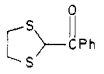
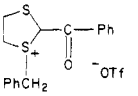
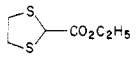
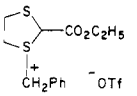
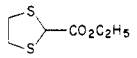
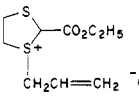
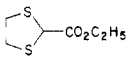
Table I. Alkylation of Sulfides Using Trimethylsilyl Triflate and Allyl or Benzyl Ethers

entry	sulfide	ether	product		% yield[c]
1[a]	$PhCH_2SCH_2CO_2C_2H_5$	$(CH_2{=}CHCH_2)_2O$	$PhCH_2\overset{+}{S}(CH_2CH{=}CH_2)CH_2CO_2C_2H_5\ {}^-OTf$	(6)	34
2[a]	$PhCH_2SCH_2CO_2C_2H_5$	$CH_2{=}CHCH_2OSiMe_3$	$PhCH_2\overset{+}{S}(CH_2CH{=}CH_2)CH_2CO_2C_2H_5\ {}^-OTf$	(6)	43
3[a]	$CH_2{=}CHCH_2SCH_2CO_2C_2H_5$	$PhCH_2OSiMe_3$	$PhCH_2\overset{+}{S}(CH_2CH{=}CH_2)CH_2CO_2C_2H_5\ {}^-OTf$		48
4[b]		$PhCH_2OSiMe_3$		(7)	89
5[a]		$PhCH_2OSiMe_3$		(8)	70
6[a]		$(CH_2{=}CHCH_2)_2O$		(9)	55
7[a]		$CH_2{=}CHCH_2OSiMe_3$		9	56

[a] Alkylation performed in acetonitrile, 24 h, 20 °C. [b] Alkylation in CH_2Cl_2, 24 h, 20 °C. [c] Yields refer to isolated crystalline salts.

groups is essential, either in the ether activation step or in the alkylation step. Previous applications of trimethylsilyl triflate as an activating agent for replacement of an oxygen substituent in acetals or ketals by various nucleophiles are no doubt related mechanistically.[2]

Experimental Section

General Procedures. (1) Alkylation with $(CH_2{=}CHCH_2)O/Me_3SiOTf$. A solution of trimethylsilyl triflate (Petrarch, 0.68 g, 3.1 mmol) in CH_3CN (4 mL, distilled from P_2O_5) was combined with allyl ether (0.17 g, 1.7 mmol) and the sulfide substrate (2.9 mmol). After 24 h, the solvents were removed and the dark residue was triturated with ether (3 × 15 mL). The residue was crystallized from $CHCl_3$–ether. The following products were made by this medhod for characterization: $C_6H_5CH_2S^+(CH_2CH{=}CH_2)CH_2CO_2C_2H_5\ {}^-O_3SCCF_3$[3] (6), mp 62.5 °C; 1-allyl-2-(carboethoxy)-1,3-dithiolanium triflate[3] (9), mp 83–83.5 °C.

(2) Alkylation with $CH_2{=}CHCH_2OSiMe_3/Me_3SiOTf$. A solution of the sulfide (2 mmol) and allyl trimethylsilyl ether (2.2 mmol) in CH_3CN (1.5 mL, distilled from P_2O_5) was combined with Me_3SiOTf (0.49 g, 2.2 mmol). After 24 h at ambient temperature, the salts were isolated as above.

(3) Alkylation with $PhCH_2OSiMe_3/Me_3SiOTf$. The sulfide (2.2 mmol) and benzyl trimethylsilyl ether (0.4 g, 2.2 mmol) were dissolved in acetonitrile (2 mL). Trimethylsilyl triflate (0.47 g, 2.1 mmol) was added and the reaction was allowed to proceed for 24 h at room temperature. After removal of solvent and trituration with ether, the salts were isolated by crystallization from ether–$CHCl_3$ as before.

