acetone–cupric sulfate at 55 °C for 2 h as described previously. Workup and chromatography on silica gel gave 37 mg (93%) of **14:** ir ($CHCl_3$) 1733, 1710, 1655, 1612 cm^{-1}; NMR ($CDCl_3$) 0.87 (s, 3 H), 1.27 (s, 3 H), 1.30 (t, 3 H, J = 7 Hz), 1.35 (s, 3 H), 1.45 (s, 3 H), 3.90 (m, 1 H), 4.18 (q, 2 H, J = 7 Hz), 12.15 ppm (s, 1 H).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.38; H, 8.69.

Cuauhtemone Acetonide (18). To 33 mg (1.38 mmol) of sodium hydride (from 66 mg of 50% mineral oil dispersion) in 18 ml of ether was added 0.148 g (0.46 mmol) of keto ester acetonide **14.** When hydrogen evolution was complete an ethereal solution of 1.6 M methyllithium[11] (32 mmol) was added at 0 °C over a period of 10 min and the resulting solution was then heated at reflux for 4.5 h. The recooled mixture was then added to 50 ml of an ice-cooled 20% ammonium chloride solution. Following the usual workup removal of the solvent gave 0.135 g of oily product. Rapid chromatography on silica gel gave 70 mg of unreacted keto ester **14** and 40 mg of ketol acetonide **17:** NMR ($CDCl_3$) 0.82 (s, 3 H), 1.22 (s, 3 H), 1.27 (s, 3 H), 1.38 (s, 3 H), 1.53 (s, 3 H), 3.90 (m, 1 H). Recycling of the recovered **14** gave a total of 60 mg of partially purified **17.**

The ketol **17** (60 mg, 0.194 mmol) was dissolved in 10 ml of cold pyridine (0 °C) to which was added 0.2 ml of thionyl chloride.[13] After stirring for 3 h at 0 °C the mixture was added to cold saturated sodium bicarbonate solution. The usual workup (extraction with ether) gave 54 mg of oily product which was chromatographed on silica gel to yield 26 mg of cuauhtemone acetonide (**18**): ir ($CHCl_3$) 1677, 1600 cm^{-1}; NMR ($CDCl_3$) 0.89 (s, 3 H), 1.39 (s, 3 H), 1.50 (s, 3 H), 1.82 (s, 3 H), 1.98 (s, 3 H), 2.19 (s, 3 H), 3.95 ppm (m, 1 H); MS M^+ 292.20133 (calcd for $C_{18}H_{28}O_3$, 292.20377).

Preceding the elution of **18** there was obtained 11 mg of an oil having the spectral characteristics attributable to the isopropenyl isomer **19:** ir ($CHCl_3$) 1707, 1600 cm^{-1}.

Cuauhtemone (1). A solution of 0.38 g of **18** in 5 ml of 80% aqueous acetic acid was warmed to 60 °C for 15 h. The solution was then extracted with methylene chloride and the extracts washed with saturated sodium bicarbonate solution. Removal of the solvent after drying over sodium sulfate afforded 0.34 g of a crude oil. The latter was chromatographed on an EM Reagents size A silica gel 60 prepacked column to give 15 mg of racemic cuauhtemone (**1**):[1] ir ($CHCl_3$) 3530, 2930, 1675, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) 0.92 (s, 3 H), 1.20 (s, 3 H), 1.77 (broad s, 2 H), 1.82 (s, 3 H), 2.01 (s, 3 H), 2.20 (s, 3 H), 2.92 (d, 1 H, J = 12 Hz), 3.63 ppm (t, 1 H, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$) 203.11, 144.37, 131.36, 74.35, 73.07, 60.17, 45.61, 36.29, 32.95, 25.75, 23.41, 22.69, 21.35, 18.62 ppm; uv (CH_3OH) max 254 nm (ϵ 7500); MS M^+ (base peak) 252.1713 (calcd for $C_{15}H_{24}O_3$, 252.1725).

Registry No.—*rac*-**1,** 58616-76-5; **2,** 4746-97-8; **3,** 54316-77-7; **4,** 3944-80-4; **5,** 58540-78-6; **6,** 54316-78-8; **7,** 58540-79-7; **8,** 58540-80-0; **9,** 58540-81-1; **11,** 58540-82-2; **12,** 58540-83-3; **13,** 58540-84-4; **14,** 58540-85-5; **17,** 58540-86-6; **18,** 58540-87-7; **19,** 58540-88-8.

