Stereospecific Tautomerism in a 1,2-Dihydropyridine. A β-Benzomorphan Synthesis

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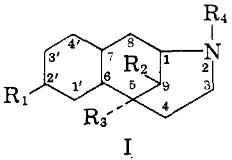
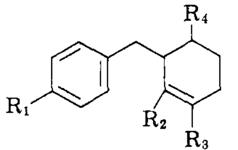
Received December 6, 1962

Bond tautomerism of 2-benzyl-1,3,4-trimethyl-1,2-dihydropyridine salts, controlled by salt form and solvent conditions, leads to *cis*- and *trans*-forms of 2-benzyl-1,3,4-trimethyl-2,3-dihydropyridinium salts which were used for stereospecific benzomorphan syntheses. A novel benzyl-migration is also described.

The configuration of the alkyl groups at position 9 of benzomorphans significantly affects the analgesic potency of these substances.[1] The more desirable *trans*- or β-form (I) is usually the lesser isomer in the Grewe syntheses,[2] where starting materials are Δ^3-tetrahydropyridines (II).



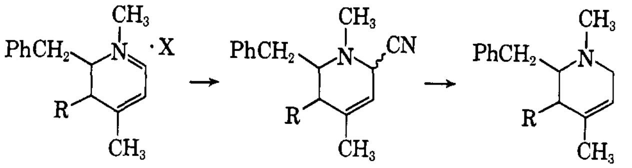
I



II

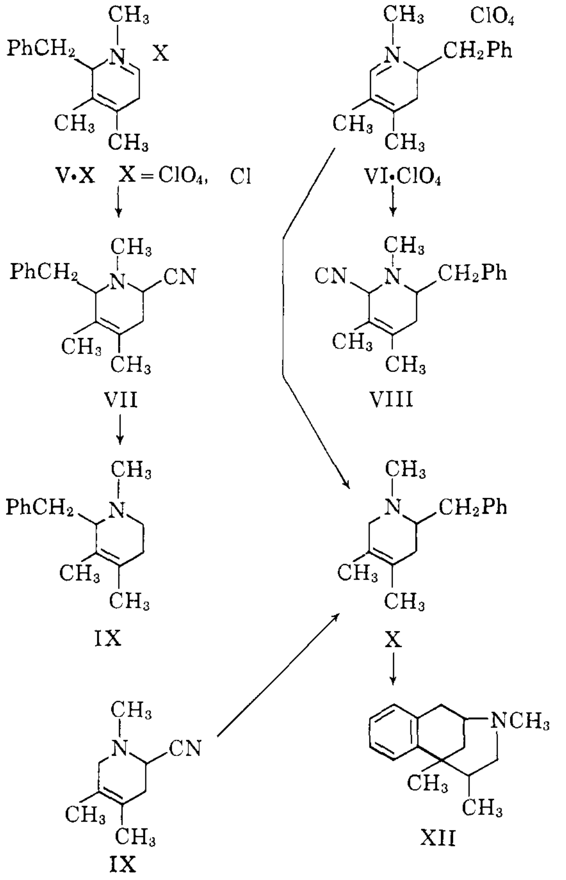
R_1 = H, -OH, -OCH$_3$
R_3, R_4 = -alkyl
R_2 = -H, -alkyl

The desirability of having an intermediate which would undergo stereospecific ring closure to the β-benzomorphan prompted this investigation, and to this end the Δ^4-*cis* and Δ^4-*trans* isomers of 2-benzyl-1,3,4-trimethyl-1,2,3,6-tetrahydropyridine (IV) were prepared by way of the corresponding imminium dienes (III). Migration of the benzyl group from position 2 to position 6 of the dihydropyridine ring also is described.



III·X III·CN IV

R = *cis*- or *trans*-CH$_3$
X = ClO$_4$, Cl



V·X X = ClO$_4$, Cl; VI·ClO$_4$; VII; VIII; IX; X; IX; XII

The crystalline perchlorate obtained from the reaction of the benzyl Grignard reagent with 1,3,4-trimethylpyridinium bromide proved to be a mixture of V-perchlorate and its isomer VI-perchlorate. The isomers could be cleanly separated by way of the salts of the cyano derivatives VII and VIII. Reduction with sodium borohydride gave IX and X and both oils were characterized through crystalline picrates. The structure of IX has been determined[3] and that of its precursor V-perchlorate is assigned by reason of the lack of a maximum in its ultraviolet absorption above 220 mμ. The structure of X is based on the degradation of its derived benzomorphan (XII) to 1-methylnaphthalene and on its n.m.r. spectrum which showed no vinylic hydrogen. It (X) was also synthesized by the action of the benzyl Grignard reagent on the cyano compound XI.[4] The structure of VI-perchlorate follows from its ultraviolet absorption maximum at 307 mμ (ε 4500), and from its lack of an ammonium band at *ca.* 4 μ in the infrared.[5]

The absence of a maximum in the ultraviolet absorption of V applies only to the salt freshly formed by acidifying a solution of the base. A freshly prepared solution of the perchlorate showed developing maxima at 265–270 mμ and at 300 mμ, thereby giving clear testimony to its instability in solution.[6,7] Attempts were made to force this transformation, and it was

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[1] S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).

[2] R. Grewe, A. Mondon, and E. Nolte, *Ann.*, **564**, 161 (1949).

[3] E. M. Fry and E. L. May, *J. Org. Chem.*, **26**, 2592 (1961).

[4] This compound is representative of a class of tetrahydropyridine derivatives not yet in the literature. This type compound is obtained readily by the action of sodium borohydride on a pyridinium salt in the presence of cyanide ion and will be the subject of a later report.

[5] B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956).