The following salts were prepared by this method for characterization: 1-benzyl-2-benzoyl-1,3-dithiolanium triflate[3] (7), mp 135.5 °C,[3] 1-benzyl-2-(carboethoxy)-1,3-dithiolanium triflate (8), mp 85.5–87 °C.[3]

Conversion of 1,3-Dithiane into 5. A solution of 1,3-dithiane (0.24 g, 2 mmol, Aldrich) and allyl trimethylsilyl ether (0.29 g, 2.2 mmol) in toluene (3 mL) and acetonitrile (0.5 mL, distilled from P_2O_5) was stirred with Me_3SiOTf. After 48 h, a brown oil had precipitated. The solvents were evaporated and dry THF (3 mL, distilled from Na–Ph_2CO) was added, followed by KOC$(CH_3)_3$ (0.25 g)(magnetic stirring). After the exothermic reaction had subsided (ca. 5 min), the mixture was diluted with ether (10 mL) and extracted once with water (5 mL), and the organic phase dried over $MgSO_4$. After solvent removal (aspirator) the residual oil was purified by preparative layer chromatography over silica gel, 30% ether–hexane, to give 5 (R_f 0.5): 0.22 g; 69%. Spectral comparisons with literature data established the identity of 5.[4]

Acknowledgment. This work was supported by the National Institutes of Health (CA 17918).

Registry No. 5, 63382-29-6; 6, 77903-20-9; 7, 77903-22-1; 8, 77966-19-9; 9, 77903-24-3; trimethylsilyl triflate, 27607-77-8; 2-benzoyl-1,3-dithiolane, 21504-08-5; ethyl 1,3-dithiolane-2-carboxylate, 20461-99-8; 1,3-dithiane, 557-22-2; $PhCH_2SCH_2CO_2C_2H_5$, 2899-67-4; $CH_2{=}CHCH_2SCH_2CO_2C_2H_5$, 15224-05-2; $(CH_2{=}CHCH_2)_2O$, 557-40-4; $CH_2{=}CHCH_2OSiMe_3$, 18146-00-4; $PhCH_2OSiMe_3$, 14642-79-6.

(2) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248; *Tetrahedron Lett.* **1980**, 2527. Murata, S.; Noyori, R. *Ibid.* **1980**, 767. Tsunoda, T.; Suzuki, M.; Noyori, R. *Ibid.* **1980**, 71; *Ibid.* **1979**, 4679.

(3) Satisfactory C, H analysis was obtained.

(4) Harding, K. E.; Nash, W. D. *Synth. Commun.* **1977**, *7*, 19.

(5) Note added in proof: the generation of benzyl triflate in situ from $PhCH_2Br + CF_3SO_3Ag$ has recently been reported: Booth, B. L.; Haszeldine, R. N.; Laali, K. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2287.

Folate Analogues. 19. Construction of Some 6-Substituted 7,8-Dihydro-8-thiopterins[1]

M. G. Nair,* Loretta H. Boyce, and Michael A. Berry

Department of Biochemistry, College of Medicine, University of South Alabama, Mobile, Alabama 36688

Received March 25, 1981

As part of our continuing interest in developing synthetic substrates of dihydrofolate reductase[2] (EC 1.5.1.3) whose enzymatic reduction products are potentially capable of interfering with tetrahydrofolate utilization,[2,3] we have

(1) For the previous papers in this series see: Nair, M. G.; Bridges, T. W.; Henkel, T. J.; Kisliuk, R. L.; Gaumont, Y.; Sirotnak, F. M. *J. Med. Chem.*, in press; Nair, M. G.; Adapa, S. R.; Bridges, T. W. *J. Org. Chem.*, in press. The pterins are 6-substituted derivatives of the 2-amino-4-hydroxy-pyrimido[4,5-*b*](1,4)thiazine ring system.

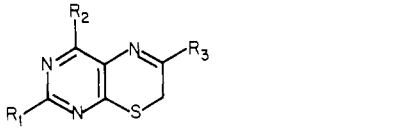
(2) Nair, M. G.; Colleen, S.; Chen, S. Y.; Kisliuk, R. L.; Gaumont, Y. *J. Med. Chem.* **1980**, *23*, 59.

(3) Misra, D. K.; Humphreys, S. R.; Friedkin, M.; Goldin, A.; Crawford, E. J. *Nature (London)* **1961**, *189*, 39.

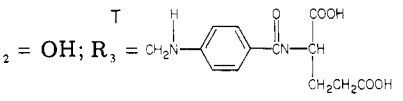
0022-3263/81/1946-3354$01.25/0

been interested in the construction of certain analogues of folic acid possessing the pyrimido[4,5-*b*](1,4)thiazine ring system (1).