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Studies on the Adduct of 4-Phenyl-1,2,4-triazoline-3,5-dione with Vitamin D_3

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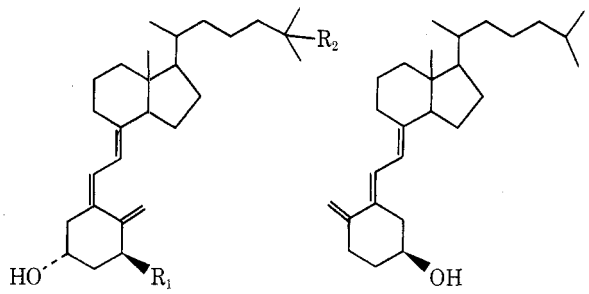
Vitamin D_3 reacted rapidly with 4-phenyl-1,2,4-triazoline-3,5-dione at the $\Delta^{5,10(19)}$-diene system to give the α-face adduct **7** (95%) and β-face adduct **9** (5%). The adduct mixture gave a crystalline ketone **14** with Jones reagent. Ketone **14** was unaffected by HCl in dioxane or ethanol, but gave a dimethyl ketal **15** with HCl in methanol. Sodium borohydride reduction of **14** gave a mixture of **7** and the crystalline epimer **16.** Adduct **7** was unaffected by lithium aluminum hydride or sodium bis(2-methoxyethoxy)aluminum hydride, but reacted with diisobutylaluminum hydride to give a dihydrodeoxy compound **17.** With KOH in ethylene glycol–water, 5,6-*trans*-vitamin D_3 was recovered.

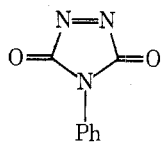
The chemistry of vitamin D has a history of over 50 years.[1] Nonetheless, there remains considerable interest in the chemistry of vitamin D, in particular as a result of recent investigations on the metabolism of vitamin D_3 (**1**) and related compounds.[2] It is now clear that this vitamin undergoes hydroxylation (in the liver) at C-25, followed by hydroxylation (in kidney) at C-1α position to form 1α,25-dihydroxycholecalciferol (**2**), which appears to be the biologically active agent responsible for stimulation of the production of the calcium-binding protein. The activity of **2** is manifested even in nephrectomized rats, which are incapable of carrying out the 1α-hydroxylation step,[3] where in contrast cholecalciferol (**1**) and 25-hydroxycholecalciferol (**3**) are ineffective. The primary requirement for activity in vitamin D analogues appears to be the presence of a 1α-hydroxyl, or, as in 5,6-*trans*-cholecalciferol (**4**), a hydroxyl in the same position, relative to the transoid diene system, as the 1α-hydroxyl.[1a,4] Synthetic 1α-hydroxycholecalciferol (**5**) is now being used in the clinical treatment of nephritic bone disease in humans.[5]

With the foregoing facts in mind, we and many others[6,7] have been studying synthetic routes to the preparation of hydroxylated (or otherwise modified) vitamin D analogues, particularly compounds **2** and **5.** All studies reported to date, with the exception of a total synthesis[8] of **5** have involved the synthesis of steroidal precursors convertible into $\Delta^{5,7}$-steroids, from which the vitamins can be obtained by the usual photochemical–thermal isomerization process. In the present work, we have approached the problem from a different angle, namely via the direct modification of vitamin D_3 itself. Our first objective was the preparation of a derivative in which the heat-, light-, and air-sensitive calciferol triene system is protected in such a way that oxidative reactions, or other trans-



1, $R_1 = R_2 = H$
2, $R_1 = R_2 = OH$
3, $R_1 = H$; $R_2 = OH$
5, $R_1 = OH$; $R_2 = H$

4



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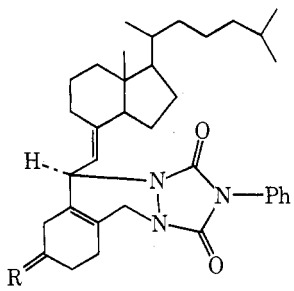
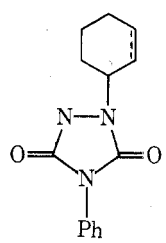


7, R = 

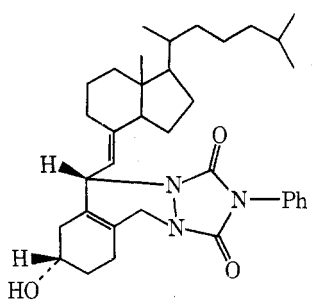
14, R = O=

15, R = 

16, R = 



8a, Δ 2′
b, 2′, 3′-H_2



9

formations, could be performed in ring A. An important requirement was that the calciferol triene system be easily recoverable after such transformations.

We were attracted by recent reports[9] on the protection of steroidal 5,7-dienes by formation of adducts with 4-phenyl-1,2,4-triazoline-3,5-dione (**6**). The diene system was recoverable from such adducts by treatment with lithium aluminum hydride. We therefore investigated the reaction of cholecalciferol with **6**.

