3-methylthianaphthene[5] in 30 ml. of ether was added slowly with stirring an ethereal solution containing 0.045 mole of *n*-butyllithium, the concentration of which was determined by the procedure of Gilman and Haubein.[9] The mixture was stirred and heated to reflux for 45 minutes and carbonated with crushed solid carbon dioxide in the usual manner. After hydrolysis and addition of excess dilute hydrochloric acid the ether layer was separated and the aqueous layer extracted twice with ether. The combined ether solutions were extracted with 10% aqueous sodium hydroxide and the extracts acidified to precipitate 5.1 g. (65%) of 3-methyl-2-thianaphthenecarboxylic acid, m.p. 244–246°. Gaertner[5] reports m.p. 244–244.5°. Reprecipitation from aqueous base changed the melting point to 244.5–246°.

Anal. Calcd. for $C_{10}H_8O_2S$: S, 16.67; neut. equiv., 192. Found: S, 16.78; neut. equiv., 189.

3-Methyl-2-thianaphthenecarboxamide.—The amide was prepared from the above acid in usual fashion involving treatment with thionyl chloride and ammonia. There was obtained after crystallization from ethanol 2.1 g. (70%) of amide, m.p. 181–183°.

Anal. Calcd. for $C_{10}H_9NOS$: N, 7.33. Found: N, 7.55.

The amide was desulfurized[2] in 85% yield to β-phenylbutyramide, m.p. 105–106°. This amide has been reported to melt 105°[10] and 106–107°.[11] The β-phenylbutyramide was further characterized by nitration to its *p*-nitro derivative by the method of Schroeter.[12] The product melted at 164° which is in agreement with the literature value.[12]

2-Nitro-3-methylthianaphthene.—To a solution of 5 g. (0.034 mole) of 3-methylthianaphthene in 10 ml. of glacial acetic acid was added slowly with stirring a solution of 10 ml. of concentrated nitric acid and 10 ml. of acetic acid. The mixture was allowed to stand at room temperature for 15 hours and then poured into excess water. The precipitated solid was separated and crystallized from ethanol to give 1.65 g. (25%) of 2-nitro-3-methylthianaphthene, m.p. 148–149°.

Anal. Calcd. for $C_9H_7NO_2S$: N, 7.25. Found: N, 7.46.

2-Acetamino-3-methylthianaphthene.—Reduction of the nitro compound as described previously gave the acetamino compound, m.p. 182.5–183° in 55% yield.

Anal. Calcd. for $C_{11}H_{11}NOS$: N, 6.86. Found: N, 7.05.

Desulfurization[2] of a small amount of the acetamino compound followed by alkaline hydrolysis of the product gave 2-phenylpropylamine identified as its picrate, m.p. 184–185°, and its N-benzoyl derivative, m.p. 87.5–88°. Both of these derivatives have been prepared previously and the melting points reported approximately as above.[10,13,14]

N-Benzoyl-2-amino-3-methylthianaphthene.—This compound was prepared by reduction of 2-nitro-3-methylthianaphthene with Raney nickel at 50 p.s.i. hydrogen pressure. The reduction was carried out in ether solution and the ether evaporated followed by immediate treatment of the amine with benzoyl chloride in the presence of aqueous alkali. The product was crystallized once from ether and

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[4] For example see E. M. Crook and W. Davies, *J. Chem. Soc.*, 1698 (1937).

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[6] All melting points were taken on a Fisher-Johns apparatus and are uncorrected.

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once from ethanol to give the N-benzoyl-2-amino-3-methylthianaphthene melting at 167.5–170°.

Anal. Calcd. for $C_{16}H_{13}NOS$: N, 5.24. Found: N, 5.37.

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Studies on Carcinogenic Hydrocarbons: Dissociation Constants and Free Energies of Formation of Complexes with 2,4,7-Trinitrofluorenone[1]

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The reasons for the synthesis of appreciable amounts (about 20–25 g. of each) of all of the monomethyl-1,2-benzanthracenes and monomethylbenzo(c)phenanthrenes have been stated.[2] In an attempt to find some physical or chemical property of these hydrocarbons which might be correlated with their cancer producing activities, we have studied spectrophotometrically the equilibrium of the reaction between these hydrocarbons and 2,4,7-trinitrofluorenone[3] (TNF) in chloroform solution. From the data we have calculated the dissociation constants for the reaction

$$X{\cdot}TNF \rightleftharpoons X + TNF$$

We also have calculated the free energy of formation of the complexes X·TNF. The results of these calculations are summarized in Table I.