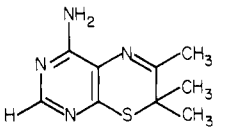
Although three 6-aryl-substituted 7,8-dihydro-8-thiopterins[1] were recently described in the literature[4] and were found to be relatively stable, no corresponding data are available on the desired 6-alkyl-substituted 7,8-dihydro-8-thiopterins. The stability and spectral characteristics of the 6-alkyl- and 6-aryl-substituted 7,8-dihydro-8-thiopterins are expected to differ considerably due to the presence of extended conjugation in the structure of the latter. Furthermore, the structures of the pterins described by Fenner and Opperman[4] have not been rigorously established (vide infra). Taylor and Garcia[5] reacted 5-amino-4-methoxy-6-mercaptopyrimidine with α-chloroacetophenone and prepared 4-methoxy-6-phenyl-8-thiodihydropteridine (**2**). When Mirza and co-workers[6] attempted to prepare a dihydropteridine by reacting 5,6-diamino-4-mercaptopyrimidine with α-bromoisopropyl methyl ketone, they obtained 4-amino-6,7,7-trimethyl-8-thiodihydropteridine (**3**) in good yield. In addition, Safanova and co-workers[7] have described this ring system with a 4-methoxy substituent in the pyrimidine ring. However, reaction of 2,5-diamino-4-hydroxy-6-mercaptopyrimidine (**6**) with an appropriately substituted α-halo ketone can give rise to products which can theoretically have either the 7,8-dihydro-8-thiopterin or the alternate structure **3b**. Therefore, investigations pertaining to the unambiguous construction of both the 6-aryl- and 6-alkyl-substituted 7,8-dihydro-8-thiopterin ring system were undertaken.



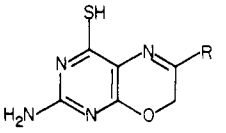
1, $R_1 = NH_2$; $R_2 = OH$; R_3 = T



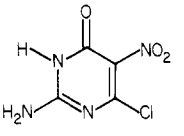
2, $R_1 = H$; $R_2 = OCH_3$; $R_3 = C_6H_5$



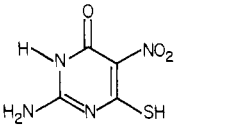
3



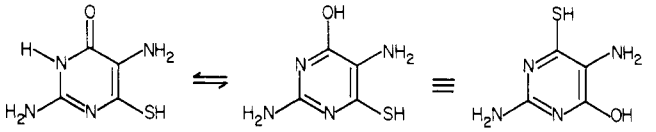
3b



4

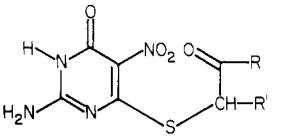


5



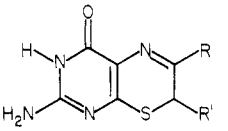
6

The general method[5,6] for the preparation of 7,8-dihydro-8-thiopteridine ring system consists of reacting an appropriately substituted 5-amino-6-mercaptopyrimidine with an α-halo ketone. Substituents such as the amino and the hydroxyl groups at the 4-position of the pyrimidine ring need to be protected prior to its reaction with α-halo ketones to avoid formation of products with alternate structures. Our attempts toward the unambiguous construction of the 6-substituted 7,8-dihydro-8-thiopterin ring system were based on the following strategy. The known 2-amino-6-chloro-4-hydroxy-5-nitropyrimidine was reacted with equimolar amounts of sodium sulfide, acidified to the 6-mercapto-5-nitropyrimidine **5**, and treated with α-bromopropiophenone to give **7**. Alternately, this pyrimidine **7** was prepared by the reaction of the sodium salt of **5** generated in situ with α-bromopropiophenone in MeOH. Dithionite reduction of the sodium salt of **5** in aqueous solutions gave 5-amino-6-mercaptopyrimidine **6** which was found to be relatively stable.



7, $R = C_6H_5$; $R' = CH_3$

Our next attempt was to convert intermediates **7** to the known 7,8-dihydro-8-thiopteridine structures **8** and establish their identities. This was accomplished by reducing **7** to the corresponding amino compound which cyclized after several days to the 7,8-dihydro-8-thiopteridine **8** in 60% yield. Reaction of 2,5-diamino-4-hydroxy-6-mercaptopyrimidine (**6**) with α-bromopropiophenone in aqueous methanol at reflux temperature gave a product whose NMR and UV spectral characteristics were identical with those of the product obtained by the elaboration of intermediate **7**, thus confirming structure **8**.

