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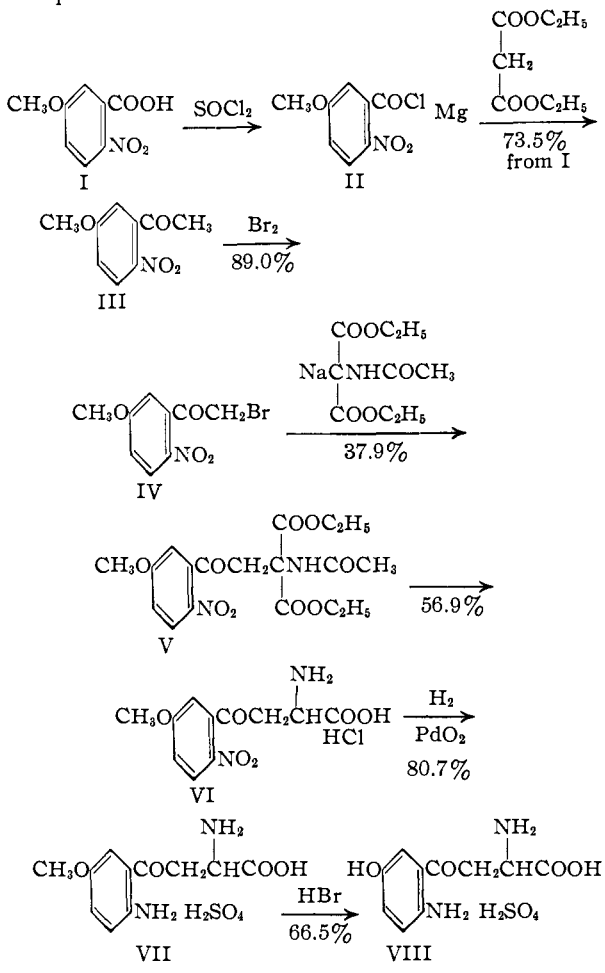
The Kotake[1] isolation of 5-hydroxyanthranilic acid from urine of rabbits injected with anthranilic

(1) Y. Kotake, *J. Japan. Biochem. Soc.*, **22**, 173 (1950).

acid and the isolation of 5-hydroxytryptophan[2] metabolites (bufotenine[3] and serotonine[4]) from natural sources motivated the authors to synthesize 5-hydroxykynurenine (VIII). The synthesis was performed as



This work was aided by a grant from the Scientific Research Fund of the Ministry of Education of Japan. We wish to thank the Takeda Research Laboratory for making the elementary analyses.

Experimental

6-Nitro-3-methoxybenzoic Acid (I).—6-Nitro-3-methoxybenzoic acid was prepared by the method of Blaikie and Perkin[5] from *m*-cresol, and the crystal water removed under reduced pressure at 80°, m.p. 132°.

6-Nitro-3-methoxybenzoyl Chloride (II).—6-Nitro-3-methoxybenzoic acid (6.6 g.) was converted to the chloride by warming with thionyl chloride; the excess reagent was distilled off *in vacuo* and the resultant chloride (m.p. 34°) used immediately in the next reaction.

6-Nitro-3-methoxyacetophenone (III).—To 0.95 g. of Mg turnings in a dry flask were added 0.15 ml. of dry carbon tetrachloride and 0.9 ml. of absolute ethanol; as soon as the reaction began, 10.5 ml. of dry chlorobenzene was cautiously added; then a mixture of diethyl malonate (6.3 g.), dry chlorobenzene (6.0 ml.) and absolute ethanol (4.5 ml.) was added in several portions. During this treatment the Mg turnings dissolved either spontaneously or by warming to 60 ~ 65°. After the reaction was complete, the flask was allowed to cool. Then the 6-nitro-3-methoxybenzoyl chloride (prepared above), dissolved in 10.6 ml. of dry chlorobenzene, was added in several portions. The mixture, which was shaken, changed slowly into a gelatinous mass and then solidified. This was cooled and dissolved in 3 ml. of sulfuric acid in 21 ml. of water; the chlorobenzene layer which separated was dried over sodium sulfate and evaporated *in vacuo*. The residue was decomposed by heating with a mixture of acetic acid (12 ml.), hydrochloric acid (1.5 ml.) and water (9 ml.) for 5 hours on the water-bath. On cooling, light tan crystals separated, which were purified by boiling with dilute sodium bicarbonate solution for a short time. The oily product solidified quickly, m.p. 67°, yield 4.8 g.

