[CONTRIBUTION FROM THE UNIVERSITY OF TEXAS, BIOCHEMICAL INSTITUTE, AND THE CLAYTON FOUNDATION FOR RESEARCH, AUSTIN, TEXAS, AND THE DEPARTMENT OF CHEMISTRY, NATIONAL UNIVERSITY OF PEKING, CHINA]

Syntheses of Compounds Related to Vitamin K. III. 4-(3′-Methyl-4′-hydroxynaphthylazo)-benzenesulfonamide and Related Compounds[1,2]

BY EDITH JU-HWA CHU

In continuation of the work on 4-(3′-alkyl-4′-hydroxynaphthylazo)-benzenesulfonamides,[3] the methyl derivative has been synthesized and found to possess an antihemorrhagic activity almost equal to that of 2-methyl-1,4-naphthoquinone by a preliminary test,[4] while other alkyl derivatives are inactive. It would be interesting to study the antihemorrhagic action of its analogs derived from albucid (N-acetylsulfanilamide), sulfapyridine, sulfathiazole, sulfadiazine and sulfaguanidine. This paper is reporting the syntheses of 4-(3′-methyl-4′-hydroxynaphthylazo)-benzenesulfonamide, 4-(3′-methyl-4′-aminonaphthylazo)-benzenesulfonamide and their analogs, respectively. Also the corresponding acetyl derivatives were prepared.

The antihemorrhagic activities and the antibacterial effects of these compounds and 4-(3′-methyl-4′-carboxylnaphthylazo)-benzenesulfonamide and related compounds will be reported elsewhere.

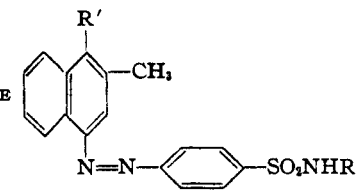
Experimental

4-(3′-Methyl-4′-aminonapththylazo)-benzenesulfonamide, 4-(3′-Methyl-4′-hydroxynaphthylazo)-benzenesulfonamide and Analogs.—Several methods[5,6] of reduction of 2-methyl-1-nitronaphthalene to 2-methyl-1-naphthylamine were tried. Although the catalytic hydrogenation process of Baker and Carlson gave the most satisfactory result, it was found the use of hydrogen in a hydrogenator was unnecessary in this case. The refluxing of 2 g. of 2-methyl-1-nitronaphthalene with 10 g. of Raney nickel[7] on a steam-bath for an hour gave a 96% yield of 2-methyl-1-naphthylamine.

2-Methyl-1-naphthol was prepared according to the

TABLE I

DERIVATIVES OF 4-(3′-METHYLNAPHTHYLAZO)-BENZENESULFONAMIDE



R′ = OH, R′ = NH₂

R	Solvent for recrystn.	Color[a]	Cryst. form	Yield, %	M. p., °C.	N Analyses, % Calcd.	Found
Hydrogen	Acetone	Orange	Needles	100	247 dec.[b]	12.31	11.93
Acetyl	Acetone	Orange-red	Needles	100	232–233 dec.	10.96	11.12
2-Pyridyl	Acetone	Orange-red	Prisms	60	224 dec.	13.40	13.38
2-Thiazolyl	Ethylene glycol	Orange	Fine prisms	78	224 dec.	13.20	13.55
2-Pyrimidyl	Acetone	Yellow-orange	Prisms	98	248 dec.	16.70	16.82
Guanyl	Acetone	Yellow-orange	Cluster of needles	66	249 dec.	18.27	18.07
Hydrogen	Acetone or ethylene glycol	Orange	Cluster of prisms	69	228–229 dec.[c]	16.47	16.60
Acetyl	Acetone	Red	Needles	50	194.5–195.5 dec.	14.66	14.52
2-Pyridyl	Acetone	Red	Cubes	84	230 dec.[d]	16.78	17.05
2-Thiazolyl	Acetone or acetic acid + alc.	Red	Plates	94	280 dec.[e] (acetone) 218 dec. (acetic acid + alc.)	16.54	16.77
2-Pyrimidyl	Acetone, alc. or acetic acid	Orange-red (283°) Orange (248–249°)	Prisms	72	283 dec. (acetone or alc.) 248–249 dec. (acetic acid)	20.09	20.31
Guanyl	Acetone or acetic acid	Black (acetone) Orange-red (acetic acid)	Needles	100	253 dec.	21.99	21.73

[a] Color of the compounds differ with different solvents for recrystallization. [b] Harry Willstädt, *Svensk. Kem. Tidskr.*, 54, 223 (1942); *Chem. Zentr.*, 114; I, 750 (1943), reported a m. p. 235° dec. [c] Harry Willstädt, *ibid.*, reported a m. p. 226°. [d] Harry Willstädt, *ibid.*, reported a m. p. 239°. [e] Harry Willstädt, *ibid.*, reported a m. p. of only 218°.

(1) The author is indebted to Miss Zoh-Ing Shen in testing Lesser's procedure of preparing 2-methyl-1-naphthylamine and 2-methyl-1-naphthol.

(2) The author wishes to thank Drs. Joseph Needham and Harry Sobotka for supplying 2-methylnaphthalene; Dr. E. Schwenk for albucid and Dr. K. K. Chen for sulfapyridine.

(3) E. J.-H. Chu, Z. I. Shen, T. L. Chien and T. S. Tuan, THIS JOURNAL, 66, 653 (1944).

(4) The author is indebted to Drs. P. Ewing, C. D. Leake and G. Emerson for the preliminary test.

(5) R. Lesser, *Ann.*, 402, 1 (1913).

(6) B. R. Baker and G. H. Carlson, THIS JOURNAL, 64, 2657 (1942).

