Selective *N*-Methylations of Heterocycles with Dimethyloxosulfonium Methylide

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Studies in this laboratory on methyltransferases[2] and nonenzymatic methylations of nucleotides[3] have shown the need for model systems capable of preferential or selective methylation. Thus, dimethyloxosulfonium methylide[4] is known to react with acidic NH or OH groups to give the corresponding methylation compounds[5] and also methylates aromatic hydrocarbons, such as anthracene and nitrobenzene.[6]

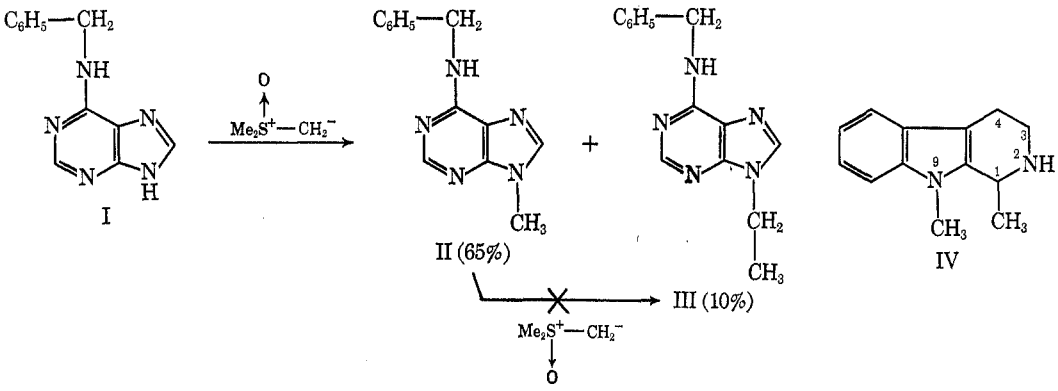
We have extended these observations to *N*-methylation of heterocycles, such as pyrimidines, imidazoles, and pyrroles. In connection with the preparation of cyclothymine nucleosides,[7] we reported that the dimethyloxosulfonium ylide smoothly methylates uracil derivatives at the 1 or 3 positions to give 1-methyluracil or 3-methyluridine, and, in one special case, the sugar hydroxyls were also methylated.[8]

As a model compound for building stones of nucleic acids, 6-benzyladenine (I) reacted with 3 mol of ylide in tetrahydrofuran to give 9-methyl-6-benzyladenine (II), mp 127°, *m/e* 239 (M), in 63% yield, whose structure was confirmed by direct comparison with that of an authentic sample prepared from benzylamine and 6-chloro-9-methylpurine ($\delta_8 - \delta_2 = 9$ Hz in DMSO).[9]

By-product, mp 144°, *m/e* 253 (M), obtained in 10% yield, was identified as 6-benzyl-9-ethyladenine (III) on the basis of nmr, uv, and ir spectra. This ethylation to III indicates alkylation by the rearranged ylide, dimethyloxosulfonium ethylide, since direct treatment of II with excess ylide did not afford the ethyl compound III.

Similarly, benzimidazole was converted to the 1-methyl derivative in 80% yield. In the cases of indole and 1,2,3,4-tetrahydroharman only the pyrrole ring was methylated to give 1-methylindole and 9-methyltetrahydroharman (IV) in almost 90% yield (corrected). This provides a convenient method for *N*-methylation of indole derivatives.[10] Oxindole underwent both *N*- and competitive *C*-alkylation.[11] With an equimolar amount of ylide 1-methyloxindole was obtained (66% yield), while 3 mol of ylide gave 1,3,3-trimethyloxindole (69% yield) in addition to traces of mono- and dimethyl derivatives. By contrast *N*-phenethylbenzamide was completely unreactive.

While *N*-methylase from rabbit lung converts adenine to 3-methyladenine,[12] the ylide reagent leads to 9-methyladenine derivatives. In analogy to the *in vivo* methylation of tRNA from yeast to a 1-methyladenine-containing species by an enzyme from rat tissue,[13] we recently found a methylating model that converts adenosine to 1-methyladenosine and very little 3-methyladenine with concomitant loss of the ribose moiety.[14]



Experimental Section

Melting points are uncorrected. Nmr and mass spectra were determined on a Varian A-60 and a Hitachi RMU-6D instrument, respectively. Chemical shifts and J values are given in τ and hertz, respectively.

