consequently bears the C_6 group on the right, while in the 20β-hydroxy epimer (4) the C_6 group must be on the left. Further weight to this conclusion is given by the fact that C-21 would be in a different environment in the two epimers, and the NMR signals for this carbon atom differ (by δ 0.15) in the two cases.

We conclude from these various facts that rotation about the 17(20) bond occurs when C-20 is in the trigonal state. However, when C-20 is tetrahedral and fully substituted, conformational preference is enhanced. It is interesting that in the presence of two substituents on C-20 with the same structure, the addition of restricted rotation could confer asymmetry. This has actually been observed[10] with 20-methyl-20-(2-hydroxyethoxy)pregn-5-ene-3β,17-diol. Despite the fact that C-20 bears two methyl groups, the substance exists as two separable isomers, and they have spectroscopic properties consistent with the ether group lying toward or away from C-13.

Experimental Section

The NMR spectra were performed in 2% solutions of deuterated chloroform at ambient temperature on a 220-MHz instrument through the services of Morgan-Schaffer of Montreal, Canada, who also supplied the mass spectral data. Melting points were determined on a Kofler hot stage. Gas–liquid chromatography was performed on a column of 1% of nitrile silicone gum (XE-60) on Chromosorb W in a 6-ft U-tube at 235 °C.

Grignard Reaction with Pregnenolone Acetate (3 and 4 from 1a and 2a). A benzene solution of pregnenolone acetate was added to 4-methylvalerylmagnesium bromide in ether. After the reaction had subsided the mixture was refluxed for 2 h. The product was acetylated (Ac_2O–pyridine, room temperature) and submitted to GLC analysis. Two substances were present with retention times relative to cholesteryl acetate of 2.07 and 1.95 in a ratio of 1.8:1.0 based on peak heights. The NMR spectrum also showed the presence of two substances, one with a C-21 signal at δ 1.28 and the other with the analogous signal at δ 1.13 in a ratio of about 1.6:1.0. The major component was 20α-hydroxycholesteryl acetate (3) and the minor one 20β-hydroxycholesteryl acetate (4) as shown by a comparison of the retention times and NMR values with those of authentic samples which are described in what follows.

The product mixture was crystallized from ethanol, and the precipitate was recrystallized several times, giving 5.1 g (from 14.6 g of pregnenolone acetate) of authentic 20α-hydroxycholesteryl acetate (3) with a retention time relative to cholesteryl acetate of 2.07. The melting point (153–155 °C), NMR spectrum [δ 0.87 (d, J = 6 Hz, 6 H, C-26 and C-27), 0.87 (s, 3 H, C-18), 1.03 (s, 3 H, C-19), and 1.28 (s, 3 H, C-21)], and mass spectrum [m/e 384 (M^+ − CH_3COOH, 61%), 366 (384 − H_2O, 88%), 351 (366 − CH_3, 63%), 299 (384 − C_6H_{13}, 100%), 281 (299 − H_2O, 86%), 256 (87%), 253 (46%), 241 (37%), 228 (61%), 213 (73%), and 211 (52%)] were in agreement with the corresponding values for the product (20α-hydroxycholesteryl acetate) reported earlier.[5,6] The free alcohol derived from hydrolysis (KOH in methanol, 10 min at reflux) of the 20α-hydroxycholesteryl acetate melted at 133–134 °C, δ 0.87 (d, J = 6 Hz, C-26 and C-27), 0.86 (s, C-18), 1.01 (s, C-19), and 1.28 (s, C-21) as previously reported.[5] Although the mother liquor from the first crystallization of the 20α-hydroxycholesteryl acetate was enriched in the β epimer, attempts to obtain the latter pure by concentration and recrystallizations of the succeeding crops of crystals failed. The best material was a mixture in which the β epimer had twice the concentration of the α epimer by GLC analysis.

