is possible that this minor product, III, could have arisen from a rearrangement of the cyclopropyl derivative II during the course of the electrochemical process; however, Reusch has shown the transformation to be effected by acid or base catalysis,[1] and our reduction conditions are neutral. The two diastereomers corresponding to IV were isolated as crystalline substances and their structures assigned on the basis of their IR (hydroxyl, carbon to carbon double bond, saturated carbonyl), NMR (vinyl proton), and mass spectra (no molecular ion but peaks at m/e 322, molecular ion less 2 mol of water, and m/e 179, dimer cleaved to monomer) and the C and H analysis.

It is thus apparent that the electrochemical reduction of I does not parallel the lithium/ammonia reduction. This result does not rule out the polarographic data as being indicative of a homoconjugative interaction as put forth by Reusch.[1]

Experimental Section

Analyses were performed by Atlantic Microlab, Inc. Infrared spectra were recorded on either a Perkin-Elmer Model 257 or a Model 467 spectrometer. NMR spectra were obtained on a Varian Model EM-360 spectrometer. Mass spectra were obtained on a Finnigan 4000 GC/MS system.

A Princeton Applied Research Model 170 was used for the controlled-potential electrolysis. The electrolysis cell was a conventional three-electrode system: a mercury (instrumental grade) pool working electrode (cathode), a saturated calomel reference electrode, and a silver auxiliary electrode (anode) which was separated from the solution by a fritted glass disk. The reduction was carried out under a nitrogen atmosphere. The mercury pool was stirred rapidly throughout the electrolysis with a magnetic stirrer. KCl was used as a supporting electrolyte. Prior to the electrolysis the system was purged with nitrogen for approximately 20 min until a steady background current for the solvent system, 1000 mL of 50:50 methanol–water, was obtained. The ketone (1.67 g, 0.009 mol), which had been dissolved in methanol, was added slowly to the solution. The electrolysis was conducted at -1.7 V vs. the SCE and 500 μA and was complete in 14 h, as indicated by a return to background levels of current. The methanol was rotoevaporated off and the aqueous solution extracted with ether. The ether layers were dried over Na_2SO_4 and concentrated to yield 1.43 g of yellow oil. This oil was chromatographed on 200 g of Silicar CC-7 with a gradient elution of hexanes/ether. Four main fractions were separated, the first two as oils (a total of 0.123 g) and then two as crystalline fractions (0.46 g and 0.51 g, respectively). Intermediate cuts between these two crystalline fractions contained 0.046 g of material.

The early-eluted materials showed carbonyl absorptions in the IR at 1700 cm^{-1}, were devoid of vinyl protons in the NMR, and exhibited no methyl resonances below 1.27 ppm. Their mass spectra contained a molecular ion peak at m/e 180. This evidence is consistent with these fractions being mixtures of the cis and trans isomers of III.

The major amount of product (89%) consisted of two crystalline fractions. In the IR the first of these (0.46 g, mp 163–164 °C) had a broad hydroxyl absorption (3580 cm^{-1}), a carbonyl absorption at 1700 cm^{-1}, and a double bond absorption at 1650 cm^{-1}. The NMR in $CDCl_3$ had a vinyl proton resonance at 5.87 ppm and no resonances below 1.23 ppm. The mass spectrum had peaks at m/e 322 (molecular weight of dimer less two H_2O's) and m/e 179 (half of the molecular weight). Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.71; H, 8.47.

In the IR the second crystalline product (0.51 g, mp 125–126 °C) had a broad hydroxyl absorption (3600 cm^{-1}), a carbonyl absorption at 1700 cm^{-1}, and a double bond absorption at 1650 cm^{-1}. The NMR in $CDCl_3$ had a vinyl proton resonance at 5.70 ppm and no resonances below 1.23 ppm. The mass spectrum had peaks at m/e 322 (molecular weight of dimer less two H_2O's) and m/e 179 (half of the molecular weight). Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.77; H, 8.46.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We also thank the National Science Foundation for help in the purchase of the Finnigan GC-MS-Data System.

