

ation with formalin and NaBH_4 gave a product (IV), mp 220—222° (decomp.). O-Methylation of IV with diazomethane resulted in the compound III, mp 139—141°, which was proved to be completely identical with O-methylerybidine by mixed mp and comparisons of IR (CHCl_3) and NMR spectra.

The position of a hydroxyl group in the molecule of erybidine was defined by the comparison of NMR spectra of compounds III, IV and erybidine.

The methoxyl signals of compound III showed at 6.08 τ and 6.14 τ as two six-proton singlets, and in the compound IV, lacking 3,11-methoxyls, only one six-proton singlet at 6.15 τ was observed. Then, it is deduced that the signal at 6.08 τ is attributable to 3- and/or 11-methoxyls and that at 6.14—6.15 τ to 2- and/or 12-methoxyls, respectively. We suggested, by comparison with these assignments, that in the NMR spectrum of erybidine, three-proton singlet at 6.08 τ would be due to 3- or 11-methoxyl, and six-proton singlet at 6.13 τ is to 2- and 12-methoxyl groups, and hence the hydroxyl group must be attached to 3-(or 11-)position of dibenz(*d,f*)azonine moiety.

On the basis of these evidences, the structure of erybidine should be assigned to the formula II.

From the view point of biosynthesis, it is interest that we isolated the dibenz(*d,f*)azonine type base which was postulated as one of the intermediates of Erythrina alkaloids biosynthesis,⁶⁾ in addition to some erythrinan type bases.

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5) This compound was supplied generously by Dr. D.A. Widdowson.

6) D.H.R. Barton, R. James, G.W. Kirby, D.W. Turner, and D.A. Widdowson, *J. Chem. Soc. (C)*, **1968**, 1529.

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Metabolism of Benzydamine Hydrochloride

Benzydamine hydrochloride (BZY) is a non-steroid anti-inflammatory agent. It has been reported that about 50% of the administered drug in men and about 30% in rats were excreted in the urines,¹⁾ but the conclusive information concerning its metabolites are not available. We studied the metabolic pathway of BZY by means of its strong fluorescence and identified some metabolites.

BZY was administered orally at a dose of 200 mg/kg to rabbits and the 24 hr urine adjusted pH 5 was extracted with CHCl_3 . About 20% of fluorescence excreted in the urine was extracted into this fraction. After concentrating and dissolving the residue into a small amount of CHCl_3 , thin-layer chromatography (TLC) was carried out on Silica gel HF₂₅₄ (0.25 mm) developing by a solvent system of benzene: CHCl_3 : MeOH: EtOH: conc. NH_4OH (15: 15:10:5:0.5). At least four spots were visualized with Dragendorff reagent ($R_f=0.13, 0.25, 0.40, 0.80$). A spot of $R_f 0.80$ was indistinguishable with authentic BZY. The main spot,

1) B. Catanese, A. Grasso, and B. Silvestrini, *Arcneim.-Forsch. (Drug Res.)*, **16**, 1354 (1966).

Rf 0.40, was purified by means of polyamide column chromatography (eluted with 50–60% CHCl_3 in benzene) and of preparative TLC. The spot was scraped off under ultraviolet (UV) light and extracted with MeOH. After removing the solvent completely, the remaining material was subjected to mass and nuclear magnetic resonance (NMR) spectrometry. Mass spectrum of *m/e* 285 (M^+) indicated the reduction of CH_2 from BZY. The NMR spectrum of this material in CDCl_3 was the τ values being 7.40 (3H, singlet, $-\text{NCH}_3$), 6.84 (4H, multiplet, $-(\text{CH}_2)_2-$), 5.50 (2H, triplet, $-\text{OCH}_2-$) and 4.70 (2H, singlet, $>\text{NCH}_2-$), while NMR spectrum of BZY was the τ values being 7.77 (6H, singlet, $-\text{N}(\text{CH}_3)_2$), 6.84 (4H, multiplet, $-(\text{CH}_2)_2-$), 5.60 (2H, triplet, $-\text{OCH}_2-$) and 4.70 (2H, singlet, $>\text{NCH}_2-$). Therefore, the spot of *Rf* 0.40 was N-demethylated BZY (nor-BZY). These data were identical with those of authentic nor-BZY²⁾

After extracting with CHCl_3 , the remaining urine was extracted with *n*-butanol saturated with 0.1 M acetate buffer (pH 5.0), but about half of fluorescence still remained in aqueous layer. After removing butanol *in vacuo*, the residues were dissolved into 0.1 M acetate buffer (pH 5.0). No fluorescence was extracted with CHCl_3 from this solution. The incubation of this solution with β -glucuronidase (Tokyo Zokikagaku Co. 300 Fishman U/ml) at 37° for 24 hr. gave several new spots on TLC, *Rf*=0.25, 0.62, 0.70, visualized with Dragendorff, Gibbs and Folin reagents. This fact suggests that these metabolites are phenolic substances and excreted as glucuronides. These metabolites were extracted with CHCl_3 and purified by means of polyamide column chromatography (eluted with 5–15% CHCl_3 in benzene) and of preparative TLC. The main spot, *Rf* 0.62, was scraped off and eluted with MeOH. After removing the solvent completely, the remaining substance was subjected to mass spectrometry. The parent peak was M^+/e 325 indicating the addition of one oxygen atom. Other peaks at *m/e* 107 and 85 corresponded to the molecular ion $\text{H}_2\text{C}^+-\text{C}_6\text{H}_4-\text{OH} \leftrightarrow \text{H}_2\text{C}=\text{C}_6\text{H}_4=\text{OH}^+$ and base ion $\text{CH}_2=\text{CHCH}_2\text{N}^+(\text{CH}_3)_2$, respectively. These data indicated the addition of one oxygen atom into *para*-position³⁾ on benzyl ring of BZY (HO-benzyl-BZY). Another spot, *Rf*, 0.53, which showed pink color by Gibbs reagent was indistinguishable with the authentic