[6] Previous work on double-bond mobilities in dihydropyridines has been limited to examples of 1,2- and 1,4-dihydropyridines substituted on the 3-position by groups capable of resonance interaction with ring unsaturation. The results were not useful in the present work. (a) K. Wallenfels, H. Schüly, and D. Hofmann, *Ann.*, **621**, 106 (1959). (b) K. Schenker and J. Druey, *Helv. Chim. Acta*, **42**, 1960, 2571 (1959). (c) W. Traber and P. Karrer, *ibid.*, **41**, 2066 (1958).

[7] Nucleophilic adducts have not been observed in the course of this work. However, see K. Wallenfels, H. Schüly, and D. Hofmann, *Ann.*, **621**, 188 (1959); A. G. Anderson and G. Berkelhammer, *J. Am. Chem. Soc.*, **80**, 992 (1958); ref. 6b.

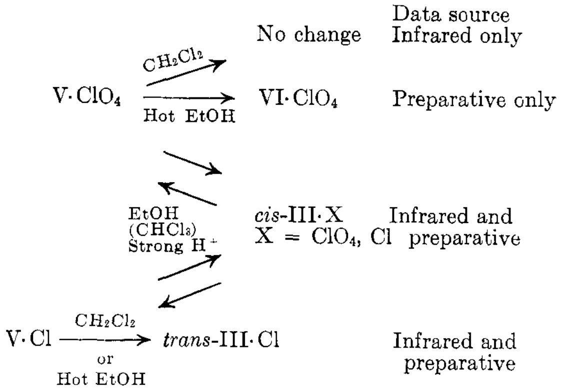


Figure 1

found that, by heating an alcohol solution of V-perchlorate for an hour under reflux, a 28% rearrangement to VI-perchlorate could be achieved. The remainder of the material was an oil with properties of a quaternary salt; it remains unidentified. The forcing conditions necessary to effect this isomerization rule out the possibility that VI-perchlorate originally isolated from the Grignard product was derived from V-perchlorate in the work-up. This unexpected and unwanted rearrangement was suppressed in strongly acid solutions, and was not that giving rise to the 300-mμ absorption mentioned.

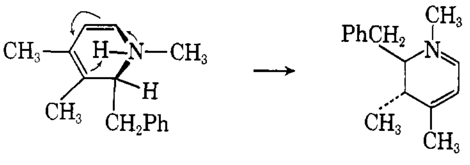
This latter material formed readily at room temperature, and was separated from unchanged V-perchlorate by way of the cyano derivatives,[8] crystalline VII-hydrobromide being separated from the unknown oily hydrobromide which was then transformed into a perchlorate. In this state it spontaneously lost hydrogen cyanide to give a crystalline perchlorate isomeric with V-perchlorate. The new salt had a maximum in the ultraviolet at 298 mμ (ε 4200). It easily reverted to starting material in solution and never amounted to more than 30% in an equilibrated acid solution. Reduction of the perchlorate gave a new tetrahydro isomer which readily isomerized in IX in hot hydrobromic acid, and which showed two C-methyl groups and one vinylic hydrogen. It gave the known benzomorphan,[9] isolated as the methiodide in 67% yield, on ring closure. Comparison of the benzomorphan with its β isomer (see text following) put its configuration on a firm basis and permitted assignment of the *cis* structure to the precursor diene (*cis* III-perchlorate).

When a hydrochloric acid solution of the V-chloride–*cis*-III-hydrochloride mixture was layered with chloroform and refluxed, the nature of the bond rearrangements was profoundly altered. By the action of sodium cyanide on the resulting salt, a crystalline base was obtained in 70% yield. An acid-induced loss of hydrogen cyanide was followed by formation of a crystalline perchlorate isomeric with V-perchlorate. It showed a maximum absorption in the ultraviolet at 282 mμ (ε 5800). Its reduction gave a tetrahydro derivative which showed vinylic hydrogen and two C-methyl groups by n.m.r. spectra and which readily isomerized to IX in hot hydrobromic acid. Ring closure of the hydrochloride with aluminum chloride gave an 82% recovery of a benzomorphan, the structure of which was confirmed by degradation to 1,2-dimethylnaphthalene.[9] On the basis of the rate of methiodide formation[1] relative to that of the previously obtained isomer, it was assigned the β configuration. Thus the rearrangement of the hydrochloride under these conditions yielded *trans*-III-chloride. In contrast to *cis*-III-chloride, *trans*-III-chloride is stable in acid solution and a return to V-chloride could not be effected.

The experimental evidence cited so far has included only as much as was necessary for describing the conditions of the three rearrangements and identification of the compounds involved. The relationships shown in Fig. 1 are taken in part from infrared data, and repeat what has been described except for calling attention to the differences in the behavior of V-perchlorate and V-chloride. As can be seen, the perchlorate is stable in the aprotic solvent methylene chloride, but isomerizes in the presence of a proton source, namely the alcohol usually present in chloroform, to the extent of 0.75%.

In like manner *cis*-III-perchlorate is stable in methylene chloride, but reverts to V-perchlorate in chloroform–0.75% ethanol. The equilibrium is thus approached from both sides, and the infrared diagrams become equivalent. The chloride of V, on the other hand, shows only as transients those bands at 5.86 and 5.96 μ, which characterize V-perchlorate. Within an hour, bands at 6.01 and 6.26 μ characteristic of *trans*-III-chloride become dominant. Even in the hot alcohol solution which promoted the V-perchlorate to VI-perchlorate isomerization, V-chloride again yields *trans*-III-chloride.

The key to these differences probably lies in the absorption, or lack of it, in the 4-μ region of the infrared.[5] The perchlorate of V lacks absorption in this region, whereas V-chloride has a broad band at 4.0–4.3 μ. If, on the basis of the ammonium bands, V-chloride is partly thus,



III

with *trans* arrangement of benzyl and N-methyl groups, a 1,5-hydrogen transfer[10] would account for the formation of *trans*-III. In the case of the immonium salt, V-perchlorate, or with V-chloride in a strongly acid solution where the immonium structure might be favored, an equilibrium between Δ^3 and Δ^4 is obviously not only easily achieved, but strongly favors the *cis* arrangement for the alkyl groups; the most obvious implication is that the benzyl group inhibits the approach of the proton donor to the sterically less favored position.

