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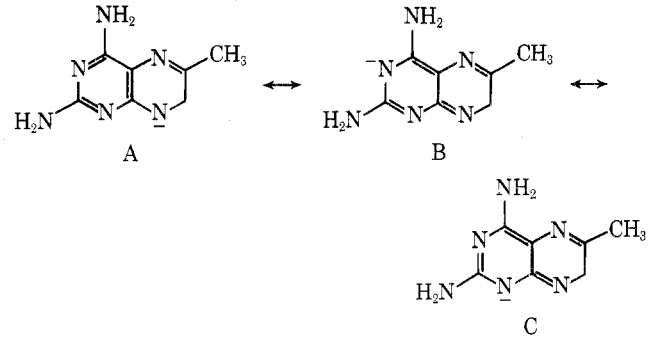
Direct N^8-Alkylation of 2,4-Diamino-7,8-dihydropteridines. Preparation of 7,8-Dihydro-8-methylmethotrexate[1]

Summary: A method is described for the N^8-alkylation of 2,4-diamino-7,8-dihydropteridines by reaction of these compounds with *n*-butyllithium in DMSO followed by treatment with an alkyl halide.

Sir: Dihydro and tetrahydropteridines in which the pyrazine ring is the reduced site are intermediates in many biological reactions in diverse living organisms.[2] The study of the chemical and biological properties of reduced pteridines is complicated by the fact that they are readily oxidized to the parent aromatic compounds, even upon standing in air. Substitution of methyl groups for hydrogen at N^8 in 7,8-dihydropteridines[3] and at N^5 and/or N^8 in 5,6,7,8-tetrahydropteridines[4] results in derivatives which resist facile oxidative degradation at the 5,6 and/or 7,8 positions. Although direct substitution at N^5 in 5,6,7,8-tetrahydropteridines can be accomplished rather easily under mild conditions,[4-7] N^8 is resistant to alkylation[6] and can be acylated only under drastic conditions.[5] In this communication we describe a method by which 2,4-diamino-7,8-dihydropteridines can be directly monoalkylated at N^8 without substitution either in the pyrimidine ring or on the 2- or 4-amino groups. The resulting products can then be hydrogenated catalytically to tetrahydropteridines.

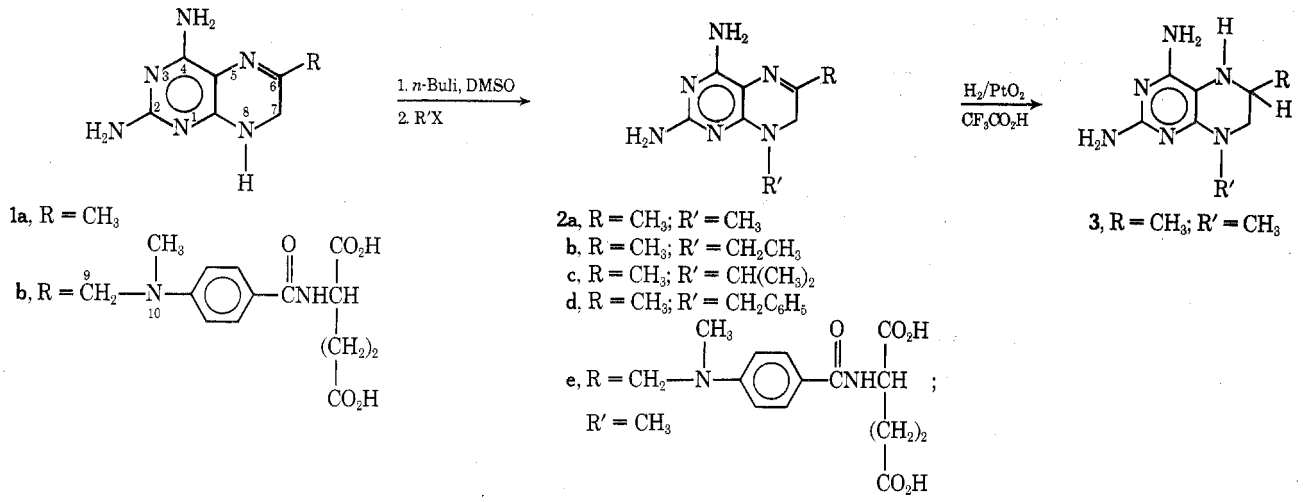
Since most of the biologically important pteridines are substituted at the 6 position, we chose to experiment with 2,4-diamino-7,8-dihydro-6-methylpteridine (**1a**)[8] as a model compound. The nmr spectrum of this compound in DMSO-d_6 (TMS internal standard) shows the C^6 CH_3 at δ 1.86 (s), the 7-CH_2 at 3.96 (s), the amino groups at 5.53 and 5.65 (overlapping singlets), and the N^8 H at 6.27 (s). This spectrum indicates that the N^8 H is deshielded with respect to the hydrogens on the amino groups. It was expected that if **1a** were treated with a powerful base, nucleophilic attack with proton abstraction would occur at N^8 H rather than at either of the amino groups. What is more important is that the resulting anion could be stabilized by resonance forms such as B and C in which the charge is accommodated on the nitrogens of the pyrimidine ring. Treatment of this anion with an alkylating agent should result in attack preferentially at the least hindered N^8 position.