General Procedure of Methylation.—Dimethyloxosulfonium methylide was prepared by gently refluxing a suspension of sodium hydride and trimethyloxosulfonium chloride in THF for 2–2.5 hr under N_2.[4] The heterocyclic compounds were added as solids and the mixture was kept boiling gently overnight. After filtration, the solution was evaporated *in vacuo*, and the residue was taken up in organic solvent and washed with H_2O. The products were purified by chromatography on silica gel or by recrystallization.

6-Benzyl-9-methyladenine (II) and 6-Benzyl-9-ethyladenine

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(III).—6-Benzyladenine (I, 1.0 g) was reacted with the ylide prepared from NaH (0.7 g) and trimethyloxosulfonium chloride (4.2 g) in THF. The two main products were obtained pure by chromatography on silica gel (acetone). The minor product (150 mg) eluted faster and was recrystallized from benzene–ligroin to give 9-ethyl-6-benzyladenine III (110 mg) as colorless prisms, mp 141–144°. The nmr spectrum ($CDCl_3$) showed peaks at 8.53 (t, J = 7.5, CH_3), 5.81 (q, J = 7.5, CH_2), 5.07 (d, J = 7.0, benzylic methylene), 2.68 (aromatic), 2.52 (s, H_2), and 1.57 (s, H_8); mass spectrum m/e 253 (M^+); uv λ_{max}^{MeOH} 270 nm.

Anal. Calcd for $C_{14}H_{15}N_5$: C, 66.40; H, 5.93; N, 27.67. Found: C, 66.12; H, 5.98; N, 27.86.

Recrystallization of the major product (670 mg) from benzene–ligroin gave 6-benzyl-9-methyladenine (II) as colorless needles: mp 127–128°; nmr ($CDCl_3$) 6.27 (s, CH_3), 5.09 (d, J = 6.0, $ArCH_2$), 2.70 (aromatic), 2.60 (s, H_2), 1.60 (s, H_8); nmr (DMSO-d_6) 1.90 (s, H_2), 1.76 (s, H_8); mass spectrum m/e 239 (M^+); uv λ_{max}^{MeOH} 270 nm.

Anal. Calcd for $C_{13}H_{13}N_5$: C, 65.27; H, 5.44; N, 29.29. Found: C, 65.28; H, 5.23; N, 28.96.

This product was identical with an authentic sample (mp 128°, nmr, ir, and uv spectra), which was prepared by boiling 6-chloro-9-methylpurine and benzylamine in methyl Cellosolve.

1-Methylbenzimidazole.—Benzimidazole (0.8 g) was reacted with the ylide prepared from NaH (0.8 g) and sulfonium chloride (4.8 g) in THF. 1-Methylbenzimidazole was obtained as an oil (0.74 g), which showed singlet peaks at 6.61 (NCH_3) and 2.33 (H_2) in addition to aromatic protons in the nmr spectrum ($CDCl_3$). The picrate formed in ether was recrystallized from EtOH as yellow needles, mp 250–251°.

Anal. Calcd for $C_8H_8N_2 \cdot C_6H_3N_3O_7$: C, 46.54; H, 3.07; N, 19.38. Found: C, 46.80; H, 3.13; N, 19.21.

1-Methylindole.—Indole (1.17 g) was allowed to react with the ylide prepared from NaH (0.7 g) and sulfonium chloride (4.5 g). The product obtained as a reddish yellow oil was purified by chromatography on silica gel (hexane–benzene). The product obtained as a pale yellow liquid was identical with authentic 1-methylindole with regard to ir and nmr spectra. The nmr spectrum showed peaks at 6.47 (s, NCH_3), 3.60 (d, J = 3.0, 3 H), and 3.16 (d, J = 3.0, 2 H).

9-Methyl-1,2,3,4-tetrahydroharman.—1,2,3,4-Tetrahydroharman (1.0 g) was treated with the ylide prepared from NaH (0.75 g) and sulfonium chloride (4.5 g). The nmr spectrum of the crude products showed a mixture of starting material and 9-methylharman in a ratio of 2:3. The unchanged compound was removed as a solid by treatment with benzene–ligroin. Evaporation of the mother liquor gave the pure N-methylation product (0.6 g) whose nmr spectrum ($CDCl_3$) showed peaks at 8.75 (d, J = 7.0, CCH_3) and 6.77 (s, NCH_3). The picrate was obtained from EtOH–ether as reddish yellow prisms, mp 243–245° dec (lit.[5] 242°).