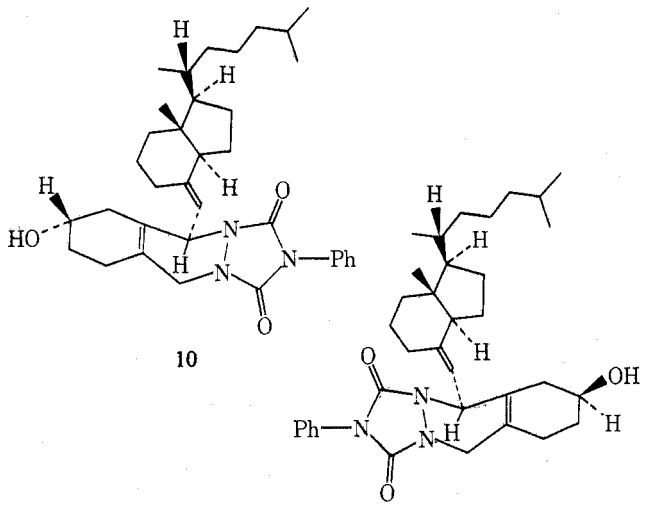
Cholecalciferol (**1**) reacted rapidly with **6**, the reaction being complete within a few minutes at 0 °C (as judged by the disappearance of the red color of **6**). Qualitatively, however, the reaction was significantly slower than the corresponding reaction of **6** with 7-dehydrocholesterol, in which the reaction is practically complete in the time required for mixing. The slower rate of reaction of **1** may be attributed in part to some noncoplanarity of the reactive 5,6 and 10,19 double bonds, as shown in the x-ray analysis of a vitamin D_2 derivative.[10] The product was a noncrystalline glass, but gave a single spot in several TLC solvent systems, and single peaks on high-pressure liquid chromatograms. The NMR spectrum of the product supported the expected structure **7** (without stereochemical implications). Thus, in particular, the C-7 vinyl H, δ 4.98, and the C-6 proton (attached to nitrogen and doubly allylic, δ 4.73) formed an AB pattern, J = 10 Hz, with additional weaker long-range coupling. Also, the C-19 hydrogens formed a distinctive broadened AB pattern, δ 3.85 and 4.20. The chemical shifts are consistent with the location of the protons on an allylic carbon bonded to nitrogen. This system may reasonably be compared with that in 1-(2′-cyclohex-1′-yl)-4-phenylbicarbamimide (**8a**) (prepared from **6** and cyclohexene in benzene at room temperature) in which the C-1′ hydrogen appears at δ 4.80. (In the saturated compound **8b**, this hydrogen appears at δ 3.98). The NMR thus clearly supported structure **7**, as opposed to **12** which would have resulted from addition of **6** to the transoid diene system of **1** after a preliminary conformational change to the cisoid form.

Structure **7** is in fact closely related to the Diels–Alder adduct **13** of ergocalciferol with maleic anhydride reported 30 years ago by Windaus and Thiele.[11] In that case, the product was apparently a mixture, convertible into two crystalline acetyl dimethyl esters designated α and β. The stereochemistries of these products still remain unknown. It is reasonable to assume that the mixture consisted of products formed by addition of maleic anhydride in an endo fashion,[12] from the upper (β) and lower (α) faces of the triene system which does not bear the usual α-directive 19-methyl group.[13] With such precedent, one might expect to obtain a similar mixture in the reaction of **1** with triazolinedione **6**. An examination of models indicates that while the 18-methyl and side chain would have little influence on the addition of maleic anhydride, they present significant interference with the approach of **6** to the β face of **1**, at least in the transition state in which the phenyl group is oriented toward rings C and D. Such interference is not presented upon approach to the α face; consequently, an "α-face adduct" **7** is formed almost exclusively. After the majority of the present work was completed, however, a minor product (ca. 5%) designated **9** was detected by TLC using a modified solvent system, and isolated in low yield by preparative TLC. The NMR spectrum of this presumably "β-face adduct" was very similar to that of **7**, except for small differences in the chemical shifts of the vinyl protons. The specific rotations of the compounds were markedly different, however, the major (α-face) isomer **7** being strongly dextrorotatory ([α]D + 196°), while the minor isomer **9** was, as expected, strongly levorotatory ([α]D −187°). The ring systems in these compounds (structures **10** and **11**, written in identical, reasonable conformations) are essentially mirror images of one another, even though they are identical in rings C and D and in the configuration of the hydroxyl group.

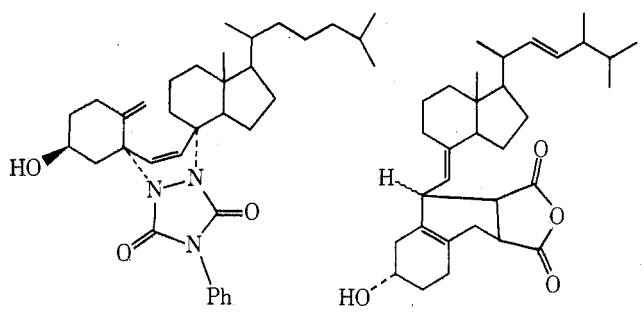
In support of the assigned structure **9** for the minor product of the addition reaction is the fact that treatment of 5,6-*trans*-cholecalciferol (**4**) with **6** gave an approximately equal mixture of **7** and **9**. In this case, the reactive cisoid diene is more remote from the 18-methyl and side chain, and not subject to steric hindrance to the approach of **6** from the β face. Although larger quantities of **9** were formed in this reaction, its isolation in pure form proved to be quite difficult, and no chemical studies were performed on this compound.