Registry No. I, 20007-72-1; *cis*-III, 4707-05-5; *trans*-III, 4707-04-4; IV, 72952-32-0.

Use of (Pivaloyloxy)methyl as a Protecting Group in the Synthesis of Antigenic Theophylline (1,3-Dimethylxanthine) Derivatives†

Mae W. Hu, Prithipal Singh,* and Edwin F. Ullman

Syva Research Institute, Palo Alto, California 94304

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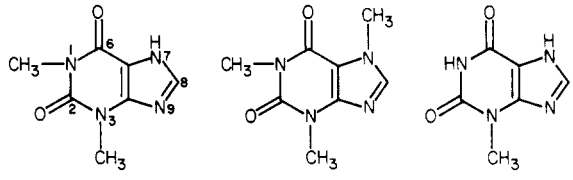
In the course of constructing a homogeneous enzyme immunoassay[1] for theophylline (1,3-dimethylxanthine, **1**)[2] in human serum, it became necessary to prepare an analogue of the drug that could be attached to an immunogenic protein carrier. Of primary concern is the design of such an analogue (hapten) which when attached to a carrier protein and injected into animals would afford antibodies to distinguish theophylline not only from its demethylated metabolites[3] but also from the ubiquitous presence of caffeine (1,3,7-trimethylxanthine, **2**). Since



1 **2** **3**

portions of the molecule that are least sterically encumbered by the protein carrier should most effectively interact with lymphocytic receptors, it seemed important to avoid attachment through the five-membered ring which bears the only structural feature that differentiates theophylline from caffeine. The choice between the remaining two sites of attachment to the drug at the 1- and 3-methyl groups was dictated in a similar way by the need to distinguish theophylline from 3-methylxanthine (**3**), a major metabolite.[3] For these reasons we wished to prepare 1-methyl-3-(carboxalkyl)xanthines in which the carboxyl group could serve as a linking function to ϵ-amino groups of the lysines of the protein carrier.[4]

Xanthines with identical alkyl substituents at the 1 and 3 positions are generally prepared from disubstituted ureas.[5] The use of unsymmetrical *N,N'*-dialkylureas[6] for the preparation of 1,3-dialkylxanthines would be expected to yield a mixture of products. Perhaps for this reason few unsymmetrical 1,3-dialkylxanthines have been reported. We wish to report a selective alkylation of 1-methylxanthine which makes 1-methyl-3-alkylxanthines[7] readily available.

Spectroscopic studies[8] indicate that the order of acidity of the N-bonded protons of xanthine is 3 > 7 > 1. This order suggests that controlled alkylation of 1-methylxanthine might give primarily 1-methyl-3-alkylxanthines. However only 1,7-dialkyl- and 1,3,7-trialkylxanthines have been observed under a variety of experimental conditions,[9] presumably because the higher rate of alkylation of the

† Contribution No 81.

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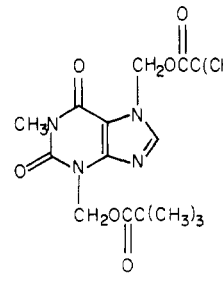
less hindered 7 position outweighs the effect of the higher acidity of the 3 position. These results suggested that the more reactive N-7 position must be protected prior to alkylation of N-3.

The use of the trialkylsilyl protecting group was not practical. When tris(trimethylsilyl)xanthine was treated with methyl iodide, a mixture of 7-methyl- and 3,7-dimethylxanthines was obtained.[10] Moreover, we observed that the reaction of 1,3-dimethyl-7-(trimethylsilyl)xanthine, prepared from theophylline (1) with ethyl bromoacetate, afforded 7-(carbethoxymethyl)-1,3-dimethylxanthine in high yield. Presumably these reactions occur as a result of cleavage of the weak N–Si bond by halide ion released during alkylation.