Anal. Calcd for $C_{13}H_{16}N_2 \cdot C_6H_3O_7N_3$: C, 53.15; H, 4.43; N, 16.32. Found: C, 53.39; H, 4.36; N, 16.37.

1-Methyloxindole.—Oxindole (2.6 g) was reacted with the ylide prepared from NaH (0.5 g) and sulfonium chloride (3.2 g). The crude products were chromatographed on silica gel (benzene–acetone) to give two main products.

An oily product, which eluted faster, was identified as 1,3-dimethyloxindole by the nmr spectrum ($CDCl_3$) which showed signals at 8.57 (d, J = 8.0, C-CH_3), 6.85 (s, NCH_3), and 6.67 (q, J = 8.0, 3 H).

The subsequently eluted product (1.9 g) was obtained as colorless needles from ligroin, mp 89–90° (lit.[6] 88°). The nmr spectrum ($CDCl_3$) showed peaks at 6.80 (s, N-CH_3), 6.51 (s, CH_2), and around 3.0 (m, aromatic).

1,3,3-Trimethyloxindole.—Oxindole (0.9 g) was treated with the ylide prepared from NaH (0.5 g) and sulfonium chloride (3.0 g). A major product obtained by chromatography on silica gel ($CHCl_3$) was further purified by distillation at 0.5 mm (120°) to give trimethyloxindole (0.8 g) as a slightly yellow oil. The nmr spectrum ($CDCl_3$) showed singlet peaks at 8.64 (6 H) and 6.80 (3 H), mass spectrum m/e 175 (M^+). The uv and ir spectral data were identical with those reported.

Registry No.—II, 5440-16-4; III, 25870-60-4; dimethyloxosulfonium methylide, 5367-24-8; 1-methylbenzimidazole picrate, 25870-61-5.

Reaction of Aliphatic Nitro Compounds with Carbon Monoxide. A New Route to Trialkylpyridines

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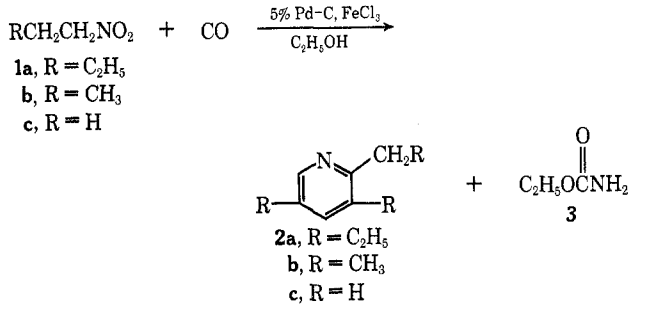
Recently, Bennett, Hardy, and coworkers[1] reported that carbon monoxide reacts with aromatic nitro, nitroso, azo, and azoxy compounds in the presence of a noble metal and ferric chloride to yield the corresponding isocyanates. In a patent issued to Mountfield[2] it is stated that urethans may be produced from the reaction of carbon monoxide, aromatic or aliphatic nitro compounds, and alcohols in the presence of a metal carbonyl catalyst system. We have found that certain primary aliphatic nitro compounds yield trisubstituted pyridines when treated with carbon monoxide under pressure using a noble metal–ferric chloride catalyst system. For example, treatment of an ethanol solution of 1-nitrobutane (**1a**) with carbon monoxide in the presence of palladium on carbon and ferric chloride yields 2-propyl-3,5-diethylpyridine (**2a**) and ethyl carbamate (**3**). Likewise, 1-nitropropane (**1b**) gives rise to 2-ethyl-3,5-dimethylpyridine (**2b**) and **3**. The pyridines were



identified by spectral methods (nmr, uv, and mass spectra), from their picrate derivatives and by comparison of their nmr spectra with the spectra of the authentic samples prepared by Falbe.[3,4] It is apparent from the structure of the pyridines that this reaction must involve a trimerization process wherein three molecules combine in a specific fashion to form the heterocyclic ring. The pyridine formation is markedly dependent upon the structure of the nitro compound as indicated by the results summarized in Table I. Although the reaction of aromatic nitro compounds under these conditions gives high yields of the corresponding N-arylurethans,[5] N-alkylurethans are probably not involved in the cyclization since N-1-butylurethan was recovered

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