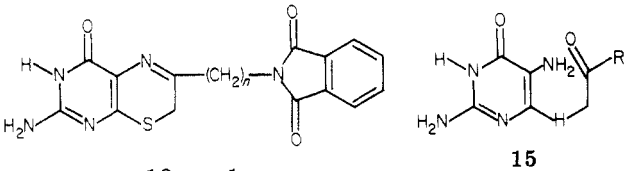


8, $R = C_6H_5$; $R' = CH_3$
9, $R = p\text{-}CH_3C_6H_4$; $R' = H$
10, $R = p\text{-}ClC_6H_4$; $R' = H$
11, $R = m\text{-}CH_3OC_6H_4$; $R' = H$
12, $R = o\text{-}CH_3OC_6H_4$; $R' = H$

A series of hitherto unknown 6-aryl-substituted 7,8-dihydro-8-thiopterins, **9**–**12**, were then prepared. All these compounds had very similar UV spectra, with their λ_{max} ranging from 370 to 380 and 255 to 265 nm in 0.1 N NaOH, and exhibited NMR resonances expected of these structures. These compounds were also found to be relatively stable in acidic and basic conditions—in contrast to 6-alkyl-substituted 7,8-dihydropterins whose instability is quite well-known.[10,11] Reactions of **6** with (1-bromo-2-oxopropyl)phthalimide[8,9] or (1-bromo-2-oxobutyl)phthalimide[12] under conditions which were successfully employed for the preparation of **8**–**12** gave mixtures of tarry products which were unsuitable for characterization. This observation substantiated the expected instability of the 6-alkyl-substituted 7,8-dihydro-8-thiopterin ring system to

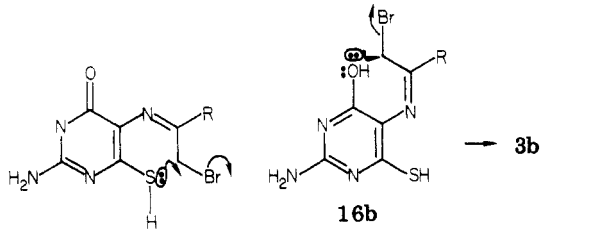
(4) Fenner, H.; Oppermann, W. *Arch. Pharm.* **1979**, *312*, 76.
(5) Taylor, E. C.; Garcia, E. E. *J. Org. Chem.* **1964**, *29*, 2121.
(6) Mirza, J.; Pfleiderer, W.; Brewer, A. D.; Stuart, A.; Wood, H. C. S. *J. Chem. Soc. C* **1970**, 437.
(7) Safanova, T. S.; Nemeryuk, M. P.; Myshkina, L. A.; Traven, N. I. *Khim. Geterotsikl. Soedin.* **1972**, *7*, 944.
(8) Nair, M. G.; Campbell, P. T.; Baugh, C. M. *J. Org. Chem.* **1975**, *40*, 1745.
(9) Nair, M. G.; Campbell, P. T. *J. Med. Chem.* **1976**, *19*, 825.
(10) Hillcoat, B. L.; Nixon, P. F.; Blakley, R. L. *Anal. Biochem.* **1967**, *21*, 178.
(11) Chippel, D.; Scrimgeour, K. G. *Can. J. Biochem.* **1970**, *48*, 999.
(12) Chen, S. Y.; Nair, M. G. *J. Org. Chem.* **1978**, *43*, 4143.

acidic conditions resulting from the generation of HBr in the reaction mixture. Addition of 1 equiv of bicarbonate and use of anhydrous methanol for aqueous ethanol as the reaction medium gave the desired products which had UV spectra similar to those of a 6-alkyl-7,8-dihydropterine. The apparent lack of formation of **3b** (R = alkyl or aryl) from the direct reaction of 2,5-diamino-4-hydroxy-6-mercaptopyrimidine (**6**) with various α-halo ketones, indicates that the reaction might proceed through the initial formation of intermediate **15** and subsequent ring closure, rather than via **16a** and **16b**.



