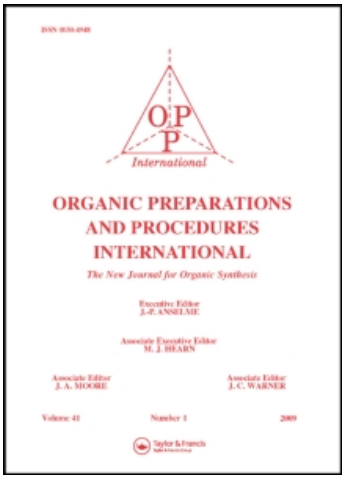

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THE SYNTHESIS OF α-ACETOXYBENZYLBENZYLNITROSAMINE†

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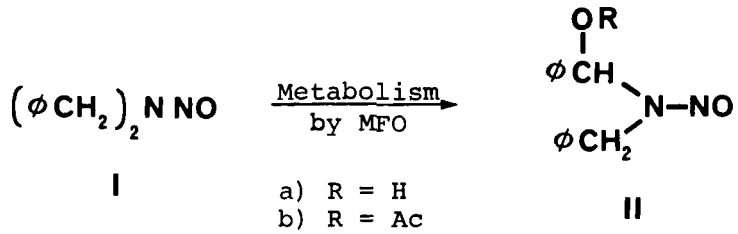
N-Nitrosodibenzylamine (I) is one of only a few nitrosamines which have been shown to be both non-mutagenic[1] and non-carcinogenic.[2] These results were unexpected since this compound should be readily metabolized to the α-hydroxy derivative in view of the highly acidic nature of its α-hydrogens.[3] This lack of activity could result from the failure of the N-nitrosodibenzylamine (I) to undergo metabolic oxidation to IIa (Eq. 1) or could reflect the failure of the benzyl carbocation to alkylate the nucleic acids because of its stability.[4] In order to elucidate this point, the "chemical oxidative metabolism" of I was attempted. The α-acetoxybenzylbenzylnitrosamine (IIb) was chosen as the stabilized metabolite and this paper describes its synthesis.



I

a) R = H
b) R = Ac

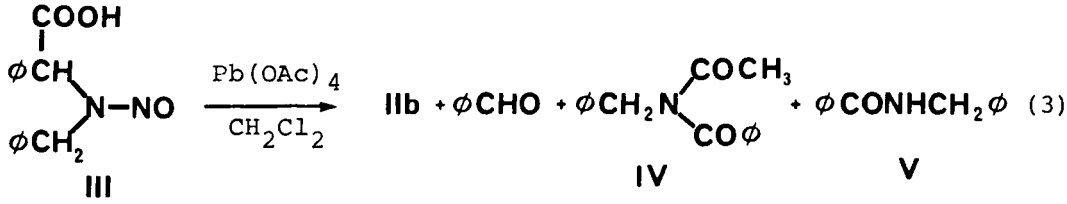
II

(1)

Adaptation of the synthesis of α-acetoxy dimethylnitrosamine[5] to the preparation of α-acetoxybenzylbenzylnitrosamine (IIb) did not give useful results (Eq. 2). Only trace amounts of IIb were detected in the product mixture by TLC along with several compounds which were not characterized.

$$\phi CHO + \phi CH_2NH_2 \cdot HCl \xrightarrow[AcOH]{NaNO_2} IIb + \phi CHO + \text{Other Products} \quad (2)$$

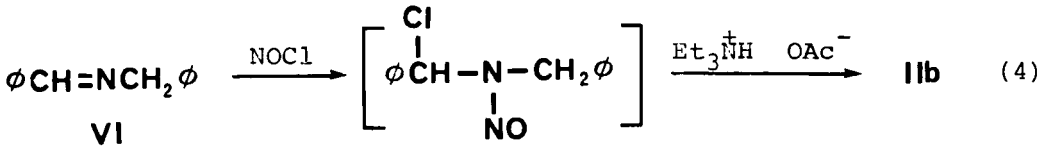
Although the oxidative decarboxylation of N-nitroso-N-benzyl-α-phenylglycine (III) with lead tetraacetate[6] gave a 25-29% yield of IIb, the product mixture also contained benzaldehyde, N-acetyl-N-benzylbenzamide (IV) and N-benzylbenzamide (V).