The bases of the salts which have been described can be obtained by decomposition of the salts with strong alkali, but insufficient base or even a trace of weak base in suspensions of V-perchlorate or VI-perchlorate in alcohol yields the corresponding pyridinium and tetra-

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[8] N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957).

[9] E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).

[10] A six-center concept has been used to explain the thermal isomerization of 1,3-dienes. J. Wolinsky, B. Chollar, and M. D. Baird, *J. Am. Chem. Soc.*, **84**, 2775 (1962). G. Büchi and E. M. Burgess, *ibid.*, **84**, 3104 (1962).

hydropyridine salts.[11] The identities of the former follow from their quaternary nature, analytical values, and absorption characteristics. Heating in alcohol solution alone is enough to cause disproportionation of VI-perchlorate.

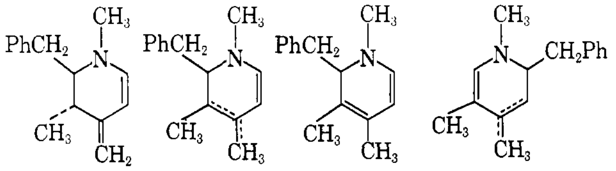
A prediction based on the relative stabilities of the carbanions[12] would favor initial formation of the *exo–endo* diene from VI-salts and from the *cis*- and *trans*-III-salts. In fact only *trans*-III-base was clearly *exo–endo* as shown by its n.m.r. spectrum, with four vinylic hydrogens and one C-methyl group. The other two bases were mixtures, as shown by comparison of their infrared data with those of the bases, V and *trans*-III. The relevant data are given in Fig. 2.

Bases V and VI were recovered unchanged from ethereal solutions of lithium aluminum chloride, but *trans*-III was reduced to *trans*-IV in 71% yield under these conditions. Reduction by hydride reagent in solvents incapable of supplying the proton necessary to form the immonium ion appears anomalous. (The possibility of a pseudobase appears ruled out by the absence of 2.7–2.8-μ absorption.) Compounds V and VI were readily reduced by sodium borohydride in alcohol to give IX and X, respectively. It will be noted that in two of these examples, *trans*-III and VI, the reduction must have occurred after migration of both bonds and raises the question of a possible concerted tautomerism. It is interesting that the single bond shift implicit for V in the basic reduction medium, can also be observed on acidification of a solution of the base (disappearance of ultraviolet maxima), whereas development of salt maxima are rapid in the other two cases, *trans*-III and VI, where concerted migration in basic media is suspected. Analogous systems provide examples of stepwise,[13] or possibly concerted[6b] bond migrations, and Opitz and Merz[14] give an example of initial N-protonation, followed by two probable stepwise bond shifts.[15]

The successful use of cyanide ion[4] as a competitor nucleophile in hydride reductions may eventually yield more information, and another potentially useful approach was initiated by Lyle, Nelson, and Anderson[16] in the use of deuterium to mark the nucleophilic site on the dihydropyridine ring. But because of the possibility of bond shifts due to proton abstraction, both methods seem limited to disproving an apparently concerted diene tautomerism.

Experimental

Microanalyses are by the Analytical Services Unit of this laboratory, Harold McCann, director. N.m.r. spectra, 60 Mc., are with tetramethylsilane as internal reference standard; τ values are averaged; integrated benzene areas were used as standards. Ultraviolet spectra are by a Cary recording spectrophotometer, Model 14, and infrared spectra are by a Perkin-Elmer Infracord, Model 137. Melting points are uncorrected.



trans-III	*cis*-III	V	VI
302 (14200)	282 (4600)	275 (4100)	
	300–315 (4400)	325 (3800)	312 (3600)
6.17 (s)	6.06 (s)	6.05 (s)	6.04 (s)
	6.18 (m)		6.14 (m)
6.25 (sh)	6.32 (s), 6.24 (sh)	6.32 (s), 6.23 (sh)	6.32 (s), 6.24 (sh)

Fig. 2. Ultraviolet maxima, mμ (ε). Infrared μ, (s)trong, (m)edium, (sh)oulder.

Mixture of 2-Benzyl-1,3,4-trimethyl-2,5-dihydropyridinium (V) and 6-Benzyl-1,3,4-trimethyl-5,6-dihydropyridinium (VI) Perchlorates.—The Grignard reagent from 64 ml. (0.56 mole) of benzyl chloride in 500 ml. of ether solution was added to 68 g. (0.34 mole) of N-methyl-3,4-lutidinium bromide, previously layered with ether, and the suspension stirred for 1 hr. The grey adduct no longer showed a yellow spot on mashing with a stirring rod. The suspension was poured onto a mixture of 105 ml. of 60% perchloric acid and ice while agitating vigorously. The salt partly crystallized, and the ether was decanted and crystallization aided by triturating the oily solid several times with 30–60° petroleum ether. It was recovered by filtering through a sintered-glass funnel, washing twice with water, and twice with chloroform. After drying overnight, it was again washed twice with chloroform. The solid weighed 62 g. and melted at 150–154°. From the aqueous acid–chloroform mother liquors, another 12 g. was obtained, m.p. 130–180°. The total crystalline yield was 70%. The main fraction could not be completely freed of the isomer (infrared evidence) by recrystallization from acetic acid, and the melting point was variable. The analytical sample melted at 143–146°.

Anal. Calcd. for $C_{15}H_{20}ClNO_4$: C, 57.41; H, 6.42. Found: C, 57.45; H, 6.37.

