(95 mm)], *N*-chloropiperidine [bp 54.5–55° (35 mm)], and *N*-chloromorphorine [bp 47° (17 mm)] were isolated by fractional distillation. *N*-Chloro-*N*-methylbenzylamine was prepared from *N*-methylbenzylamine–HCl and sodium hypochlorite in an aqueous medium. The oily layer which was separated from the reaction mixture was dried over calcium chloride and subjected to the carbonylation reaction without purification by distillation. *N*-Chloromonoalkylamines were prepared from the monoalkylamine–HCl and sodium hypochlorite in the presence of ether. The ether layer was dried over calcium chloride and was subjected directly to the carbonylation reaction.

Carbonylations of Dialkylchloramines (Tables I and II).—A typical procedure is as follows. In a 50-ml stainless steel tube, palladium metal (commercial palladium metal was used directly), 0.0106 g (0.1 g-atom), *N*-chlorodimethylamine (10 mmol), and solvent (1,2-dimethoxyethane was usually employed) (5 ml) were placed and then carbon monoxide was compressed. The tube was closed and was heated at a desired temperature for about 20 hr. Then carbon monoxide was purged off and the reaction mixture was subjected to glpc analysis (a column packed with silicon on Celite was used). The products were identified by comparison of the glpc retention time and ir spectrum with the authentic *N*,*N*-dimethylcarbamoyl chloride. In the cases of *N*-chloropiperidine, *N*-chloromorphorine, and *N*-chloro-*N*-methylbenzylamine, the yields of the products were determined by the glpc analysis of the corresponding urethanes which were formed by treatment of the reaction mixture with excess ethanol in the presence of triethylamine.

Carbonylations of Monoalkylchloramines (Table III).—The following example illustrates the procedure used in the carbonylations of monoalkylchloramines. In a 50-ml stainless steel tube, palladium metal, 0.0053 g (0.05 g-atom), and *N*-chloromethylamine ether solution (5 mmol) were placed, and then carbon monoxide was compressed up to 60 kg/cm² at −78°. The tube was closed and was heated at 50° for 20 hr. The carbon monoxide was purged off, and excess methanol and triethylamine were added to the reaction mixture. The product was identified and its yield was estimated by the form of methyl *N*-methylcarbamate by glpc.

Registry No.—**1** ($R_1 = R_2 = H$), 10599-90-3; **1** ($R_1 = R_2 = CH_3$), 1585-74-6; **2** ($R_1 = R_2 = H$), 463-72-9; carbon monoxide, 630-08-0.

A Convenient Synthesis of Pteroic Acid[1]

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Previous syntheses of pteroic acid[2-10] result in preparations that are contaminated with simple pteridines, presenting a formidable problem of purification. The reductive condensation of 2-acetylamino-4-hydroxy-6-formylpteridine with *p*-aminobenzoic acid or with ethyl *p*-aminobenzoate by formic acid or aryl thiols[11] was found to be unsatisfactory, giving variable yields of pteroic acid containing large amounts of pteridine impurities. The present note describes an improved version of the latter synthesis in which pteroic acid is obtained free of contaminating pteridines, thus avoiding the problem of purification.

Ethyl *p*-aminobenzoate and 2-acetylamino-4-hydroxy-6-formylpteridine in glacial acetic acid afforded the corresponding Schiff's base, which without isolation was reduced to ethyl N^2-acetylpteroate by dimethylamine borane, a procedure introduced by Billman and McDowell[12] for the reduction of aromatic Schiff's bases. Saponification of the ethyl ester of N^2-acetylpteroic acid so obtained gave pure pteroic acid which traveled as a single spot on paper chromatography and was free of all fluorescent pteridines. Conversion of this pteroic acid to dihydrofolic and tetrahydrofolic acids gave compounds that showed full enzymatic activity with dihydrofolate reductase of the L 1210 murine leukemia and with thymidylate synthetase of *E Coli*.

