with 25 vol.% methanol–benzene) which, on standing several hours, deposited crystals identified as 1,2-diphenylethanol (VII, m.p. 64.5–65°, lit. 65°). *Anal.* Calcd. for $C_{14}H_{14}O$: C, 84.8, H, 7.07, O, 8.1. Found: C, 84.5, H, 7.14, O, 8.8. The presence of both stilbene and 1,2-diphenylethanol suggested that a substantial part of the reaction in tetrahydrofuran involved the formation of α-chlorobibenzyl (V) as an intermediate product (the 1,2-diphenylethanol arising from a small amount of hydrolysis of V during the work-up of the reaction) according to the following reaction sequence.[5]

(2)
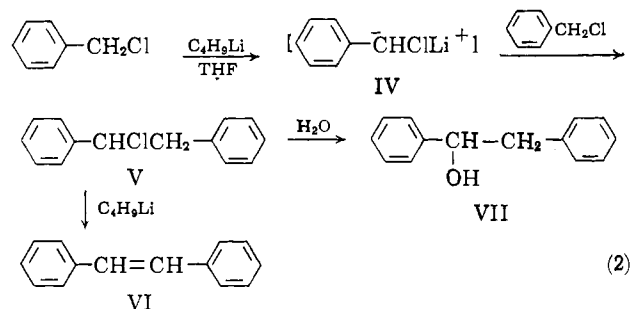
This reaction mechanism is formally similar to that suggested by Kharasch, *et al.*,[6] and others,[7] for the reaction of benzyl chloride with alkali metal amides in liquid ammonia.

We set out to isolate the α-chlorobibenzyl intermediate by adjusting the stoichiometry of the reagents (2 moles of benzyl chloride per mole of *n*-butyllithium), by adding the *n*-butyllithium to the tetrahydrofuran solution of the benzyl chloride, and by using very low reaction temperatures ($-100°$). After 2 hr. reaction, the yield of α-chlorobibenzyl (V) isolated was over 80% (b.p. 110–112° at 0.5 mm.). *Anal.* Calcd. for $C_{14}H_{13}Cl$: Cl, 16.4. Found: Cl, 16.2. Hydrolysis of V yielded the 1,2-diphenylethanol and base-catalyzed or thermal dehydrochlorination gave *trans*-stilbene. In agreement with the related observation of Wittig and Witt,[8] this reaction occurs only with α-chlorosubstituted phenylmethanes. The reaction of benzyl bromide with butyllithium under the same conditions[3] gave only bibenzyl (88% yield) and amylbenzene, presumably *via* reaction 1.

These data indicate that at low temperatures in tetrahydrofuran *n*-butyllithium reacts with benzyl chloride, practically exclusively by attack of the α-hydrogen atoms (eq. 2), to form α-chlorobenzyllithium (IV) (or perhaps more accurately, the α-chlorobenzyl carbanion) as a transient intermediate. It is suggested that the unique effect of tetrahydrofuran may be related to its superior solvating ability for the metal cation, and that we are observing the reaction of the dissociated butyllithium (butyl anion displacement on the α-hydrogen). On this basis, one might expect the

nature of alkali metal to be of subordinate importance; a point presently being studied. We are also studying the utility of this reaction scheme as a general synthesis for substituted α-chlorobibenzyls and stilbenes.

Acknowledgment.—Infrared and ultraviolet spectral data, which were of considerable help in the identification of these products, were obtained by Mr. John E. Forrette.

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Total Synthesis of *dl*-Garryine and *dl*-Veatchine[1]

Sir:

Very recently we reported[2] the total synthesis of *dl*-atisine performed in a stereospecific manner. This communication presents a total synthesis of garryine and veatchine, representative garrya alkaloids, in the racemic form.

The pentacyclic dimesyl derivative II, synthesized from the tricyclic conjugated ketone I as described in the preceding paper,[2] was refluxed with collidine to afford the olefin III,[3] m.p. 200–200.5°, in 78% yield.