(Pivaloyloxy)methyl chloride represents an attractive alternative to trimethylsilyl chloride as a protecting agent. This reagent generates a carbon–nitrogen bond that was shown to be stable under alkylating conditions. Leonard and co-workers[11] had previously reported its use as a protecting group for selective alkylation of adenine. When 1-methylxanthine was treated with sodium hydride and (pivaloyloxy)methyl chloride, the 3,7-disubstituted and 7-substituted derivatives **4** and **5a** were formed in 39% and 41% yield, respectively. Since **4** could be quantitatively hydrolyzed back to 1-methylxanthine, the effective yield of **5a** was about 65%. The xanthine **5a** was readily alkylated in over 90% yield to give 1-methyl-3-alkylxanthines **5b–d** and also underwent Michael addition of acrylonitrile to afford **5e**. Removal of the protecting group to yield theophylline derivatives **6b–e** was accomplished by treatment of **5b–e** with 2 M aqueous sodium hydroxide.

Structural assignments for the xanthine derivatives are based primarily on their ultraviolet spectra which are diagnostic of the position of the substituents on the xanthine ring.[8,12] While 1,3,7-trialkylxanthines have absorption maxima near 270 nm that are nearly pH independent, the maxima of 1,3- and 1,7-dialkylxanthines shift from ~270 nm to longer wavelength at high pH. The observed bathochromic shifts are more pronounced (~10–15 nm) in the 1,7-dialkylxanthines than in the 1,3-dialkylxanthines (~3–5 nm). In accord with these generalizations **5a** exhibited a maximum at 269 nm at pH 6.5



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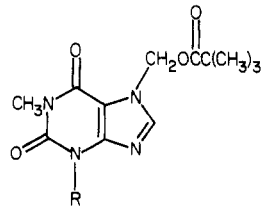

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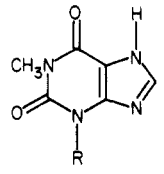

6

a, R = H, b, R = CH_3; c, R = $CH_2CH(CH_3)_2$; d, R = $(CH_2)_3COOC_2H_5$(H); e, R = CH_2CH_2CN

which shifted to 285 nm at pH 8.8. On the other hand the 1,3,7-trisubstituted xanthines **4** and **5b–e** had maximal absorption at 272 ± 1 nm which was pH independent, while the 1,3-disubstituted derivatives had absorption maxima at 272 nm that shifted to 275 nm at pH 8.8. All the compounds **4–6** were further characterized by their molecular ions in their mass spectra and by characteristic infrared carbonyl absorptions at 1657 ± 8 and 1704 ± 5 cm^{-1}.

Hydrolysis of the (pivaloyloxy)methyl group of **5d** with sodium hydroxide yielded the acid derivative **6d**, R = $(CH_2)_3COOH$. Conversion to the corresponding *N*-hydroxysuccinimide ester and conjugation to the carrier protein, bovine serum albumin, yielded an immunogen that elicited a highly specific immune response in sheep. These antibodies bind theophylline 160 times more strongly than caffeine and 1000 times more strongly than 3-methylxanthine.[13]

Experimental Section[14]

1-Methyl-7-[(pivaloyloxy)methyl]xanthine (5a). A partial solution of 1-methylxanthine (1.0 g, 6.02 mmol) in dry *N,N*-dimethylformamide (DMF, 40 mL) was prepared by heating the mixture at 80 °C for 30 min. To the cooled mixture was added 630 mg of sodium carbonate followed by the addition of a solution of chloromethyl pivalate (1.0 g, 6.6 mmol) in DMF (3 mL) over 60 min. After 16 h, the suspension was filtered and the residue washed with 1 N hydrochloric acid and water to give unreacted 1-methylxanthine (193 mg, 19%). The filtrate was evaporated under vacuum and chromatographed on silica TLC plates (chloroform–methanol, 9:1). 1-Methyl-7-[(pivaloyloxy)methyl]-xanthine (**5a**) was obtained in 41% yield (566 mg), R_f ~0.5, mp 194–195 °C, by recrystallization from hexane–dichloromethane; NMR ($CDCl_3$) δ 1.18 (s, 9 H), 3.40 (s, 3 H), 6.22 (s, 2 H), and 7.9 (s, 1 H); and 1-methyl-3,7-bis[(pivaloyloxy)methyl]xanthine (**4**) was obtained in 39% yield (750 mg), R_f ~0.9, mp 89–90 °C, by recrystallization from hexane–dichloromethane; NMR ($CDCl_3$) δ 1.20 (s, 18 H), 3.4 (s, 3 H), 6.10 (s, 2 H), 6.22 (s, 2 H), and 7.82 (s, 1 H).