13, n = 1
14, n = 2

15



16a

8-14

16b

3b

In conclusion, these results show that the direct reaction of 2,5-diamino-4-hydroxy-6-mercaptopyrimidine (**6**) with various conjugated α-halo ketones results in the formation of relatively stable 6-aryl-substituted 7,8-dihydro-8-thiopterins. The reaction of nonconjugated α-halo ketones with **6** should be carefully controlled to obtain the desired 6-alkylpterins which are reasonably stable under neutral conditions in N_2 but are unstable in both alkaline and acidic conditions. These 6-alkyl-substituted 7,8-dihydro-8-thiopterins exhibit chemical and spectroscopic properties similar to those of dihydrofolate.

Experimental Section

Melting points were determined on a Fisher Model 355 digital melting point analyzer and NMR spectra were run in $CDCl_3$ or CF_3COOH on a 90-MHz Perkin-Elmer R-32 spectrometer with Me_4Si as internal lock signal. Field strengthes of the various proton resonances are expressed in δ (parts per million) and coupling constants in hertz. Ultraviolet spectra were determined on a Beckman Model 25 spectrophotometer. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN.

Preparation of 2,5-Diamino-4-hydroxy-6-mercaptopyrimidine (6). In a typical experiment, a solution of 1.33 g (7.35 mmol) of 2-amino-6-chloro-4-hydroxy-5-nitropyrimidine[13] (**4**) in 150 mL of methanol under nitrogen was slowly added to a refluxing solution of 2.16 g (9 mmol) of $Na_2S{\cdot}9H_2O$ in 170 mL of methanol, during a period of 3 h, and the refluxing continued for 30 min more after the addition was complete. The solvent was removed by evaporation under reduced pressure, and the bright yellow residue thus obtained was dissolved in 150 mL of warm distilled water (50 °C), stirred, and reduced with the portionwise addition of 4 g of sodium dithionite during a period of 20 min, while maintaining the temperature between 50 and 55 °C. On cooling a solid residue began to separate; the mixture was filtered; the filtrate was acidified to pH 4.0 with glacial HOAc and chilled overnight in the refrigerator. The cream colored crystals thus formed were filtered, washed with distilled water, and dried: yield 500 mg (37%); mp >300 °C; UV (0.1 N NaOH) λ_{max} 310 nm. Anal. Calcd for $C_4H_6N_4OS{\cdot}1.5H_2O$: C, 25.94; H, 4.86; N, 30.27; S, 17.29; O, 21.62. Found: C, 26.39; H, 4.64; N, 30.09; S, 17.12; O, 21.43.

Preparation of 2-Amino-4-hydroxy-6-mercapto-5-nitropyrimidine (5) and α-[(2-Amino-4-hydroxy-5-nitropyrimidin-6-yl)thio]propiophenone (7). The reaction between the chloronitropyrimidine **4** and sodium sulfide was carried out as described above for the preparation of **6**. After the addition of the pyrimidine to sodium sulfide solution was complete the reaction mixture was refluxed for 1 h in N_2 and then evaporated to dryness. The residue was dissolved in 50 mL of distilled water, chilled, and acidified to pH 3.0 with 1.0 N HCl. A bright yellow precipitate of **5** was formed, which was separated by filtration, washed with 1% acetic acid in water, and dried: yield 800 mg (58%); UV (0.1 N NaOH) λ_{max} 345, 275 nm.

However, reaction of equimolar amounts (7 mmol each) of chloronitropyrimidine **4** and sodium sulfide, in methanol as described above, gave a methanolic solution of the sodium salt of **5**. Without isolation of **5**, the solution was refluxed with 7 mmol of commercial α-bromopropiophenone for 1.5 h, and the reaction mixture was concentrated to ~100 mL by rotary evaporation at reduced pressure and chilled, whereupon compound **7** crystallized as a yellow solid: yield 1.57 g (68%); mp >300 °C; NMR (TFA) δ 7.05 (s, 5 H, aromatic), 4.15 (q, 1 H, benzyl), 0.85 (d, 3 H, methyl); UV (0.1 N NaOH) λ_{max} 340, 285 nm. Anal. Calcd for $C_{13}H_{12}N_4O_4S{\cdot}0.5H_2O$: C, 47.27; H, 4.24; N, 16.96; S, 9.69. Found: C, 47.16; H, 4.04; N, 17.03; S, 9.54.