Sterically controlled hydroboration[4] of III with bis-3-methyl-2-butylborane followed by oxidation and hydrolysis yielded the desired 1,2-diol V, m.p. 242–245°, purified *via* its acetonide (m.p. 228–230°), in 53% yield, and the isomeric 1,3-diol VI, m.p. 262–263°, in 18% yield. Here, no epimeric *endo*-hydroxy compounds were isolated. The 1,2-diol V was smoothly rearranged by refluxing a methanolic dioxane solution of its monobrosyl derivative VII with aqueous potassium hydroxide to the bridged ketone VIII having a desired configuration, m.p. 215–217° ($\nu_{max}^{CHCl_3}$ 1739 cm.$^{-1}$), in 70% yield. This compound was also synthesized by the following alternative route involving more reaction steps but with higher selectivity. The acetoxy olefin III after hydrolysis (IV, m.p. 189–191°, 203–204°) was epoxidized with perbenzoic acid to give exclusively the *exo*-epoxide IX, m.p. 258–259.5°, which was rearranged with diethyl aluminum chloride to the ketol X, m.p. 242–243° ($\nu_{max}^{CHCl_3}$ 1744 cm.$^{-1}$). This compound after ketalization (XI, m.p. 220–221°) was oxidized to the ketone XII, m.p. 205–206° ($\nu_{max}^{CHCl_3}$ 1738 cm.$^{-1}$), which on a modified Wolff–Kishner reduction[5] (XIII, m.p. 198.5–200°) and subsequent deketalization led to the ketone VIII mentioned earlier. By this route the last compound was obtained from the olefin III in an over-all yield (32%) comparable to that (37%) in the former procedure.

Wittig condensation of VIII afforded the *exo*-methylene derivative XIV, m.p. 136–137° ($\nu_{max}^{CHCl_3}$ 1659, 882 cm.$^{-1}$), in 90% yield. At this stage it was necessary to replace the protecting N-mesyl group by another suitable one. Thus XIV was demesylated by Birch reduction and the resulting secondary amine XV, m.p. 68–71°, was converted into the N-carbethoxy derivative XVI, an oil. Introduction of the hydroxyl group at the 19α position was carried out in a way similar to that previously reported[2]: XVI underwent bromination with N-bromosuccinimide followed by epoxidation and debromination with zinc to give the allylic alcohol

(5) It has been known for a long time that symmetrically substituted stilbenes are formed in the reaction of substituted benzyl chlorides with base in aqueous acetone or dioxane, when the substituents on the benzyl chloride are strong electron attractors. Thus, 4,4'-dinitrostilbene is formed from 4-nitrobenzyl chloride and alkali in aqueous acetone or dioxane. Recent evidence has been presented [S. B. Hanna, Y. Iskander, and Y. Riad, *J. Chem. Soc.*, 217 (1961)] indicating that this reaction proceeds *via* α-elimination to form phenylmethylene which dimerizes to form the stilbene. In the early part of this work, we suspected that a similar mechanism could be involved. We attempted to "trap" any carbene as phenylnorcarane by using tetrahydrofuran containing cyclohexene (*ca.* 70 vol.% cyclohexene at $-10°$) as the reaction solvent. No phenylnorcarane was detected, nor was any appreciable difference noted in the product distribution, using the same procedure as in ref. 3.

(6) M. S. Kharasch, W. Nudenberg, and E. K. Fields, *J. Am. Chem. Soc.*, **66**, 1276 (1944).

(7) C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *ibid.*, **78**, 1653 (1956).

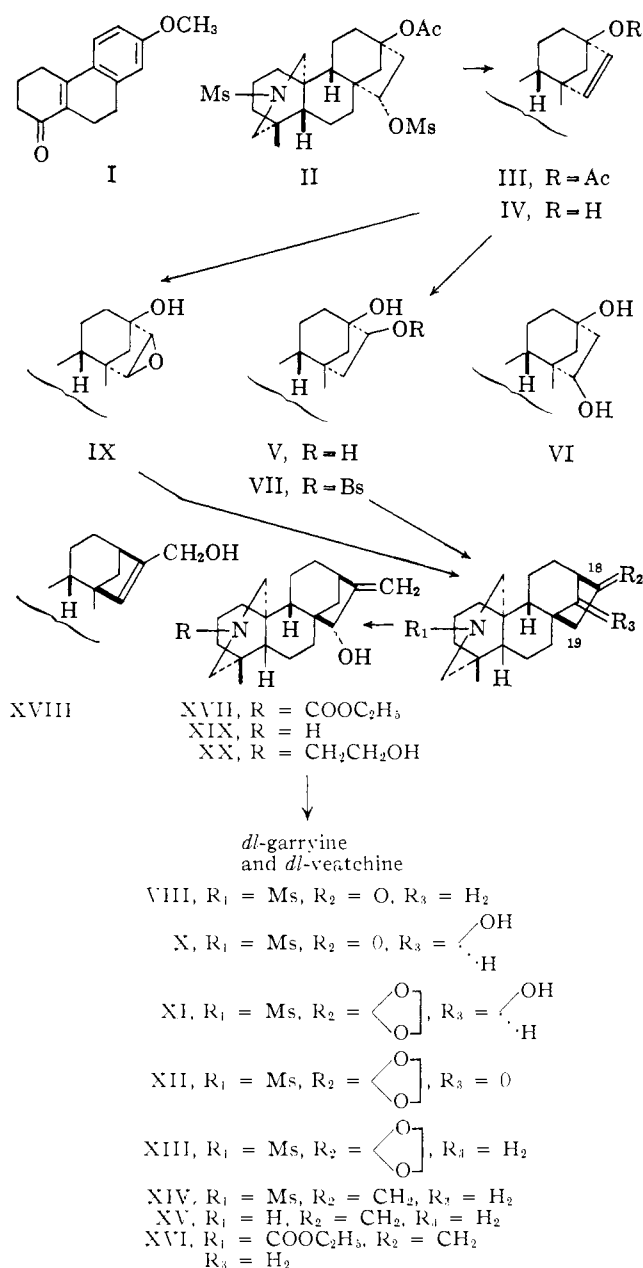(8) G. Wittig and H. Witt, *Ber.*, **74B**, 1474 (1941).

