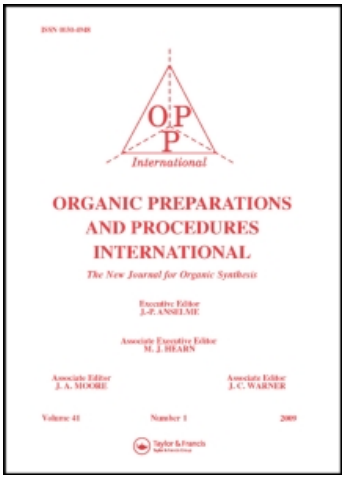

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SYNTHESIS OF DIBENZHYDRYLNITROSAMINE

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SYNTHESIS OF DIBENZHYDRYLNITROSAMINE

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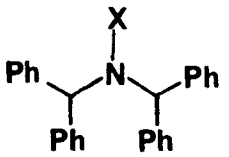
It is now well-accepted that the mutagenic and carcinogenic activity of nitrosamines is due to their α-hydroxylated metabolites.[1] Observable α-hydroxynitrosamines were first synthesized by mild reduction of α-peroxynitrosamines.[2] We had unsuccessfully sought to prepare α-hydroxynitrosamines by direct low-temperature oxygenation[3] of N,N-dibenzylnitrosamine and N,N-dibenzhydrylnitrosamine (1b). While the former is well-known, the latter could not be prepared by standard methodology.[4]



a) X = H b) X = NO c) $X = NO_2$

In contrast to all other dialkylamines (including diisopropylamine) which react virtually instantaneously with nitrosyl chloride in methylene chloride at 0°, dibenzhydrylamine (1a) was totally inert. Lyle et al.[5] have used nitrosyl chloride to nitrosate the sodium salts of secondary amines (tetrahydrofuran (THF) solution at -78°). Although lithium dibenzhydrylamide was unreactive at -78°, it eventually gave an acceptable yield of the desired nitrosamine (1b) with an excess of nitrosyl chloride at ambient temperature.

Acknowledgement.- Financial support was provided by grants from the National Institute of Environmental Health Sciences and the National Science Foundation.

EXPERIMENTAL SECTION

Dibenzhydrylamine (1a).- This compound was prepared from benzhydrylamine and benzhydryl bromide on a 0.2 mol scale. A slight modification (addition of triethylamine to capture the hydrogen bromide liberated during the reaction) of the method of Hauser et al.[7] led to an improved yield (72%). Recrystallization from ethanol-chloroform gave white crystals, mp. 138.5-140.5°, lit.[7] 138-139°; IR ($CHCl_3$): 3300 (w) cm^{-1}; NMR ($CDCl_3$): δ 2.11 (s, 1 H), 4.73 (s, 2 H), and 7.1-7.45 (m, 20 H).

Dibenzhydrylnitrosamine (1b).- n-Butyllithium in hexane (55.0 mmol) was added at -78° under nitrogen to a stirred solution of dibenzhydrylamine (17.5 g, 50.0 mmol) in THF (400 ml). A THF solution of nitrosyl chloride (110 mmol) was added to the lithium amide at -78°, then the mixture was stirred under nitrogen at ambient temperature for 48-72 hrs. The mixture was concentrated to approximately 75 ml, then quenched by pouring it into water (500 ml). The combined ethereal extracts (3 x 200 ml) were washed with brine (1 x 200 ml) and dried ($MgSO_4$). The solvent was removed in vacuo to give a crude reddish-brown oil. Purification was accomplished by flash column chromatography (silica gel H; hexane-benzene (1:1)) to give

14.4 g (76%) of a yellow oil which crystallized on standing. Recrystallization from hexane gave 12.3 g (65%) of white crystals, mp. 96-97°; IR ($CHCl_3$): 1490 (m) cm^{-1}; NMR ($CDCl_3$) δ 5.92 (s, 1 H), 6.9-7.4 (m, 20 H), and 7.10 (s, 1 H); MS (70 eV): m/e 378 (M^+). The assignment of the singlet at δ 7.10 is somewhat speculative. Chemical shift arguments based on diisopropylnitrosamine[7] would place the syn methine hydrogen at nearly this position in the spectrum.

Anal. Calcd for $C_{26}H_{22}N_2O$: C, 82.51; H, 5.86; N, 7.40.

Found: C, 82.74; H, 6.13; N, 7.45.

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ethyl acetate-chloroform gave 2.49 g (63%) of white crystals. By raising the temperature rapidly (~20°/min), the unusually broad melting range could be narrowed to 193-200°. The clear melt soon solidified at this temperature and remelted to a yellow liquid at 255-290° similar to that obtained by slowly heating the substance (~2°/min) to these temperatures. NMR ($CDCl_3$): δ 5.20 (s, 2H) and 7.1-7.8 (m, 20 H); MS (70 eV): m/e 349 (M-45), 272 (M-122), 242 (M-152), 212 (M-182), and 167 (M-227).

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PREPARATION OF THE PALMITATES OF KAHWEOL AND CAFESTOL

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The diterpene esters, kahweol palmitate (1a) and cafestol palmitate (2a), isolated from green coffee beans have been found to induce increased activity of the detoxifying enzyme system, glutathione S-transferase.[1] Administration of compounds 1a and 2a to Sprague-Dawley rats treated with 7,12-dimethylbenz(a)anthracene, resulted in a decrease in the incidence of mammary tumor formation.[2] To study further the effects of 1a and 2a as inhibitors of chemically-induced tumorigenesis, large quantities were required. The yield of 1a and 2a isolated from green coffee beans was less