Anal. Calcd. for $C_9H_9NO_4$: C, 55.4; H, 4.7; N, 7.19. Found: C, 55.07; H, 5.44; N, 6.79.

6-Nitro-3-methoxyacetophenone Bromide (IV).—To 4.8 g. of 6-nitro-3-methoxyacetophenone dissolved in 35 ml. of acetic acid was added a mixture of bromine (4.0 g.), acetic acid (12 ml.) and $AlCl_3$. The mixture was warmed (50 ~ 55°) and after about 15 minutes, the color disappeared; it was then poured into cold water and white crystals separated, m.p. 90°, yield 6.0 g.

Anal. Calcd. for $C_9H_8NO_4Br$: C, 39.42; H, 2.92; N, 5.11. Found: C, 39.43; H, 3.19; N, 4.72.

Ethyl Acetamino-6-nitro-3-methoxyphenacyl Malonate (V).—To a solution of 0.38 g. of sodium in 20 ml. of absolute alcohol was added 3.9 g. of ethyl acetaminomalonate. After cooling in an ice-bath, 4.0 g. of dry crude 6-nitro-3-methoxyacetophenone bromide was added, the mixture was shaken overnight. After cooling (−3 ~ −5°) for five hours, the yellow-white crystals which separated were filtered, and washed with water, dried and recrystallized from ethyl acetate; m.p. 145°, yield 2.3 g.

Anal. Calcd. for $C_{18}H_{22}N_2O_9$: C, 52.7; H, 5.37; N, 6.83. Found: C, 53.21; H, 5.69; N, 6.68.

D,L-6-Nitro-3-methoxyphenacylglycine Hydrochloride (VI).—Ethyl acetamino-6-nitro-3-methoxyphenacyl malonate (9.0 g.) was decomposed by heating with a mixture of acetic acid (18 ml.) and hydrochloric acid (18 ml.) for 5 hours, during which 18 ml. of additional hydrochloric acid was added. When the cooled mixture was poured into water, a flocculent precipitate formed which was filtered and extracted with ether. The aqueous phase was evaporated *in vacuo*, and the residue boiled with absolute alcohol and filtered. After cooling, ether was added to the filtrate which yielded, on cooling at 0° for several hours, a crystalline substance, m.p. 199°, yield 3.8 g. This amino acid gave a yellow color with ninhydrin.

D,L-5-Methoxykynurenine Sulfate (VII).—6-Nitro-3-methoxyphenacylglycine hydrochloride (915 mg.), dissolved in 6 ml. of *N* H_2SO_4 and 11 ml. of *N*/25 H_2SO_4, was hydrogenated with 0.25 g. of palladium black catalyst; 3 moles of hydrogen was absorbed. After removal of the catalyst, the filtrate was concentrated to a small volume in an atmosphere of carbon dioxide and then stored in an ice-box; it yielded small prismatic needles; m.p. 191°, yield 815 mg. The ninhydrin reaction gave a reddish-purple, the diazo reaction a yellow, and ferric chloride test a weak brown color. A paper chromatogram developed with butanol–acetic acid–water showed two spots (R_f 0.32 and 0.36) which presumably correspond to the D- and L-isomer.

D,L-5-Hydroxykynurenine Sulfate (VIII).—5-Methoxykynurenine sulfate (1.3 g.) was boiled with hydrobromic acid (42%, 25 ml.) in an atmosphere of carbon dioxide. After ten hours it was diluted with 100 ml. of water and decolorized with charcoal. The filtrate was concentrated under carbon dioxide gas to a small volume; 30 ml. of *N*/10 H_2SO_4 was added and the solution again concentrated. This procedure was repeated twice. After cooling in an ice-box, small crystals of 5-hydroxykynurenine sulfate were obtained. Recrystallization from water gave colorless prismatic needles which darkened at 225° and carbonized at 255°; yield 830 mg.

Anal. Calcd. for $C_{10}H_{14}N_2O_8S$: C, 37.27; H, 4.34; N, 8.69. Found: C, 37.28; H, 4.26; N, 8.35.

