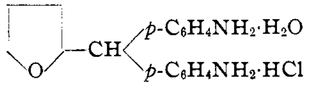
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF BUFFALO]

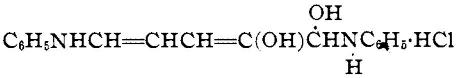
# The Constitution of the Condensation Product of Furfural and Aniline (Schiff Base)[1]

BY EMIL R. RIEGEL AND MILICENT HATHAWAY

To the violet solid produced by the interaction of furfuraldehyde, aniline, and aniline hydrochloride (1 mole of each),[1a] there was assigned[2] the formula (I), chiefly because of the analogy of its formation to that of the triphenylmethane dyes. Later the structure (II)[3] was proposed.



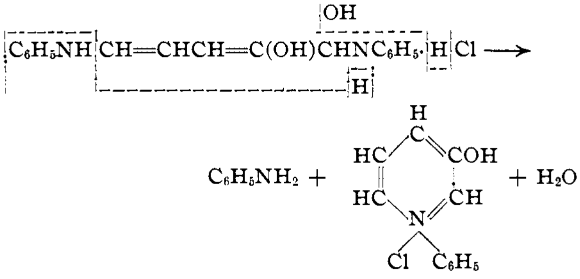
I



$$C_6H_5NHCH{=}CHCH{=}C(OH)\overset{OH}{C}H\underset{H}{N}C_6H_5\cdot HCl$$

II

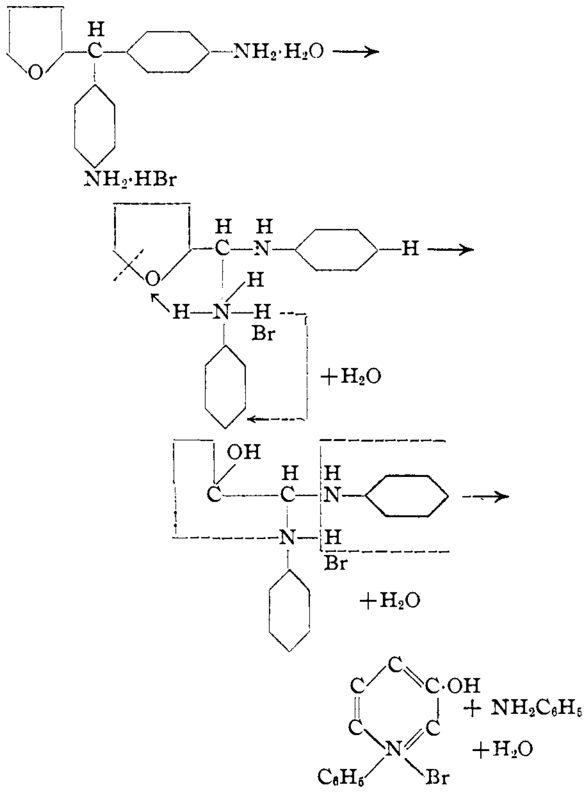
On boiling with glacial acetic acid, Schiff base gives free aniline, and a tarry residue, from which 1-phenyl-3-hydroxypyridinium bromide (or chloride) may be extracted. Zincke and Mühlhausen use formula (II) and show how satisfactorily it fits this decomposition



A further support of formula II is the reputed synthesis of Schiff base by the interaction of bromocyanogen, 3-hydroxypyridine and aniline, a synthesis due to König. A violet solid results, which[4] on treatment with boiling acetic acid, or with hydrochloric acid in closed tubes, gives free aniline and 3-hydroxy-1-phenylpyridinium bromide.

It will be noted that formula (I) has two free amino groups. We tested for their presence by diazotizing. The base is insoluble in water, but suspended and partly dissolved in alcohol, the diazotizing reaction takes place smoothly. By using weighed amounts and a standard nitrite solution, we found two free groups. The tetrazo body so formed was successfully coupled to a number of intermediates, the dyes isolated, and dye test performed. On the strength of this direct evidence, therefore, formula (I) must be accepted. An objection to it remains, however, unless an acceptable scheme for the formation from it of 1-phenyl-3-hydroxypyridinium bromide can be presented. For this we propose the following.