Dimethylamine borane appears to be the reagent of choice for the reduction of this Schiff's base. The complete reduction of the 9,10 double bond before reaction at the 5,6 or 7,8 positions is noteworthy. Continued reduction with more amine borane gives dihydro- and tetrahydropteroates. Under these conditions, the acetylpteridine aldehyde alone is reduced in the pyrazine ring before reaction at the carbonyl group takes place.

Experimental Section[13]

Glacial acetic acid (5 ml) was added to a mixture of 330 mg (2 mmol) of ethyl *p*-aminobenzoate and 307 mg (1 mmol) of 2-acetylamino-4-hydroxy-6-formylpteridine dimethylformamide monosolvate.[14] The mixture was stirred briefly. Then a solution of 100 mg of dimethylamine borane in 1.5 ml of glacial acetic acid was added. The suspension turned bright yellow. Stirring was continued at ambient temperature for 20 min. The suspension was warmed to 60° for 10 min and cooled to 25°. The solid was filtered and washed with 5 ml of glacial acetic acid, then with 10 ml of anhydrous ether. The solid was dried at ambient temperature in the dark to give 384 mg (100%) of pale yellow ethyl N^2-acetylpteroate. The solid was dissolved in 5 ml of hot (100°) dimethylformamide and cooled to 30°. Then 2 ml of anhydrous ether was added with stirring to give a homogeneous solution. After standing at ambient temperature, ethyl N^2-acetylpteroate began to crystallize. The flask was stored in a freezer (−35°) overnight. The solid was filtered, washed with anhydrous ether, and dried. This procedure gave 322 mg (84%) of the ethyl ester. The nmr spectrum in deuterated trifluoroacetic acid showed a triplet at δ 0.97 (3 H, J = 7 cps, ester CH_3), singlet at 2.0 (3 H, acetyl CH_3), quartet at 4.07 (2 H, J = 7 cps, ester CH_2), singlet at 4.84 (2 H, bridge CH_2), doublet at 7.35 (2 H, J = 9 cps, benzene CH), doublet at 7.88 (2 H, J = 9 cps, benzene CH), and a singlet at 8.67 (1 H, pteridine CH).

Anal. Calcd for $C_{18}H_{18}N_6O_4$: C, 56.53; H, 4.74; N, 21.98. Found: C, 56.5; H, 5.0; N, 21.8.

The solid ester was saponified with 50 ml of 0.10 *N* sodium hydroxide solution at 100° (under N_2) for 0.5 hr while protected

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(2) C. W. Waller, B. L. Hutchings, J. H. Mowat, E. L. R. Stokstad, J. H. Boothe, R. B. Angier, J. Semb, Y. SubbaRow, D. S. Cosulich, M. J. Fahrenbach, M. E. Hultquist, E. Kuh, E. H. Northey, D. R. Seeger, J. P. Sickels, and J. M. Smith, Jr., *J. Amer. Chem. Soc.*, **70**, 19 (1948).

(3) M. E. Hultquist, E. Kuh, D. B. Cosulich, M. J. Fahrenbach, E. H. Northey, D. R. Seeger, J. P. Sickels, J. M. Smith, Jr., R. B. Angier, J. H. Boothe, B. L. Hutchings, J. H. Mowat, J. Semb, E. L. R. Stokstad, Y. SubbaRow, and C. W. Waller, *ibid.*, **70**, 23 (1948).

(4) F. E. King and P. C. Spensley, *Nature*, **164**, 574 (1949).

(5) H. S. Forrest and J. Walker, *J. Chem. Soc.*, 2002 (1949).

(6) F. Weygand and V. Schmied-Kowarzik, *Chem. Ber.*, **82**, 333 (1949).

(7) F. E. King and P. C. Spensley, *J. Chem. Soc.*, **2**, 144 (1952).

(8) D. I. Weisblat, B. J. Magerlein, A. R. Hanze, D. R. Myers, and S. T. Rolfson, *J. Amer. Chem. Soc.*, **75**, 3625 (1953).

(9) D. I. Weisblat, B. J. Magerlein, D. R. Myers, A. R. Hanze, E. J. Fairburn, and S. T. Rolfson, *ibid.*, **75**, 5893 (1953).

