Anal. Calcd. for $C_{12}H_{19}O_2N$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.93; H, 9.18; N, 6.33.

N-(3,4-Diethoxyphenylacetyl)-β-(3,4-diethoxyphenyl)-ethylamine.—A mixture of 10.45 g. of β-(3,4-diethoxyphenyl)-ethylamine (0.05 mole) and 11.65 g. of technical grade 3,4-diethoxyphenylacetic acid[8] (0.052 mole) was held at 180–195° for one hour. The water formed was swept out with a current of nitrogen. The reaction mixture was dissolved in 50 cc. of hot toluene and chilled at 2°. The crystals were collected and washed with petroleum ether; yield 16.5 g. (79.5%), m. p. 102–103°.

Anal. Calcd. for $C_{24}H_{33}O_5N$: C, 69.37; H, 8.00; N, 3.37. Found: C, 69.43; H, 8.27; N, 3.46.

6,7-Diethoxy-1-(3′,4′-diethoxybenzyl)-3,4-dihydroisoquinoline.—Forty-eight grams of N-(3,4-diethoxyphenylacetyl)-β-(3,4-diethoxyphenyl)-ethylamine (0.115 mole) was suspended in 200 cc. of benzene; the air was replaced with carbon dioxide, then 23 cc. of phosphorus oxychloride (about 0.25 mole) was added, and the mixture was stirred mechanically and refluxed in a carbon dioxide atmosphere for one hundred minutes. The benzene and excess phosphorus oxychloride was distilled *in vacuo*, and the residual sirup was dissolved in 150 cc. of benzene and poured on cracked ice. Then an excess of concd. ammonia was added and the mixture agitated thoroughly. The ammoniacal layer was separated and again extracted with 100 cc. of benzene. The combined benzene extracts were washed with 2–150-cc. portions of 5% ammonia water, then water, and dried over anhydrous sodium sulfate. The benzene was distilled *in vacuo*, the residue was agitated with 400 cc. of petroleum ether and chilled at 2° overnight. The crystals were filtered and washed with petroleum ether; yield 44.5 g. (97%), m. p. 74–75°.

6,7-Diethoxy-1-(3′,4′-diethoxybenzyl)-isoquinoline.—Forty-two grams of crude 6,7-diethoxy-1-(3′,4′-diethoxybenzyl)-3,4-dihydroisoquinoline (0.1056 mole) was dissolved in 168 cc. of diisopropylbenzene, 2 g. of 5% palladium-on-charcoal was added, the air was replaced with carbon dioxide, and the mixture refluxed for two hours. The catalyst was filtered, the filtrate was cooled to 30° and mixed with 350 cc. of petroleum ether, then chilled at 2° overnight. The crystals were washed with petroleum ether; yield 37.5 g. (90%), m. p. 95–96°. After suitable purification the base melted at 99–100°.

Anal. Calcd. for $C_{24}H_{29}O_4N$: C, 72.88; H, 7.39; N, 3.54. Found: C, 73.08; H, 7.81; N, 3.79.

The hydrochloride, prepared by adding alcoholic hydrochloric acid to an alcoholic solution of the base, melted at 186–188°.

Anal. Calcd. for $C_{24}H_{30}O_4NCl$: C, 66.72; H, 7.00; N, 3.24. Found: C, 66.69; H, 7.12; N, 3.42.

(8) Kindler and Gehlhaar, *Arch. d. Pharm.*, **274**, 377 (1936).

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RECEIVED OCTOBER 22, 1948

A Michael Reaction of Lawsone

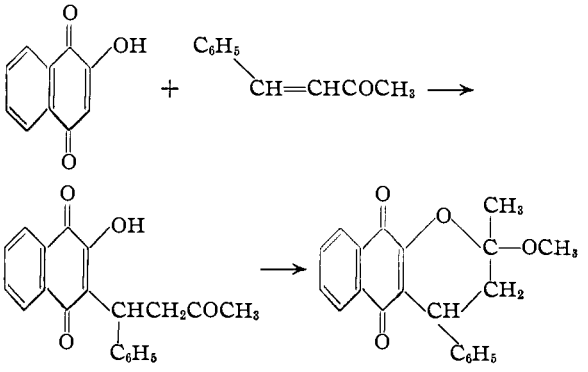
BY HAROLD E. ZAUGG

In connection with the preparation of various 3-substituted-2-hydroxy-1,4-naphthoquinones for application to antimalarial studies,[1] the present author found that lawsone (2-hydroxy-1,4-naphthoquinone) would react with benzalacetone in pyridine to give an addition product resulting from a Michael type reaction. In this respect, lawsone is similar in reactivity to 4-hydroxycoumarin which likewise has been found[2] to add to various α,β-unsaturated ketones.