The following chemical studies were carried out on the unseparated adduct **7** (actually ca. 95% **7** and ca. 5% **9**). However, all products obtained were characterized as recrystallized compounds which are presumed to be homogeneous. None showed any evidence of being a mixture of isomers.

On treatment of **7** with Jones reagent, the ketone **14** was prepared in good yield. The NMR spectrum of **14**, which possessed two AB patterns practically identical with those in the NMR of **7**, indicated the unchanged positions of the Δ^7 and $\Delta^{5,10}$ double bonds. However, the C-4 protons, now adjacent



10 11



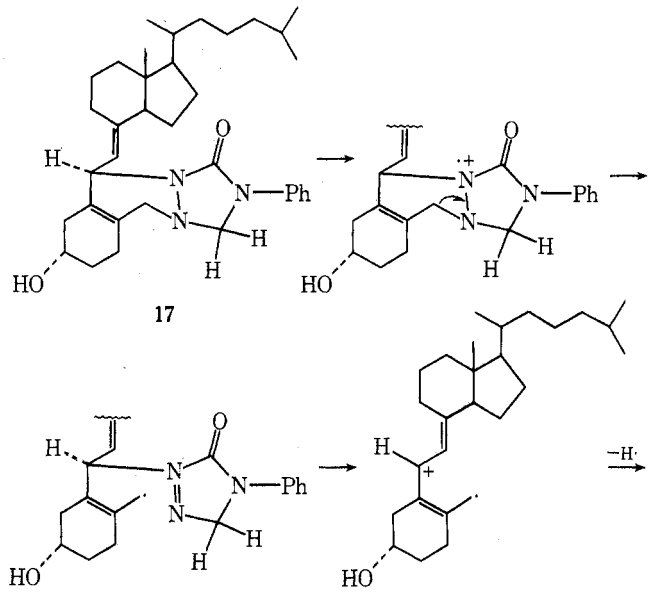
12 13

to carbonyl as well as allylic, moved downfield forming a new AB pattern, δ 3.91 and 4.29, J = 16 Hz.

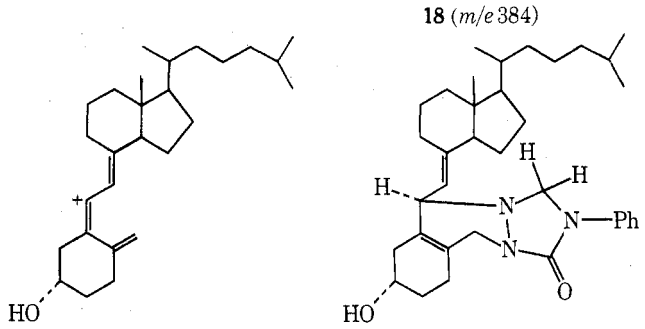
It appeared possible that this β,γ-unsaturated ketone **14** could be isomerized to the corresponding α,β-unsaturated ketone. Furthermore, the possibility existed that the Δ^7 double bond might be isomerized into ring A, which would produce a phenolic system. On treatment of **14** with aqueous HCl in dioxane or ethanol, even under vigorous conditions, no change occurred and the starting material was recovered. In contrast, treatment of **14** with aqueous HCl in methanol led within 15 min at room temperature to the crystalline dimethyl ketal **15.** Again, the NMR showed the continued presence of the Δ^7 and $\Delta^{5,10}$ double bonds, as well as signals for two methoxyls, δ 3.18 and 3.25. When this ketal was further treated with aqueous HCl in dioxane, ketone **14** was regenerated.

Since we were interested in synthesizing the 3α epimer of vitamin D_3,[7] ketone **14** was treated with sodium borohydride, affording a mixture, resolvable by multiple elution TLC and easily resolvable by liquid chromatography, of approximately equal amounts of the 3β alcohol **7** and a crystalline isomer, **16.** Thus, in this reaction, no particular preference was observed for attack of the borohydride from one side or the other of the carbonyl, in contrast to our observations[7] with the ketone derived from the adduct of **6** with 7-dehydrocholesterol. The NMR of **16** was very similar to that of **7,** particularly in the low-field signals characteristic of the triene–adduct system.

