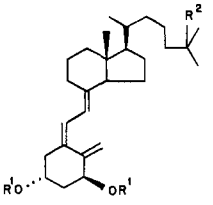
A Convenient Synthesis of 1α-Hydroxy-Vitamin D_3

Sir:

There has been much recent interest in 1α,25-dihydroxycholecalciferol (**1**),[1] the polar, biologically active, metabolite of vitamin D_3. A particularly interesting property of this metabolite is an extremely rapid onset of physiological activity.[2] We wish to describe the synthesis of a new vitamin D_3 analog—1α-hydroxyvitamin D_3 (**2b**), which exhibits many features of the biological activity associated with **1**, in particular a notably rapid onset of physiological activity (*vide infra*).

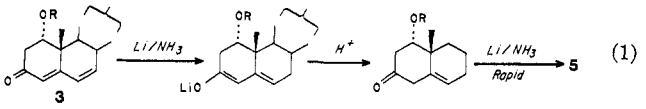


1 R^1=H, R^2=OH

2a R^1=Ac; R^2=H

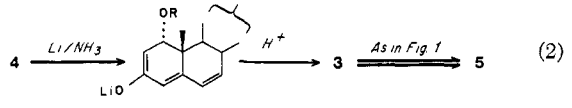
2b R^1=R^2=H

Although 1α-hydroxy steroids are available through conjugate addition to a Δ^1-3-keto system, transformation of these into vitamin D precursors has proved cumbersome.[1,3] The well-known deconjugation reactions of Δ^4-3-keto steroids[4] led us to speculate that if a $\Delta^{4,6}$-dien-3-one such as **3** were reduced with lithium and ammonia in the presence of an effective proton source an alternating sequence of reductions and protonations as expressed in eq 1 might lead ultimately to



(1)

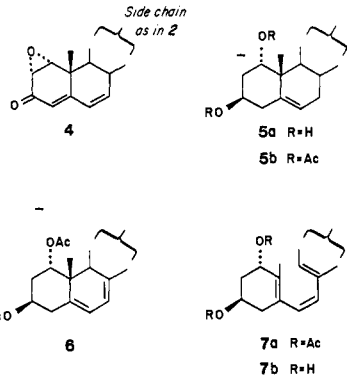
the required 3β-hydroxy-Δ^5-sterol **5**. An attractive feature of this scheme (which presupposes a rate of reduction much faster than enolization, etc.) was the expectation of stereospecific formation of the required 3β-hydroxyl in the final step.[5] A modest extrapolation of this scheme, expressed in eq 2, leads to an efficient



(2)

synthesis of 1α-hydroxycholesterol.

Treatment of 1α,2α-epoxycholesta-4,6-dien-3-one (**4**) (available in 45% yield (two steps) from cholesterol[6]) with large excesses each of lithium metal and ammonium chloride in ammonia–tetrahydrofuran (*ca.* 1:1) at reflux led to 1α-hydroxycholesterol (**5a**) (60% yield), mp 162–163°. The optical rotation observed for 1α-hydroxycholesterol, $[\alpha]D$ −38°, was in keeping with the required structure.[7] The structure of **5a** was confirmed[9] by hydrogenation (5% Pd/C in ethanol, room temperature) to the known 1α,3β-dihydroxy-5α-cholestane.[10]