Dithionite Reduction of 7. Preparation of 2-Amino-4-hydroxy-7-methyl-6-phenylpyrimido[4,5-*b*](1,4)thiazine (8). A solution of 200 mg (0.625 mmol) of **7** in 4 mL of DMF at 55 °C was stirred with 2 g of sodium dithionite in a 50-mL Erlenmeyer flask. To this stirred suspension was added 5 mL of distilled water dropwise, during a period of 20 min. The clear yellow solution thus obtained was diluted to 50 mL with ice-cold water and chilled in the refrigerator. During the next 4 days, a bright yellow precipitate formed, which was filtered, washed with water, and dried. This compound cochromatographed with the product obtained by reacting **6** with α-bromopropiophenone on silica gel TLC plates in two different systems, and both products gave identical UV (MeOH) and NMR (Me_2SO) spectra: yield 102 mg (60%); NMR (TFA) δ 7.6–7.18 (c, 5 H, aromatic), 4.65 (q, 1 H, C_7H), 1.35 (d, 3 H, C_7-CH_3); UV (0.1 N NaOH) λ_{max} 375 nm (ϵ 9548), 238 (13575).

General Method for Preparation of 8–12 from 6. To a solution of 300 mL of refluxing 20% aqueous ethanol was added 2 mmol of **6** under N_2 followed by the introduction of 2 mmol of the appropriate bromomethyl ketone. This mixture was refluxed under N_2 for 4 h, concentrated to ~75 mL by rotary evaporation, and chilled. The precipitated pterins were collected by filtration, washed with distilled water, and dried to obtain analytical samples. Yields ranged from 70 to 80%.

The UV spectrum in MeOH and melting point of **8** were found to be identical with those reported in the literature. The chemical and physical characteristics of **8** were also identical with those of the product obtained by the dithionite reduction of **7**. (See preceding experiment for data.)

Compound 9: NMR (TFA) δ 7.6, 7.1 (d, d, 4 H, aromatic), 4.22 (s, 2 H, C_7H), 2.05 (s, 3 H, methyl); UV (0.1 N NaOH) λ_{max} 378 nm (ϵ 10900), 271 (15530), 242 (14710); mp >300 °C. Anal. Calcd for $C_{13}H_{12}N_4OS{\cdot}H_2O$: C, 53.79; H, 4.82; N, 19.31; S, 11.03. Found: C, 53.64; H, 4.74; N, 18.82; S, 11.14.

Compound 10: NMR (TFA) δ 8.13, 7.75 (d, d, 4 H, aromatic), 4.73 (s, 2 H, C_7H); UV (0.1 N NaOH) λ_{max} 380 nm (ϵ 10002), 270 (13014), 248 (13511); mp >300 °C. Anal. Calcd for $C_{12}H_9ClN_4OS{\cdot}0.75H_2O$: C, 47.05; H, 3.43; N, 18.30; S, 10.45. Found: C, 47.13; H, 3.59; N, 18.23; S, 10.43.

Compound 11: NMR (TFA) δ 7.6–7.8 (C, 4 H, aromatic) 4.65 (s, 2 H, C_7H), 4.0 (s, 3 H, methoxy); UV (0.1 N NaOH) λ_{max} 378 nm (ϵ 8064), 264 (10225); mp >300 °C. Anal. Calcd for $C_{13}H_{12}N_4O_2S{\cdot}1.5H_2O$: C, 50.24; H, 4.67; N, 18.03; S, 10.30. Found: C, 50.46; H, 4.41; N, 18.08; S, 9.90.

Compound 12: NMR (TFA) δ 7.2–8.1 (c, 4 H, aromatic), 4.4 (s, 2 H, C_7H), 4.0 (s, 3 H, methoxy); UV (0.1 N NaOH) λ_{max} 375 nm (ϵ 8065), 260 (9245); mp >300 °C. Anal. Calcd for $C_{13}H_{12}N_4O_2S{\cdot}0.75H_2O$: C, 51.74; H, 4.45; N, 18.57; S, 10.61. Found:

(13) Stuart, A.; Wood, H. C. S. *J. Chem. Soc.* **1963**, 4186.