In addition to the above studies, we examined procedures capable, in principle, of converting adducts such as **7** or **16** back to the vitamin D triene system. All studies to date have been conducted on the original adduct, **7.** Contrary to expectations, this compound proved to be highly resistant to reduction with lithium aluminum hydride in THF or sodium bis(2-methoxyethoxy)aluminum hydride in benzene, and was recovered unchanged after 3 days refluxing. However, **7** did react under relatively mild conditions with diisobutylaluminum hydride to give a major product, tentatively assigned structure **17.** In particular, this structure is supported by the



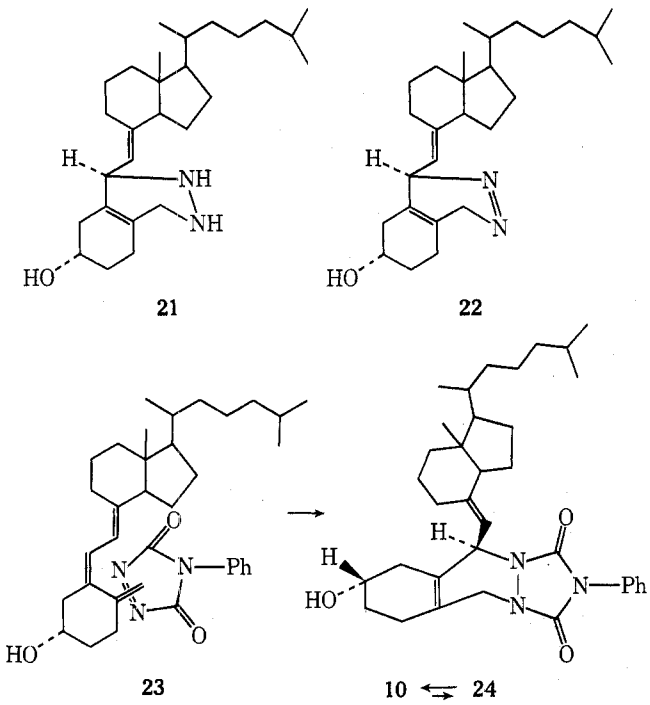
17 18 (m/e 384)



19 (m/e 383) 20

mass spectrum, M^+ m/e 545, which indicates a loss of 14 mass units from the starting material **7.** The production of fragment ions at m/e 384, structure **18,** and m/e 383, **19,** clearly indicates that this 14 mass unit difference is located in the triazoline system. The structure is supported by the NMR spectrum, which allows a distinction between **17** and the isomeric structure **20.** Thus, signals persist for the C-7 vinyl H (δ 4.84) and C-6 H (δ 4.42). Although the latter signal is 0.3 ppm upfield from its position in **7,** this is minor in comparison with the upfield shift of ca. 0.9 ppm exhibited by the C-19 hydrogens. This is consistent with their attachment to an amine nitrogen, rather than to an amide nitrogen. A new signal for the $-NCH_2N-$ protons appears at 5.03 ppm. Efforts to force the reduction with diisobutylaluminum hydride to completion have not been successful to date. Under forcing conditions, other products are formed, but none appears to predominate.

In an alternative approach to the regeneration of the vitamin D_3 triene system, adduct **7** was treated with aqueous alkali.[15] It was expected that the imide system of **7** could be hydrolyzed to the hydrazine **21,** oxidation of which (by air, or other oxidizing agent) would give the azo derivative **22** which might be expected to readily eliminate N_2 forming a mixture of vitamin D_3 and 5,6-*trans*-cholecalciferol (**4**). Under relatively mild conditions, no vitamin D_3 or **4** was formed with this reagent, although several uncharacterized intermediates were detected. However, under vigorous conditions (ca. 100 °C), 5,6-*trans*-cholecalciferol (**4**) was formed in good yield. Under such conditions, vitamin D_3 would have been converted into a mixture of pyrocalciferol and isopyrocalciferol.[1a] However, these compounds were not detectable among the minor byproducts of this process, and it appears that 5,6-*trans*-cholecalciferol (**4**) is the only triene formed. Furthermore, when the process was applied to the mixture of **7** and **9** formed by addition of **6** to 5,6-*trans*-cholecalciferol (**4**), again the only



major product recovered was **4**. Thus, the original Diels–Alder addition reaction and the above cycloreversion process were observed to follow different stereochemistries. The addition presumably occurs as shown, **23**, to yield initially an axially substituted adduct **24**, which undergoes conformational change to the more stable structure **10**. Cycloreversion from **22** occurs via a conformation resembling **10** thereby leading directly to 5,6-*trans*-cholecalciferol (**4**). The observed results seem to preclude the application of these procedures in the preparation of modified derivatives of vitamin D_3 itself.

