and water–ethanol–ethyl acetate, m.p. 258–259° (slow heating) or 278–281° (rapid heating), with decomposition. It gave a strong blue ninhydrin test.

Anal. Calcd. for $C_8H_{19}N_3O_2Cl_2$: C, 36.93; H, 7.36; Cl, 27.25. Found: C, 37.12; H, 7.86; Cl, 27.60.

2-(4-Benzylpiperazino)-propanol.—The reduction of 31 g. (0.112 mole) of ethyl 2-(4-benzylpiperazino)-propionate by 7.6 g. (0.2 mole) of lithium aluminum hydride in ether was carried out in the usual way. After 5 hours under reflux, the solution was treated with 18 ml. of water which must be added *dropwise* with stirring, initially at a maximum rate of one drop each few seconds, since the reaction mixture tends to foam as the hydrogen is involved. After the water had been added and the reaction mixture stirred an additional 10 minutes to ensure the destruction of all of the hydride, 9 g. of Dry Ice in small pieces was added through the condenser over 5 minutes with stirring, to decompose any lithium alkoxide. Filtration, washing of the solids with anhydrous ether, removal of the solvent and distillation of the remaining oil gave 22.5 g. (86%), b.p. 111–130° at 0.3 mm. The dihydrochloride was recrystallized from absolute ethanol, m.p. 239.8° dec.

Anal. Calcd. for $C_{14}H_{24}N_2OCl_2$: C, 54.72; H, 7.87. Found: C, 54.73; H, 8.20.

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Hydroxylation of Benzene in a Solution of Hydrogen Peroxide and Copper Sulfate

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The formation and reactions of hydroxyl radicals in aqueous solutions have been the object of numerous investigations.[1] Wieland[2] observed that hydrogen peroxide in the presence of cupric ions degrades stable organic compounds, like benzoic acid, to carbon dioxide and water. Since Baxendale[1c] reported that cuprous ions generate hydroxyl radicals from hydrogen peroxide, it seemed probable that the reaction described by Wieland proceeds through the intermediate formation of phenols. On treating benzene under suitable conditions with aqueous hydrogen peroxide and copper sulfate we were able to isolate phenol from the reaction mixture. Salicylic acid was obtained by treating sodium benzoate in a similar manner.

Experimental

Hydroxylation of Benzene.—Two grams of copper sulfate in 100 ml. of distilled water and 25 ml. of 30% hydrogen peroxide was vigorously agitated on a shaking machine for 14 hr. with 150 ml. of benzene. After 14 hours the mixture was filtered in order to break up the emulsion. The black aqueous layer was acidified with 6 *M* sulfuric acid and then extracted with successive portions of methylene chloride. The benzene and the methylene chloride were extracted with dilute sodium hydroxide and the alkaline extracts were acidified and treated with decolorizing carbon. The resulting clear solution was extracted with methylene chloride. The organic layer was dried and the solvent was removed leaving 0.14 g. of long needles, m.p. 37°, with the characteristic odor of phenol. It was converted into tribromophenol (0.30 g.) by bromine water, and recrystallized from dilute alcohol, m.p. 92° (uncor.). The experiment was repeated with a reaction time of 65 hr. and gave 0.37 g. of the crude product and 0.86 g. of the brominated derivative.

Hydroxylation of Sodium Benzoate.—Fifty ml. of a 0.2 *M* solution of sodium benzoate, adjusted to *p*H 4 with excess acid, was mixed with an equal volume of a 0.4% solution of hydrated copper sulfate. On the addition of 12 ml. of 30% hydrogen peroxide the solution turned green and some green precipitate settled out. The volume of the system was made up to 500 ml. with distilled water and it was allowed to stand for 13 hr. At the end of that period the yellow brown solution was acidified with 6 *M* sulfuric acid and extracted with ethyl ether. After drying the extract the solvent was removed, leaving 1 g. of a light brown crystalline residue. On the addition of dilute ferric nitrate to an aqueous solution of the product, an intensely violet color developed. The absorption spectra in 0.00040 *M* aqueous ferric nitrate of a 0.014% solution of salicylic acid and a 0.19% solution of the product were compared. At the 530 mμ absorption maximum the values of log I/I_0 were 0.63 and 0.55, respectively. The yield of 0.04 g. of salicylic acid was estimated colorimetrically.