A solution of **1a** in DMSO, under nitrogen at room temperature, was treated with 1.1 equiv of *n*-butyllithium in hexane,[9] followed after a few minutes by the addition of 1.2 equiv of methyl iodide. Addition of water after 15 min precipitated a white solid (71%, mp 260–280° dec) which appeared as a single new compound on tlc (silica gel, 8% MeOH–$CHCl_3$). The product was stable in air and was unchanged upon treatment with hydrogen peroxide in DMF for 30 min, conditions which rapidly oxidized **1a** to the fully aromatic pteridine. Elemental analysis gave the formula $C_8H_{12}N_6$ for this compound, in accordance with the introduction of a single CH_3 group into the starting material, and the uv spectrum [$\lambda_{max}^{0.1\,N\,HCl}$ 236 nm (ϵ 26,700), 263 (sh, 8130), 292 (13,600)] showed little change from that of **1a**.[8] The nmr spectrum in DMSO-d_6 was similar to that of **1a** except that the N^8 H peak was absent and a new singlet appeared at δ 2.78 (3 H). In CF_3CO_2H, the nmr spectrum consisted of singlets at δ 2.61 (C^6 CH_3), 3.24 (N^8 CH_3), and 4.86 (7-CH_2), almost identical with the reported spectrum of 2-amino-4-hydroxy-6,8-dimethyl-7,8-dihydropteridine, prepared by Wahlefeld, *et al.*,[3] by an unambiguous synthesis. These data are consistent with the assignment of structure **2a** for the new product. Hydrogenation of **2a** with PtO_2 in CF_3CO_2H gave the tetrahydropteridine **3**: nmr (CF_3CO_2H) δ 1.67 (d, J = 6 Hz, C^6 CH_3), 3.36 (s, N^8 CH_3), 3.67–4.20 (m, C^6 H and 7-CH_2). This product was isolated as a fairly stable white solid as its dihydrochloride monohydrate.

Compounds **2b**, **2c**, and **2d** were prepared in the same manner as **2a** in yields of 60, 24, and 80%, respectively, by the use of ethyl bromide, isopropyl bromide, and benzyl chloride as the alkylating agents. The relatively low yield for **2c** may be the result of extensive dehydrohalogenation of the sterically hindered isopropyl bromide during the reaction. Elemental and spectral analyses of these compounds substantiated the proposed structures.

