The amount of product obtained in both procedures is about the same—yields amount to about 55% of theoretical. However, the derivative prepared in acetic acid (Procedure II) usually required less recrystallization and consequently gave higher yields. This may be attributed to the fact that in heating the reaction mixture, some disproportionation products must be removed by recrystallization.

In general it was found that the aliphatic amides gave purer initial products than the aromatic amides, possibly due to their greater solubility in the condensing medium and consequent decreased contamination of the derivative with amide.

Summary

The N-xanthyl derivatives of 22 amides have been prepared by one or both of two standard, very simple procedures. These procedures eliminate the necessity for hydrolysis of the amides in the process of their identification. The N-xanthyl derivatives are crystalline, easily purified compounds, well adapted to identification purposes.

CAMBRIDGE, MASSACHUSETTS
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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, FACULTAD DE CIENCIAS EXACTAS, FÍSICAS Y NATURALES, UNIVERSITY OF BUENOS AIRES]

Alkoxyl Interchange by γ-Alkoxyquinoline Derivatives in Alcoholic Alkali

BY B. BERINZAGHI, V. DEULOFEU, R. LABRIOLA AND A. MURUZABAL

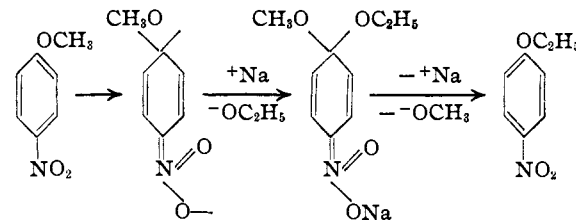
In a preliminary study of the alkaloids of *Fagara coco*, skimmianine (β-fagarine) and γ-fagarine whose structures were then unknown, De Langhe found that they were altered by the action of alcoholic alkali. The demonstration that β-fagarine is identical with skimmianine and that γ-fagarine is a methoxy-dictamine[1] has prompted us to make a more detailed study of the reaction involved.

We have demonstrated that under the influence of alcoholic alkali, there is produced an interchange of the methoxyl group at the γ position of the pyridine ring and the alkoxyl group of the particular alcohol used. In this manner skimmianine has been transformed into the corresponding ethoxy and propoxy derivatives and γ-fagarine into an ethoxy analog. The new alkoxy derivatives so obtained may be reconverted into the original alkaloids by the action of alkali in methanol.

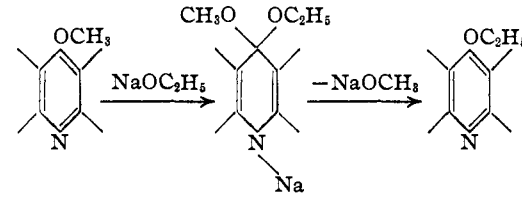
That the interchange alters no other portion of the molecule is also demonstrated by the observation that oxidative degradation of the new derivatives yields the same dihydroxyquinoline as the original compounds.[1,2] The ethoxy analog of skimmianine, moreover, when treated with methyl iodide, eliminates the ethoxyl group and is converted into the known compound iso-skimmianine[2] in which the γ-position is occupied by a carbonyl group.

Interchange of alkoxy groups in alkaline media apparently has not been studied among alkoxypyridines or -quinolines. Similar reactions have been described, however, among other compounds. Fox and Bogert[3] recently described analogous reactions of 6-methoxy-7-nitrobenzothiazole, and Hodgson and Habeshaw[4] have made similar observations upon ethers of 4-nitrophenol.

We believe that many of these cases are similar in nature and may be given a common explanation. According to classical theory, nitro derivatives give rise to quinonoid structures, permitting the addition of the reagent with a subsequent reversion to the benzoid form by loss of sodium alkoxide.



Similar transformations also may be postulated for the alkoxyquinolines



Hodgson and Habeshaw explain this inter-

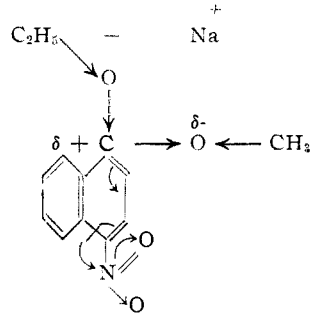
(1) Deulofeu, Labriola and De Langhe, THIS JOURNAL, 64, 2326 (1942).

(2) Asahina and Inubuse, *Ber.*, 63, 2052 (1930).

(3) Fox and Bogert, THIS JOURNAL, 63, 2996 (1941).