During the prolonged boiling with acetic acid (twelve hours), at 118°, the molecule reaches a state of predissociation which permits the aniline groups to reverse their position; one group is detached altogether and forms free aniline. The other group remains attached through its nitrogen while, at the same time, the furan ring opens, allowing its oxygen to form a hydroxyl, and satisfying the momentarily unsatisfied fourth bond of the oxygen-adjacent carbon by allowing its union with the nitrogen, in the right position to form a six-membered ring. These changes are outlined below.



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[1] This article, except for additions and further analytical data on freshly prepared samples of a number of the substances, is an abridged edition of a manuscript received on February 11, 1935.—*The Editor.*

[1a] Stenhouse, *Ann.*, **156**, 199 (1870).

[2] H. Schiff, *ibid.*, **201**, 355 (1880), and *ibid.*, **239**, 349 (1887).

[3] Zincke and Mühlhausen, *Ber.*, **38**, 3825 (1905).

[4] W. König, *J. prakt. Chem.*, **69**, 105 (1904).

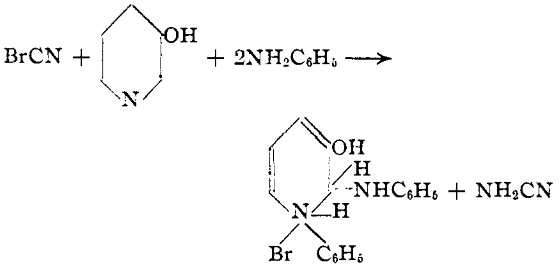
(a) In this proposal, contrary to the assumption of Zincke and Mühlhausen, the furan ring is preserved during the formation of Schiff base. This is reasonable, for furfuraldehyde, aniline, and aniline hydrochloride (or bromide), in molecular proportions, dissolved in alcohol, react almost instantaneously even at room temperature. There is an evolution of heat, and the temperature rises to not more than 35°. At such low temperature, the furan ring may well persist during the gentle reaction.

(b) The furan ring persists in the condensation with dimethylaniline, in the presence of dehydrating and oxidizing agents, with formation of the furyl analog to Malachite Green,[5] also in the formation of the analog to Brilliant Green.[6] There are no additional influences present in the synthesis of Schiff base which would tend to open the ring; such reagents as zinc chloride, oxalic acid, or lead peroxide are absent.

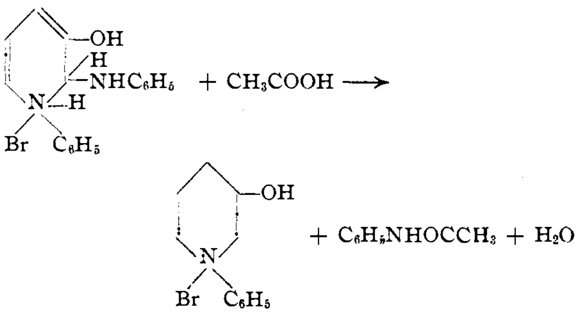
(c) During the boiling with glacial acetic acid, according to our explanation, the aniline group is assumed to reverse; a similar reversal is considered commonplace in the formation of benzidine. It is not said that every molecule undergoes just this reversal but only a certain percentage corresponding to the yield of the pyridinium bromide; many molecules are disturbed to an even greater extent, and in other directions, as is shown by the great amount of tarry and resinous matter simultaneously formed. The best yield of N-phenyl-$\beta$-hydroxypyridinium bromide was 30%.

(d) The formation of a six-membered ring from a five-membered one was demonstrated by Ciamician and Dennstedt[7] by acting upon pyrrole with sodium ethylate and bromoform, $\beta$-bromopyridine was formed. Again, Dennstedt and Zimmermann found that pyrrole with methylene iodide and sodium methylate gave pyridine, although in very small yields.[8] The pyrogenic transformation of N-benzylpyrrole to $\beta$-phenylpyridine and that of $\alpha$-methylpyrrole to pyridine apply also, even though in those cases the temperatures were higher.[9] These transformations show the readiness of formation of six-membered rings containing nitrogen.

