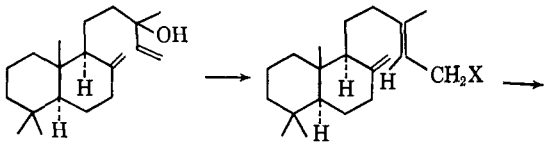
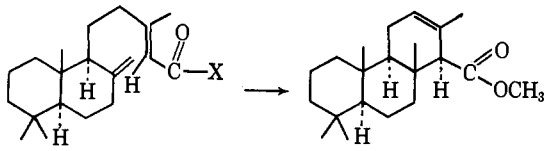
quence. Purification (tlc) of the *p*-nitrobenzoate (V, R = COC_6H_4-*p*-NO_2) was employed in order to obtain tricyclic alcohol which, as the acetate, appeared substantially homogeneous (single peak with a slight shoulder on vpc over Apiezon at 270°). Alternatively, alcohol V resulted from the synthetic sequence VI → VII (X = Br) → VII (X = OAc) → VIII (X′ = H) → VIII (X′ = OCH_3) → IX → V, the penultimate step closely resembling the cyclization of agathic acid



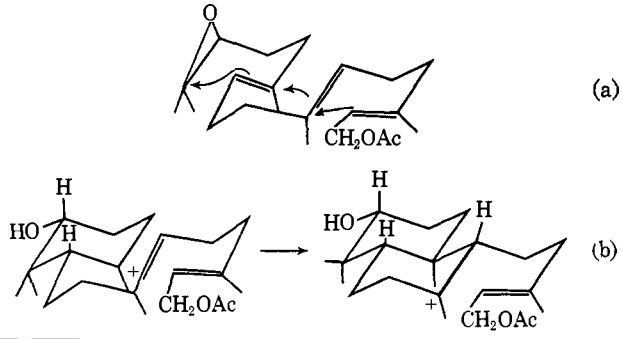
VI VII



VIII IX

to isoagathic acid, substances of established structure and stereochemistry.[6] The unsaturated methyl ester IX, a well-defined crystalline substance of mp 108–110°, provided on lithium aluminum hydride reduction noncrystalline but stereochemically homogeneous tricyclic alcohol V (R = H). The vpc, infrared, and mass spectral behavior of the alcohols (II, R = H) derived from the two sources were, within experimental error, identical. Since the nmr spectrum of synthetic II reveals axial hydrogen (broad peak τ 6.67–7.15, J = ~7 cps) at C-3,[7] the stereochemistry of II is established at all positions as shown.[8]

Although the methyl substitution pattern of squalene oxide directs laboratory cyclization principally to tricyclic product with a five-membered C ring,[9] the "head-to-tail" arrangement of all isoprene units in geranylgeraniol permits formation of a hydrophenanthrene system through involvement of three centers with chemically preferred, *t*-carbocationic properties. In the sesquiterpene series, it has been demonstrated that monocyclic products obtained by cyclization of terminal epoxide are not separately converted under original cyclization conditions to bicyclic products formed concurrently from the epoxide, and therefore are not intermediates.[7] By the same token, further



(a)

(b)

cyclization under original conditions of mono- or bicyclic material produced from geranylgeranyl acetate epoxide is unlikely; consequently we believe that the tricyclic diol II monoacetate arises from epoxide I by (a) a synchronized cyclization, (b) a stepwise sequence involving mono- or bicyclic carbonium ions, or (c) a sequential combination of mechanisms a and b.

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Reactions of Deprotonated Ligands. II. The *in Situ* Synthesis of Bipyridyl(N,N,N′,N′-tetramethylethylenediamine)platinum(II) Chloride[1,2]

Sir:

In connection with studies on the effect of methyl substitution upon the deprotonation of coordinated ethylenediamine, we had need for an authentic specimen of [Pt(bipy)(tetmen)]Cl_2. Conventional methods of synthesis, *e.g.*, treatment of [Pt(bipy)X_2] with tetmen or [Pt(tetmen)X_2] with bipy, and other direct approaches that seemed reasonable failed to provide the desired product.