(1) Fieser, Leffler, *et al.*, THIS JOURNAL, **70**, 3151 (1948).

(2) Ikawa, Stahmann and Link, *ibid.*, **66**, 902 (1944).

The structure of the product was demonstrated by analysis and by ring-closure to a cyclic ketal.[2] The two reactions are summarized as



Since both the quinone adduct and its cyclization product were found[3] to be entirely inactive against *P. lophurae* in ducks, no extension of this reaction to other α,β-unsaturated ketones was attempted.

Experimental

The Michael Condensation.—A solution of 34.8 g. (0.2 mole) of lawsone and 29.2 g. (0.2 mole) of benzalacetone in 150 cc. of pyridine was refluxed for five hours and poured into ice-water containing 200 cc. of concentrated hydrochloric acid. The tarry precipitate was then taken up in ether, washed with dilute hydrochloric acid and filtered from insoluble material. The ether solution was extracted with two 400-cc. portions of saturated sodium bicarbonate solution. These deep red solutions were combined to form fraction I. Six more extractions with 300-cc. portions of saturated bicarbonate were combined to form fraction II. The ether layer was concentrated to dryness and the residue dissolved in 250 cc. of 5% sodium hydroxide solution and filtered from insoluble material to form fraction III.

Fraction I was acidified with hydrochloric acid to give 7.0 g. of yellow precipitate of m. p. 130–160° apparently containing a considerable proportion of starting material. This solid was warmed gently with 300 cc. of a 10% sodium bisulfite solution and any insoluble material was filtered off and dissolved in ether. The ether solution was washed successively with 10% sodium acetate, dilute hydrochloric acid and water, and dried over anhydrous magnesium sulfate. Filtration and concentration of the ether to a volume of about 40 cc. followed by cooling in ice and filtering gave 1.7 g. of light yellow powder, m. p. 143–144°.

Fraction II was acidified with concentrated hydrochloric acid, the brown precipitate was filtered off and triturated with a large excess of saturated sodium bicarbonate solution until no more solid appeared to dissolve. The solution was filtered through a thin layer of Norite and acidified again with hydrochloric acid. The precipitate was taken up in a relatively large volume of ether, washed with water and dried over anhydrous magnesium sulfate. Filtration and treatment of the ether solution in the same way as that of fraction I gave 2.3 g. of light yellow powder, m. p. 142–144°.

Fraction III was stirred with 50–75 g. of Nuchar at room temperature and filtered through a layer of Nuchar. The filtrate was discarded and the filter cake was stirred at room temperature with 300 cc. of 5% sodium hydroxide, filtered and washed with 700 cc. of water. The filtrate was acidified and the brown precipitate formed was treated in exactly the same manner as was the brown product

(3) Antimalarial tests were carried out by Drs. A. P. Richardson and R. Hewitt at the University of Tennessee, Department of Pharmacology.

obtained from fraction II. There was obtained 1.4 g. of yellow powder, m. p. 140–143°.

For analysis the 5.4 g. of product was purified by dissolving in about one liter of refluxing ether. The solution was dried over anhydrous magnesium sulfate, filtered and concentrated to about 30–40 cc. The mixture containing the product, already partly precipitated, was cooled in ice and filtered. The pure product consisted of a light yellow powder, m. p. 143–144°.

Anal.[4] Calcd. for $C_{20}H_{16}O_4$: C, 74.98; H, 5.04. Found: C, 74.97; H, 5.24.

Cyclization.—Two grams of the quinone adduct was refluxed in 50 cc. of 6% methanolic hydrogen chloride for sixteen hours. The quinone went into solution slowly and, on cooling, the mixture crystallized to give a product (1.6 g.) of m. p. 141–143°. Two recrystallizations from methanol gave shiny yellow platelets, m. p. 144–145°.

Anal. Calcd. for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.52; H, 5.52.

It is interesting to note that the cyclized product gave an apparent exaltation of melting point when mixed with a sample of starting material. A mixture of the two quinones (each melting at 144°) softened at 140° but melted completely at 151–155°.

The cyclized product was further differentiated from the starting material by the fact that in cold alcoholic alkali, the former did not give the deep red color characteristic of the free hydroxy-group present in the uncyclized quinone.