6-Benzyl-1,3,4-trimethyl-5,6-dihydropyridinium perchlorate ($VI \cdot ClO_4$) was readily obtained from the lesser fraction by recrystallization from acetic acid. It melted at 196–199° with a slight sinter at 193°. Ultraviolet data for this salt was obtained by dissolving the sample in a little alcohol containing a drop of 60% perchloric acid, λ_{max} 307 mμ (ε 4500); λ_{min} 235 mμ (ε1100). Without acid, absorption at 275 mμ was evident. Disproportionation evidence is presented (p. 1872). Infrared bands (μ) in Nujol were at 5.96 (m), 6.26 (s), 8.09 (m), and 8.36 (m). The last two peaks were valuable in detecting this compound in mixtures.

Anal. Calcd. for $C_{15}H_{20}ClNO_4$: C, 57.41; H, 6.42. Found: C, 57.55; H, 6.35.

Base from VI-perchlorate was obtained as an oil from the action of sodium hydroxide in dilute alcohol and was recovered from ether. In an ethereal solution it was held for 30 min. with lithium aluminum hydride, recovered, and converted back to the perchlorate for a 60% recovery. The neat oil showed an infrared (μ) pattern of peaks 6.04 (s), 6.14 (m), 6.24 (sh), 6.32 (s) which varied with different samples and, together with n.m.r. results, indicates a mixture. In ethanol, λ_{max} 312 mμ (ε3600); λ_{min} 245 mμ (ε 2800).

N.m.r. data: 4.25 τ (=CH—) 0.7H; 5.2 τ (=CH—) 0.7H; 8.25 τ [=C(CH$_3$)—C(CH$_3$)=] 5.5H.

A sample of the cyano derivative made from the perchlorate was found to be an oil; hence there is no question of contamination of the cyano base described next.

2-Benzyl-6-cyano-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (VII).—To 31.8 g. of crude VII-perchlorate, wet with water and layered with ether, was added a solution of 7.5 g. (1.5 × theory) of sodium cyanide dissolved in 35 ml. of water. The solid disappeared on shaking. Hydrogen chloride was passed into the ethereal solution with precipitation of an oil which crystallized. Instability precluded solution in a hot solvent. It was purified by triturating in acetone, wt., 24.9 g. (89%), m.p. (rapid heating) 119–121° (gas). The oil from the acetone filtrate yielded 0.92 g. (2.9%) of VI-perchlorate.

Anal. Calcd. for $C_{16}H_{21}N_2Cl$; C, 69.42; H, 7.65. Found: C, 69.55; H, 7.56.

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[11] For disproportionation of a Hantzsch base see O. Mumm, *Ann.*, **529**, 115 (1937); O. Mumm and J. Diederichsen, *ibid.*, **538**, 195 (1939).

[12] See A. Schriesheim and C. A. Rowe, Jr., *J. Am. Chem. Soc.*, **84**, 3160 (1962).

[13] J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford, and F. W. Heyl, *ibid.*, **78**, 430 (1956); W. S. Johnson, V. J. Bauer, and R. W. Frank, *Tetrahedron Letters*, 72 (1961).

[14] G. Opitz and W. Merz, *Ann.*, **652**, 139 (1962).

[15] For other examples of C- and N-protonation see R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1962), and references therein.

[16] R. E. Lyle, D. A. Nelson, and P. S. Anderson, *Tetrahedron Letters*, (13) 553 (1962).

The weakness of the cyano base is shown by dissociation of the salt in aqueous solution yielding the free base. The base was obtained solid from ether solution and was purified by recrystallization from petroleum ether (30–60°). It melted at 59.5–62°.

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 80.06; H, 9.03; N, 11.69.

In ethanolic solution at room temperature the hydrochloride rapidly underwent change. Ultraviolet absorption at 262 mμ increased to a maximum value, ϵ 4400, in 20 min. The base showed no peak above 220 mμ except for benzene peaks at about 260 mμ (ϵ 500).

2-Benzyl-1,3,4-trimethyl-1,2-dihydropyridine (V) and Its Perchlorate ($V \cdot ClO_4$).—(The cyano group was eliminated without accompanying tautomerism by means of stannic chloride. The crystalline tin salt was not characterized.) The hydrochloride of VII, 0.26 g., partly dissolved in 4 ml. of dilute alcohol, was treated with 0.2 ml. of stannic chloride. The tin salt separated from the solution crystalline, m.p. 157–159°. It was converted to the base with sodium hydroxide and the base recovered with ether. Infrared bands (μ) for the neat oil were at 6.05 (s), 6.23 (sh), 6.32 (s). Conversion to the perchlorate gave a salt which, in Nujol mull or chloroform, showed no absorption at about 4 μ, with bands at 5.86 and 5.96 μ, with only weak absorption at 6.25 μ, and no maxima in 8.0–8.4-μ region (Nujol mull). These were the criteria used in establishing the absence of its isomers. The perchlorate, dissolved in ethanol acidified with perchloric acid, showed only benzene maxima above 220 mμ. Made alkaline with sodium hydroxide, the solution showed two peaks in ultraviolet, λ_{max} 275 mμ (ϵ 4100), 325 (3800); λ_{min} 240 (3000), 302 (3100).[17] Reacidification gave back the original curve. When the perchlorate was dissolved in ethanol, absorption at 268 mμ rose to a constant value, ϵ 4500, in 2 hr. at room temperature. The perchlorate was recovered (93%) from base held for 8 min. in ethereal lithium aluminum hydride solution.

