in 100 cc. of glacial acetic acid was added a solution of 800 mg. of chromic anhydride in 10 cc. of 90% acetic acid keeping the temperature at 20°. After standing thirty minutes water was added and the product was extracted with ether. The solvent was removed and the residue was refluxed for thirty minutes with 100 cc. of 3% alcoholic potassium hydroxide. Water was added, the solution was neutralized and the product was filtered and washed with water. It was recrystallized from ether, m. p. 275–278°, yield 0.9 g.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.6; H, 8.4. Found: C, 70.0; H, 8.6.

Acetylation with boiling acetic anhydride followed by crystallization from ether gave a diacetate, m. p. 264–265°. Upon shaking with hydrogen and palladium catalyst in ethyl acetate the product was recovered unchanged.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.1: H, 7.7. Found: C, 67.4; H, 7.8.

A solution of 200 mg. of the above diacetate in 25 cc. of acetic acid containing 100 mg. of platinum oxide catalyst was shaken with hydrogen at 40 pounds pressure for fifteen minutes. After filtration, water was added and the product was extracted and crystallized from ether, m. p. 265–267°. It gave no depression in melting point when mixed with the 2,3-diacetate of *allo*-pregnantriol-2,3.17-dione-12,20 prepared from the potassium hydroxide hydrolysis of the oxidation product of pseudomanogenin triacetate followed by acetylation. Mixtures of both products with the unreduced diacetate from kammogenin gave depressions in melting point of 12–18°.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.8: H, 8.1. Found: C, 67.0; H, 8.4.

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RECEIVED OCTOBER 26. 1949

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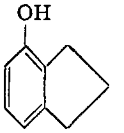
[6] Now with Hormosynth. S. A.. Cervantes Saavedra. No. 5. Mexico City.

Partition Studies on Phenols. III. Steric Effects

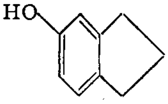
BY MILTON ORCHIN[1] AND CALVIN GOLUMBIC[1]

It has been previously suggested that the partition coefficient of a phenol between water and an organic phase provides a sensitive index of the degree of steric hindrance around the phenolic group.[2] This arises from the fact that an important factor affecting the solubility of a phenol in the aqueous phase often is the degree of hydrogen bonding between the phenol and the water molecules; if the approach to the phenolic group is sterically inhibited, hydrogen bonding and, hence, solubility in water is reduced.

Arnold and co-workers have shown in a series of papers[3] that the relative steric influence of methylene groups in six-membered rings is greater than that of five-membered rings. In the course of our investigations on partition coefficients, we have obtained information on the same subject.



I



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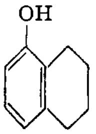
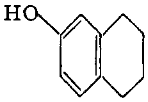


III



IV

The partition coefficients of the indanols, I and II, and the tetrahydronaphthols, III and IV, were determined in the system cyclohexane–water (Table I). The partition coefficient (*k*) of 5-hydroxy-1,2,3,4-tetrahydronaphthalene, III, is 5.6 times that of 4-indanol, I. It would be expected, of course, that III would have less solubility in water than I solely on the basis of its greater molecular weight, but that III's high partition coefficient is due mainly to steric inhibition of hydrogen bonding is shown by comparison with its isomer IV, the hydroxyl group of which is unhindered. The ratio of partition coefficients of IV/I is only 1.9 as compared to III/I of 5.6. These results agree with Arnold's contention that methylene groups in five-membered rings offer less steric hindrance than those in six-membered rings. Further evidence of the correctness of this view is provided by the infrared specta of I and III in the hydroxyl group region. The spectrum of I shows a rather broad band at 2.93μ, while that of III shows only a weak shoulder at 2.91μ. This significant difference between the two spectra indicates the greater association through hydrogen bonding in the case of 4-indanol.[4] The slightly higher *k* value of I as compared to II indicates some steric interference of hydrogen bonding by the five-membered ring. This is consistent with the fact that I is the lower boiling of the two isomers.