4 **5a** R=H **5b** R=Ac **6** **7a** R=Ac **7b** R=H

Acetylation (acetic anhydride–pyridine–*N*,*N*-dimethyl-4-aminopyridine at room temperature) of **5a** afforded the diacetate **5b**, which was brominated (dibromodimethylhydantoin in hexane[11]) and then dehydrobrominated [$(MeO)_3P$ in refluxing xylene[11]] to afford the diene diacetate **6**: mp 118–119°; λ_{max} 262 (ε 8300), 271 (11,800), 282 (12,700), 294 (7500) nm; $[\alpha]D$ −31° (34%). The diene **6** was irradiated in ether at 0° to 50% conversion with a 200-W medium pressure mercury lamp filtered to largely remove radiation between 300 and 330 nm as well as radiation shorter than 275 nm. The reaction product was separated into two fractions by chromatography on $AgNO_3$ impregnated silica gel. The more polar fraction was unchanged **6**. The other fraction was largely the diacetate of 1α-hydroxy-vitamin D_3 (λ_{max} 260, λ_{min} 232 nm), **7a**, approximately 70% pure based on the change of the ultraviolet spectrum attendant upon the iodine-catalyzed conversion of the previtamin to the tachysterol analog[12] [λ_{max} 272 (sh), 282, 292 (sh) nm; 100% purity requires a threefold enhancement of absorbance; found, 2.2]. The crude **7a** was heated at 75° in isooctane for 2.25 hr to effect equilibration of **7a** and the vitamin diacetate **2a**. The product mixture was then carefully saponified (methanolic KOH at room temperature) and the diols **7b** and **2b** were resolved by chromatography on silica gel. The 1α-hydroxy-vitamin D_3 (**2b**) thus obtained had

(1) (a) M. F. Holick, H. K. Schnoes, H. F. DeLuca, T. Suda, and R. J. Cousins, *Biochemistry*, **10**, 2799 (1971); (b) A. W. Norman, J. F. Myrtle, R. J. Midgett, and H. G. Nowicki, *Science*, **173**, 51 (1971); (c) D. E. M. Lawson, D. R. Fraser, E. Kodicek, H. R. Morris, and D. H. Williams, *Nature (London)*, **230**, 228 (1971); (d) E. J. Semmler, M. F. Holick, H. K. Schnoes, and H. F. DeLuca, *Tetrahedron Lett.*, **40**, 4147 (1972).

(2) M. R. Haussler, D. W. Bayce, E. J. Littledike, and H. Rasmussen, *Proc. Nat. Acad. Sci. U. S.*, **68**, 177 (1971).

(3) B. Pelc and E. Kodicek, *J. Chem. Soc.*, 1624 (1970).

(4) (a) H. J. Ringold and S. K. Malhotra, *J. Amer. Chem. Soc.*, **84**, 3402 (1962); (b) A. L. Nussbaum, G. Brabazon Topliss, T. L. Popper, and E. P. Oliveto, *J. Amer. Chem. Soc.*, **81**, 4574 (1959); (c) R. E. Schaub and M. J. Weiss, *Chem. Ind.*, 2003 (1961).

(5) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

(6) E. Glotter, M. Weissenberg, and D. Lavie, *Tetrahedron*, **26**, 3857 (1970); A. B. Turner, *J. Chem. Soc. C*, 2568 (1968).

(7) Cholesterol has $[\alpha]D$ −39°[8a] and a 1α-hydroxy group was shown to have a small positive contribution in a number of 3-substituted androst-5-enes.[8b]

(8) (a) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 178; (b) R. M. Dodson, A. H. Goldkamp, and R. D. Muir, *J. Amer. Chem. Soc.*, **82**, 4026 (1960).

(9) Our data (mp 162–163°, $[\alpha]D$ −38°) are not in agreement with those (mp 195–200°, $[\alpha]D$ 0°) reported by Kodicek.[3] In fact, the microanalytical data reported by these authors[3] do not accord with the required composition. The latter, in fact, has been incorrectly calculated.

(10) (a) P. R. Striebel and C. Tamm, *Helv. Chim. Acta*, **37**, 1094 (1954); C. W. Shoppee, S. K. Roy, and B. S. Goodrich, *J. Chem. Soc.*, 1583 (1961). (b) We are indebted to Professor H. B. Henbest for the authentic specimen of 1α,3β-dihydroxy-5α-cholestane. We also thank Professor C. W. Shoppee for a specimen of 1α,3β-dihydroxy-5α-cholestane 3-acetate.

(11) F. Hunziker and F. X. Muller, *Helv. Chim. Acta*, **41**, 70 (1958).