We have, however, produced the complex by an indirect route which, as far as we are aware, is unprecedented in the sense of producing *in situ* a ligand that apparently cannot be introduced directly. This was done by producing [Pt(bipy)(sdmen)]I_2 by a known method,[3] removing both remaining protons from the nitrogen atoms using methods described elsewhere[4]

$$[Pt(bipy)(sdmen)]^{2+} + 2NH_2^- \longrightarrow [Pt(bipy)(sdmen\text{-}2H)] + 2NH_3 \quad (1)$$

and methylating the deprotonated species as described in an earlier communication.[5]

$$[Pt(bipy)(sdmen\text{-}2H)] + 2CH_3Cl \longrightarrow [Pt(bipy)(tetmen)]Cl_2 \quad (2)$$

Attempts to form the corresponding iodide by using methyl iodide in reaction 2 led to the desired product, but (as shown by X-ray diffraction and infrared spectral data) it was contaminated with [Pt(bipy)$_2$$I_2$]. By taking advantage of the lesser tendency for chloride to coordinate with platinum(II) and carrying out reaction 2 at 7°, only very small quantities of by-product [Pt(bipy)Cl_2] resulted; this was eliminated essentially completely by carrying out the reaction at −12°. The experimental evidence is as follows.

To establish that [Pt(bipy)(sdmen)]I_2 is unreactive toward the deprotonation reaction medium, a 0.54-g sample was treated with anhydrous liquid ammonia

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(7) *Cf.* E. E. van Tamelen and E. J. Hessler, *Chem. Commun.*, 411 (1966).
(8) Spectral (mass, infrared, and/or nmr) characteristics of all substances described are consistent with the assigned structures.
(9) E. E. van Tamelen, J. Willett, M. Schwartz, and R. Nadeau, *J. Am. Chem. Soc.*, **88**, 5937 (1966).

(1) This work was supported by the U. S. Atomic Energy Commission and the Robert A. Welch Foundation.
(2) bipy = 2,2′-bipyridyl; en = ethylenediamine; en-H = a deprotonated en ligand, and similarly for sdmen; sdmen = N,N′-dimethylethylenediamine; tetmen = N,N,N′,N′-tetramethylethylenediamine.
(3) G. W. Watt and D. G. Upchurch, *Inorg. Nucl. Chem. Letters*, **2**, 363 (1966).
(4) G. W. Watt and J. K. Crum, *J. Am. Chem. Soc.*, **87**, 5366 (1965).
(5) G. W. Watt and D. G. Upchurch, *ibid.*, **87**, 4212 (1965).

at −65° for 2 hr. The solvent was removed and the yellow solid residue was dried *in vacuo* for 12 hr at 25°. *Anal.* Calcd for [Pt(bipy)(sdmen)]I_2: Pt, 28.2. Found: Pt, 28.1. The infrared spectrum of this residue was identical with that of the starting material.

A 1.50-g sample of [Pt(bipy)(sdmen)]I_2 was slurried in 45 ml of liquid ammonia at −35°, and 13 ml of potassium amide solution (prepared from 0.1951 g of potassium) was added over 0.5 hr. After digestion for 2 hr, the intensely purple solution was filtered and the residual purple-black solid was washed four times with 25-ml portions of ammonia. This product was dried *in vacuo* for 27 hr and maintained thereafter in a dry, oxygen-free helium atmosphere. *Anal.* Calcd for [Pt(bipy)(sdmen-2H)]: Pt, 44.5; C, 38.4; H, 4.11; N, 12.8. Found: Pt, 44.7; C, 38.5; H, 4.29; N, 12.6. This product was iodine-free, and analysis of the residue remaining after evaporation of the solvent from the combined filtrate and washings accounted for 100% of the iodine in the starting material.

A 0.4-g sample of [Pt(bipy)(sdmen-2H)] was treated with 5 ml of methyl chloride in a sealed tube at −12° for 6 days during which the color of the solid changed from purple-black to pink-red. The methyl chloride was evaporated and the yellow-tan residue was dried *in vacuo*. *Anal.* Calcd for [Pt(bipy)(tetmen)]Cl_2: Pt, 36.2; C, 35.7; H, 4.45. Found: Pt, 35.7; C, 35.6; H, 4.37.