Grignard Reaction with 20-Keto-21-norcholesteryl Acetate (3 and 4 from 1b and 2b). Authentic 20β-hydroxycholesteryl acetate (4) was prepared by the Grignard reaction of 20-keto-21-norcholesteryl acetate with methylmagnesium iodide. This reaction is reported[5] to give both epimers in a ratio of about 1:10 (α to β). The GLC analysis of our reaction product was in agreement with this. After acetylation, chromatography on alumina, and crystallization from methanol the β epimer (530 mg from 1.04 g of ketone) had a retention time relative to cholesteryl acetate of 1.95. Its melting point (110–111 °C), NMR spectrum [δ 0.88 (d, J = 6 Hz, 6 H, C-26 and C-27), 0.87 (s, 3 H, C-18), 1.03 (s, 3 H, C-19), and 1.13 (s, 3 H, C-21)], and mass spectrum [m/e 384 (M^+ − CH_3COOH, 33%), 366 (384 − H_2O, 89%), 351 (366 − CH_3, 77%), 299 (384 − C_6H_{13}, 40%), 281 (299 − H_2O, 100%), 256 (65%), 253 (50%), 241 (32%), 228 (84%), 213 (90%), and 211 (63%)] agreed with the literature.[5,6] The free alcohol melted at 115–117 °C as previously reported.[5] Since the melting point of the β epimer is much lower than that of the α epimer, it is not surprising that the β epimer was missed by earlier workers in the Grignard reaction with pregnenolone. It was easily isolated only when the α epimer was present in very small concentration.

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Registry No.—**1a,** 1778-02-5; **1b,** 6570-97-4; **3,** 7484-20-0; **4,** 7429-99-4; 4-methylvaleryl bromide, 58298-91-2.

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Attempted Synthesis of 2-Methylalanyl-L-prolyl-L-tryptophan. An Unexpected Result

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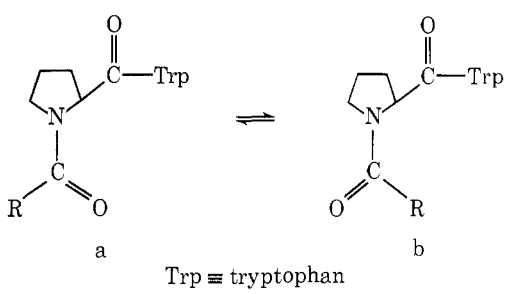
A program in our laboratory required the synthesis of tripeptides containing proline or 4-fluoroproline[1] as the central amino acid residue and an N-terminal group which biased the conformational equilibrium shown in eq 1



(1)

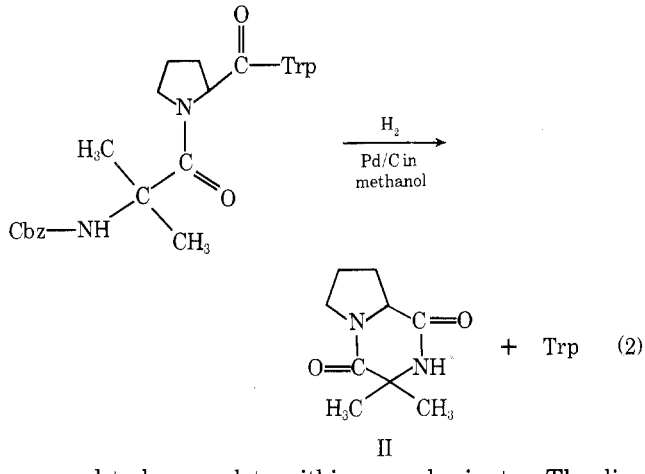
Trp ≡ tryptophan

strongly in favor of one conformer. A recent ^1H NMR study has demonstrated that pivaloylproline exists as essentially one rotational isomer.[2] This corresponds to R = $(CH_3)_3C$ in eq 1, and we reasoned that 2-methylalanine [R = $(CH_3)_2CNH_3^+$] as the N-terminal would provide a tripeptide which meets the above specification since the pivaloyl and 2-methylalanyl groups would be expected to be nearly isosteric. Our attempts to synthesize 2-methylalanyl-L-prolyl-L-tryptophan and 2-methylalanyl-4-fluoro-L-prolyl-L-tryptophan by conventional methods did not cleanly afford these tripeptides but culminated, instead, in the results described here.