As to the violet body produced by the König synthesis,[4] we repeated the condensation and tested the resulting material for the presence of free amino groups; they were found to be absent. The reaction, following König's own interpretation, must, therefore, be written



On heating the König substance with glacial acetic acid, there is indeed formed 3-hydroxy-1-phenyl-pyridinium bromide



but this shows merely that the six-membered pyridine, present in the first place, persisted unchanged through the several steps of reaction and decomposition.

Zincke and Mühlhausen emphasize that, from both bodies, 1-phenyl-3-hydroxypyridinium bromide is obtained, and that a mixed sample of the products still gives the proper melting point. That the two violet substances (both bromides) are alike, is less clearly claimed in the article of Zincke and Mühlhausen, but Dieckman and Beck make the statement that both substances,[10] after drying *in vacuo* at 50° to constant weight, melt with decomposition at 166°. No melting point of mixed samples of the base is reported. We consider our test with nitrous acid as more searching.

## Experimental

**Schiff Base.**—Example of preparation, using tenth mole: 12.95 g. recrystallized aniline hydrochloride was dissolved in 150 cc. of 95% alcohol on the water-bath. After cooling, 9.3 g. of freshly redistilled aniline was added, followed by 9.6 g. of freshly redistilled furfural. The solution turned red immediately, heat was evolved, and in two to three minutes violet crystals in the form of rosettes formed on the

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(5) Renshaw and Naylor, This Journal, **44**, 862 (1922).

(6) Mahood and Harris, *ibid.*, **46**, 2810 (1924); Mahood and Harris, *ibid.*, **52**, 4477 (1930).

(7) Ciamician and Dennstedt, *Ber.*, **14**, 1153 (1881).

(8) Dennstedt and Zimmermann, *ibid.*, **18**, 3316 (1885).

(9) Ciamician and Silber, *ibid.*, **20**, 1368 (1887).

(10) Dieckman and Beck, *ibid.*, **38**, 4122 (1905).

TABLE I

DYES MADE BY COUPLING TETRAZOTIZED DIANILINOFURYLMETHANE HYDROBROMIDE WITH THE LISTED INTERMEDIATES

| | Color of powdered dye | Nitrogen, % Found | Calcd. | 2% dye test on wool |
|---|---|---|---|---|
| S-acid dye | Dark maroon | 10.29 | 10.40 | Dark maroon |
| Schaeffer's acid dye | Brick-red | 7.08 | 7.218 | Dull orange |
| Chromotropic acid dye | Maroon | 5.67 | 5.774 | Vieux rose |
| H acid dye | Dark maroon | 8.25 | 8.32 | Cold red |
| α-Naphthol dye | Brick-red | 9.91 | 10.02 | .... |
| J acid dye | Red-brown | 10.1 | 10.397 | Burnt orange |
| R acid dye | Red powder, dull scarlet | 5.59 | 5.70 | Orange |
| S-S acid dye | Dark red | 8.12 | 8.32 | Magenta |
| Koch acid dye | Red powder | | | Orange |

walls of the dish. In five minutes, the dish was filled with crystals, which were filtered, washed with cold alcohol, and dried. The yield was 24 g., or 80%.

The bromide prepared from aniline hydrobromide was white. The other reactants were not far from colorless. The product made from the hydrochloride was violet, but the product made from the hydrobromide consisted of blue black crystals. Crystallization from hot absolute alcohol was satisfactory.

**Titration.**—As an example, 2.92 g. of the hydrochloride was suspended in 200 cc. of 95% alcohol, acidified with 1 cc. of concd. hydrochloric acid and kept cold by immersion in ice and water. Normal sodium nitrite was then run in from a buret; more acid was added at intervals, after tests with congo paper. Free nitrous acid was detected by a smear on filter paper, with freshly prepared iodide-starch paste, compared in every case to a test with the starch paste alone, in order to discount more readily the effect of the yellow tetrazotization product. After 18 cc. had been added, the violet color had vanished, the solution was brown, with a yellow brown solid in suspension. After 20.5 cc. of nitrite solution had been added, a positive test for free nitrous acid was obtained; this volume indicates the presence of two amino groups. Calcd. for two amino groups, 20.0 cc. of nitrite solution; consumed, 20.5, 20.2 cc.