(12) A. L. Koevoet, A. Verloop, and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **74**, 788 (1955).

mp 132–133°,[13] $[\alpha]D$ (ether) +26°, λ_{max} (ether) 264 nm (20,200), and on treatment with iodine underwent smooth isomerization attended by spectral changes [λ_{max} 270 nm (20,000)] completely analogous to those accompanying the conversion of vitamin D_3 into 5,6-*trans*-vitamin D_3.[14] The pmr spectrum of **2b** showed the 6 and 7 protons as an AB quartet (J_{AB} = 11.5 Hz) centered at δ 6.20 while the 19 protons appeared as a pair of one-proton multiplets at δ 4.85 and 5.30. These spectral parameters are completely analogous to those observed for vitamin D_3 itself and are not compatible with any of the other triene isomers encountered in the vitamin D series.

We have found that 1α-hydroxy-vitamin D_3 possesses potent vitamin D activity and in particular is associated with an onset of activity fully as rapid as that observed for the natural polar metabolite **1** of D_3.[15] The important implications of this biological activity to vitamin D biochemistry and therapy will be discussed fully in a subsequent paper.[17–19]

(13) The cited melting point was obtained by placing the specimen on the hot stage preheated to 100° and increasing the temperature at the rate of 1°/4 sec (the block thermometer and specimen are in reasonable equilibrium at this rate).

(14) A. Verloop, A. L. Koevoet, and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, 74, 1125 (1955).

(15) 1α-Hydroxy-vitamin D_3 was >10 times as effective as vitamin D_3 in raising the serum calcium of thyroidectomized–parathyroidectomized rats. A direct comparison between 1α-hydroxy-vitamin D_3 and biosynthetic 1,25-dihydroxy-vitamin D_3 demonstrated that the former was fully as effective as the latter in stimulating calcium transport across the chick intestines.[16,17] Essentially identical time courses were observed.

(16) M. E. Coates and E. S. Holdsworth, *Brit. J. Nutr.*, **15**, 131 (1961).

(17) In collaboration with M. R. Haussler whom we thank for preliminary biological data in the chick assay.

(18) All new compounds exhibited appropriate and expected spectral characteristics and (with the exception of **7a**) were of the required composition as established by microanalysis.

(19) NOTE ADDED IN PROOF. Application of the synthesis reported in this paper to 25-hydroxycholesterol has led to 1α,25-dihydroxycholecalciferol (**1**). The details will comprise a future communication.

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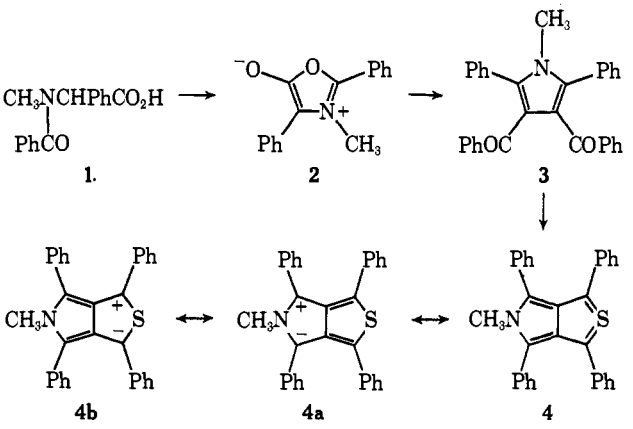
The Thieno[3,4-*c*]pyrrole System, a "Tetravalent Sulfur" Heterocycle Showing Both Azomethine Ylide and Thiocarbonyl Ylide Dipolar Characteristics

Sir:

The title ring system **4** is one of several 10π-electron heterocyclic systems containing "tetravalent sulfur" atoms that have been reported recently in the literature.[1,2] Described as a bright red powder, it formed a 1:1 adduct with dimethyl acetylenedicarboxylate, shown to be **8** (R = $COOCH_3$) by its oxidation to the benzo[*c*]thiophene (**9**) (R = $COOCH_3$).