An alternative approach to the protection of the vitamin D triene system was recently reported.[16]

Experimental Section

Infrared spectra were taken on a Perkin-Elmer Model 337 spectrometer. Ultraviolet spectra were taken on a Beckman DB-G instrument. NMR spectra were taken on a Varian A-60 instrument. Specific rotations were measured on a Rudolph Model 80 polarimeter. Camag Kieselgel DF-0 was used for thin layer chromatography (TLC). Liquid chromatography was performed using a Waters Associates ALC-202 liquid chromatograph with 2 ft × 0.125 in. columns packed with Waters Corasil II or Bondapak Carbowax 400. Melting points were taken on a hot stage apparatus and are uncorrected. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

Cholecalciferol 4-Phenyl-1,2,4-triazoline-3,5-dione Adducts 7 and 9. Cholecalciferol (Sigma, 1 g, 2.6 mmol) in ethyl acetate (30 ml) cooled in ice–water was treated with 4-phenyl-1,2,4-triazoline-3,5-dione (500 mg, 1 equiv) in ethyl acetate (30 ml) added dropwise over 15 min until a pink color persisted for 10 min. After stirring for an additional 1 h at room temperature, the straw-colored solution was evaporated to a glass, which became a hard froth upon pumping under high vacuum.

A sample was purified by preparative TLC (ethyl acetate/hexane 2/3, followed by ethyl acetate/benzene 1/4 with multiple elution) and the major product **7** (95%) isolated as a noncrystalline glass. It had $[\alpha]^{27}D$ +196° (*c* 1.4, $CHCl_3$); ν_{max} ($CHCl_3$) 3600, 3450 (br), 1760, 1705, 1420, 853, 690, 649 cm^{-1}; NMR ($CDCl_3$) δ 0.50 (3 H, s), 0.85 (6 H, d, J = 6 Hz), 0.88 (3 H, d), 1.0–3.0 (m, ca. 27 H), 3.85 and 4.20 (2 H, AB, J_{AB} = 15 Hz, peaks broadened through additional coupling), 4.1 (1 H, –OH, D_2O exchangeable), 4.73 and 4.98 (2 H, AB, J_{AB} = 10 Hz, broadened through additional coupling), 7.45 (s, 5 H).

Anal. Calcd for $C_{35}H_{49}N_3O_3$: C, 75.10; H, 8.82; N, 7.51. Found: C, 74.99; H, 8.94; N, 7.50.

The minor product (5%) was also a noncrystalline glass: $[\alpha]^{27}D$ −187° (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3620, 3480 (br), 1760, 1705, 1420, 1134, 1040 cm^{-1}; NMR ($CDCl_3$) δ 0.51 (3 H, s), 0.85 (6 H, d, J = 6 Hz), 1.0–3.0 (ca. 30 H, m), 3.78 and 4.21 (2 H, AB, J_{AB} = 16 Hz, broadened by additional coupling), 4.1 (1 H, D_2O exchangeable), 4.75 and 5.04 (2 H, AB, J_{AB} = 10 Hz), 7.48 (5 H, br s).

1-(2′-Cyclohexen-1′-yl)-4-phenylbicarbamimide (8a). Cyclohexene (1 g, distilled) and 1,2,4-triazoline-3,5-dione (1 g) in benzene (100 ml) was kept at room temperature in the dark for 12 h. The colorless solution was evaporated to a crystalline residue, recrystallized from MeOH, blades, mp 168–169 °C (lit.[14] mp 168–169 °C).

The dihydro compound, **1-cyclohexyl-4-phenylbicarbamimide (8b),** was prepared by hydrogenation of **8a** (280 mg) in ethyl acetate (20 ml) over PtO_2 (50 mg) in a Parr Model 3910 shaking hydrogenation apparatus at 30 psi for 2 h. After filtration and evaporation of the solvent, the product was crystallized from ethyl acetate, needles: mp 204–206 °C; ν_{max} ($CHCl_3$) 3365, 1755, 1695, 1425 cm^{-1}; NMR ($CDCl_3$) δ 0.9–2.0 (broad m, 10 H), 3.98 (1 H, br m, $W_{1/2} \sim 20$ Hz). 7.49 (5 H, s).

Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61. Found: C, 64.75; H, 6.47.

Cholecalciferone 4-Phenyl-1,2,4-triazoline-3,5-dione Adduct (14). Adduct **7** (1.0 g) in acetone (100 ml) in an ice–water bath was treated with Jones reagent (1.8 ml) for 5 min. Then water (100 ml) was added, followed by 5% $NaHSO_3$ to destroy the excess oxidant. The mixture was extracted with ether, and the extract washed twice with 5% $NaHCO_3$ and with saturated NaCl, dried (Na_2SO_4), and evaporated to a gum, 0.8 g. This was purified by preparative TLC (ethyl acetate/hexane 2/3, R_f 0.37) and crystallized from MeOH, white prisms: mp 158–160 °C; $[\alpha]^{28}D$ +224° (*c* 1.8, $CHCl_3$); ν_{max} ($CHCl_3$) 1760, 1710, 1700, 1410, 1145, 853, 810, 688, 648 cm^{-1}; NMR ($CDCl_3$) δ 0.50 (3 H, s), 0.80 (3 H, s), 0.90 (3 H, s), 1.0–2.2 (25 H, m), 2.51 (3 H, br s, $W_{1/2}$ = 5 Hz), 2.8 (3 H, br s, $W_{1/2}$ = 9 Hz), 3.91 and 4.29 (2 H, AB, J_{AB} = 16 Hz, with smaller long-range coupling), 4.74 and 5.04 (2 H, AB, J_{AB} = 10 Hz, with additional smaller coupling), 7.4 (5 H, s).