TABLE I

PARTITION COEFFICIENTS AND IONIZATION CONSTANTS OF PHENOLS[a]

Compound	$k(H_2O)$	*m*	*pK*
4-Indanol (I)	4.5	0.98	10.2
5-Indanol (II)	3.7	1.03	10.2
5-Hydroxy-1.2.3,4-tetrahydronaphthalene (III)	25.3	1.04	10.1
6-Hydroxy-1.2.3.4-tetrahydronaphthalene (IV)	8.6	1.08	9.9

[a] Measurements at 25°.

Table I also lists the *pK* values of the four phenolic compounds calculated from observed partition coefficients at various *p*H values in the manner previously described.[2] The slopes (*m*) of the straight lines obtained by plotting the logarithms of the observed partition coefficients against *p*H are also listed in Table I. These values are in good agreement with the theoretical slope of one for monobasic phenols.

Experimental[5]

4-Indanol (I) was isolated by Dr. E. O. Woolfolk from the products of the hydrogenation of coal at the Bureau of Mines. It had a melting point of 47–48°.

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[1] Organic Chemist. Bureau of Mines. Research and Development Branch. Office of Synthetic Liquid Fuels. Pittsburgh. Pa.

[2] Golumbic. Orchin and Weller. THIS JOURNAL. **71**. 2624 (1949).

[3] For the most recent paper in this series see Arnold and Richter. *ibid.*. **70**. 3505 (1948).

[4] We wish to thank Dr. R. A. Friedel. Lois Harnack and Marion Springer for the spectral data. Both spectra were determined in a 7% carbon disulfide solution and will be published in greater detail with other material in another article. We are indebted to George Goldbach for assistance with the experimental work.

[5] All melting points corrected.

5-Indanol (II) was also isolated by Dr. Woolfolk from coal-hydrogenation oils. It had a melting point of 52.4–53.8°.

5-Hydroxy-1,2,3,4-tetrahydronaphthalene (III) was prepared from pure 1-naphthol by hydrogenation.[6] Repeated crystallization gave a spectroscopically pure sample, m. p. 67.8–69.0°.

6-Hydroxy-1,2,3,4-tetrahydronaphthalene (IV) was prepared by the hydrogenation of 2-naphthol according to the directions of Stork.[7] We experienced considerable difficulty in freeing the tetrahydro compound from its aromatic precursor. Purification was achieved by distributing the mixture between cyclohexane and an aqueous alkaline buffered (*p*H 12.5) solution. In such a system all the 2-naphthol and a portion of the tetrahydronaphthol is retained in the aqueous phase and the organic phase contains pure tetrahydronaphthol. The tetrahydro compound was recovered from the organic phase by distillation and recrystallization. The pure material had a melting point of 57.2–58.4° and its ultraviolet absorption spectrum indicated the absence of naphthol.

Partition Experiments.—The phenols were dissolved in 20 ml. of spectrographic grade cyclohexane (0.5 mg. per ml.) and shaken with an equal volume of water for two minutes. After phase separation, the concentration of the phenol in the organic phase was determined by ultraviolet spectrophotometry in the usual way.[4]

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[6] Musser and Adkins, THIS JOURNAL, **60**, 664 (1938).

[7] Stork, *ibid.*, **69**, 576 (1947).

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The Reaction of Sodium Hypobromite with Arylcyanopyruvic Esters

BY SIGVARD WIDEQVIST

The appearance of a paper on the bromination of esters of arylcyanopyruvic acid[1] has prompted us to report some experiments, carried out some years ago, on the reaction between sodium hypobromite and certain organic compounds having labile hydrogen atoms. One of these was ethyl phenylcyanopyruvate. It was found that a cleavage of the ester took place with the production of phenylbromoacetonitrile, probably according to the equation

$$C_6H_5\text{—}CH(CN)\text{—}COCOOC_2H_5 + NaOBr \longrightarrow C_6H_5\text{—}CH(CN)Br + NaOCOCOOC_2H_5$$

This reaction was later used for synthetic purposes.