(10) F. Weygand and H. Bestman, *Chem. Ber.*, **88**, 1992 (1955).

(11) M. Sletzinger and M. Tishler, U. S. Patent 2816109 (1957).

(12) J. H. Billman and J. W. McDowell, *J. Org. Chem.*, **26**, 1437 (1961).

(13) Microanalyses were performed by Dr. C. K. Fitz, Needham Heights, Mass. Paper chromatography was on Whatman No. 1 paper, ascending. Pteroic acid was observed as a spot that quenches ultraviolet light. Nmr spectra were taken on the Varian T-60 with tetramethylsilane as external standard.

(14) M. Sletzinger, D. Reinhold, J. Grier, M. Beachem, and M. Tishler, *J. Amer. Chem. Soc.*, **77**, 6365 (1955). The nmr spectrum of the acetylpteridine aldehyde revealed that it crystallized as a monosolvate from dimethylformamide.

from light. The solution was cooled to 20°. Upon adjusting to pH 3 with concentrated hydrochloric acid, pteroic acid separated as a bright yellow solid. This was centrifuged at 3000 rpm and washed thoroughly by suspension and centrifugation with three to five 10-ml portions of water. The moist solid was freeze-dried to give 263 mg of pteroic acid (84%). The nmr spectrum in deuterated trifluoroacetic acid showed a singlet at δ 4.90 (2 H, bridge CH_2), doublet at 7.49 (2 H, J = 9 cps, benzene CH), doublet at 7.85 (2 H, J = 9 cps, benzene CH), and a singlet at 8.54 (1 H, pteridine CH).

Anal. Calcd for $C_{14}H_{12}N_6O_3$: C, 53.85; H, 3.88; N, 26.92. Found: C, 53.7; H, 4.2; N, 26.8.

Paper chromatography (0.10 N ammonium bicarbonate) showed R_f 0.17 (quench), pteroic acid, free of all fluorescent compounds.

The sample of pteroic acid was acylated with trifluoroacetic anhydride and converted to folic acid by the mixed anhydride method as previously described.[15] Upon reduction to the dihydro form with sodium dithionite, the sample showed full activity with the two enzymes listed above.

Registry No.—Pteroic acid, 119-24-4; N^2-acetylpteroic acid ethyl ester, 27345-61-5.

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(15) L. T. Plante, E. J. Crawford, and M. Friedkin, *J. Biol. Chem.*, **242**, 1466 (1967).

Effects of 4-Alkyl Substitution on the Photoreduction of Benzophenone

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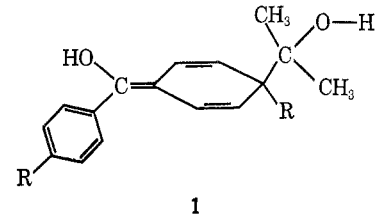
We recently investigated the photoreduction of benzophenone[2] (B) and its di-*p*-*tert*-butyl derivative[3] (TBB) in isopropyl alcohol. Both the photoreduction of TBB and the reactions of its long-lived intermediates with coreactants were surprisingly more complex than those of B. Therefore, it was of interest to examine the analogous reactions of symmetrical benzophenones with gradually increasing size of the alkyl substituent. Here we report on a similar spectroscopic investigation of the photolysis of di-*p*-methylbenzophenone (MB), di-*p*-ethylbenzophenone (EB), and di-*p*-isopropylbenzophenone (IPB) in degassed isopropyl alcohol.[4] The experimental methods, the designation of intermediates, and methods of calculation of extinction coefficients, stoichiometry, and rate constants were described previously.[2,3]

Successive short irradiations of degassed ketone solutions indicated formation of an intermediate species In_1 with λ_{max} between 330 and 350 nm. That this transformation was free of side reaction was shown by the isosbestic points at 237 and 298 nm (MB), 238 and 299 nm (EB), and 237 and 302 nm (IPB). The dark reaction of MB paralleled that of B; namely, the absorption band characteristic of In_1 decreased gradually to complete disappearance (for initial photoconversion less than 50%) or to an unchanging concentration (for conversion in excess of 50%). The spectral changes in the dark indicated that In_1 reacted bimolecularly with the residual benzophenone until one or the other was consumed. The plot of the second-order rate expression gave an excellent fit with the rate constant given in Table I. Product analysis identified only acetone and the tetramethyl-substituted benzopinacol. As for B, In_1 was oxygen sensitive and reverted to MB on exposure to air, as shown by both the uv absorption and reappearance of the characteristic ketone phosphorescence in the emission spectrum of refrozen samples at 77°K.