(7) R. Mozingo, C. Spencer and K. Folkers, *ibid.*, 66, 1859 (1944).

TABLE I (*Concluded*)

R (R′ = OCOCH$_3$, R′ = NHCOCH$_3$)								
Acetyl	Alcohol	Orange	Prisms	100[a]	85[b]	198–199	9.88	9.95
2-Pyridyl	Acetone	Yellow-orange	Prisms		100	203.5	12.17	12.00
2-Thiazolyl	Acet. + alc.	Red-orange	Cluster of heavy plates		100	207	12.01	12 14
2-Pyrimidyl	Acetone	Yellow-orange	Fine needles		100	195–196	15.18	15.46
Acetylguanyl	Acetone	Orange	Needles		67	205–206	14.99	15.14
Acetyl	Acet. + alc.	Orange	Prisms	64[c]	90[d]	213.5–214.5	13.21	13.34
2-Pyridyl	Acetone	Orange	Cluster of needles		91	149–150	15.25	15.28
2-Thiazolyl	Acet. + alc.	Orange-red	Clusters of needles		100	160–161[e]	15.05	15.12
2-Pyrimidyl	Acet. + alc.	Yellow-orange	Cluster of prisms		99	208–209[f]	18.26	18.36
Acetylguanyl	Alc. + petr. ether	Orange	Fine needles		87	246	18.02	18.14

[a] Acetylation of 4-(3′-methyl-4′-hydroxynaphthylazo)-benzenesulfonamide. [b] Acetylation of 4-(3′-methyl-4′-hydroxynaphthylazo)-N-acetylbenzenesulfonamide. [c] Acetylation of 4-(3′-methyl-4′-aminonaphthylazo)-benzenesulfonamide. [d] Acetylation of 4-(3′-methyl-4′-aminonaphthylazo)-N-acetylbenzenesulfonamide. [e] Two polymorphic forms m. p. 280° and m. p. 218° yielded the same acetyl derivative. [f] Two polymorphic forms m. p. 283° and m. p. 248–249° yielded the same acetyl derivative.

procedure of Lesser[5] with slight modification. The yield was about 80–90%.

2-Methyl-1-naphthylamine hydrochloride and 2-methyl-1-naphthol were, respectively, coupled with sulfanilamide. The hydrochloride of 4-(3′-methyl-4′-aminonaphthylazo)-benzenesulfonamide thus obtained was treated with a 10% sodium hydroxide solution to liberate the free amine. The analogs from albucid, sulfapyridine, sulfathiazole, sulfadiazine and sulfaguanidine were similarly prepared. The yields and properties of these compounds are listed in Table I.

Acetyl Derivatives of 4-(3′-Methyl-4′-aminonaphthylazo)-benzenesulfonamide, 4-(3′-Methyl-4′-hydroxynaphthylazo)-benzenesulfonamide and Analogs.—A sample of 0.001 g. mole of 4-(3′-methyl-4′-aminonaphthylazo)-benzenesulfonamide was refluxed with 1 cc. of acetic anhydride and about 3 drops of pyridine for an hour. It was poured into cold water and then filtered. The precipitate was recrystallized from a suitable solvent. This was identified as the diacetyl derivative by analysis and mix-melting point with the acetyl derivative obtained by acetylation of 4-(3′-methyl-4′-aminonaphthylazo)-N-acetylbenzenesulfonamide. 4-(3′-Methyl-4′-aminonaphthylazo)-sulfanilylguanidine also forms diacetyl derivative which occludes acetic acid tenaciously and has to be stirred with a 10% NaOH before recrystallization. Acetyl derivatives of 4-(3′-methyl-4′-hydroxynaphthylazo)-benzenesulfonamide and analogs were similarly prepared. 4-(3′-Methyl-4′-hydroxynaphthylazo)-benzenesulfonamide and 4-(3′-methyl-4′-hydroxynaphthylazo)-sulfanilylguanidine yielded diacetyl derivatives, respectively. The properties of these acetyl derivatives are listed in Table I.

Summary

4-(3′-Methyl-4′-aminonaphthylazo)-benzenesulfonamide, 4-(3′-methyl-4′-hydroxynaphthylazo)-benzenesulfonamide and their analogs derived from albucid, sulfapyridine, sulfathiazole, sulfadiazine and sulfaguanidine have been respectively synthesized. Also corresponding acetyl derivatives have been prepared.

A preliminary test has shown that 4-(3′-methyl-4′-hydroxynaphthylazo)-benzenesulfonamide possesses an antihemorrhagic activity almost equal to that of 2-methyl-1,4-naphthoquinone. An extensive study of antihemorrhagic activities of these compounds is in progress.

2-Methyl-1-naphthylamine has been prepared by refluxing 2-methyl-1-nitronaphthalene with Raney nickel only, in a yield of 96%.

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The Polymerization of Allyl Compounds. I. Factors Governing the Acyl Peroxide-Induced Polymerization of Allyl Acetate, and the Fate of the Peroxide

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If pure allyl acetate is heated at 80° with 6% of its weight of benzoyl peroxide, the slow decomposition of the peroxide induces polymerization of the ester. The peroxide is 90% decomposed after thirteen hours; only an undetectable amount remains after forty-eight hours, at which time about 50% of the original allyl acetate has polymerized. The soft, transparent polymer is obtained by distillation of the volatile monomer. It is soluble in a number of organic solvents and has an average molecular weight of about 1300, hence an average degree of polymerization of 13. This low degree of polymerization and high requirement of initiating peroxide makes allyl acetate a favorable material for studying the mechanism of polymerization, especially with regard to the fate of the peroxide.

Different samples of allyl acetate, prepared with care to remove free alcohol and acid and distilled in the absence of air, yielded reproducible results. The polymerizations described in this paper were followed by bromometric titration of

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