The bis-protected xanthine was refluxed with 10 mL of 2 N sodium hydroxide for 18 h. The reaction mixture was cooled, acidified (pH 2–3), and extracted with chloroform. Evaporation of the aqueous layer afforded 1-methylxanthine in quantitative yield.

1-Methyl-3-(carboxypropyl)xanthine (6d). A mixture of 1-methyl-7-[(pivaloyloxy)methyl]xanthine (**5a**, 568 mg, 2.0 mmol), sodium carbonate (430 mg, 4.06 mmol), and ethyl 4-iodobutyrate

(1) (a) K. E. Rubenstein, R. S. Schneider, and E. F. Ullman, *Biochem. Biophys. Res. Commun.*, **47**, 846–851 (1972); (b) K. E. Rubenstein, and E. F. Ullman, U.S. Patent 3 817 837 (1974).

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(8) L. F. Cavalieri, J. J. Fox, A. Stone, and N. chang, *J. Am. Chem. Soc.*, **76**, 1119–1122 (1954).

(9) Reaction of 1-methylxanthine with ethyl bromoacetate under basic conditions (Na_2S, K_2CO_3, or Et_3N) and a variety of solvents afforded in addition to the starting material, 1-methyl-7-[(carbethoxy)methyl]-xanthine, mp 225–226 °C, and 1-methyl-3,7-bis[(carbethosy)methyl]-xanthine, mp 140.5–142 °C, as the only soluble products.

(10) (a) L. Birkofer, A. Ritter, and H. Kuehltau, *Chem. Ber.*, **97**, 934–945 (1964); (b) M. J. Covill, H. G. Garg, and T. L. V. Ulbricht, *Tetrahedron. Lett.*, 1033–1034 (1968).

(11) (a) M. Rasmussen and N. J. Leonard, *J. Am. Chem. Soc.*, **89**, 5437–5455 (1967); (b) B. N. Holmes and N. J. Leonard, *J. Org. Chem.*, **41**, 568–571 (1976).

(12) (a) S. F. Mason, *J. Chem. Soc.*, 2071–2081 (1954); (b) W. Pfleiderer, *Justus Liebigs Ann. Chem.*, **647**, 161–166 (1961).

(13) P. Singh, M. W. Hu, J. B. Gushaw, and E. F. Ullman, unpublished results.

(965 mg, 4.0 mmol) in DMF (9.4 mL) was stirred under nitrogen at room temperature. After 18 h water was added and the product extracted with chloroform. The extract was washed with water, dried, evaporated, and chromatographed on silica TLC (chloroform–ethanol, 9:1) to give **5d** as a pale yellow oil (789 mg, 98%); NMR ($CDCl_3$) δ 1.22 (s overlapping J = 7 Hz, total 12 H), 1.8–2.6 (m, 4 H), 3.40 (s, 3 H), 4.15 (q, 4 H, J = 7 Hz), 6.21 (s, 2 H), and 7.8 (s, 1 H). Similar procedures were used to prepare **5c** (91% yield, mp 108–109 °C) and **5b** (100% yield, mp 69–71 °C).