The dark reactions of the In_1 intermediates of EB and IPB paralleled those of B and MB only when the initial photoconversion was less than 50% but resembled that of TBB for higher conversions. The rate constants for the former reaction, derived again from excellent second-order fits, are listed in Table I. For high initial photoconversions, another slower dark reaction, competing with the In_1 + ketone reaction, was detected which converted the In_1 intermediates to yellow species designated In_2. The $In_1 \rightarrow In_2$ dark reaction of EB and IPB proved to be first order (see Table I). The yellow In_2 species were stable indefinitely (months) in the absence of oxygen but reacted rapidly on admission of air. Multicomponent absorption spectroscopy allowed calculation of the extinction coefficients of In_1 as a symmetrical broad band with λ_{max} at 333 (MB), 338 (EB), and 348 nm (IPB) and of In_2 again as an unstructured band with λ_{max} 382 nm for both EB and IPB.

Elementary molecular orbital calculations of expected electronic absorption,[5] ionic-like reaction with $(CH_3)_2CHONa$ (see below) accompanied by corresponding bathochromic shift in uv absorption, oxygen sensitivity, absence of paramagnetism,[6-11] and analogy with other unsymmetrical coupling reactions of radicals[12] suggest enol structure **1** for In_1 intermediates. Such a configuration has been proposed by several independent investi-



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gators.[2,13,14] An attempt was made to obtain direct confirmation of the nature of In_1 by recording nmr spectra of photolyzed solutions of TBB in degassed perdeu-

(1) Taken from work done in partial fulfillment of the requirements for the Ph.D. Degree at The George Washington University, 1970.

(2) N. Filipescu and F. L. Minn, *J. Amer. Chem. Soc.*, **90**, 1544 (1968).

(3) N. Filipescu and F. L. Minn, *J. Chem. Soc. B*, 84 (1969).

(4) MB was obtained from commercial sources. EB and IPB were prepared from the alkylbenzene and oxalyl chloride in the presence of $AlCl_3$, as described by Koslov, *et al.*, in *J. Gen. Chem. USSR*, **6**, 259 (1956).

(5) G. O. Schenck, M. Cziesla, K. Eppinger, G. Matthias, and M. Pape, *Tetrahedron Lett.*, 193 (1967); G. O. Schenck and G. Matthias, *ibid.*, 699 (1967).

(6) J. N. Pitts, R. L. Letsinger, R. P. Taylor, J. M. Patterson, G. Recktenwald, and R. B. Martin, *J. Amer. Chem. Soc.*, **81**, 1068 (1959).

(7) V. Franzen, *Justus Liebigs Ann. Chem.*, **633**, 1 (1960).

(8) H. Mauser and H. Heitzer, *Naturwissenschaften*, **50**, 568 (1963).

(9) H. Mauser, U. Sprösser, and H. Heitzer, *Chem. Ber.*, **98**, 1639 (1965).

(10) H. L. J. Bäckström, K. L. Applegren, and R. J. V. Nicklasson, *Acta Chem. Scand.*, **19**, 1555 (1965).

(11) H. L. J. Bäckström and R. J. V. Nicklasson, *ibid.*, **22**, 2589 (1968).

(12) S. F. Nelsen and P. D. Bartlett, *J. Amer. Chem. Soc.*, **88**, 137 (1966).

(13) H. L. J. Bäckström, *Acta Chem. Scand.*, **20**, 2617 (1966).

(14) D. C. Neckers, "Mechanistic Organic Chemistry," Reinhold, New York, N. Y., 1967, p 71.