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Nitrohydroxy Aromatic Ketones. I. Nitrohydroxyacetophenones

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Though simple in structure, only a few nitrohydroxyacetophenones are described in the literature. These have been prepared in general by nitration of hydroxyketones or their derivatives and by acetylation of nitrophenols. By direct nitration, 3-nitro-4-hydroxy-,[1] 3-nitro-6-hydroxy-[2] and 3-nitro-2-hydroxy-5-methylacetophenones[2,3] were obtained. The oximes and acetyl derivatives of hydroxyacetophenones have also been employed.[4–6]

It has been reported that the nitro group inhibits direct acetylation[7] or migration of the acetyl group under the influence of aluminum chloride.[8,9] However, 3-nitro-4-hydroxyacetophenone has been obtained recently by both reactions.[10] It had been obtained earlier from 2-nitroanisole[11,12] and by hydrolysis of 4-bromo-3-nitroacetophenone.[13] The present investigation confirms other reports[14,15] that inhibition due to the nitro group may be overcome by proper experimental conditions.

The literature also records the formation of picric acid during the attempted dinitration of *o*-hydroxyacetophenone.[5] 3,5-Dinitro-6-hydroxyacetophenone was obtained in this Laboratory as a result of

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TABLE I

Starting reagent	3-Nitro-acetophenone	M.p., °C.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found	Phenylhydrazone Color	Phenylhydrazone M.p., °C.	Phenylhydrazone Nitrogen, % Calcd.	Phenylhydrazone Nitrogen, % Found
Acetophenone									
2-OH	2-OH	82–83[b]	1.88	7.73	7.43	Sepia yellow	221–222	15.53	15.34
	6-OH	99.5[a,c]	18.8	7.73	7.65	Dull yellow	223	15.53	15.21
	2-OH 5-NO_2	123–124	27.1	12.39	12.12	Orange needles	224	17.72	17.38
2-OH 3-Me	6-OH 5-Me	114–114.5	71.8	7.18	6.91	Yellow needles	226–227	14.74	14.63
3-Me 4-OH	4-OH 5-Me	131.5	66.6	7.18	7.01	Violet needles	161	14.74	14.47
2-OH 4-Me	4-Me 6-OH	99.5	71.8	7.18	6.94	Canary yellow	228	14.74	14.52
2-Me 4-OH	4-OH 6-Me	125–126	61.5	7.18	6.87	Scarlet needles	147	14.74	14.62
2-OH 5-Me	2-OH 5-Me	132	64.2	7.18	6.99	Saffron yellow	189	14.74	14.68
Phenol acetate									
2-NO_2	4-OH	132[d]	45	7.73	7.62	Scarlet needles	195	15.53	15.37
4-NO_2	6-OH	99.5[a,c]	35	7.73	7.50				
2-NO_2 4-Me		162							
3-Me 4-NO_2		182							
2-Me 6-NO_2	Tar								
2-NO_2 5-Me	Tar								
Phenol									
4-NO_2	6-OH	99.5	43.8	7.73	7.59				
2-NO_2	4-OH	132	46.5	7.73	7.60				
6-NO_2 2-Me	4-OH 5-Me	131.5	49.6	7.18	6.98				

[a] Lindemann and Romanoff[4] give 111–112°; Allan and Loudon[5] give 98–99°. [b] Lindemann and Romanoff[4] give 89–90°; Allan and Loudon give 83°. [c] Wittig[2] has incorrectly identified this compound as 3-nitro-2-hydroxyacetophenone. [d] The following melting points are recorded: Borsche,[13] 130°; Pope,[1] 135°; Edkins and Linnell,[6] 129.5; Brown,[10] 132–132.5°.

this reaction. However, direct acetylation of dinitrophenols has not been found possible.