Results

The protected tripeptide, carbobenzyloxy-2-methylalanyl-L-prolyl-L-tryptophan (I), was synthesized in ade-

quate yields by standard methods.[3] Attempts to remove the carbobenzyloxy (Cbz) group by hydrogenolysis at room temperature or 0 °C did not generate the expected tripeptide but rather a mixture of the diketopiperazine (II) and tryptophan (Trp). The reaction was followed by TLC and



II

appeared to be complete within several minutes. The disappearance of the protected tripeptide occurred simultaneously with the appearance of a spot (R_f 0.63) which could readily be identified as L-tryptophan by comparison to an authentic sample. A second product (R_f 0.72) was ninhydrin negative and stained only slightly with iodine. A third component (R_f 0.49), ninhydrin positive, was observed in low amounts. Attempts to isolate and identify this latter material were unsuccessful but comparison of the R_f to those of glycylprolyltryptophan (R_f 0.50) and alanylprolyltryptophan (R_f 0.51) suggested that this spot may have represented the desired tripeptide.

The ^{1}H NMR spectrum of the reaction product mixture in basic D_2O indicated, by signal positions and relative intensities, the presence of the three amino acids that were initially linked in the starting material. Several extractions of this sample with deuteriochloroform left an aqueous solution containing predominantly free tryptophan, as shown by the ^{1}H NMR spectrum. The combined organic extracts gave a ^{1}H NMR spectrum which exhibited resonances assignable to 2-methylalanine and proline and a resonance at ~7.5 ppm from Me_4Si assigned to amide protons. A mass spectrum of the extracted material showed a molecular ion at *m/e* 182; the molecular weight of 2-methylalanylprolyldiketopiperazine (II) is 182.2. Thus, although the anticipated tripeptide may initially form during hydrogenolysis, it must rapidly react to give free tryptophan and II.

Similar results were obtained in attempts to reduce carbobenzyloxy-2-methylalanyl-*cis*-4-fluoro-L-prolyl-L-tryptophan and carbobenzyloxy-2-methylalanyl-*trans*-4-fluoro-L-prolyl-L-tryptophan; TLC analysis of the reaction mixtures indicated that the same decomposition reaction had occurred as observed with the nonfluorinated protected tripeptide. However, carbobenzyloxyglycylprolyltryptophan and carbobenzyloxyalanylprolyltryptophan (R = NH_2CH_2 and NH_2CHCH_3 respectively, in eq 1) both reduced smoothly to the expected tripeptides under our conditions.

Carbobenzyloxy-2-methylalanylprolyltryptophan also was treated with a solution of hydrogen bromide in glacial acetic acid at room temperature. TLC of the residue obtained upon removal of the reaction medium showed a ninhydrin-positive spot at R_f 0.47 which might correspond to the hoped-for tripeptide. However, an unidentified broad band (R_f 0.3–0.4), intensely stained by iodine but ninhydrin negative, was also apparent.

Discussion

Previous synthetic studies have indicated that steric hindrance can be a major problem in the chemistry of 2-methylalanine and some atypical results have been described.[4,5] Many examples of peptide cleavages are known when peptides or their derivatives are subjected to conditions used to form cyclic peptides; these conditions include high temperatures and solvents such as pyridine, phenol, and *sec*-butyl alcohol. Cyclization of this type can be particularly prevalent when proline or sarcosine are present.[6,7] However, the reaction described here occurs under very mild conditions and is apparently without precedent.