The oily suspension of xanthine **5d** (760 mg, 1.93 mmol) in 2 N aqueous sodium hydroxide (54 mL) was refluxed under nitrogen for 2 h. The reaction mixture was cooled, acidified (pH 2–3) with 10% hydrochloric acid, and extracted with chloroform. The aqueous layer was evaporated to dryness and recrystallized from water to give the title compound, **6d**, as colorless crystals (210 mg, 43%): mp 220–222 °C; NMR (Me_2SO-d_6/$CDCl_3$) δ 1.7–2.3 (m, 4 H), 3.27 (s, 3 H), 4.10 (t, J = Hz, 2 H), 8.02 (s, 1 H).

Anal. Calcd for $C_{10}H_{12}N_4O_4 \cdot 0.5H_2O$: C, 45.97; H, 4.98; N, 21.45. Found: C, 46.09; H, 4.88; N, 21.72.

Hydrolysis of **5b** and **5c** in a similar fashion gave theophylline (1, 68% yield, mp >280 °C) and **6c** [76% yield, mp 200–201 °C (lit.[15] mp 199–201 °C)].

1-Methyl-3-(cyanoethyl)xanthine (6e). A mixture of 1-methyl-7-[(pivaloyloxy)methyl]xanthine (**5a**, 100 mg), sodium carbonate (44 mg), and acrylonitrile (38 mg) in DMF (1 mL) was heated at 100 °C under nitrogen. After 16 h water was added and the product extracted with chloroform. The organic layer was washed with water, dried, evaporated, and chromatographed on silica TLC (chloroform–ethanol, 9:1) to give **5e** as a heavy oil (109 mg) which after crystallization from methylene chloride–hexane gave white needles: mp 118–120 °C; NMR ($CDCl_3$) δ 1.18 (s, 9 H), 2.8 (t, J = 7 Hz, 2 H), 3.40 (s, 3 H), 4.20 (t, J = 7 Hz, 2 H), 6.20 (s, 2 H), and 7.85 (s, 1 H).

Hydrolysis of **5e** (100 mg) with 1 N sodium hydroxide (0.35 mL) at room temperature for 4 h gave 50 mg (70%) of 1-methyl-3-(cyanoethyl)xanthine (**6e**, mp 229–230 °C, crystallized from methylene chloride–hexane–ethanol); NMR (Me_2SO-d_6/$CDCl_3$) δ 2.85 (t, J = 7 Hz, 2 H), 3.34 (s, 3 H), 4.35 (t, J = 7 Hz, 2 H), and 7.81 (s, 1 H).

Anal. Calcd for $C_9H_9N_5O_2$: C, 49.31; H, 4.11; N, 31.99. Found: C, 48.76; H, 4.16; N, 31.44.

1,3-Dimethyl-7-[(carbethoxy)methyl]xanthine. To a partial solution of 1,3-dimethylxanthine (1, 3.6 g) in benzene (60 mL) was added under nitrogen triethylamine (2.78 mL) and trimethylchlorosilane (2.64 mL). The reaction mixture was stirred at room temperature for 16 h, filtered, and evaporated to give 1,3-dimethyl-7-(trimethylsilyl)xanthine (3.3 g, mp 158–161 °C); NMR (CCl_4) δ 0.5 (s, 9 H), 3.28 (s, 3 H), 3.50 (s, 3 H), 7.50 (s, 1 H).

A solution of the silylated product (252 mg) in benzene (2.5 mL) was treated at room temperature under nitrogen with dry sodium carbonate (211 mg) and ethyl bromoacetate (182 mg). The reaction mixture was stirred, quenched after 90 h with water, and extracted with chloroform to give 1,3-dimethyl-7-[(carbethoxy)-methyl]xanthine (mp 139–140 °C, 182 mg, 68%); NMR ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3 H), 3.4 (s, 3 H), 3.63 (s, 3 H), 4.3 (q, J = 7 Hz, 2 H), 5.13 (s, 2 H), 7.57 (s, 1 H). Anal. Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.26; N, 21.05. Found: C, 49.31; H, 5.27; N, 21.08.