We wish to report a very convenient synthesis of **4** which now makes it readily available in quantities sufficient to study a variety of cycloaddition reactions. Utilizing cycloaddition reactions[3] as a route to the penultimate product of **4**, *N*-benzoyl-α-phenylsarcosine[4] (**1**) was treated with dibenzoylacetylene in the presence of acetic anhydride, affording[5] a 63% yield of 3,4-dibenzoyl-2,5-diphenyl-1-methylpyrrole (**3**) as colorless, matted needles from ethanol, mp 200–202° (ν_{CO} 1655, 1635 cm^{-1}; nmr ($CDCl_3$) τ 6.62 (s, 3, NCH_3), 3.15–2.36 (m, 20, aromatic); $M\cdot^+$ 441 (55)). The mesoionic anhydro-2,4-diphenyl-5-hydroxy-3-methyloxazolium hydroxide (**2**) was undoubtedly the intermediate in this reaction which may be utilized for the synthesis of a variety of 1,2,5-substituted pyrroles.[4,6] Treatment of **3** with P_2S_5 in refluxing pyridine over 5 hr, followed by quenching the reaction mixture in 10% sodium hydroxide solution, gave 5-methyl-1,3,4,6-tetraphenylthieno[3,4-*c*]pyrrole (**4**) in 60% yield as small, brilliant



red needles, mp 110–112° ($\lambda_{max}^{CHCl_3}$ 256 nm (log ϵ 4.41), 533 (3.15); $M\cdot^+$ 441 (61), M^{2+} 220.5 (15), $PhC{\equiv}S^+$ *m/e* 121 (37), Ph^+ *m/e* 77 (100)).

In the crystalline state the thienopyrrole **4** is quite stable. In solution or on a tlc plate its color is rapidly bleached by light which, together with its poor solubility, precludes successful recrystallization.

We have found that the substitution pattern of the pyrrole moiety is critical for the formation of this ring system by the action of P_2S_5, those pyrroles with 1-methyl-2-phenyl or 1,2-diphenyl substituents being converted into the corresponding 3,4-dithiobenzoyl products.

The ring system **4** is a reactive substrate for cycloadditions, behaving both as an azomethine ylide **4a** and a thiocarbonyl ylide **4b**, depending on the reaction conditions. Olefinic dipolarophiles exhibited a temperature-dependent mode of addition to **4**. Fumaronitrile in refluxing toluene (12 hr) formed the primary 1:1 cycloadduct **5** in 67% yield, colorless needles from acetonitrile, mp 244–245° (dec) ($\lambda_{max}^{CH_3OH}$ 278 nm, log ϵ 4.06; ν_{CN} 2250 cm^{-1}; nmr ($CDCl_3$) τ 6.87 (s, 3, NCH_3), 5.88 (d, 1, J = 3.9 Hz, H_3), 5.42 (d, 1, J = 3.9 Hz, H_2), 3.34–2.40 (m, 20, aromatic); $M\cdot^+$ 519 (2)), together with the isoindole **6** (5%) which also crystallized from acetonitrile forming yellow needles, mp 332–334° ($\lambda_{max}^{CHCl_3}$ 245 nm (log ϵ 4.58), 269 (4.51), 408 (3.31); ν_{CN} 2225 cm^{-1}; nmr ($CDCl_3$) τ 6.54 (s, 3, NCH_3), 3.28–2.65 (m, 20, aromatic); $M\cdot^+$ 485 (100)). In refluxing xylene, the yield of the cycloadduct **5** decreased to 10% with an accompanying increase in the yield of **6** to 53%, suggesting the formation of **6** from **5** by the thermal elimination of the elements of H_2S. The conversion could also be effected in quantitative yield by

(1) K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.*, **94**, 6215 (1972).

(2) M. P. Cava and M. A. Sprecker, *ibid.*, **94**, 6214 (1972).

(3) For earlier references, see K. T. Potts, A. J. Elliott, and M. Sorm, *J. Org. Chem.*, **37**, 3838 (1972).

(4) H. O. Bayer, R. Huisgen, R. Knorr, and F. C. Schaefer, *Chem. Ber.*, **103**, 2581 (1970).

(5) All products described gave satisfactory analytical data.

(6) K. T. Potts and U. P. Singh, *Chem. Commun.*, **66** (1969).