(3)

The procedure for the synthesis of a variety of derivatives of α-hydroxynitrosamines reported by Wiessler[7] was adapted to the synthesis of IIb. Addition of nitrosyl chloride across the double bond of N-benzylbenzaldimine (VI)[8] followed by treatment of the product with triethylammonium acetate (VII) produced IIb in 40% yield. The compound was separated from side-products by crystallization from petroleum ether. This procedure is by far superior to the other two methods with respect to yield, ease of isolation and purification of product, low cost of reagents, and reproducibility. This method

has also been found to be applicable for the preparation of both ^{3}H and ^{14}C labeled α-acetoxybenzylbenzylnitrosamine (IIb).[9]



(4)

In principle, the oxidative procedure of Okada and coworkers,[10] which involves the oxidation of the nitrosamine anion to the hydroperoxide could also provide a convenient route to IIb. Since this route was not as convenient for the preparation of isotopically labeled IIb in the dibenzylamine fragment, this route was not explored.

EXPERIMENTAL

Direct Preparation of α-Acetoxybenzylbenzylnitrosamine (IIb).- To a solution of 31.6 g (0.22 mole) of benzylamine hydrochloride and 23.3 g (0.22 mole) of benzaldehyde in 350 ml of glacial acetic acid in a 1 ℓ round-bottom flask at room temperature was added 27.6 g (0.4 mole) of sodium nitrite in about 70 ml of water over a period of 6 hrs. The warm reaction mixture was cooled in an ice bath and neutralized with a saturated solution of aqueous sodium carbonate. The yellow oil which separated was extracted into methylene chloride. Drying over sodium sulfate followed by evaporation of the solvent gave a yellow, sweet smelling oil. TLC on a silica gel plate and elution with a 3:1 hexane-ether mixture showed the presence of benzaldehyde as the major component and traces of α-acetoxybenzylbenzylnitrosamine (IIb) and several other components.

N-Nitroso-N-benzyl-α-phenylglycine (III).- The synthesis was accomplished by a modification of the procedure of Fraser[11] by using an excess of n-butyllithium (0.052 mole) to form the anion of dibenzylnitrosamine (10 g., 0.044 mole) in 400 ml of

dry THF at -78°. Then solid carbon dioxide (Dry Ice) (40 g) was added at -78°. Work-up gave 9.33 g (79%) of III, mp. 121-123°, lit.[12] 121.5-123°.

Preparation of IIb by Oxidative Decarboxylation of N-Nitroso-N-benzyl-α-phenylglycine (III).- In a 250 ml, three-neck round-bottomed flask was placed 100 ml of dry methylene chloride, and the system was purged with nitrogen for 1 hr. To this oxygen-free system was added 1.6 g (6 mmoles) of N-nitroso-N-benzyl-α-phenylglycine (III) and 0.56 g (7.2 mmoles) of pyridine (dried over KOH and distilled). While a nitrogen atmosphere was maintained over the reaction, 2.5 g (7.2 mmoles) of lead tetraacetate was added and the reaction mixture immediately turned to a gold color. The solution was stirred at 4° for approximately 12 hrs and the precipitated solid was removed by filtration. The organic layer was washed with water, aqueous $NaHCO_3$, 1% HCl and finally water. The methylene chloride layer, after drying, was concentrated under reduced pressure to give a yellow oil which was subjected to preparative HPLC; elution with 3:1 hexane-THF afforded 0.4 g (23%) of a yellow oil which failed to crystallize. The nmr spectrum[1] indicated that the oil consisted of IIb, benzaldehyde and N-acetyl-N-benzylbenzamide (IV).