Registry No. 1, 58-55-9; 4, 43018-00-5; **5a**, 69150-36-3; **5b**, 64210-71-5; **5c**, 73018-01-6; **5d**, 69150-37-4; **5e**, 73018-02-7; **6a**, 6136-37-4; **6c**, 28822-58-4; **6d**, 73017-77-3; **6e**, 69150-39-6; 1,3-dimethyl-7-[(carboethoxy)methyl]xanthine, 7029-96-1; 1,3-dimethyl-7-(trimethylsilyl)xanthine, 62374-32-7; 1-methyl-7-[(carboethoxy)-methyl]xanthine, 73017-78-4; 1-methyl-3,7-bis[(carboethoxy)-methyl]xanthine, 73017-79-5; chloromethyl pivalate, 18997-19-8; ethyl 4-iodobutyrate, 7425-53+-8.

(14) Melting points are determined in capillary tubes with a Thomas–Hoover Uni-Melt apparatus and are uncorrected. Solutions in organic solvents were dried over anhydrous sodium sulfate. UV spectra were recorded on a Cary 15 spectrophotometer, while IR spectra were recorded on a Perkin-Elmer instrument. Unless specified otherwise, the NMR spectra were recorded on a Varian T-60 instrument and the values are given in parts per million downfield from tetramethylsilane as an internal standard.

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Use of Vinylogous Urethanes in Alkaloid Synthesis: Formal Synthesis of Ipalbidine

Arthur S. Howard,* Graeme C. Gerrans, and Joseph P. Michael

Department of Chemistry, University of the Witwatersrand, Johannesburg 2001, South Africa

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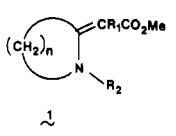
Fused five- and six-membered rings containing nitrogen at the bridgehead position are a common structural feature in a wide variety of alkaloidal systems. We are at present developing a reaction sequence which should be of general use in the synthesis of such systems. The key intermediates in this sequence are exocyclic vinylogous urethanes such as 1 (R_1 = H, R_2 = H or alkyl, n = 3 or 4), which are most conveniently prepared by means of the "sulfide contraction" procedure developed by Eschenmoser.[1] Vinylogous urethanes are stabilized enamines, and it is in this sense that we use them in intramolecular cyclizations to form bicyclic structures. Depending on the needs of the particular synthesis being carried out, the cyclization may be an alkylative one (as shown in our earlier synthesis of lupinine (**2**)[2]) or an acylative one (as in the present case). The bicyclic systems (**3**, R = O or 2H) produced in this way retain the vinylogous urethane grouping, and hence further annulation is possible.[2] The alkoxycarbonyl group, introduced initially to stabilize the exocyclic enamine, may readily be removed after the cyclization if this is desired, but in many cases it is correctly positioned for conversion to a functionality present in a particular alkaloid (e.g., lupinine, **2**).



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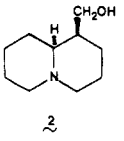

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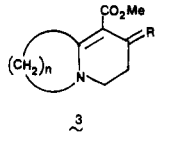

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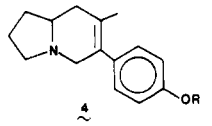

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Ipalbidine (**4**, R = H), the aglycon of the alkaloid ipalbine (**4**, R = β-D-glucosyl), isolated from *Ipomoea alba L.*[3] has been synthesized by several groups of workers.[4-7] In two of these syntheses[5,6] the bicyclic ketone (**12**) was prepared and converted to ipalbidine; our synthesis of compound (**12**), outlined in Scheme I, thus constitutes a formal synthesis of ipalbidine.

The key feature of our sequence is the acylative ring closure (**7**) to (**9**). In principle, it should be possible to attach the appropriate substituent for the annulation step to the nitrogen atom of the vinylogous urethane system (1, R_1 = R_2 = H, n = 3), but in practice, we have not found

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(3) J. M. Gourley, R. A. Heacock, A. G. McInnes, B. Nikolin, and D. G. Smith, *J. Chem. Soc. D.*, 709 (1969).

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