For the hydrobromide, calcd. for 3.37 g., 20 cc.; found, 20.1, 20.5.

In order to eliminate any possibility of consumption of nitrite by an impurity, 2.92 g. of the hydrochloride was rubbed with 150 g. of ether in several portions, filtered and the ether evaporated. The loss of weight for the solid was 0.04 g. The residue from the ether extract weighed less than 0.04 g., and did not have the odor of aniline. The 2.84 g. of washed solid was titrated, and found to consume the proper volume of nitrite solution.

The tetrazotized dianilinofurylmethane hydrobromide was coupled with a number of intermediates, as listed in Table I. The procedures were the standard ones. The dyes were purified, and the analysis and dye test were made on the powder. The regular Dumas method was used; the results confirmed earlier ones run with a micro-Dumas method.

Several other condensation products were prepared in order to establish the persistence, if possible, of the primary amino group, using homologs of aniline, substituted anilines and related substances. The following three were titrated with the result indicated, in agreement with the proposed formula and theory:

| Condensation product using tenth moles of each substance named | Number of amino groups present by titration | Appearance of condensation product |
|---|---|---|
| *p*-Toluidine, *p*-toluidine hydrochloride, furfural | Two | Glossy violet crystals |
| Xylidine, xylidine hydrochloride, furfural | Two | Violet crystals |
| Dimethylaniline, aniline hydrochloride, furfural | One | Light violet flat crystals |

For a successful condensation leading to a crystallized product, there seems to be necessary the aromatic amine, an amine hydrochloride or bromide, and furfural. The amine or its salt may be substituted, but not both. Two moles of dimethylaniline, one mole of hydrochloric acid and one mole of furfural gave no reaction.

| Condensation product using a tenth mole of each substance named | Result |
|---|---|
| *m*-Nitraniline, aniline hydrochloride, furfural | Small dark-red crystals |
| *m*-Nitraniline, *m*-nitraniline hydrochloride, furfural | Small copper colored crystals |
| *p*-Nitraniline, aniline hydrochloride, furfural | Bluish-purple crystals |
| Sulfanilic acid, aniline, furfural | Dark green crystals |
| Benzidine two-tenth moles, hydrochloric acid, furfural | Dark brown crystals |

Benzidine and furfural, without acid addition, also reacted, in disagreement with the suggestion made above. It may be that the character of benzidine permits it to act like aniline hydrochloride in this respect.

The *p*-toluidine body, ditoluidinofurylmethane hydrochloride, was tetrazotized, and couplings performed with six intermediates; the dyes were isolated in powder form, but not purified. Similarly, dixylidinofurylmethane hydrochloride was tetrazotized and coupled with five intermediates.

β-Pyridine sulfonate was prepared by the method of Hans Meyer in the form of the ammonium salt; the yield was 17%.[11] β-Hydroxypyridine was prepared by fusing the β-pyridine sulfonate with sodium hydroxide in a silver crucible, at 170–178°[12]; the yield was very low. The modification suggested by Fischer[13] was no better. Just enough product melting at 129° was obtained for the synthesis which follows.

**Pyridine Dyestuff According to König.**—10.6 g. of bromocyanogen (one-tenth mole) and 18.6 g. of aniline (two-

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[11] Hans Meyer and Wolfgang Ritter, *Monatsh.*, **35**, 765 (1914).

[12] Weidal and Murmann, *ibid.*, **15**, 761 (1895).

[13] Fischer and Renouf, *Ber.*, **17**, 763 (1884).

tenths mole), both in water, were added to 7.9 g. of pyridine (one-tenth mole) in the cold; a red color appears at once, and after a few moments, a red-violet solid separates. The yield is nearly quantitative. The same reaction takes place in ether. The product was recrystallized from alcohol. Suspended in alcohol with the proper acidity provided, neither the crude product nor the purified material reacted with nitrous acid.

The same reaction was performed with $\beta$-hydroxypyridine, bromocyanogen and aniline in ether. The product was a bluish-black crystal mass, which did not react with nitrous acid. Bromocyanogen was prepared by the method of of Scholl[14] with excellent results, provided the potassium cyanide solution was added drop by drop, to the bromide covered with a little water, and well-cooled in an ice-bath.