Preparation of α-Acetoxybenzylbenzylnitrosamine (IIb).- To a solution of 2.0 ml (0.043 mole) of nitrosyl chloride in 100 ml of methylene chloride was added dropwise with stirring 8.4 g (0.043 mole) of freshly distilled N-benzylbenzaldimine (VI)[8] at -30°. The red color of nitrosyl chloride soon disappeared leaving a clear yellow solution which was allowed to stir at -30° for 10 minutes. To this solution was added dropwise, 6.93 g (0.043 mole) of triethylammonium acetate (VII) in 25 ml of methylene chloride. After addition of the salt was complete, the solution was allowed to stir at -30° for 15-20 min; the cooling bath was removed and the temperature was gradually allowed to become ambient. The solution was washed with three 100 ml portions of tap water and dried over anhydrous sodium sulfate. Filtration followed by evaporation of the solvent under reduced pressure gave an amber oil which crystallized

upon trituration with petroleum ether. Recrystallization from ether-petroleum ether afforded 5.0 g (40%) of IIb as pale yellow prisms, mp. 46.5-48°, lit.[1] mp. 52-53°. ^{1}H NMR ($DCCl_3$): δ 1.88 (s, $C\underline{H}_3CO$), 3.70, 3.98, 4.70, 4.98 (q, $C\underline{H}_2Ph$), 7.0 (m, Ar$\underline{H}$), 7.93 (s, C$\underline{H}$Ph).

BIOLOGICAL ACTIVITY

Chronic Administration of α-Acetoxybenzylbenzylnitrosamine to Female F344 Rats.- To assess the carcinogenicity of α-acetoxybenzylbenzylnitrosamine (II) it was administered to each of a group of twenty 8-week old female F344 rats of the colony of the NCI-Frederick Cancer Research Facility as a solution in corn oil (25 mg/ml) by gavage. Treatment was 0.2 ml of solution twice a week for 102 weeks, amounting to a total dose of approximately 1 gram per animal equivalent to 5 grams per kilogram body weight. The treatment did not appear to reduce the lifespan compared with untreated animals and there were 17 animals alive at 106 weeks, 12 alive at 120 weeks, and the survivors were killed at 127 weeks. The animals were carefully necropsied and all lesions and major organs were fixed for histologic examination. Even though it did not lead to life-shortening, most of the rats bore tumors, many of which were of the endocrine system or leukemias which are commonly found in untreated animals of this strain and are not, therefore, attributable to the treatment.

Of the treated animals, 10 died with tumors attributable to the treatment. Nine rats had carcinomas of the forestomach, possibly due to local action of the nitrosamine, and one rat had a carcinoma of the tongue. In addition, one rat had a cholangiocarcinoma of the liver, four had hepatocellular carcinomas in the liver; two rats had alveolar cell carcinomas of the lung, and three had squamous cell or undifferentiated carcinomas of the lung; the lung and liver tumors are seen only very rarely in untreated animals of this strain and can be attributed to the systemic action of the nitrosamine.

α-Acetoxybenzylbenzylnitrosamine (IIb) is definitely carcinogenic to female F344 rats, but is relatively weak since the tumors induced did not lead to life-shortening. The α-acetoxybenzylbenzylnitrosamine was highly mutagenic in the Ames test.[1,14] On the other hand, the parent compound, dibenzylnitrosamine (I), failed to induce tumors in rats after administration of a total of 30 to 40 grams per kilogram body weight[2] and was not mutagenic.[1] In contrast, nitrosomethylbenzylamine is one of the most potent carcinogenic nitrosamines, leading to death of F344 rats with tumors of the esophagus, forestomach and tongue after administration of 70 mg/kg within 6 months[13] or after adminis-

tration of 200 milligrams per kilogram body weight to BD rats during 7 or 8 months.[2]

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