HCl–acetic acid and converted to the free base with triethylamine as described above. A solution of 0.38 g. (1.5 mmoles) of *t*-BOC-L-methionine[10,11] in 4 ml. of DMF was added to the washed resin and the suspension was stirred for 10 min. This was followed by the addition of 0.62 ml. (1.5 mmoles) of a 0.5 g./ml. solution of N,N′-dicyclohexylcarbodiimide in DMF. After the mixture was shaken for 2 hr. the product was filtered and washed with DMF, ethanol, and acetic acid. A 50-mg. sample of the protected undecapeptide–resin was hydrolyzed and analyzed for amino acids by quantitative column chromatography.[18] The ratios were arg, 2.0; phe, 2.3; pro, 3.2; ser, 1.2; gly, 1.2; lys, 1.0; and met, 1.0. The average value of each of the eleven amino acid residues was 0.13 mmole/g.

L-Methionyl-L-lysyl-L-arginyl-L-prolyl-L-prolyl-glycyl-L-phenylalanyl-L-seryl-L-prolyl-L-phenylalanyl-L-arginine.—The protected undecapeptide–resin, while still in the reaction vessel, was suspended in a mixture of 8 ml. of trifluoroacetic acid and 2 ml. of methyl ethyl sulfide, and a slow stream of hydrogen bromide was bubbled through for 90 min. The solution was withdrawn by suction and the resin was washed three times with 10 ml. of trifluoroacetic acid. The combined filtrates were evaporated to dryness under reduced pressure in the rotary evaporator and then in a desiccator over KOH. The solid was dissolved in acetic acid and lyophilized, and this step was repeated in order to free the product of volatile sulfur compounds.

The crude undecapeptide derivative was dissolved in 40 ml. of methanol containing 2 ml. of acetic acid and hydrogenated at 40 p.s.i. in the presence of palladium-black which had been prepared from 2 g. of $PdCl_2$.[19] The mixture was filtered and washed and the filtrate was evaporated to dryness. The undecapeptide was dissolved in acetic acid and lyophilized. For purification, 15% of the peptide was placed on a 2 × 98 cm. column of the cation-exchange resin, Amberlite IRC-50, and eluted at a rate of 15 ml./hr. with a gradient of acetic acid[6] (Fig. 1). The elution was followed by the Sakaguchi reaction,[20] carried out on 0.2-ml. aliquots of 7.5-ml. fractions. For isolation the fractions between 0.91 l. and 1.07 l. were combined, concentrated, and lyophilized to give 55 mg. of peptide. This was equivalent to an over-all yield of 366 mg. (65%) of purified undecapeptide from the 2.5 g. of starting *t*-BOC-nonapeptide–resin. The mobility relative to arginine (R_{arg}) was 0.75 (bradykinin, R_{arg} 0.62) by paper electrophoresis in 0.1 *M* (pH 5.0) pyridine acetate; and by paper chromatography, R_f 0.12 (propanol–H_2O, 2:1) and 0.19 (isoamyl alcohol–pyridine–H_2O, 35:35:30); $[\alpha]^{25}D$ −80° (*c* 0.5, *M* acetic acid). Amino acid ratios were arg, 2.00; phe, 2.11; pro, 2.89; gly, 1.09; ser, 1.05; lys, 1.05; and met, 0.95.

Anal.[21] Calcd. for $C_{61}H_{94}N_{18}O_{13}S\cdot 2CH_3COOH\cdot 2H_2O$: C, 52.9; H, 7.2; N, 17.1; CH_3COOH, 8.1. Found: C, 52.9; H, 7.1; N, 17.1; CH_3COOH, 8.5.

Acknowledgment.—The author wishes to thank Dr. D. W. Woolley for his interest and advice, and Miss Angela Corigliano for her technical assistance.

(18) S. Moore, D. H. Spackman, and W. H. Stein, *Anal. Chem.*, **30**, 1185 (1958).
(19) H. Wieland, *Ber.*, **45**, 484 (1912).
(20) C. J. Weber, *J. Biol. Chem.*, **86**, 217 (1930).
(21) Elemental analyses were by Mr. T. Bella.

A Stable Intermediate in the Hantzsch–Beyer Reaction

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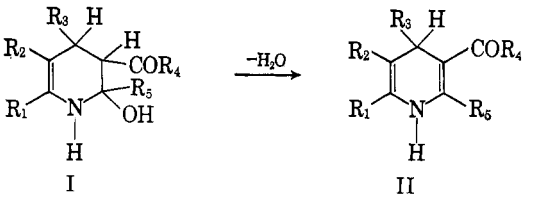
The occasional isolation of stable tetrahydropyridinols such as Ia and Ib, formed under Hantzsch–Beyer[1–3] reaction conditions, has been reported.[4] However, the structural assignments for these compounds are based upon little or no information other than combustion analysis. Hence, rather serious doubts have been expressed concerning the correctness of these structural assignments[5] since the compounds have not been clearly distinguished from the isomeric Michael adducts, their open-chain tautomers, or other isomeric ring structures.