This amino acid was slightly soluble in water giving a yellow solution with a strong green fluorescence; it became black upon the addition of alkali. On a paper chromatogram, it gave a purple color with ninhydrin, a purple color

(2) B. Witkop and A. Ek, THIS JOURNAL, **75**, 500 (1953).

(3) H. Wieland, W. Konz and H. Mittasch, *Ann.*, **513**, 1 (1934).

(4) M. M. Rapport, A. A. Green and I. H. Page, *Science*, **108**, 329 (1948).

(5) K. G. Blaikie and W. H. Perkin, *J. Chem. Soc.*, **125**, 307 (1924).

with diazotized sulfanilic acid, an orange color with dimethylaminobenzaldehyde in hydrochloric acid, a brown color with ferric chloride solution and decolorized a dilute chameleon solution. Its R_f value was 0.24 on a paper chromatogram developed with butanol–acetic acid–water; 4:1:5. The ultraviolet absorption spectra had a maximum at 405 mμ at *p*H 11.4, and a maximum at 378 mμ at *p*H 4.8.

Our synthetic 5-hydroxykynurenine is said[6] to have no influence upon the eye color of the *vbw* strain, one of the Drosophila mutants, but to show some effect on the *cnbw* strain.

(6) Kikkawa, private communication.

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Elimination of *p*-Ethylbenzenesulfonamide from N-*t*-Octyl-*p*-ethylbenzenesulfonamide. Some N-Substituted *p*-Ethylbenzenesulfonamides

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During a study of the relative ease of acid hydrolysis of a variety of N-substituted *p*-ethylbenzenesulfonamides, we have observed an apparently previously unreported type of elimination reaction in which N-(*t*-octyl)-*p*-ethylbenzenesulfonamide was converted to *p*-ethylbenzenesulfonamide and isoöctene (2,4,4-trimethyl-2-pentene). In this note we wish to record the data substantiating this unusual reaction and the data characterizing nine previously undescribed N-substituted *p*-ethylbenzenesulfonamides.

On refluxing N-(*t*-octyl)-*p*-ethylbenzenesulfonamide with 9% hydrochloric acid, a reaction takes place with the separation of an oily liquid. This liquid boils at 95–98° and gives typical unsaturation tests. Refractionation gave four fractions with refractive indices (n^{20}D 1.4086–1.4131) and boiling ranges (98–101°) indicating that the material was a mixture of 2,4,4-trimethyl-2-pentene and 2,4,4-trimethyl-1-pentene. The yield of crude liquid was 54% of the theoretical amount assuming it to be the mixture of isomeric pentenes. The other product of this reaction is *p*-ethylbenzenesulfonamide obtained in 96.7% yield. Elimination reactions are common with the tertiary alcohols and have been encountered in attempts to acylate *t*-octylamine. Apparently this is the first time a reaction of the type described has been encountered.

The N-substituted *p*-ethylbenzenesulfonamides were prepared from the sulfonyl chloride, prepared as previously described,[1] and the amine by three different techniques. With morpholine, dimethylamine, diethylamine and piperidine, excess amine was heated with the sulfonyl chloride. The diluted reaction mixture was acidified to precipitate the amide in 44.9–81.2% yields of recrystallized product. With diphenylamine, diisopropylamine and *t*-octylamine (2,4,4-trimethyl-2-aminopentane), equimolar quantities of amine and sulfonyl chloride were refluxed in pyridine. Dilute (10%) sulfuric acid was added to the reaction mixture to complete the precipitation of the amide in 21.2–49.8% yields of recrystallized product. With piperazine the reactants were refluxed together in benzene using excess amine. The reaction mixture was filtered to collect the precipitated bis-sulfonamide and then extracted with 10% sulfuric acid. The benzene layer was evaporated to obtain additional bis-sulfonamide. The total yield of recrystallized bis-amide was 39.7%. The monoamide, which precipitated on making the acid layer basic, was obtained in 5.2% yield of recrystallized product. The yields and analytical data are summarized in the Table and typical experimental details are given in the Experimental section.