(1) Angularly Substituted Polycyclic Compounds. XII.

(2) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Am. Chem. Soc.*, **85**, 2342 (1963).

(3) All compounds show reasonable infrared spectra and those for which melting points are recorded give satisfactory compositional analyses.

(4) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 3222 (1960); G. Zweifel, N. R. Ayyangar, and H. C. Brown, *ibid.*, **85**, 2072 (1963).

(5) W. Nagata, *et al.*, to be published.

I   II   III, R = Ac
IV, R = H

IX   V, R = H   VI
VII, R = Bs

XVIII   XVII, R = COOC$_2$H$_5$
XIX, R = H
XX, R = CH$_2$CH$_2$OH

↓

dl-garryine
and dl-veatchine

VIII, R$_1$ = Ms, R$_2$ = O, R$_3$ = H$_2$

X, R$_1$ = Ms, R$_2$ = 0, R$_3$ = ⟨OH / ·H

XI, R$_1$ = Ms, R$_2$ = ⟨O / O⟩, R$_3$ = ⟨OH / ·H

XII, R$_1$ = Ms, R$_2$ = ⟨O / O⟩, R$_3$ = 0

XIII, R$_1$ = Ms, R$_2$ = ⟨O / O⟩, R$_4$ = H$_2$

XIV, R$_1$ = Ms, R$_2$ = CH$_2$, R$_4$ = H$_2$
XV, R$_1$ = H, R$_2$ = CH$_2$, R$_4$ = H$_2$
XVI, R$_1$ = COOC$_2$H$_5$, R$_2$ = CH$_2$
R$_3$ = H$_2$

XVII, m.p. 151–152°, together with the isomeric allylic alcohol XVIII, m.p. 129–130.5°. The over-all yields of XVII and XVIII from the N-mesyl olefin XIV were 9 and 10%, respectively (five steps). The hydrolytic elimination of the carbethoxy group was effected by refluxing[6] a solution of XVII in diethylene glycol with potassium hydroxide and a trace of hydrazine to afford the secondary base XIX, m.p. 182–182.5° ($\nu_{max}^{CHCl_3}$ 3606, 1661, 906 cm.$^{-1}$). Finally, the base XIX was alkylated with ethylene chlorohydrin, according to the process described in the literature,[7] to afford dl-dihydroveatchine (XX), m.p. 138–141° ($\nu_{max}^{CHCl_3}$ 3618, 3479, 1662, 905 cm.$^{-1}$), in 56% over-all yield (from XVII). Both bases XIX and XX were proved to be the racemic forms of the naturally derived dihydro pyrolysis base B[7–9] and dihydroveatchine[7,8] by the identity of infrared spectra (CHCl$_3$). Since transformation of di-

(6) Cf. S. W. Pelletier and P. C. Parthasarathy, Tetrahedron Letters, No. 4, 205 (1963).

(7) K. Wiesner, W. I. Taylor, S. K. Figdor, M. F. Bartlett, J. R. Armstrong, and J. A. Edwards, Chem. Ber., 86, 800 (1953).