Anal. Calcd for $C_{35}H_{47}N_3O_3$: C, 75.37; H, 8.49. Found: C, 75.09; H, 8.48.

Cholecalciferone 4-Phenyl-1,2,4-triazoline-3,5-dione Adduct Dimethyl Ketal (15). Ketone **14** (700 mg) in MeOH (30 ml) was treated with 1 N HCl (5 drops). The reaction was complete after 15 min stirring at 25 °C and crystallization commenced. Ether (60 ml) was added and the solution was washed with H_2O twice and saturated NaCl, dried (Na_2SO_4), and evaporated to a gum, 660 mg, which crystallized from MeOH, white needles: mp 154–156 °C; $[\alpha]^{27}D$ +218° (*c* 1.4, $CHCl_3$); ν_{max} ($CHCl_3$) 1762, 1707, 1430, 1135, 1105, 1050, 910, 855, 690, 648 cm^{-1}; NMR ($CDCl_3$) δ 0.50 (3 H, s), 0.81 (3 H, s), 0.90 (6 H, br s), 1.0–2.3 (26 H, m), 3.17 (3 H, s), 3.23 (3 H, s), 3.80 and 4.22 (2 H, AB, J_{AB} = 16 Hz, with additional smaller coupling), 4.76 and 5.00 (2 H, AB, J_{AB} = 10 Hz, with additional smaller coupling), 7.92 (5 H, s).

Anal. Calcd for $C_{37}H_{53}N_3O_4$: C, 73.60; H, 8.85; N, 6.96. Found: C, 73.31; H, 8.72; N, 7.12.

On treatment of **15** (150 mg) in dioxane (20 ml) with 1 N HCl (5 drops) for 6 h at 25 °C, the ketone **14** (100 mg) was obtained after extraction with ether and purification by preparative TLC.

3-*epi*-Cholecalciferol 4-Phenyl-1,2,4-triazoline-3,5-dione Adduct (16). Ketone **14** (800 mg) in MeOH (80 ml) was treated with sodium borohydride (200 mg) and stirred at room temperature for 10 h. Water (80 ml) and ether (150 ml) were added, and 1 N HCl was added to acidify the aqueous phase. The ether extract was washed with H_2O and saturated NaCl, dried (Na_2SO_4), and evaporated.

The 3-epi compound **16** (R_f 0.52) was separated from **7** (R_f 0.44) by preparative TLC (ethyl acetate/benzene 1/4, developed three times); 244 mg of **16** was isolated, which slowly formed needles from MeOH: mp 143–145 °C; $[\alpha]^{27}D$ +175° (*c* 1.6, $CHCl_3$); ν_{max} ($CHCl_3$) 3600, 3470 (br), 1775, 1710, 1425 cm^{-1}; NMR ($CDCl_3$) δ 0.50 (3 H, s), 0.81 (3 H, br s), 0.90 (6 H, br s), 1.0–2.3 (26 H, m), 2.6 (1 H, br s, $W_{1/2}$ = 6 Hz), 3.8 (1 H, br m), 3.78 and 4.17 (2 H, AB, J_{AB} = 16 Hz, with additional smaller coupling), 4.72 and 4.88 (2 H, , J_{AB} = 10 Hz, with additional smaller coupling), 7.41 (5 H, s).

Anal. Calcd for $C_{35}H_{49}N_3O_3$: C, 75.10; H, 8.82; N, 7.51. Found: C, 74.98; H, 8.99; N, 7.56.

Diisobutylaluminum Hydride Product 17. The adduct **7** (200 mg) in anhydrous ether (16 ml) under N_2 at 0 °C was treated with diisobutylaluminum hydride (neat, 1 ml). The mixture was stirred for 3 h at 20 °C. The mixture was cooled, and additional ether (20 ml) was added, followed by MeOH (2 ml) and water (1 ml). The mixture was filtered, and the filtrate dried ($MgSO_4$) and evaporated. The main product was isolated by preparative TLC (25% EtOAc–hexane, R_f 0.4) giving 40 mg of **17**, needles from MeOH: mp 162–165°; ν_{max} ($CHCl_3$) 1695, 1685, 1490, 1395 cm^{-1}; NMR ($CDCl_3$) δ 0.55 (3 H, s), 0.7–3.0 (36 H, m), 3.12 (1 H, m), 3.33 (1 H, m), 4.0 (1 H, m), 4.42 (1 H, d, J = 6 Hz), 4.84 (1 H, d, J = 6 Hz), 5.03 (2 H, br s, $W_{1/2}$ = 6 Hz), 7.41 (5 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 547 (4), 546 (18), 545

(M^+, 45), 384 (20), 383 (20), 369 (3), 368 (2), 367 (2), 366 (2), 365 (6), 284 (27), 271 (10), 259 (8), 253 (8), 247 (17), 165 (42), 162 (32), 136 (100), 135 (28), 119 (40), 118 (88).