Treatment of an alkaline solution of ethyl phenylcyanopyruvate with an iodine–potassium iodide solution yielded a crystalline iodo compound, presumably phenyliodoacetonitrile, which, however, was very unstable and decomposed with the liberation of iodine. Ethyl α-naphthylcyanopyruvate was also cleaved in the same manner.

Phenylbromoacetonitrile.—Twenty-one and seven-tenths grams (0.1 mole) of ethyl phenylcyanopyruvate was dissolved in 200 cc. of water containing 5 g. of sodium hydroxide. The solution was cooled to 0°, and an ice-cold mixture of 16 g. of bromine, 9 g. of sodium hydroxide and 100 cc. of water was added. Phenylbromoacetonitrile immediately separated as a heavy, lemon-yellow oil; yield 16 g. (82%). It was converted into diphenylacetonitrile by the Friedel–Crafts reaction.

α-Naphthylbromoacetonitrile.—Ethyl α-naphthylcyanopyruvate (m. p. 114–115°, prepared from α-naphthylacetonitrile and diethyl oxalate; yield 73%) 5.0 g. (0.019 mole) was dissolved in 35 cc. of 2 *N* sodium hydroxide solution and cooled to 0°. A cold mixture of 5 g. of bromine and 40 cc. of 2 *N* sodium hydroxide was added. α-Naphthylbromoacetonitrile immediately separated as an orange-yellow oil which solidified in a few minutes; yield 4 g. (87%). It was recrystallized from hot alcohol (m. p. 101–102°).

Anal. Calcd for $C_{12}H_8NBr$: C, 58.54; H, 3.28; N, 5.69; Br, 32.49. Found: C, 58.80; H, 3.42; N, 5.59; Br, 32.92.

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RECEIVED JULY 11, 1949

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[1] Skinner, Kleibacker, Rosenberg, Gladner and Reed, THIS JOURNAL, **70**, 4011 (1948).

The Synthesis of 2-Fluoro-4- and 2-Fluoro-6-pyridinecarboxylic Acid and Derivatives

BY ARTHUR ROE, P. H. CHEEK AND G. F. HAWKINS[1]

The synthesis of 2-fluoronicotinamide,[2] 5-fluoronicotinamide[3] and 6-fluoronicotinamide[2] has been reported; preliminary reports indicate that at least one of them acts as a growth inhibitor for some microörganisms. It was therefore of interest to prepare some fluorinated isomers of nicotinic acid; this note reports the preparation of 2-fluoro-4-pyridinecarboxylic acid and 2-fluoro-6-pyridinecarboxylic acid together with their methyl esters and amides. The synthesis involved preparation of 2-fluoro-4-methylpyridine and 2-fluoro-6-methylpyridine followed by oxidation to the fluoro acids.

The authors are indebted to Eli Lilly and Company for generous support of this and related projects.

Experimental

The preparation of the fluoromethylpyridines and fluoro acids was carried out as described[2,3] for the fluoronicotinic acids, except that the water solubility of the 2-fluoro-6-pyridinecarboxylic acid made it necessary to remove the water from the acidified oxidation concentrate: this was accomplished by addition of ethanol and benzene, with subsequent distillation, in a manner somewhat similar to that reported by Black, Depp and Corson.[4] The acid was extracted from the inorganic material with benzene-alcohol. The methyl esters were obtained by allowing the acids to react with diazomethane[3]; the amides were prepared by the reaction of the methyl esters with 1:1 methanol-liquid ammonia mixture. The properties and analyses of the compounds prepared are given in Table I.

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[1] Present address: Tennessee Eastman Corporation, Kingsport, Tennessee.

[2] Minor, Hawkins, VanderWerf and Roe, THIS JOURNAL, **71**, 1125 (1949).

[3] Hawkins and Roe, *J. Org. Chem.*, **14**, 328 (1949).

[4] Black, Depp and Corson, *ibid.*, **14**, 14 (1949).