I II

	R_1	R_2	R_3	R_4	R_5
Ia,	Me	CO_2Et	Ph	OEt	Ph
b,	Me	CN	Ph	OEt	Me
c,	Ph	CO_2Et	Ph	OEt	Me
IIa,	Me	CO_2Et	Ph	OEt	Ph
b,	Me	$COCH_3$	Ph	OEt	Ph

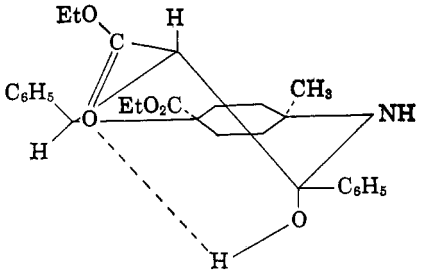
We have restudied one such reported compound, 2-hydroxy-2,4-diphenyl-3,5-dicarbethoxy-6-methyl-1,2,-3,4-tetrahydropyridine (Ia),[4] and have carefully examined its ultraviolet, infrared, and n.m.r. spectra for structural information.

Compound Ia was prepared in 78% yield by heating ethyl benzylidenebenzoylacetate and ethyl β-aminocrotonate for 3 days at 50–60° in absolute ethanol in the presence of a small amount of diethylamine. The ultraviolet spectrum showed a maximum at 278 mμ (log ε 4.21) which is near that for ethyl β-aminocrotonate [λ_{max} 276.5 mμ (log ε 4.21)] and therefore consistent with Ia. The infrared spectrum also supports the structure Ia, and pertinent band assignments are at 3410, NH; 1685, α,β-unsaturated ester carbonyl; 1720, hydrogen-bonded ester carbonyl[6]; and 1612 cm.$^{-1}$, carbonyl conjugated double bond. No free hydroxyl absorption was apparent, but the broadening of the NH band indicated overlap with hydrogen-bonded OH absorption.

The n.m.r. data are completely compatible with the structure Ia. The spectrum shows two ethyl ester groups, an olefinic methyl, two spin-coupled tertiary protons, a peak appropriate for exchanging OH and NH protons, and an aromatic resonance pattern, all with relative areas in accord with the given structure. The indirect spin–spin couplings and chemical shifts of the olefinic methyl and the two tertiary protons suggest the conformation illustrated in structure III. The doublet of closely spaced quartets located at 4.26 p.p.m. (benzyl hydrogen) has a chemical shift appropriate for the given structure, while the spin-coupling pattern indicates a large diaxial coupling to a single other proton and a small coupling typical of longer range couplings to three other protons. The olefinic methyl resonance at 2.32 p.p.m. is a doublet and shows a reciprocal coupling to the group at 4.26 p.p.m. A simple doublet

(1) A. Hantzsch, *Ber.*, **17**, 1515 (1884); **18**, 1774, 2579 (1885).
(2) C. Beyer, *ibid.*, **24**, 1662 (1891).
(3) E. Knoevenagel and W. Ruschhaupt, *ibid.*, **31**, 1025 (1898).
(4) (a) J. N. Chatterjea, *J. Indian Chem. Soc.*, **29**, 323 (1952); (b) N. Palit and J. N. Chatterjea, *ibid.*, **27**, 667 (1950).
(5) F. Brody and P. R. Ruby, "Pyridine and its Derivatives," part 1, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 440.
(6) For a similar example, see J. F. Grove and B. J. Riley, *J. Chem. Soc.*, 1105 (1961).

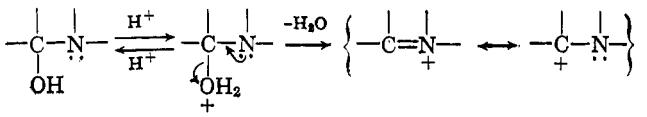
located at about 3.05 p.p.m. shows the reciprocal diaxial coupling. 2,4-Diphenyl-3-carbethoxy-5-acetyl-6-methyl-1,4-dihydropyridine (IIb) was used as a model compound in this investigation.



III

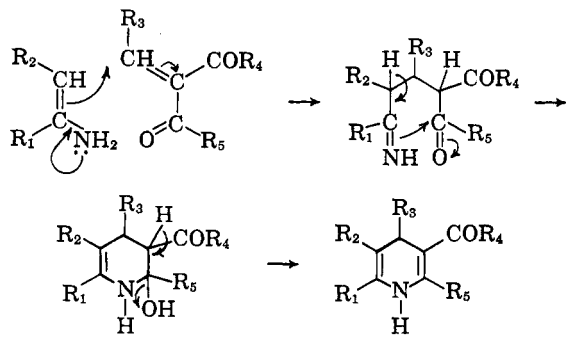
Molecular models of III show the ring hydrogen at position 3 to be well shielded by the two flanking phenyl groups.