Rearrangement of 2-Benzyl-1,3,4-trimethyl-2,5-dihydropyridinium (V) Perchlorate to 6-Benzyl-1,3,4-trimethyl-5,6-dihydropyridinium (VI) Perchlorate.—2-Benzyl-6-cyano-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (VII) hydrochloride (1.0 g.) was converted to the base and thence to the perchlorate. (This crystalline material was blank in the 6-μ region, hence still retained the cyano group, but subsequent attempts to make it showed the characteristic absorption of the dihydro salt.) It was dissolved in 1.0 ml. of 95% ethanol and 0.05 ml. of acetic acid and the solution refluxed for 1.5 hr. The solution yielded 0.33 g. of crystals melting at 165–185°. Recrystallized from acetic acid, it weighed 0.26 g. (28%) and melted at 185–191°. The infrared diagram and a mixture melting point established its identity. The remainder of the material was principally a quaternary salt which in alcohol absorbed at 265–270 mμ.

2-Benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (IX) has been obtained in 72% yield by the action of sodium borohydride on a solution of V in alcohol, in 78% yield by a similar reduction of VII, and in 71% yield by reduction of V-perchlorate with lithium aluminum hydride. All yields are as the picrate which has been reported.[3]

6-Benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (X). A.—This compound was obtained by the action of lithium aluminum hydride on a suspension of VI-perchlorate in ether in 85% yield, and by sodium borohydride reduction of its derived base in alcohol in 73% yield. Both yields are as the picrate salt which was purified from alcohol, m.p. 130–132°.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.73; H, 5.21.

N.m.r. data: No absorption in the 4–6-τ region; 8.45 τ $[-C(CH_3){=}C(CH_3)-]$ 6H.

B.—The cyano compound, obtained by action of sodium borohydride and cyanide ion on 3,4-lutidine methiodide, reacted with the benzyl Grignard reagent to yield an oil which gave a picrate. By means of mixture melting point and infrared diagram of the derived base, it was found to be identical to the previously described X-picrate.

Disproportionations. A.—2-Benzyl-1,3,4-trimethyl-2,5-dihydropyridinium (V) perchlorate, 0.5 g. (0.0016 mole), in 0.5 ml. of 95% alcohol and 0.005 g. (0.00025 equiv.) of magnesium oxide on heating gave a solution which was boiled for 10 min. The solvent was removed and the remaining oil shaken with aqueous sodium carbonate solution and ether. The oil from the ether was converted to 0.14 g. of picrate, identified by mixture melting point and the infrared diagram of the derived base as the tetrahydro compound IX. The material unaffected by base crystallized. Purified from alcohol, it weighed 0.16 g. (64%), m.p. 113–115°. In ethanol solution, it showed a maximum at 275 mμ (ϵ 8000), unchanged by alkali. A Nujol mull had bands (μ) at 6.17 (s) and 6.35 (m).

Anal. Calcd. for $C_{15}H_{18}ClNO_4$: C, 57.78; H, 5.82. Found: C, 57.65; H, 5.88. On this evidence the compound is **2-benzyl-1,3,4-trimethylpyridinium perchlorate.**

B.—6-Benzyl-1,3,4-trimethyl-5,6-dihydropyridinium (VI) perchlorate, 0.5 g. in 1.5 ml. of 95% ethanol, and 0.005 g. of magnesium oxide was boiled for 15 min. On cooling the solution, crystals separated, wt., 0.24 g. (97%), m.p. 193–197°. Recrystallized, it melted at 195–197°. It had λ_{max}^{EtOH} 272 mμ (ϵ 6700). On making the solution alkaline, this peak was not affected but broad absorption appeared at 355 mμ (ϵ 1100). Bands (μ) in a Nujol mull were at 6.11 (s) and at 6.24 (m).

Anal. Calcd. for $C_{15}H_{18}ClNO_4$: C, 57.78; H, 5.82. Found: C, 57.64; H, 5.80. This evidence identifies this compound as **6-benzyl-1,3,4-trimethylpyridinium perchlorate.**

Alcohol was removed from the preceding filtrate; the remaining oil decomposed with sodium carbonate as before. The base yielded a picrate, wt., 0.29 g. (82%), m.p. 128–130°. By mixture melting point it was proved to be identical with the sample of X-picrate described earlier. Disproportionation (about 10%) also resulted from refluxing an alcohol solution of VI-perchlorate for 3 hr.

Rearrangements Using 2-Benzyl-6-cyano-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (VII) Hydrochloride.—The facile loss of hydrogen cyanide made use of this compound equivalent to that of its parent V-salt in acid solution.

A. *cis*-2-Benzyl-1,3,4-trimethyl-2,3-dihydropyridinium (III) Perchlorate.—The hydrochloride of VII, 3.0 g., dissolved on heating in 27 ml. of 2.2 *N* hydrochloric acid; the solution was boiled for 6 min. with loss of hydrogen cyanide. The yellow solution was chilled to 7° and an equally cold solution of 4.0 g. of sodium cyanide in 20 ml. of water was added rapidly. The yellow color vanished and an oil separated. The oil was taken into ether and the solution shaken with 1.8 ml. of 8.8 *N* hydrobromic acid. The crystalline hydrobromide of VII separated. After filtering, washing with 3 ml. of water, and drying under reduced pressure, it weighed 2.2 g. (63%), m.p. 138–140° (gas). Identity was established by reconversion to VII.

Anal. Calcd. for $C_{16}H_{21}N_2Br$: C, 59.82; H, 6.59. Found: C, 59.75; H, 6.43.

Sodium cyanide, 1.0 g., in 4 ml. of cold water was then added to the cold filtrate and the separated oil (*cis*-III·CN) shaken into ether. It was recovered by removing the ether under reduced pressure, taken up in petroleum ether (30–60°) to remove aqueous material, and recovered again under reduced pressure. The yellow cyano derivative weighed 0.85 g. (33%). It was converted to the perchlorate by triturating with 0.6 ml. of 60% perchloric acid and then adding water. Hydrogen cyanide was lost and the salt crystallized. It was washed with water, dried, and washed with acetic acid to remove a little color, wt., 0.9 g. (26% over-all), m.p. 118–125°. In ethanol containing perchloric acid, λ_{max} 298 mμ (ϵ 4400); λ_{min} 235 mμ (ϵ1300). Infrared bands (μ) in Nujol at 6.01 (s), 6.29 (s), and 8.18 (m). A weak band at 5.86 μ is due to V-perchlorate and is increased by recrystallization from acetic acid or from alcohol.