It seems likely that the ability of *gem*-dimethyl groups to enhance the rate of cyclization reactions by "stereopopulation control"[8,9] plays a role in the reaction of the 2-methylalanylpeptides reported here. Consideration of space-filling models of 2-methylalanylprolyltryptophan suggests that in rotational isomer b the *gem*-dimethyl group could force a free amino group very close to the carbonyl carbon of the proline–tryptophan peptide bond, thus favoring the formation of a tetrahedral intermediate at this position. Expulsion of tryptophan from the intermediate would lead to the diketopiperazine observed. Conformer b is expected to be present in low, but not zero, concentration.[2]

We have abandoned attempts to obtain the title compound and its fluorinated analogues since it seems likely that, even if these materials could be prepared and purified, they would decompose according to eq 2 in aqueous solution.

Experimental Section[10]

2-Methylalanine (Baker), L-proline (Mann), L-tryptophan (Mann), carbobenzyloxy chloride (Aldrich), and dicyclohexylcarbodiimide (Aldrich) were used as obtained from commercial sources. The cis and trans isomers of 4-fluoroproline were prepared by the method of Gottlieb et al.[1] as previously described.[11] Preparation of carbobenzyloxy-2-methylalanine followed published procedures;[5] amino acid methyl ester hydrochlorides were prepared with methanolic HCl.[12]

Carbobenzyloxy-2-methylalanyl-L-proline Methyl Ester. To a solution of proline methyl ester hydrochloride (1.65 g, 0.010 mol) in 15 ml of dichloromethane was added triethylamine (1.4 ml), and the solution was mixed with a solution of carbobenzyloxy-2-methylalanine (2.60 g, 0.011 mol) in 15 ml of dichloromethane at 0 °C. Then dicyclohexylcarbodiimide (2.10 g, 0.010 mol) was added and the solution was stirred overnight at room temperature. Dicyclohexylurea was removed by filtration, and the filtrate was washed with 1 M HCl, water, and 1 M sodium bicarbonate, and finally dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo to yield 2.86 g (82%) of the protected dipeptide as an oily product. Additional dicyclohexylurea was removed by dissolving the oil in ethyl acetate and filtering. A ^{1}H NMR spectrum ($CDCl_3$) of the crude oil showed δ 1.5 (doublet, 6 H), 1.8 (broad band, 4 H), 3.6 [broad band, 5 H including a singlet at 3.6 ppm (~3 H)], 4.5 (broad peak, ~1 H), 5.1 (singlet, 2 H), 6.2 (broad singlet, 1 H), and 7.1 (singlet, ~5 H).

Carbobenzyloxy-2-methylalanyl-L-proline. Crude carbobenzyloxy-2-methylalanyl-L-proline methyl ester (1.02 g, 0.015 mol) was dissolved in 10 ml of methanol, and 1.0 ml of 4 M NaOH was added. The resultant solution was let stand for 16 h at room temperature. At the end of this time, the solution was diluted with 20 ml of water and extracted with ether. The ether layer was discarded. The aqueous layer was acidifed with concentrated HCl and extracted twice with ethyl acetate. The organic layer was washed with saturated NaCl solution and dried over anhydrous sodium sulfate, and the solvent was evaporated to yield 0.70 g (72%) of the oily carbobenzyloxy dipeptide. The ^{1}H NMR spectrum ($CDCl_3$) of the crude oil showed the disappearance of the singlet (3 H) at 3.6 ppm, but the rest of the spectrum was virtually the same as that of the corresponding carbobenzyloxy dipeptide methyl ester.

Carbobenzyloxy-2-methylalanyl-L-prolyl-L-tryptophan Methyl Ester. The preceding crude carbobenzyloxy dipeptide was coupled to tryptophan methyl ester hydrochloride by the same procedure described above for formation of the 2-methylalanyl–

prolyl peptide bond. The product was recrystallized from chloroform to obtain white crystals, mp 155–156 °C. The ^{1}H NMR spectrum in CD_3OD had resonances at δ 1.5 (doublet, 6 H), 1.8 (broad multiplet, 4 H), 3.6 (singlet, 3 H), 5.1 (singlet, 2 H), and 7.3 [multiplet, 10 H, including a singlet in the center (~5 H)]; other peaks were obscured by residual protons in the solvent.