C, 51.70; H, 4.37; N, 18.48; S, 10.65.

Preparation of 2-Amino-4-hydroxy-6-(phthalimidomethyl)pyrimido[4,5-*b*](1,4)thiazine (13). To 200 mL of anhydrous methanol was added 398 mg (2.15 mmol) of **6** under nitrogen and the mixture was stirred under reflux. When this suspension began refluxing, 181 mg (2.15 mmol) of $NaHCO_3$ was added, followed by 606 mg (2.15 mmol) of (1-bromo-2-oxopropyl)phthalimide. This mixture was refluxed for 2 h in N_2, concentrated to ~50 mL by rotary evaporation, and cooled. Crystals of **13**, thus formed, were collected by filtration, washed with distilled water followed by a small amount of MeOH, and dried: yield 660 mg (96%); mp 228 °C; UV (0.1 N NaOH) λ_{max} 340 nm (ϵ 4740), 255 (12410); NMR (TFA) δ 7.4 (c, 4 H, phthalimido), 4.65 (s, 2 H, C_6 methylene), 3.55 (s, 2 H, C_7H). Anal. Calcd for $C_{15}H_{11}N_5O_3S\cdot1.5H_2O$: C, 48.91; H, 3.80; N, 19.02; S, 8.69. Found: C, 49.09; H, 3.86; N, 19.23; S, 8.61.

Preparation of 2-Amino-4-hydroxy-6-(phthalimidoethyl)pyrimido[4,5-*b*](1,4)thiazine (14). This reaction was carried out exactly as described for the preparation of **13**, using (1-bromo-2-oxobutyl)phthalimide instead of (1-bromo-2-oxopropyl)phthalimide. The product was obtained in ~90% yield: mp 214-126 °C; UV (0.1 N NaOH) λ_{max} 339 nm (ϵ 4569), 256 (12274); NMR (TFA) δ 7.4 (c, 4 H, phthalimido), 3.98 (s, 2 H, C_7H), 3.8, 3.05 (br, br, 4 H, C_6 ethyl). Anal. Calcd for $C_{16}H_{13}N_5O_3S\cdot0.5H_2O$: C, 52.75; H, 3.84; N, 19.23; S, 8.79. Found: C, 52.82; H, 3.95; N, 19.13; S, 8.59.

Acknowledgment. This investigation was supported by grants from the National Institutes of Health (CA-27101 from the National Cancer Institute) and from the American Cancer Society (CH-53C).

Registry No. **4**, 1007-99-4; **5**, 77903-09-4; **5** Na, 77903-10-7; **6**, 37489-38-6; **7**, 77903-11-8; **8**, 69808-35-1; **9**, 77903-12-9; **10**, 77903-13-0; **11**, 77903-14-1; **12**, 77903-15-2; **13**, 77903-16-3; **14**, 77903-17-4; α-bromopropiophenone, 2114-00-3; 2-bromo-4'-methylacetophenone, 619-41-0; 2-bromo-4'-chloroacetophenone, 536-38-9; 2-bromo-3'-methoxyacetophenone, 5000-65-7; 2-bromo-2'-methoxyacetophenone, 31949-21-0; (1-bromo-2-oxopropyl)phthalimide, 6284-26-0; (1-bromo-2-oxobutyl)phthalimide, 51132-00-4.

Carbonation of 1-Triptycyllithium Taking Place via an Electron Transfer-Recombination Mechanism

Yuzo Kawada and Hiizu Iwamura*

Division of Applied Molecular Science, Institute for Molecular Science, Myodaiji, Okazaki 444, Japan