(4) Microanalyses were carried out by Mr. E. F. Shelberg, chief microanalyst, Abbott Research Laboratories.

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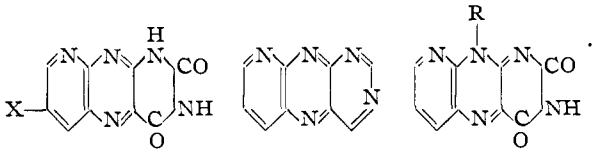
Some 9-Aza-alloxazines

BY J. BENJAMIN ZIEGLER[1]

During the course of a program of research in these laboratories it became necessary to synthesize some compounds of type (I). Substances of this structure



(Ia) X = H
(Ib) X = Cl

II

III

which may be considered to be derived from the parent compound, pyrido-[2.3-b] pyrimido-[5.4-e]pyrazine[1a] (II) appear not to have been synthesized previously, although certain closely similar 10-alkyl-9-aza-isoalloxazines (or 10-alkyl-9-aza-flavins) (III) have been prepared by Rudy and Majer.[2a,b]

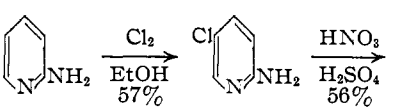
It is to be expected that condensation of 2,3-diaminopyridines with alloxan under the proper conditions would result in the removal of two molecules of water with the formation of tricyclic compounds of type I. Rudy and Majer have shown[3] that condensation of 2,3-diaminopyridine with alloxan in water or dilute acids yields bicyclic compounds formed by the removal of only one molecule of water. The reaction of *o*-phenylenediamine with alloxan with the removal of two molecules of water to yield alloxazine proceeds readily under these conditions.[4] Apparently the diminished reactivity of the 2-amino group in 2,3-diaminopyridine is responsible for the failure to remove the second molecule of water in this case.

The condensation of 2,3-diaminopyridine with alloxan in glacial acetic acid was investigated; however, the product obtained was one formed by the removal of only one molecule of water from the reactants. It is probably the 2-hydroxy-8-azaquinoxaline-3-carboxureide described by Rudy and Majer.[3]

It has been shown[2a,5] that boric acid is an effective condensing agent in reactions of this type. Condensation of 2,3-diaminopyridine with alloxan in a solution of boric acid in glacial acetic acid finally led to a product having the composition of the desired 9-aza-alloxazine (Ia). It was a dense, sandy, reddish-brown crystalline powder insoluble in water but soluble in dilute ammonia water, from which solution it could be precipitated by acidification with acetic acid. It did not melt up to 300° but at about 270° the color changed from reddish-brown to yellow.

Interestingly enough an attempt to synthesize 7-chloro-9-aza-alloxazine (Ib) by condensation of 2,3-diamino-5-chloropyridine with alloxan under these same conditions did not succeed, the product obtained being one formed by the removal of only one molecule of water. Apparently the 2-amino group is still further deactivated by the chlorine atom in the para-position. Substitution of boron trifluoride etherate for the boric acid, however, led to the desired result. The 7-chloro-9-aza-alloxazine was an orange-tan crystalline powder similar in appearance and properties to the parent 9-aza-alloxazine.

Since the various published syntheses[6] of 2,3-diaminopyridine are unsatisfactory for one reason or another we have developed a new synthesis of this difficultly accessible diamine which is believed to possess some advantage over the older methods. The procedure starts with the readily available 2-aminopyridine and proceeds to 2,3-diaminopyridine with an over-all yield of about 20% by a three-step process which is outlined below



(1) Present address: Ciba Pharmaceutical Products, Inc., Summit, N. J.

(1a) R. I. 1872. Patterson and Capell, "The Ring Index," Reinhold Publishing Co., 1940, p. 254.

(2) (a) Rudy and Majer, *Ber.*, **71**, 1243–1248 (1938); (b) *ibid.*, **72**, 933–939 (1939).

(3) Rudy and Majer, *Ber.*, **71**, 1323–1332 (1938).

(4) Kühling, *Ber.*, **24**, 2363–2369 (1891).

(5) Kuhn, Reinemund, Weygand and Ströbele, *Ber.*, **68B**, 765–774 (1935).

(6) (a) Tschitschibabin and Kirsanow, *Ber.*, **60**, 766–776 (1927); (b) Konopnicki and Plazek, *ibid.*, **60B**, 2045–2047 (1927); (c) von Schickh, Binz and Schulz, *ibid.*, **69**, 2593–2605 (1936).