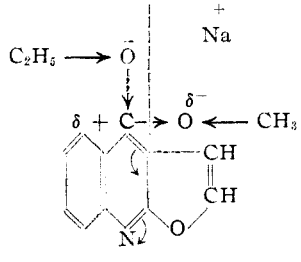
(4) Hodgson and Habeshaw, *J. Chem. Soc.*, 45 (1942).

change on a basis of the inductive effect (−I) of the nitro group, the other benzene ring, and of the methoxyl group itself which renders carbon 1

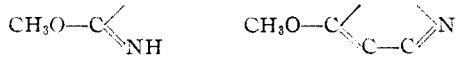


very cationoid and easily attacked, therefore, by the ethylate cation.

The same interpretation is valid for the γ-alkoxyquinolines, although the nitrogen of the ring should have less of an inductive effect than the nitro group, even though in these alkaloids the oxygen of the furan ring contributes to the inductive effect.



This substitution may also be interpreted in terms of the principle of vinylogy, considering the γ-alkoxyquinolines as vinylogs of imido esters, as is easily seen from the formulas below.



Experimental Part

Ethoxy Analog of Skimmianine.—A sample of 500 mg. of skimmianine was dissolved in 100 ml. of 10% potassium hydroxide in ethanol, and the solution heated to boiling. On throwing into 250 ml. of water, a crystalline precipitate was obtained. After twenty-four hours it was filtered, washed with water and recrystallized from ethanol as large colorless needles, melting at 138°; yield, 75%.

Anal. Calcd. for $C_{15}H_{15}O_4N$: C, 65.93; H, 5.50; N, 5.12. Found: C, 66.28; H, 6.06; N, 5.17.

Picrate of the Ethoxy Analog of Skimmianine.—Obtained by mixing a solution of the ethoxy derivative with a saturated solution of picric acid, the compound formed prisms from alcohol which melted at 194° (mixed m. p. with skimmianine picrate melting at 194°, 187°).

Anal. Calcd. for $C_{15}H_{15}O_4N \cdot C_6H_3O_7N_3$: N, 11.15. Found: N, 11.40

Iso-skimmianine.—A sample of 500 mg. of ethoxy derivative was treated for four hours in a sealed tube at 100–110° with an excess of methyl iodide. At the end of the period of heating, the solution was evaporated. The residue was dissolved in chloroform, filtered, and the filtrate treated with an excess of petroleum ether, which precipitated crystals of **iso-skimmianine.** After recrystallization from alcohol-acetone, these melted at 188–189°. The product obtained by a similar treatment of skimmianine was identical.

Ethoxy Analog of Skimmianal.—A sample of 1.2 g. of the derivative was dissolved in acetone and treated for one hour with 2.4 g. of potassium permanganate dissolved in acetone. The manganese dioxide was filtered and the ketone solution was evaporated to dryness. By recrystallizing the residue from alcohol, a product was obtained melting at 212°; yield, 200 mg.

Anal. Calcd. for $C_{14}H_{15}O_5N$: C, 60.64; H, 5.41. Found: C, 60.73; H, 5.44.

Phenylhydrazone of the Ethoxy Analog of Skimmianal.—Obtained in the usual way, this compound formed yellow needles melting at 178.5°.

Anal. Calcd. for $C_{20}H_{21}O_4N_3$: N, 11.44. Found: N, 11.54.

Ethoxy Analog of Skimmianic Acid.—The recovered manganese dioxide was treated with hot 10% sodium hydroxide solution and animal charcoal, filtered, and the filtrate was acidified with hydrochloric acid. A crystalline precipitate was obtained melting at 225°; yield, 400 mg.

Anal. Calcd. for $C_{14}H_{15}O_6N$: C, 57.33; H, 5.11. Found: C, 57.48; H, 5.38.

7,8-Dimethoxy-2,4-dihydroxyquinoline.—A sample of 0.74 g. of ethoxy derivative acid was treated with 85 ml. of 30% hydrochloric acid, and heated until total solution occurred (four hours). On chilling, crystals were obtained which melted at 249–250° after three recrystallizations from alcohol–water. There was no depression of the m. p. when mixed with authentic 7,8-dimethoxy-2,4-dihydroxyquinoline, and the nitroso derivatives (m. p. 246°) are also identical.

Propoxy Analog of Skimmianine.—One gram of skimmianine was boiled for one hour with 20 ml. of 5% potassium hydroxide in propanol. The product obtained was recrystallized from ligroin in the form of colorless needles melting at 95°.

Anal. Calcd. for $C_{16}H_{17}O_4N$: C, 66.89; H, 5.92; N, 4.87. Found: C, 67.19; H, 5.61; N, 5.17.

Picrate of the Propoxy Analog of Skimmianine.—Obtained in the usual way, this substance formed yellow prisms of m. p. 179–180°.

Anal. Calcd. for $C_{16}H_{17}O_4N \cdot C_6H_3O_7N_3$: N, 10.85. Found: N, 11.23.

Reconversion of the Analogs to Skimmianine.—The alkoxy derivatives when treated with 5% potassium hydroxide in methanol for one hour at 100° were converted into skimmianine, melting at 177–178°, which gave no depression when mixed with the original product. The picrate of recovered skimmianine melted at 194°.