Anal. Calcd. for $C_{15}H_{20}ClNO_4$: C, 57.41; H, 6.42. Found: C, 57.36; H, 6.65.

Lithium aluminum hydride reduction of residual perchlorate of this rearrangement yielded all four tetrahydro isomers, IX, *cis*-IV, X, and *trans*-IV, the latter being in trace amount. Identification was by v.p.c. The **base from *cis*-III-perchlorate** appeared in the infrared to be principally V. The neat oil showed bands (μ) at 6.06 (s), 6.18 (m), 6.24 (sh), and 6.32 (s). A return to the perchlorate gave back V-perchlorate.

B. 2-Benzyl-6-cyano-1,3,4-trimethyl-1,2,3,4-tetrahydropyridine (*trans*-III·CN).—Two grams of VII-hydrochloride in 8 ml. of 6 *N* hydrochloric acid layered with 16 ml. of chloroform was heated to the reflux temperature of the chloroform layer, with solution of the solid and loss of hydrogen cyanide. After refluxing for 4 hr., the chloroform was distilled from the pale yellow acid solution. Reduced to a small volume under reduced pressure, a little ammonium chloride separated. Sodium cyanide, 0.9 g. in 7 ml. of cold water, was added to the chilled oil and

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[17] Extensive use has been made of the double peak characteristic of 1,2-dihydropyridines as opposed to the single band shown by the 1,4-isomers, ref. 6a,c. Cross conjugation involving the 3-substituent has been considered, ref. 6b, but this explanation is obviously not relevant here.

triturated, with formation of the solid product which was dissolved in ether. After removing ether under reduced pressure, the crystalline product was filtered from cold alcohol. It weighed 1.23 g. (70.5%) and melted at 88–90°.

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 80.15; H, 8.64; N, 11.80.

To the alcohol filtrate was added dilute perchloric acid with recovery of 0.42 g. (19%) of crystalline material. The infrared diagram showed a mixture of VI- and V-perchlorates.

One gram of VII-hydrochloride was heated in 1.0 ml. of 95% ethanol and 0.05 ml. of acetic acid. These are conditions for rearranging V-perchlorate to VI-perchlorate, but none of the latter could be recovered. Instead, a 32% yield of the previous cyano derivative resulted from the action of sodium cyanide on the solution. The oily portion was converted to an oily perchlorate which showed loss of cyanide (strong absorption in the 6-μ region) but no bands at 8.09 and 8.36 μ characteristic of VI-perchlorate.

***trans*-2-Benzyl-1,3,4-trimethyl-2,3-dihydropyridinium (*trans*-III) Perchlorate.**—The previously described cyano compound, 0.51 g., was treated with 1.1 ml. of 2.2 *N* hydrochloric acid with formation of another crystalline material, probably the salt. It dissolved over the next 12 min., accompanied by liberation of hydrogen cyanide (vapor test with alkaline sodium picrate solution) and a lowering of the solution temperature. After an additional 20 min., the addition of 0.3 ml. of 60% perchloric acid gave an oil which crystallized, wt., 0.62 g. (93%), m.p. 115–118°. Recrystallized from alcohol, it melted at 116–118°. In ethanol it showed λ_{max} 282 mμ (5800); λ_{min} 230 mμ (ϵ1600). Infrared maxima (μ) in Nujol were at 6.00 (m), 6.26 (s), and 8.26 (m).

Anal. Calcd. for $C_{15}H_{20}ClNO_4$: C, 57.41; H, 6.42. Found: C, 57.50; H, 6.36.

N.m.r. data: 1.65 τ [—N(CH$_3$)=CH—] 1H; 7.9 τ [—C-(CH$_3$)=] 3H; 9.9 τ [—CH(CH$_3$)—] 3H. The perchlorate was recovered (90%) after refluxing in alcohol–acetic acid; neither the condition of the V-perchlorate–VI-perchlorate rearrangement nor did heating the hydrochloride salt in hydrochloric acid under conditions of the V-chloride–*cis*-III-chloride rearrangement result in change. The perchlorate likewise showed no rearrangement in chloroform.

Spectroscopic Evidence of the Formation of *trans*-III-Chloride from V-Chloride.—The hydrochloride made by passing hydrogen chloride into a methylene chloride solution of V showed the 5.86-μ, 5.96-μ double peaks characteristic of V-perchlorate, as well as 6.26-μ absorption with a broad band at about 4.2 μ. In an hour at room temperature peaks at 6.00 and 6.26 μ, characteristic of *trans*-III-chloride, were dominant with the 4.2-μ absorption still present. The addition of perchloric acid resulted in elimination of the 4.2-μ absorption and appearance of a peak at 3.6 μ, which was found by means of a blank to be due to hydrogen chloride. Positive identification was made by means of the crystalline cyano derivative but recovery was poor. The oily hydrochloride made from *trans*-III-base also showed absorption in the 4.2-μ region. The neat oil did *not* show absorption in this region.

Spectroscopic Evidence for the V-Perchlorate–*cis*-III-Perchlorate Tautomerism.—A solution of V-perchlorate in chloroform (alcohol stabilized) showed development of 6.01- and 6.29-μ bands, reaching an equilibrium with the original 5.86- and 5.96-μ bands in about 4 hr. This same equilibrium was reached by development of the 5.86- and 5.96-μ bands in a chloroform solution of *cis*-III-perchlorate in approximately the same time. In methylene chloride this equilibration was not observed.