Studies with models reveal no steric effects that would preclude direct synthesis of the tetmen complex. Success of the *in situ* synthesis, however, could arise from a favorable conformational situation. Thus, in the deprotonated sdmen complex, the bipy ligand may be planar with the two methyl groups below the plane; this could leave two hybrid orbitals projecting above the plane and available for a preequilibrium coordination of the methyl halide with the deprotonated complex in a manner that will be discussed in more detail elsewhere.[3]

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Synthesis of N-Hydroxysuccinimide Esters of Acyl Peptides by the Mixed Anhydride Method

Sir:

Until now, no simple method for the direct synthesis of active esters of acyl peptides without racemization has been available. We have recently shown that the mixed carbonic–carboxylic anhydride method can be used for acyl peptide activation and subsequent peptide bond formation without racemization provided that suitable conditions are chosen.[1] It has now been found that essentially the same conditions are useful for the synthesis of N-hydroxysuccinimide esters of acylamino acids and acyl peptides. Results reported here indicate that no racemization can be expected in normal cases. Since experience has shown that active esters can be used in peptide synthesis without racemization, the utility of N-hydroxysuccinimide (HOSu) esters is thus extended to acyl peptide derivatives. An alternate, racemization-free synthesis of HOSu esters by the dicyclohexylcarbodiimide method will be separately reported.

Applying our test for racemization,[2] 5 mmoles of Z-Gly-Phe-OH (L) was dissolved in 25 ml of dry ethyl acetate with 5 mmoles of N-methylmorpholine and chilled to −15°, and 5 mmoles of isobutyl chloroformate was added. After 30 sec, 5.5 mmoles of N-hydroxysuccinimide was added with rapid stirring. The mixture was allowed to warm to 0° during 5 min, then kept in a 40° bath for 2 min to assure completion of the reaction, and finally cooled to 15° for 5 min before filtering. The solution on concentration under vacuum left the active ester as a gum; extraction with isopropyl ether to remove by-products and any unreacted mixed anhydride left a semisolid. This was dissolved in dry tetrahydrofuran, and ethyl glycinate (5 mmoles) was added. After 2 hr at room temperature, the solution was concentrated and the product washed with water, dilute sodium bicarbonate solution, and water, giving 2.06 g (94% yield) of Z-Gly-Phe-Gly-OEt, mp 117–118.5°. The usual fractionation from alcohol gave no racemate.

The same procedure applied to the synthesis of Bz-Leu-OSu gave a crystalline product in 99% yield, mp 169–173°. (A product from a similar reaction had mp 172–174° after recrystallization from 2-propanol. *Anal.* Calcd for $C_{17}H_{20}O_5N_2$: C, 61.43; H, 6.07; N, 8.43. Found: C, 61.52; H, 6.08; N, 8.31.) Reaction of the crude product with ethyl glycinate gave Bz-Leu-Gly-OEt in 91% yield, mp 154–156°. Racemate determined by our separation procedure[1] was estimated at 2%. Several variations of the synthesis gave racemate in varying amounts. Although not better than ethyl acetate, tetrahydrofuran was a good solvent. Chloroform and toluene were unfavorable; the oxazolone from benzoylleucine was isolated from the isopropyl ether washes in these experiments.

Since the Bz-Leu-Gly-OEt test is considered to be unduly severe,[3] the results with both tests make it likely that HOSu esters of most acyl peptides can be made by the mixed anhydride method without racemization.

Nefkens, *et al.*,[4] have reported that N-hydroxyphthalimide esters of benzyloxycarbonylamino acids cannot be made by the mixed anhydride method. Using our improved procedure, we were unable to isolate the N-hydroxyphthalimide esters of Z-Gly-OH, Z-Pro-OH, or Z-Gly-Phe-OH. Also, no product was isolated in the attempted synthesis of the *p*-nitrophenyl and 2,4,5-trichlorophenyl esters of Z-Gly-Phe-OH. Esters of the dipeptide derivative were obtained with pentachlorophenol and 8-hydroxyquinoline, but reaction of these with H-Gly-OEt yielded partially racemized Z-Gly-Phe-Gly-OEt in both cases. N-Hydroxypiperidine gave an active ester and no racemate in the tripeptide synthesis; however, the low reactivity of such esters[5] is to their disadvantage in peptide synthesis.

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