Anal. Calcd for $C_{35}H_{51}N_3O_2$: C, 77.02; H, 9.15. Found: C, 76.75; H, 9.44.

Treatment of Adduct 7 with Alkali. Adduct **7** (800 mg) in a mixture of ethylene glycol (30 ml), water (30 ml), and KOH (630 mg) was heated at reflux under N_2 for 40 min. The mixture was cooled and extracted with ether, and the extract washed with water and saturated NaCl, dried (Na_2SO_4), and evaporated. The product (300 mg) was separated by preparative TLC (ethyl acetate/hexane 1/2) and the major product isolated. The product (110 mg) was identical with 5,6-*trans*-cholecalciferol (**4**), prepared by an alternative method.[4] No cholecalciferol or products obtained by treatment of cholecalciferol under the above conditions were detected.

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Registry No.—**1**, 67-97-0; **6**, 4233-33-4; **7**, 58581-83-2; **8a**, 15971-69-4; **8b**, 53959-00-5; **9**, 58617-26-8; **14**, 58581-84-3; **15**, 58581-85-4; **16**, 58617-27-9; **17**, 58581-86-5; cyclohexene, 110-83-8.

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Nucleophilic and 1,3 Additions to Triazolinediones[1a]

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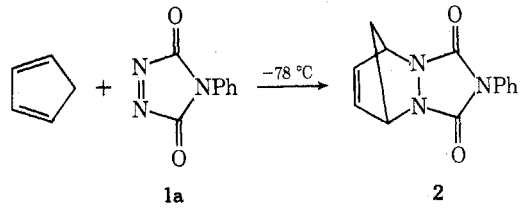
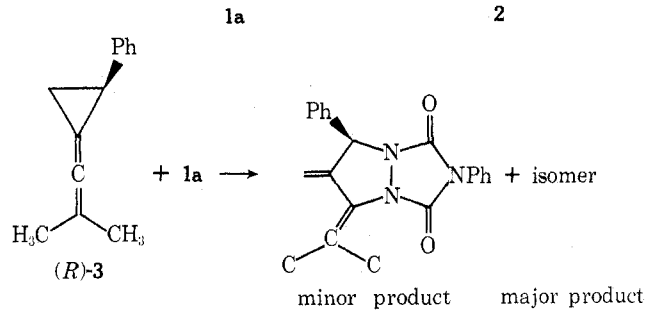
Triazolinediones **1** are shown to undergo cycloaddition to vinyl azides **5** in a 1,3 manner with loss of nitrogen to form novel bicyclic heterocycles **6**. Substituent effects on the vinyl carbons suggest nucleophilic attack by the β carbon of **5** on the N=N of **1**. Phosphorus ylides likewise undergo nucleophilic attack on **1** followed by proton abstraction to produce ylides **14**.

4-Phenyl-1,2,4-triazoline-3,5-dione (PTAD, **1a**) has been shown in recent years to be one of the most powerful dienophiles.[2] For instance, cyclopentadiene reacts with **1a** at −78 °C in a 1,4 manner to produce **2**. On the other hand, allene **3** undergoes an addition with opening of the cyclopropane ring[2d] but to form an optically active adduct **4** and an isomer. These reactions were shown to occur in a concerted manner. Furthermore, a 1,2 addition of **1a** to a methylenecyclopropane has been reported.[2e]



1a **2**



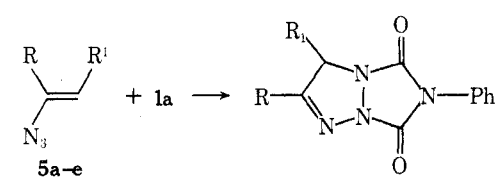
(*R*)-**3**

minor product major product

(*S*)-**4**

We now wish to report a 1,3 cycloaddition of **1a** with vinyl azides leading to the formation of novel heterocycles. This reaction can also be used as a method of derivatizing vinyl azides which are normally difficult to purify.

When vinyl azides, **5**, were allowed to react with **1a** in



5a–e **6**

5	R	R′
a	Ph	H
b	Ph	CH_3
c	*p*-MeO—C_6H_4	H
d	H	*tert*-butyl
e	*p*-NO_2—C_6H_4	