The compound is completely resistant to dehydration at 56° over P_2O_5 *in vacuo* for 1 week, and shows no signs of decomposing below its melting temperature of 206.5–207.0°, although decomposition does accompany melting. Cold, dilute acid readily converts it to the corresponding 1,4-dihydropyridine (IIa), the reaction probably being assisted by the adjacency of nitrogen to the carbinol carbon.



The important role of the sterically hindered hydrogen in the stability of Ia was further emphasized when the synthesis of Ic was attempted under reaction conditions identical with those employed in the formation of Ia, but starting instead with ethyl β-aminocinnamate and ethyl benzylideneacetoacetate. *No Ic was obtained from the reaction mixture.* The only compound isolated was IIa. The hydrogen atom in question in Ic should be *cis* to a phenyl on C-4 and to a *methyl* on C-2, the reduction in steric hindrance apparently favoring base-catalyzed elimination in this instance.

The structure of Ia would then seem to indicate that the *initial step* in ring formation is Michael addition



and would tend to rule out Schiff base formation prior to ring closure, an alternate mechanism not excluded by the work of Berson and Brown.[7] Though the latter mechanism would lead to a 3,4-dihydropyridine, such compounds would be expected to isomerize under the usual reaction conditions to the more stable 1,4-dihydro structure.

(7) J. A. Berson and E. Brown, *J. Am. Chem. Soc.*, **77**, 444 (1955).

Experimental[8]

Starting Materials.—Ethyl β-aminocrotonate,[9] ethyl benzylidenebenzoylacetate,[10] ethyl benzylideneacetoacetate,[10] and ethyl β-aminocinnamate[11] were prepared by known methods and freshly distilled prior to use.

2-Hydroxy-2,4-diphenyl-3,5-dicarbethoxy-6-methyl-1,2,3,4-tetrahydropyridine (Ia).—This compound, m.p. 206.5–207.0° dec. (lit.[4b] m.p. 190–192°), was prepared in 78.4% yield by the method of Palit and Chatterjea.[4b]

Anal. Calcd. for $C_{24}H_{27}NO_5$: C, 70.39; H, 6.65; N, 3.42. Found: C, 70.24; H, 6.61; N, 3.42.

2,4-Diphenyl-3,5-dicarbethoxy-6-methyl-1,4-dihydropyridine (IIa). **A.**—Treatment of 5.0 g. of Ia dissolved in ethanol with cold, dilute nitric acid produced IIa in 64% yield: m.p. 130–132° (aqueous ethanol), $\lambda\lambda_{max}$ 245 mμ (log ε 4.28) and 360 (3.88), NH at 3405 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.43; N, 3.58. Found: C, 73.60; H, 6.25; N, 3.75.

B.—A mixture of 12.1 g. (0.06 mole) of ethyl benzylideneacetoacetate, 13.5 g. (0.07 mole) of ethyl β-aminocinnamate, 12.1 ml. of absolute ethanol, and 1.2 ml. of diethylamine was allowed to stand at 50–60° for 3 days. Yellowish white crystals (9.5 g., 40.9% yield) of m.p. 130.5–131.5° were obtained after several recrystallizations from aqueous ethanol. The product had an infrared spectrum identical with that of the material obtained in A and melted undepressed with it.

2,4-Diphenyl-3-carbethoxy-5-acetyl-6-methyl-1,4-dihydropyridine (IIb).—A mixture of 9.0 g. (0.046 mole) of ethyl β-aminocinnamate and 8.4 g. (0.045 mole) of benzylideneacetylacetone was heated on a steam bath for 20 hr. The resulting solution was dissolved in 250 ml. of ether and allowed to dry over anhydrous calcium chloride for 1 hr. After filtration, the ether was evaporated and the resulting thick red-orange liquid was triturated with small amounts of ether. This treatment produced 11.6 g. (67.9%) of yellow crystals melting at 162.0–163.5° after repeated recrystallizations from aqueous ethanol: λ_{max} 263 mμ (log ε 4.33) and 375 (4.04), NH at 3365 cm.$^{-1}$.

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(8) Melting points were determined on a Fisher-Johns apparatus and are not corrected. Ultraviolet spectra were taken in methanol and the infrared spectra in chloroform. The n.m.r. spectra were of deuteriochloroform solutions with tetramethylsilane added to act as an internal reference. Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

(9) S. Glickman and A. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).

(10) E. F. Pratt and E. J. Werble, *ibid.*, **72**, 4638 (1950).

(11) R. Lukes and J. Kloubek, *Collection Czech. Chem. Commun.*, **25**, 607 (1960). Infrared and ultraviolet spectra indicate this compound to exist principally as the *cis*-chelated enamine rather than the imine as reported in this reference. See B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956), for a discussion of spectra of imine–enamine systems.

1,5-Dibromoadamantane-2,6-dione Synthesis and Rearrangement to Tricyclo[3.3.0.0^{3,7}]-octane-1,3-dicarboxylic Acid

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1,5-Dibromoadamantane-2,6-dione (**1**) was synthesized and rearranged by base to a dicarboxylic acid which we believe is tricyclo[3.3.0.0^{3,7}]octane-1,3-dicar-