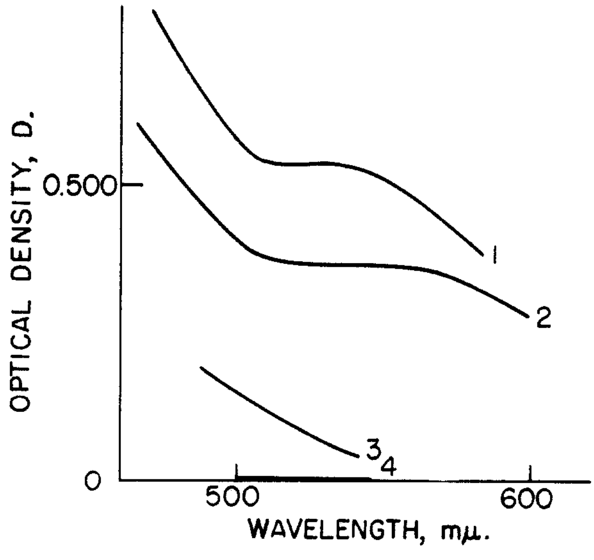

Fig. 1.—Typical absorption curves: initial concentrations in $CHCl_3$, 1, 6-methyl-1,2-benzanthracene 0.999 × 10^{-3} *M*, TNF 47.0 × 10^{-3} *M;* 2, 9-methyl-1,2-benzanthracene 1.045 × 10^{-3} *M*, TNF 46.7 × 10^{-3} *M;* 3, benzo(c)phenanthrene 0.750 × 10^{-3} *M*, TNF 38.4 × 10^{-3} *M;* 4, saturated solution of TNF.

TABLE I

DISSOCIATION CONSTANTS AND FREE ENERGIES OF FORMATION OF THE COMPLEXES OF 1,2-BENZANTHRACENES AND BENZO(C)-PHENANTHRENES IN CHLOROFORM, 25°

1,2-Benzanthracenes	Wave length,[a] mμ	*K*, mole/l.	*F*, cal./mole
4-Methyl	517	0.013	−2600
9-Methyl	546	.019	−2400
7-Methyl	517	.019	−2400
6-Methyl[b]	526	.021	−2300
	526	.023	−2200
8-Methyl	517	.023	−2200
10-Methyl[b]	546	.023	−2200
	546	.024	−2200
3-Methyl	517	.029	−2100
3′-Methyl	526	.029	−2100
4′-Methyl	517	.030	−2100
Unsubstituted	517	.034	−2000
5-Methyl[b]	517	.032	−2000
	526	.036	−2000
1′-Methyl	517	.040	−1900
2′-Methyl	526	.059	−1700
Benzo(c)phenanthrenes			
4-Methyl	500	0.035	−2000
2-Methyl[b]	526	.051	−1800
	500	.052	−1800
6-Methyl	500	.054	−1700
5-Methyl	500	.056	−1700
3-Methyl	500	.087	−1400
Unsubstituted[b]	500	.12	−1200
	500	.12	−1200
1-Methyl[b]	500	.15	−1100
	500	.15	−1100

[a] Wave length at which measurements were taken. [b] Two separate experiments were carried out and the values obtained in each are recorded.

Experimental

The general procedure for spectrophotometric determination is described below.

A solution of the hydrocarbon of known concentration (0.7–1.0 × 10^{-3} *M*) in chloroform (C.P.) was prepared. This was transferred to a series of volumetric flasks containing weighed amounts of TNF. The TNF concentrations in the resultant solutions were from 35–47 × 10^{-3} *M*. The mixtures were shaken to dissolve the TNF and then were allowed to stand overnight at room temperature. Prior to the photometric measurements the solutions were set for several hours in the spectrographic laboratory where the room temperature was held at 25°.

The solutions of the TNF complexes with the methyl-1,2-benzanthracenes varied in color from a deep red to reddish purple while the methylbenzo(c)phenanthrenes gave orange solutions. For each of the methyl-1,2-benzanthracene solutions there was a region around 517–546 mμ where the optical densities of these solutions were constant (Fig. 1). No such plateaus were found in the absorption curves of benzo(c)phenanthrene and its methyl derivatives. The absorption of TNF alone was very small at the wave lengths studied.

The optical densities of the solutions were measured with a Beckman quartz spectrophotometer, model DU, in 1-cm. quartz cells. Measurements were made at a number of wave lengths in the region of 500–546 mμ. These were taken as rapidly as possible to minimize any temperature changes of the solution in the cell compartment.

The TNF complexes were made by the method described for 1,2-benzanthracene.[3] Recrystallization involved solution in acetone, addition of alcohol, and distillation to incipient crystallization. The melting points recorded in Table II are for once recrystallized samples. All of the TNF derivatives involved a 1:1 ratio of hydrocarbon and

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[1] This work was supported by a grant, C-483-C3,4 from the U. S. Public Health Service to whom grateful acknowledgment is made.

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