TABLE I

N-SUBSTITUTED *p*-ETHYLBENZENESULFONAMIDES

Amide	M.p., °C.	Yield,[a] %	Nitrogen, % Calcd.	Found
N,N-Dimethyl	48–48.5	45 E	6.57	6.40
N,N-Diethyl	52.5–53	66 P	5.78	5.66
N,N-Diisopropyl	64–64.5	21 P	5.20	5.44
N-*t*-Octyl[b]	98–98.5	50 A	4.71	5.15
Piperidide	69.5–70	52 E	5.53	5.30
Morpholide	120–121	81 E	5.49	5.41
Piperazide				
Bis	231–232	40 E[c]	6.63	6.67
Mono	93	5 E[c]	10.99	10.90
N,N-Diphenyl[d]	133–134	29 E	4.15	4.28

[a] Yield after recrystallization to constant m.p. from E, ethanol; P, petroleum ether; A, aqueous ethanol. [b] Calcd. for $C_{16}H_{27}NO_2S$: C, 64.60; H, 9.15. Found: C, 64.84; H, 9.18. [c] Isolated in same runs. [d] Calcd. for $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.68. Found: C, 71.28; H, 5.78.

Experimental[2]

The amines used in the following experiments were obtained from various laboratory supply firms and used as received except the *t*-octylamine which was generously supplied by Dr. C. E. Denoon, Rohm and Haas Company, Philadelphia, Penna.

4-(*p*-Ethylphenylsulfonyl)-morpholine.—Twenty and five-tenths grams (0.1 mole) of *p*-ethylbenzenesulfonyl chloride was added slowly to 50 ml. of morpholine. The mixture was heated on a steam-bath for one-half hour, diluted with 100 ml. of 10% sulfuric acid to precipitate the amide. The precipitate was collected and recrystallized several times from ethanol to obtain 20.7 g., 81.2%, of 4-(*p*-ethylphenylsulfonyl)-morpholine, m.p. 120–121°.

N,N-Diphenyl-*p*-ethylbenzenesulfonamide.—Twenty and five-tenths grams (0.1 mole) of *p*-ethylbenzenesulfonyl chloride was added slowly with stirring to a solution of 16.9 g. (0.1 mole) of diphenylamine in 70 ml. of pyridine. The mixture was refluxed for 12 hours and acidified with 10% sulfuric acid. The precipitated amide was collected and recrystallized from ethanol to obtain 9.7 g., 28.6%, of N,N-diphenyl-*p*-ethylbenzenesulfonamide, m.p. 133–134°.

1-(*p*-Ethylphenylsulfonyl)-piperazine and 1,4-Bis-(*p*-ethylphenylsulfonyl)-piperazine.—Ten and four-tenths grams (0.05 mole) of *p*-ethylbenzenesulfonyl chloride was added slowly to 28.5 g. (0.15 mole) of piperazine hexahydrate in 60 ml. of benzene. The mixture was refluxed for one-half hour and filtered to collect the precipitated bis-sulfonamide. The benzene layer was extracted with 10% sulfuric acid and evaporated to obtain additional bis-sulfonamide. The collected crude material was recrystallized to give 8.4 g., 39.7%, of 1,4-bis-(*p*-ethylbenzenesulfonyl)-piperazine, m.p. 231–232°. The aqueous layers were made basic to precipitate the monosulfonamide. Recrystallization gave 0.66 g., 5.2%, of 1-(*p*-ethylbenzenesulfonyl)-piperazine, m.p. 93°.

Hydrolysis of N-(*t*-Octyl)-*p*-ethylbenzenesulfonamide.—A mixture of 10.16 g. (0.0342 mole) of N-(*t*-octyl)-*p*-ethylbenzenesulfonamide and 30 ml. of 9% hydrochloric acid was refluxed for 12 hours. During this time the amide dissolved and an oily solid separated. The reaction mixture was made basic and 2.1 g., 54%, of crude 2,2,4-trimethylpentenes separated. Distillation gave 1.55 g. of liquid, b.p. 96–99°, which gave positive unsaturation tests with bromine and potassium permanganate. Fractionation of the liquid gave four fractions: (1) b.p. −99°, n^{20}D 1.4086; (2) b.p. 99-

(1) R. H. Wiley and R. P. Davis, THIS JOURNAL, **74**, 6142 (1952).

(2) Analyses by Micro Tech Laboratories.