Carbobenzyloxy-2-methylalanyl-L-prolyl-L-tryptophan was prepared from the above carbobenzyloxy tripeptide methyl ester in the same manner as was done at the dipeptide stage of the synthesis. The product was obtained in 82% yield and was recrystallized from methanol to afford white crystals, mp 158–159 °C. The mass spectrum exhibited a parent ion at *m/e* 520 and the ^{1}H NMR spectrum, in acetone-d_6, showed signals at δ 1.5 (broad singlet, 6 H), 1.8 (multiplet partially obscured by residual solvent peaks), 3.3 (singlet, 3 H), 3.5–4.7 (broad complex region, 6 H), 5.0 (singlet, 2 H), and 7.2 [complex multiplet, 10 H, including a singlet in the center (~5 H)]. The singlet at 3.3 ppm (3 H) represents a solvating molecule of methanol found in the crystalline material.

Anal. Calcd for $C_{28}H_{32}N_4O_6 \cdot CH_3OH$: C, 63.03; H, 6.57. Found: C, 62.94; H, 6.29.

Carbobenzyloxy-2-methylalanyl-*cis*-4-fluoro-L-prolyl-L-tryptophan and carbobenzyloxy-2-methylalanyl-*trans*-4-fluoro-L-prolyl-L-tryptophan were prepared by exactly the same methods as the unfluorinated carbobenzyloxy tripeptide described above. As in the unfluorinated case, the *cis*- and *trans*-4-fluoroprolyl peptide derivatives afforded carbobenzyloxy dipeptide methyl esters (85 and 78%, respectively) and carbobenzyloxy dipeptides (70 and 73%, respectively) which were oils, whereas the carbobenzyloxy tripeptide methyl esters (79% mp 109.5–111 °C, and 76%, mp 158–159 °C, respectively) and carbobenzyloxy tripeptides (80%, mp 190–191 °C, and 85%, mp 126–127 °C, respectively) were crystalline. Each step in these syntheses went smoothly, and ^{1}H NMR spectra were consistent with the expected products at each step. The ^{1}H NMR spectrum of the protected tripeptide containing *cis*-fluoroproline showed signals at δ 1.4 (unsymmetrical doublet, 6 H), 2.1–2.6 (broad band, 2 H), 5.6 (broad peak, 0.5 H), and 7.2 (broad, complex multiplet, 10 H). A number of peaks, some partially obscured by signals from residual protons of the solvent and spinning side bands, were observed between δ 3.0 and 5.0. The ^{1}H NMR spectrum (CD_3OD) of the corresponding trans isomer had δ 1.4 (doublet, 6 H), 1.8–2.5 (broad multiplet, 2 H), 2.7–4.9 (a number of resonances, many partially obscured by residual solvent signals and spinning side bands), 5.0 (singlet, 2 H), 6.0 (broad peak, 0.5 H), and 7.2 (broad complex multiplet, 10 H).

Carbobenzyloxyglycyl-L-prolyl-L-tryptophan was synthesized from carbobenzyloxyglycyl-L-proline (Sigma) by the same reactions described above, affording the carbobenzyloxy tripeptide methyl ester in 75% yield and carbobenzyloxy tripeptide in 79% yield. Both products were solids upon exhaustive evaporation of solvent, but could not be recrystallized, possibly because of traces of dicyclohexylurea present. The impure carbobenzyloxy tripeptide product had a ^{1}H NMR spectrum ($CDCl_3$) containing signals at δ 5.0 (singlet, 2 H), 6.0 (broad peak, 1 H), and 7.1 (complex multiplet, 10 H).

Carbobenzyloxy-L-alanyl-L-prolyl-L-tryptophan was synthesized from carbobenzyloxy-L-alanyl-L-proline (Sigma) by reactions similar to those used above. The saponification of the methyl ester resulted in a solid rather than an oily precipitate on addition of concentrated HCl. This solid was not readily extracted into ethyl acetate and was collected by vacuum filtration, washed with cold water, and dried (mp 171–173 °C). ^{1}H NMR (CD_3OD) of this unpurified solid had δ 1.2 (doublet, 3 H), 1.9 (broad band, 4 H), 5.0 (singlet, 2 H), and 7.3 (complex multiplet, 10 H). The solvent signals made accurate integration of other parts of the spectrum unreliable.