***trans*-2-Benzyl-1,3-dimethyl-4-methylene-1,2,3,4-tetrahydropyridine (*trans*-III)** was obtained as an oil by the action of sodium hydroxide on *trans*-III-perchlorate. In ethanol, λ_{max} 302 mμ (ϵ14,200); λ_{min} 255 mμ (ϵ3300). Infrared maxima (neat) (μ) at 6.17 (s), and 6.25 (sh).

N.m.r. data: 4.15 τ (—CH=) 1H; 5.05 τ (—CH=) 1H; 5.40 τ, 5.65 τ (=CH$_2$) 2H.

***trans*-2-Benzyl-1,3,4-trimethyl-1,2,3,6-tetrahydropyridine (*trans*-IV).**—Sodium borohydride, 0.58 g., was added to a cold suspension of 2.7 g. of 2-benzyl-6-cyano-1,3,4-trimethyl-1,2,3,6-tetrahydropyridine with vigorous gas evolution. The temperature was maintained below 23°. After 2 hr. the suspension was chilled and 10 ml. of 3 *N* hydrochloric acid added portionwise with gas evolution. The solid in suspension successively became an oil, solidified, and dissolved. The acid solution was heated briefly to 50°. The solvent was removed under reduced pressure, sodium carbonate solution added, and the base taken into ether. The crystalline salt separated as hydrogen bromide was passed into the ethereal solution; it was washed with acetone, wt., 2.7 g. (81%), m.p. 191–197°. Recrystallized from alcohol it melted at 198–199°.

Anal. Calcd. for $C_{15}H_{22}NBr$: C, 60.81; H, 7.49. Found: C, 60.70; H, 7.31.

This hydrobromide was also recovered in 88% yield by the action of lithium aluminum hydride on *trans*-III-perchlorate, and in 71% yield by the action of lithium aluminum hydride on *trans*-III in ether solution. The picrate was made and purified from alcohol. It melted at 114–116°.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.60; H, 5.68.

N.m.r. data: 4.6 τ [—C(CH$_3$)=CH—] 1H; 8.2 τ [—C-(CH$_3$)=] 3H; 8.6 τ [—CH(CH$_3$)—] 3H.

***cis*-2-Benzyl-1,3,4-trimethyl-1,2,3,6-tetrahydropyridine (*cis*-IV).**—The perchlorate of *cis*-III, 1.3 g., was added to a cold solution of 0.2 g. of lithium aluminum hydride in 11 ml. of ether. The solid rapidly dissolved. After decomposition of the excess reagent with ethyl acetate–water, the solution of the base in ether was shaken with 0.48 ml. (1 × theory) of 8.8 *N* hydrobromic acid. The oil which separated was freed of water under reduced pressure, dissolved in absolute ethanol, and again freed of solvent. The salt was recovered crystalline from acetone–ether. A second crop brought the weight to 0.73 g. (58%). Purified by adding ether to a solution in absolute ethanol, it melted 170–171°. The same material was obtained by the action of sodium borohydride on the oily cyano derivative (*cis*-III·CN).

Anal. Calcd. for $C_{15}H_{22}NBr$: C, 60.81; H, 7.49. Found: C, 60.93; H, 7.57.

N.m.r. data: 4.7 τ (=CH—) 1H; 8.3 τ [—C(CH$_3$)=] 3H; 8.65 τ [—CH(CH$_3$)—] 3H.

Isomerizations of *cis*-IV- and *trans*-IV-Hydrobromides to IX-Hydrobromide.—A solution of 0.10 g. of *cis*-IV-hydrobromide in 0.4 ml. of 8.8 *N* hydrobromic acid was held in the steam bath for 2 hr. The base was recovered, then converted to the picrate (wt., 0.11 g.) which by mixture melting point was proved to be IX-picrate. In like manner 0.10 g. of *trans*-IV-hydrobromide yielded 0.12 g. of IX-picrate. Infrared diagrams confirmed these results.

2,4,9-Trimethyl-6,7-benzomorphan (XII) and Degradation to 1-Methylnaphthalene.—A solution of the oily hydrobromide of X in 20 ml. of 8.8 *N* hydrobromic acid was heated at reflux temperature for 5 hr. The solution was chilled, made alkaline with sodium hydroxide solution, and 3.4 g. of oil recovered with ether. In acetone solution the crude benzomorphan, 2.2 g., was converted to an oily methiodide which was heated in aqueous suspension with excess thallous hydroxide until the thallous iodide became granular. After filtering the solid, the solution was made alkaline with sodium hydroxide, boiled for 30 min., cooled, and extracted with ether to give 1.3 g. of methine base. Converted to the hydrobromide, an oil, this salt absorbed about 1 mole of hydrogen in alcohol over Adams catalyst. The oily product was converted to the base and heated with 10% palladium-charcoal at 270° with distillation of an oil which showed about 12% 1-methylnaphthalene by v.p.c.