Ethoxy Analog of γ-Fagarine.—A sample of 500 mg. of γ-fagarine was treated in the manner indicated above

with 100 ml. of alcoholic potassium hydroxide. On recrystallization from alcohol, rhombs were obtained, melting at 143° (mixed with γ-fagarine of m. p. 140°, 130°). The yield was 66%.

Anal. Calcd. for $C_{14}H_{13}O_3N$: C, 69.13; H, 5.34; N, 5.76. Found: C, 68.99; H, 5.08; N, 5.79.

Picrate of the Ethoxy Analog of γ-Fagarine.—Obtained from alcohol by the method described, in the form of large yellow prisms, the substance melted at 161°.

Anal. Calcd. for $C_{14}H_{13}O_3N \cdot C_6H_3O_7N_3$: N, 11.86. Found: N, 12.10.

Reconversion of the Ethoxy Analog to γ-Fagarine.—The ethoxy analog of γ-fagarine when treated for two hours with 10% methyl alcoholic potassium hydroxide at 90–100° is converted into γ-fagarine, m. p. 139–141°, showing no depression of m. p. when mixed with the original alkaloid. The picrate melts at 178–179°.

Ethoxy Analog of γ-Fagaric Aldehyde.—A sample of 0.5 g. of the ethoxy analog of fagarine was dissolved in 40 ml. of acetone and slowly treated while warm with 1 gram of potassium permanganate in acetone solution. After the oxidation, the manganese dioxide was filtered off and the filtrate evaporated to dryness. The residue recrystallized from alcohol as yellow needles of m. p. 192–193°. The yield was 228 mg.

Anal. Calcd. for $C_{13}H_{13}O_4N$: C, 63.15; H, 5.26. Found: C, 63.19; H, 5.37.

Phenylhydrazone of the Ethoxy Analog of γ-Fagaric Aldehyde.—Prepared essentially as described, this substance formed yellow plates, melting from 185–186°.

Anal. Calcd. for $C_{19}H_{19}O_3N_3$: N, 12.46. Found: N, 12.64.

Ethoxy Analog of γ-Fagaric Acid.—The manganese dioxide from the previous experiment was extracted with 10% sodium hydroxide. The alkaline solution was boiled for ten minutes, filtered, concentrated, and acidified with dilute hydrochloric acid. The crystalline precipitate thus obtained was recrystallized from acetic acid. Needles melting at 210–211° were obtained: yield, 210 mg.

Anal. Calcd. for $C_{13}H_{13}O_5N$: N, 5.32. Found: N, 5.49.

The same acid is obtained by further oxidation of the ethoxy analog of γ-fagaric aldehyde, m. p. 210–211°.

Methoxy-2,4-dihydroxyquinoline.—A sample of 0.38 g. of the ethoxy analog of γ-fagaric acid was treated with 50 ml. of 30% hydrochloric acid and heated with reflux until total solution. On chilling, crystals came down, which, after recrystallization from 50% alcohol, were small needles, m. p. 250°. The substance obtained from γ-fagarine following the same treatment gave no depression of the melting point, and the nitroso derivatives are also identical.

Summary

1. The action of alkali in alcohol solutions upon skimmianine (β-fagarine) and γ-fagarine has been found to consist of an interchange between the γ methoxyl of these alkaloids and the alkoxyl group of the solvent alcohol.

2. The new alkoxy analogs and several of their derivatives have been described.

3. The reconversion of the new alkoxy analogs into the original alkaloids by action of alkali in methanol has been observed.

4. Possible mechanisms of the changes have been discussed.

BUENOS AIRES, ARGENTINA RECEIVED MARCH 19, 1943

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

New Methods for the Purification of Invertase and Some Properties of the Resulting Products[1]

BY MILDRED ADAMS AND C. S. HUDSON

These investigations on the purification of invertase from yeast were undertaken to develop methods of more general applicability than those reported hitherto. For this purpose we have employed bentonite, previously reported[2] to be an excellent adsorbent for invertase, and several precipitants which we have also found useful in the purification of this enzyme

A critical study has been made of the factors important in obtaining reproducible results in the purification of invertase and our experiments have been carried out with a view to establishing methods as simple as were consistent with maximal purification. As a result, procedures were established which could be used not only for yeast from a constant source, but also for yeast from different sources, and, in spite of marked variations in the invertase content of the starting materials, relatively small differences were noted in the purity of the resulting products. Furthermore, the methods which we have developed are considerably less involved than those generally used, yet the resulting purification was equal to or greater than that produced by the majority of methods reported in the literature.

Our preparations appeared to be protein in

(1) Original manuscript received December 24, 1941.

(2) Adams and Hudson, THIS JOURNAL, **60**, 982 (1938).