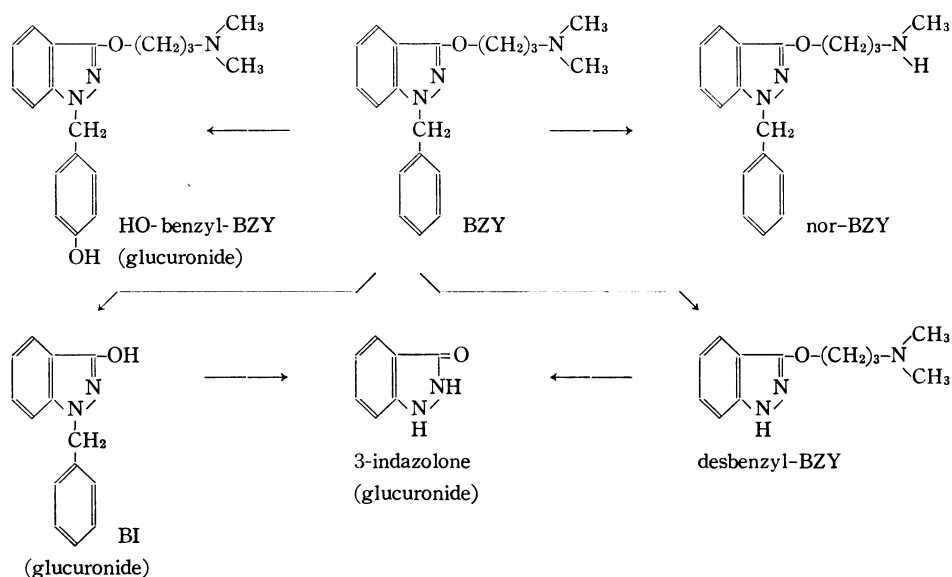


Chart 1. Metabolic Pathway of Benzylamine (BZY)

2) Gift from Dr. Silvestrini.

3) J.S. Shannon, *Austral. J. Chem.*, **15**, 265 (1962).

sample of 3-indazolone²⁾ on TLC. After extraction of hydrolysate with CHCl_3 , over half of fluorescence remained in aqueous layer and the identification for these material is in progress.

Other experiments in which the urines were extracted with ethyl acetate gave a crystalline metabolite, mp 167–168° (uncorr.). Its mass spectrum was m/e 224 (M^+). The NMR spectrum in CDCl_3 showed chemical shifts, 4.72 (2H, singlet, $\text{>NCH}_2\text{-}$) and 5.20 (1H, singlet, -OH or >NH). These data were identical with those of authentic sample of 1-benzylindazolone (BI).²⁾ TLC of ethyl acetate extract gave another spot. This metabolite was also purified by TLC. Its mass spectrum was m/e 219 (M^+) and NMR spectrum in CDCl_3 was the τ values being 5.90 (1H, singlet, -OH or >NH) and 2.30 (1H, singlet, -OH or >NH). These data indicated that this metabolite should be desbenzylated BZY (desbenzyl-BZY).

The following scheme is proposed as the metabolic pathway of BZY.

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Total Synthesis of Flavanantine and Bracteoline by a Photo-Pschorr Reaction

Previously,¹⁾ we reported a total synthesis of flavinantine (I) by debenzoylation of the morphinandienone (II), which was obtained by a modified Pschorr reaction^{2–4)} of the aminoisoquinoline (III) derived from the 1-(2-nitrobenzyl)-isoquinoline (IV). The nature of the reaction of the above synthesis, however, possessed fundamental defects. The first one was regarding the reduction of IV to the aminoisoquinoline (III); the debenzoylation occurred as a side reaction and, therefore, it was necessary to separate III from by-products. The second defect was that, in the debenzoylation of II to flavinantine (I), several rearranged products were obtained because the morphinandienone was unstable in acid. Therefore, we examined the modified synthesis of the morphinandienone alkaloids. Herein we wish to report total synthesis of flavinantine and bracteoline by a photo-Pschorr reaction.⁵⁾

The nitration of O,O-dibenzylorientaline (V),⁶⁾ followed by the reduction of the 2'-nitrobenzylisoquinoline (VI) with zinc and hydrochloric acid, gave the corresponding amino-derivative. Debenzoylation of this product in boiling hydrochloric acid, followed by separation as usual, gave 6'-aminoorientaline (VII).

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