(8) We are very grateful to Prof. Z. Valenta for his courtesy of supplying valuable authentic samples of natural compounds.

(9) The authors wish to thank Prof. S. W. Pelletier for providing a sample of dihydro pyrolysis base B.

hydroveatchine to garryine[7] and further to veatchine[10] has already been accomplished in the natural series, this work constitutes a total synthesis of the racemic forms of these alkaloids. All the reactions employed in this synthesis, although not satisfactory in yield in a few of the steps, proceeded in a desired stereochemical sense.

Acknowledgment.—We wish to express our thanks to Professor emeritus E. Ochiai and Dr. K. Takeda for showing deep interest and encouraging us throughout this work.

(10) S. W. Pelletier and K. Kawazu, Chem. Ind. (London), 1879 (1963).

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TSUTOMU SUGASAWA

Insulin Peptides. X. The Synthesis of the B-Chain of Insulin and Its Combination with Natural or Synthetic A-Chain to Generate Insulin Activity[1]

Sir:

In a previous communication[2] we have reported the synthesis of the A-chain of sheep insulin, its isolation in the S-sulfonate form, and its combination with natural B-chain to generate insulin activity. We have now completed synthesis and isolation in the S-sulfonate form of a triacontapeptide with the amino acid sequence proposed by Sanger for the B-chain of insulin.[3] The proposed structure for sheep insulin is shown in Chart I. The synthetic B-chain upon combination with natural A-chain generated insulin activity equivalent to that produced when natural B-chain was recombined with natural A-chain. In addition, insulin activity was generated when the synthetic B-chain was combined with a synthetic preparation of A-chain. This last observation appears to represent the first chemical synthesis of a naturally occurring protein.

Im-Benzyl-L-histidine benzyl ester[4] was condensed with N-carbobenzoxy-L-glutamine p-nitrophenyl ester[5] to give N-carbobenzoxy-L-glutaminyl-Im-benzyl-L-histidine benzyl ester (I), m.p. 168°; [α]^{28}D − 25.7° (c 1.0, acetic acid) (Anal. Calcd. for C$_{33}$H$_{35}$N$_5$O$_6$: C, 66.3; H, 5.90; N, 11.8. Found: C, 65.8; H, 6.12; N, 11.5); R$_f$[6] (hydrobromide) 0.40. Decarbobenzoxylation of I with HBr in acetic acid and coupling of the ensuing product with N-carbobenzoxy-L-asparagine p-nitrophenyl ester[5] afforded N-carbobenzoxy-L-asparaginyl-L-glutaminyl-Im-benzyl-L-histidine benzyl ester (II), m.p. 184°; [α]^{28}D − 20.9° (c 1.5, acetic acid) (Anal. Calcd. for C$_{37}$H$_{41}$N$_7$O$_8$: C, 62.4; H, 5.81; N, 13.8. Found: C, 62.1; H, 5.94; N, 13.8); R$_f$[6] (hydrobromide) 0.36. The tetrapeptide N-carbobenzoxy-L-valyl-L-asparaginyl-L-glutaminyl-Im-benzyl-L-histidine benzyl ester (III, m.p. 220°; [α]^{28}D − 31.1° (c 0.9, acetic acid) (Anal. Calcd. for C$_{42}$H$_{50}$N$_8$O$_9$: C, 62.2; H, 6.21;

(1) Presented in part (P. G. K.) as the first Edwin J. Cohn Memorial Lecture at the 15th Annual Scientific Conference of Protein Foundation on November 25, 1963, Cambridge, Mass.; Vox Sanguinis, in press.

(2) P. G. Katsoyannis, A. Tometsko, and K. Fukuda, J. Am. Chem. Soc., 85, 2863 (1963).

(3) F. Sanger and H. Tuppy, Biochem. J., 49, 463, 481 (1951); F. Sanger and E. O. L. Thompson, ibid., 53, 353, 366 (1953); H. Brown, F. Sanger, and R. Kitai, ibid., 60, 556 (1955); J. I. Harris, F. Sanger, and M. A. Naughton, Arch. Biochem. Biophys., 65, 427 (1956).

(4) D. Theodoropoulos and G. Fölsch, Acta Chem. Scand., 12, 1955 (1958).

(5) M. Bodanszky and V. du Vigneaud, J. Am. Chem. Soc., 81, 5688 (1959).

(6) The R$_f$ refers to the Partridge system [S. M. Partridge, Biochem. J. 42, 238 (1948)].