**1-Phenyl-3-hydroxy Pyridinium Bromide and Chloride.**—By refluxing Schiff base with glacial acetic acid for twelve hours, a black tarry material was formed which after extraction with acetone was further extracted with hot water, in order to obtain the pyridinium salt. After recrystallization from alcohol, the proper melting points were recorded. Boiling Schiff base with alcohol instead of acetic acid gave a much smaller yield, and the boiling had to be continued for forty-eight hours.

## Summary

The violet substance known as Schiff base has been shown to possess two free amino groups; therefore the formula originally suggested by Schiff representing it as a derivative of diphenylfurylmethane, should be favored over that proposed by Zincke, an open chain compound with unsaturation. The main support for this latter formula is the formation of 1-phenyl-3-hydroxypyridinium bromide or chloride, by glacial acetic acid treatment, but a reasonable explanation for its formation from the dianilinofurylmethane structure is given, so that this possible objection to the original formula of Schiff is removed.

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[14] Scholl, *Ber.*, **29**, 1822 (1896).

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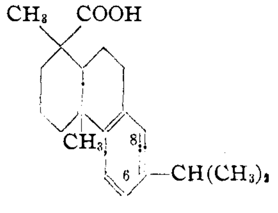
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

# Substitution Reactions of Dehydroabietic Acid. II

BY WILLIAM P. CAMPBELL AND MORLEY MORGANA

Dehydroabietic acid[1] (I) is a readily available hydrophenanthrene derivative which offers promise of becoming a useful starting material for the synthesis of industrially or physiologically important products, by the introduction of suitable substituents into the aromatic ring and by alteration of the carboxyl group. It was with this ultimate goal in mind that this series of investigations was undertaken. One derivative of the type indicated, 6-hydroxydehydroabietinol (II),[2,2a] has been found to possess considerable oestrogenic activity.

Of the limited number of substitution products of dehydroabietic acid that have been reported, only those derived from the 6- and 8-acetyl derivatives[1b,2] are of known structure. No positive evidence has been brought forward concerning the location of the substituents in sulfodehydroabietic acid (III)[1b,3] or in the dinitro (VII),[1,4] or the nitro-sulfo (XI)[5] derivatives. In this work the position of the sulfonic acid group in these compounds is established and one of the nitro groups is definitely located. In addition, new derivatives of dehydroabietic acid are reported together with a new route to the important 6-amino and 6-hydroxy compounds.



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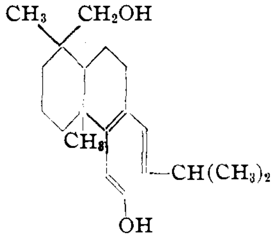

II

The sulfonic acid group of sulfodehydroabietic

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[1] (a) Fieser and Campbell, THIS JOURNAL, **60**, 159 (1938); (b) **60**, 2631 (1938).

[2] Fieser and Campbell, *ibid.*, **61**, 2528 (1939).

[2a] Another derivative, 6-dimethylaminodehydroabietinol methyl ether hydrochloride,[2] has been tested for analgesic activity by Dr. Nathan B. Eddy through the courtesy of Dr. Lyndon F. Small. His report follows: "Toxicity—Only two dose levels were given to mice, 300 and 500 mg. per kg. Only mild depression was seen, without apparent change in reflex activity or coördination, and with little muscular weakness even with the larger dose. It is presumed that the fatal dose would lie well above 500 mg. per kg. Analgesic effect —Doses of 100 and 200 mg. per kg. were administered orally to cats. Very slight depression followed the larger dose but there was no analgesic effect. The substance was not emetic in the doses administered." Thus the compound is relatively inactive in all respects.

[3] Fanica, *Bull. inst. pin*, **44**, 151 (1933); Hasselstrom, *et al.*, THIS JOURNAL, **60**, 1267, 2340 (1938).

[4] Johansson, *Arkiv. Kemi. Min. Geol.*, **6**, No. 19 (1917).

[5] Hasselstrom and Hopkins, THIS JOURNAL, **63**, 421 (1941).