We next attempted the alkylation of the more complicated folate derivative 7,8-dihydromethotrexate **1b**.[10,11] A solution of **1b** (as the diacid monohydrate), in DMSO at room temperature under nitrogen, was treated with 4.5 equiv of *n*-butyllithium in hexane followed by 3 equiv of methyl iodide. After 5 min the mixture was diluted with water and the pH adjusted to 3.5 with HCl. The precipitated solid was collected and then reprecipitated from dilute alkali in the same manner to give **2e** as a light tan solid, 50%, mp 185–195° dec. *Anal.* Calcd for $C_{21}H_{26}N_8O_5 \cdot H_2O$: C, 51.63; H, 5.78; N, 22.94. Found: C, 51.84; H, 5.35; N, 22.25. Thin layer chromatography (Eastman 13254 cellulose; 5% aqueous $NaHCO_3$) showed the presence of one major compound (R_f 0.68) with only a trace of unreacted **1b** (R_f 0.55): uv $\lambda_{max}^{0.1\,N\,HCl}$ 295 nm (ϵ 23,700); nmr (CF_3CO_2H) δ 2.3–2.9 (m, side chain CH_2CH_2), 3.24 (s, N^8 CH_3), 3.64 (s, N^{10} CH_3), 4.46 (s, 9-CH_2), 4.72 (s, 7-CH_2), 5.10 (m, side-chain CH), 8.0



(m, 4 H, phenyl CH's). The nmr spectrum was essentially identical with that of **1b** except for the N^8 CH_3 singlet at δ 3.24, which also appears at this δ value in **2a.** To confirm alkylation at N^8, **2e** was treated with excess sodium dithionite in water at reflux for 45 min—conditions which lead to reductive cleavage at the 9,10 bond.[11] The reaction mixture was then made basic and extracted with $CHCl_3$ to give **2a** (46%).

These reactions make available some 7,8-dihydro- and 5,6,7,8-tetrahydropteridine derivatives which would otherwise require lengthier synthetic procedures. The biological properties of these and similar compounds are under investigation.

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Conjugate Reduction and Reductive Alkylation of α,β-Unsaturated Cyclohexenones Using Potassium Tri-*sec*-butylborohydride

Summary: β-Unsubstituted cyclohexenones undergo 1,4 reduction and reductive alkylation to afford saturated ketones in high yield through the agency of potassium tri-*sec*-butylborohydride.

Sir: The reduction of cyclic ketones using hindered borohydrides, especially lithium and potassium tri-*sec*-butylborohydride,[1,2] has been shown to occur with a high degree of stereoselectivity for the less stable isomer. Similar selectivity has been reported in the preparation of allylic alcohols by reduction of acyclic α,β-unsaturated ketones.[3] In view of these facts we were encouraged to study the reaction of these borohydride reagents with cyclic enones. The potentially useful results we encountered prompts this preliminary communication.

We have observed that conjugated cyclohexenone systems which are unsubstituted at the β-vinylic carbon undergo exclusive 1,4-reduction in the presence of potassium tri-*sec*-butylborohydride (K-Selectride™, Aldrich Chemical Co.) to produce the corresponding saturated ketones in nearly quantitative yield.[4] No traces of allylic or saturated alcohol can be detected when 1 equiv of reducing agent is employed. If, however, an excess of 2 equiv of borohydride is present and the reaction is quenched at −78° with water, only saturated alcohols are obtained. Table I summarizes our results.

The reduction seems to occur equally well in pure tetrahydrofuran (THF) or in ether–THF mixtures and is quite rapid at −78°. 3,5-Dimethyl-2-cyclohexenone (**7**) cleanly affords a mixture of allylic alcohols and no saturated ketone or dimethylcyclohexanol whatsoever, thus demonstrating that the 1,4 addition of hydride is extremely sensitive to steric factors.[6] Not surprisingly, reduction of 10-methyl-$\Delta^{1,9}$-2-octalone (**9**) followed a similar course. Numerous attempts to effect the reduction of 2-cyclopentenone by direct or inverse admixture with Selectride™ led to a complex mixture which included cyclopentanol as a major product.

A survey of other conjugated functional groups seems to support the remarkable substrate specificity of this reagent. Ethyl crotonate, for instance, was recovered unchanged after exposure for 1 hr at −78° to an equimolar amount of K-Selectride™. This observation suggests that selective reductions may be feasible in complex polyfunctional structures containing a variety of electron-deficient olefins.