Hydrogenolyses of the carbobenzyloxy tripeptides were carried out by bubbling H_2 through a magnetically stirred solution of 0.4 mmol of the material in 14 ml of methanol; ~100 mg of 10% Pd/C was used as the catalyst.

The peptide syntheses and hydrogenolyses were monitored by TLC using Eastman Chromogram silica gel plates developed with a mixture of 1-butanol (63 ml), glacial acetic acid (23 ml), and water (14 ml). Plates were visualized with ninhydrin spray and iodine vapor.

^{1}H NMR spectra were recorded on a Varian Associates T-60 or HA-100 spectrometer using, as appropriate, deuterium oxide, acetone-d_6, deuteriochloroform, or deuterated methanol as solvents; chemical shifts are given relative to tetramethylsilane. Mass spectra were determined with an AEI MS-902 mass spectrometer. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

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Registry No.—I, 58281-74-6; Carbobenzyloxy-2-methylalanyl-L-proline methyl ester, 15030-91-8; proline methyl ester HCl, 2133-40-6; carbobenzyloxy-2-methylalanyl-L-proline, 58281-75-7; carbobenzyloxy-2-methylalanyl-L-prolyl-L-tryptophan methyl ester, 58281-76-8; carbobenzyloxy-2-methylalanyl-*cis*-4-fluoro-L-prolyl-L-tryptophan, 58281-77-9; carbobenzyloxy-2-methylalanyl-*trans*-4-fluoro-L-prolyl-L-tryptophan, 58281-78-0; *cis*-4-fluoroproline methyl ester HCl, 58281-79-1; *trans*-4-fluoroproline methyl ester HCl, 58281-80-4; carbobenzyloxy-2-methylalanyl-*cis*-4-fluoroproline methyl ester, 58281-81-5; carbobenzyloxy-2-methylalanyl-*trans*-4-fluoroproline methyl ester, 58281-82-6; carbobenzyloxy-2-methylalanyl-*cis*-4-fluoroproline, 58281-83-7; carbobenzyloxy-2-methylalanyl-*trans*-4-fluoroproline, 58281-84-8; carbobenzyloxy-2-methylalanyl-*cis*-4-fluoro-L-prolyl-L-tryptophan methyl ester, 58281-85-9; carbobenzyloxy-2-methylalanyl-*trans*-4-fluoro-L-prolyl-L-tryptophan methyl ester, 58281-86-0; carbobenzyloxyglycyl-L-proline, 1160-54-9; carbobenzyloxyglycyl-L-prolyl-L-tryptophan methyl ester, 58281-87-1; carbobenzyloxyglycyl-L-prolyl-L-tryptophan, 58281-88-2; carbobenzyloxy-L-alanyl-L-proline, 21027-01-0; carbobenzyloxy-L-alanyl-L-prolyl-L-tryptophan methyl ester, 58281-89-3; carbobenzyloxy-L-alanyl-L-prolyl-L-tryptophan, 58281-90-6.

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Diels–Alder Reactions of *trans,trans*-1,4-Diacetoxybutadiene. Observations Concerning Some Literature Reports

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Diels–Alder cycloadditions of *trans,trans*-1,4-diacetoxybutadiene (1) with electrophilic olefins provide one valuable source of highly oxygenated six-membered carbocycles[1] which we have had occasion to explore. In this note we disclose further details regarding the reactivity of 1 as a diene component. We also describe the outcome of experiments which bring important new results to bear on some previously described cycloadditions.

The condensation of 1 with acrylic acid and its esters has been the subject of some debate, focusing on the stereochemistry of the adduct 2.[2-4] Comprehensive NMR spectroscopic data have been gathered by Raphael,[5] Hill,[6] and Smissman[7] in support of the all-cis stereochemistry (shown in 2) predicted from an endo transition state. We have pre-