The nitrohydroxyacetophenones are crystalline compounds, from nearly colorless to yellow, insoluble in water, soluble in common organic solvents and alkali. They readily form phenylhydrazones. Table I records the compounds prepared, physical data, derivatives, and analyses. The Experimental section gives an illustrative preparation by each of the three methods used.

Experimental

Preparation of Nitrohydroxyacetophenones.—As indicated in Table I, all the compounds were prepared by one or more of the following methods. In each method, specific directions are given to illustrate the general use for all compounds thus prepared.

(a) **Migration of the Acetyl Group.**—A well-stirred mixture of anhydrous aluminum chloride (22 g.) in 40 cc. of nitrobenzene was added to a solution of 10 g. of 4-nitrophenyl acetate in 50 cc. of nitrobenzene. The mixture was left at room temperature for an hour and then heated on a water-bath for two hours. The temperature was then raised slowly to 130° and maintained at that temperature for an hour. After cooling, the mixture was treated with chipped ice and hydrochloric acid and steam distilled. The first distillate contained the bulk of the nitrobenzene and a small amount of 3-nitro-6-hydroxyacetophenone, which was recovered by an alkali extraction. Continued steam distillation yielded a product of sufficient purity to crystallize out in the condenser. The combined product was recrystallized from alcohol, 3.5 g., m.p. 99.5°. (From the non-steam-distillable residue 3 g. of *p*-nitrophenol was recovered.)

In some runs the above procedure was modified by adding the aluminum chloride powder slowly in small amounts while heating a nitrobenzene solution of the ester on a water-bath.

(b) **Acetylation of a Nitrophenol.**—To a solution of 14 g. of *p*-nitrophenol and 15 g. of acetyl chloride in 60 cc. of nitrobenzene was added slowly a well-stirred mixture of 40 g. of anhydrous aluminum chloride in 40 cc. of nitrobenzene. The reaction was completed and product recovered as described in method (a) above. The yield was 8 g. of 3-nitro-6-hydroxyacetophenone, m.p. 99.5°.

(c) **Nitration of Hydroxyacetophenones.**—With constant stirring, 10.5 cc. of concentrated nitric acid was added to an ice-cold solution of 10 g. of *o*-hydroxyacetophenone in 50 cc. of acetic acid over a period of 30 minutes. The temperature was allowed to rise slowly to 30°, cooling the flask when the reaction becomes too vigorous. The reaction mixture was treated with ice-water and a semi-solid mass separated. The mass was steam distilled to yield a first fraction of crude oily product which was rejected, followed by crystals of 3-nitro-6-hydroxyacetophenone (2.5 g.). After crystallization from alcohol the product melted at 99.5°. The non-steam distillable residue was extracted with alkali and the extract acidified, yielding 0.25 g. of the yellow crystals of 3-nitro-2-hydroxyacetophenone, m.p. 82–83°.

Dinitration of *o*-hydroxyacetophenone was accomplished by adding 12 cc. of nitric acid to a solution of 10 g. of the ketone in acetic acid and following the above procedure. However, after the temperature reached 30°, the reaction flask was heated on a water-bath for 30 minutes, cooled and the contents poured over ice. The 3-nitro-6-hydroxyacetophenone was removed by steam distillation, and the non-volatile residue recrystallized from alcohol. The product was 4.5 g. of pale yellow needles of 3,5-dinitro-6-hydroxyacetophenone, m.p. 123–124°. The use of a larger excess of nitric acid resulted in a purer product in lower yields.

The other compounds prepared by direct nitration were not subjected to steam distillation, but the crude product which separated out on addition of ice-water was recrystallized from acetic acid or alcohol.

Preparation of Phenylhydrazones.—An alcoholic solution of the ketone and phenylhydrazine in equivalent quantities was refluxed 30 minutes and the derivative separated. It was washed with dilute hydrochloric acid and recrystallized from alcohol.

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The Synthesis of 5-Hydroxykynurenine

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The Kotake[1] isolation of 5-hydroxyanthranilic acid from urine of rabbits injected with anthranilic

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