Received March 4, 1981

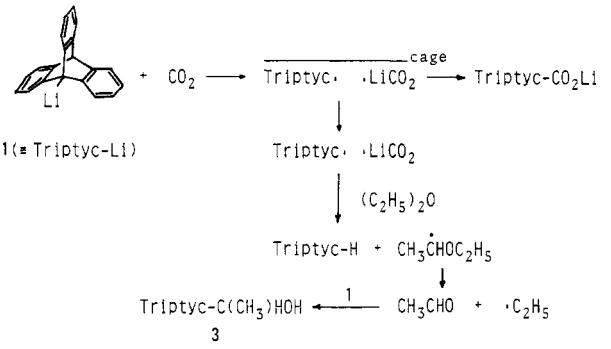
Ample evidence has been accumulating to indicate that the addition of organometallic reagents to carbonyl compounds proceeds via an electron-transfer pathway. In the case of the reaction of lithium organocuprates with a series of enones, House[1] presented the empirical rule that, in order for the two-step mechanism (the electron transfer and recombination of the resultant radical pair) to proceed at a reasonable rate, the electrode potential difference ($E_{red} - E_{ox}$) between the reactants should be more positive than -0.4 V. A number of additional factors for the occurrence of the single electron transfer pathway have been scrutinized by Ashby[2] for Grignard reactions with ketones. We have found, however, no definitive example in which one-electron transfer to carbon dioxide has been shown to be important in the carbonation of organometallic reagent.[3]

Table I. Product Yields (%) of the Reactions of 1-Triptycyllithium with Carbon Dioxide and Typical Carbonyl Compounds

carbonyl compd	normal product	1-(1-triptycyl) ethanol **3**	triptycene
CO_2[a]	85[c]	trace	15
CO_2[b]	27[c]	23	48
CH_2O	71[d]	0	22
CH_3CHO	84[e]		16
Ph_2CO	82[f]	2	16
adamantanone	83[g]	trace	10

[a] Introduced in a few minutes. [b] Introduced over 10 min. [c] 1-Triptoic acid. [d] 1-Triptycenemethanol. [e] 1-(1-Triptycyl)ethanol. [f] Diphenyl(1-triptycyl)carbinol.[7] [g] 2-(1-Triptycyl)adamantan-2-ol.[7]

Scheme I



We now report and discuss evidence for one-electron transfer from 1-triptycyllithium (**1**) to carbon dioxide taking place in a nonpolar solvent. When a suspension of **1** in benzene–ether (1:2 v/v) was saturated with dry carbon dioxide gas followed by usual workup, triptycene and 1-(1-triptycyl)ethanol (**3**) were obtained in addition to the expected 1-triptoic acid (**2**). Neither di(1-triptycyl) ketone nor di(1-triptycyl)carbinol was found.[3] The yield of the products varied, depending on the rate of introduction of CO_2 gas. When a rapid stream of carbon dioxide was employed, the suspended **1** disappeared within a few minutes and the reaction gave the highest yield of carbonation product **2**. When the addition was slow and it took more than 10 min for the starting suspension to become clear, the side reactions were prevalent (see Table I).[4]

The results are best interpreted in terms of the formation of 1-triptycyl radicals by one-electron donation from lithium reagent **1** to carbon dioxide. The radical species which has been generated independently by decomposition of ditriptoyl peroxide[5] and has the odd electron in the $sp^{8.6}$ hybrid orbital[6] is considered to be very reactive. Abstraction of a hydrogen atom from solvent ether should lead to the formation of the 1-ethoxyethyl radical which then can undergo β-cleavage to give acetaldehyde. Formation of triptycene and **3** can thus be explained. There

(1) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59.
(2) Ashby, E. C.; Wieseman, T. L. *J. Am. Chem. Soc.* **1978**, *100*, 189.
(3) Electrocatalytic reduction of carbon dioxide by using Ni and Co complexes of phthalocyanines and macrocycles has a number of precedents. See, for example: Meshitsuka, S.; Ichikawa, M.; Tamaru, K. *J. Chem. Soc., Chem. Commun.* **1974**, 158; Fischer, B.; Eisenberg, R. *J. Am. Chem. Soc.* **1980**, *102*, 7361. A referee called our attention to the carbonation of 1-norbornyllithium which gives dinorbornylcarbinol (15%) in addition to the carboxylic acid (19%): Jorgenson, M. J. *Org. React.* **1970**, *18*, 7. Most of the complexities in this reaction can be ascribed to a possible electron transfer from the lithium reagent to the dinorbornyl ketone intermediate.
(4) The reaction of **1** with carbon dioxide was reported for the first time by Wittig and Schöllkopf (*Tetrahedron Lett.* **1958**, 91) to give **2** in 41% yield, the yield midway between our two extreme values.
(5) Bartlett, P. D.; Greene, F. D. *J. Am. Chem. Soc.* **1954**, *76*, 1088.
(6) Reichel, C. L.; McBride, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 6758.

0022-3263/81/1946-3357$01.25/0