α-2,5,9-Trimethyl-6,7-benzomorphan.[18]—An oily adduct formed when 0.2 g. of *cis*-IV-hydrobromide was added to a suspension of 0.2 g. of aluminum chloride in 0.5 ml. of carbon disulfide. The adduct was gummy but on triturating became an oil in about 2 min. After 3 hr. at room temperature the suspension was chilled and water added dropwise; carbon disulfide was decanted from the white mush which was then washed with ether. Excess sodium hydroxide dissolved the aluminum hydroxide, and the basic product was recovered from petroleum ether (30–60°), wt., 0.14 g. The base in acetone solution was converted to a crystalline methiodide in 67% over-all yield, m.p. 214–220°. Recrystallized from alcohol–ethyl acetate, it melted at 218–222°, and a mixture melting point and infrared diagram showed it to be identical to the previously characterized sample.[9]

β-2,5,9-Trimethyl-6,7-benzomorphan.—The hydrobromide of *trans*-IV, 2.7 g., was added to a suspension of 2.8 g. of aluminum chloride in 8 ml. of carbon disulfide. The solids dissolved into an oily adduct on triturating. After 4 hr. the mixture was decomposed as in the above experiment to give 1.75 g. of an oil which, in acetone with methyl iodide, yielded a crystalline salt, wt., 2.7 g. (82% over-all), m.p. 225–231° (gas). Recrystallized from water, it melted at 232–239° with a sinter at 196°. Dried

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[18] Configuration assignments for the α- and β-benzomorphans were made by E. L. May and will be included in a subsequent publication.

overnight at 100° under oil pump vacuum it lost 0.97% water and melted at 240–241° with a sinter at 201°.

Anal. Calcd. for $C_{16}H_{24}NI$: C, 53.78; H, 6.77. Found: C, 53.92; H, 6.59.

1,3-Dimethyl-1-(2-dimethylaminoethyl)-1,2-dihydronaphthalene Hydrobromide.—The methiodide of the β-benzomorphan, 1.8 g., was converted to the methohydroxide with thallous hydroxide. After filtering the thallous iodide the aqueous solution was taken to an oil under reduced pressure and the base then heated in a bath at 170° (0.5 mm.) with distillation of a colorless oil at about 120° (0.5 mm.). In ether solution with hydrogen bromide it gave a crystalline salt, wt., 1.4 g. (88% over-all), m.p. 170–174° (gas). Recrystallized from acetone, it melted at 175–177°.

Anal. Calcd. for $C_{16}H_{24}NBr$: C, 61.93; H, 7.80. Found: C, 62.12; H, 8.12. An ethanol solution showed λ_{max} 265 mμ (ε 9000).

1,3-Dimethyl-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene hydrobromide was obtained by reduction of the above salt in alcohol with Adams catalyst. It was recrystallized by adding ethyl acetate to a solution in alcohol–acetone, m.p. 202–205°.

Anal. Calcd. for $C_{16}H_{26}NBr$: C, 61.53; H, 8.39. Found: C, 61.81; H, 8.47.

1,2-Dimethylnaphthalene was recovered as the picrate in 18% yield as one of the products resulting from the 280° palladium–charcoal decomposition of the tetrahydronaphthalene base from the preceding hydrobromide.[9] Identification was by a mixture melting point with a known sample.

Acknowledgment.—Nuclear magnetic resonance data were helpfully interpreted by Drs. E. D. Becker and L. A. Cohen and recorded by Mr. R. B. Bradley; configuration assignments of the benzomorphans were generously made by Dr. E. L. May.

The Synthesis of Tryptophan Peptides

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Received December 26, 1962

The preparation of blocked and free dipeptides containing tryptophan and the synthesis of tryptophan benzyl ester are described.

In connection with our work on the specific cleavage of proteins at the tryptophyl residue, we found it necessary to prepare various peptides containing tryptophan as model compounds.

The only studies so far reported in the synthesis of tryptophan peptides are the early work of Abderhalden[1] and the work of Smith[2] on the synthesis of protected tryptophyl peptides through carbobenzoxy tryptophyl chloride, and the preparation of tryptophylglycine[3] and arginyltryptophan[4,5a] as intermediates in the partial synthesis of α and β MSH.[5b]

All the protected tryptophan peptides listed in Table I and the corresponding free peptides listed in Table II previously have not been reported in the literature. They were synthesized by coupling carbobenzoxy-L-tryptophan with the appropriate amino acid benzyl ester by the dicyclohexylcarbodiimide (DCC) method.[6]

The blocked dipeptides containing C-terminal tryptophan were prepared similarly from the appropriate carbobenzoxy-L-amino acid and L-tryptophan benzyl ester, except for carbobenzoxy-L-prolyl-L-tryptophan which was synthesized from carbobenzoxypropyl chloride[7] and free L-tryptophan.

Tryptophan benzyl ester hydrochloride has not been synthesized previously probably owing to the instability of tryptophan at the acid pH values and high temperature needed for esterification. However, we succeeded in synthesizing this compound in 80% yield in one step by a modification of Erlanger's method.[8] The method was to pass phosgene through a suspension of tryptophan in dioxane until the tryptophan was completely dissolved, being converted to the N-carboxyanhydride.[9] About half the dioxane was distilled so as to remove the excess of phosgene. Benzyl alcohol–ether was added and two to three moles of gaseous hydrogen chloride per mole residue of tryptophan were passed through at 0°. After standing overnight, the ester precipitated. All of the benzyl esters used in this study were synthesized by this method.

The unblocked peptides listed were obtained by catalytic hydrogenation of the blocked peptides in the presence of palladium on charcoal.

The free peptides were chromatographically pure (butanol–acetic acid–water, 25:6:25). On basic hydrolysis all gave tryptophan and the appropriate amino acid in a 1:1 ratio.

Experimental

All melting points are uncorrected. Prior to analysis the free peptides were dried at 80° *in vacuo*, over phosphorus pentoxide. Other compounds were dried *in vacuo* over phosphorus pentoxide at room temperature.

L-Tryptophan Benzyl Ester Hydrochloride.—Dry phosgene was passed at room temperature through a suspension of L-tryptophan (20.4 g.) in anhydrous dioxane (330 ml.) until a clear solution was obtained (about 45 min.). Phosgene was removed by a stream of dry nitrogen and half of the solvent was distilled *in vacuo* at 45°.

Benzyl alcohol (50 ml.) and dry ether (250 ml.), previously saturated with 2–3 moles of gaseous hydrogen chloride per mole residue of tryptophan at 0°, were added, and the solution was left overnight at room temperature. The ester which separated was filtered off and washed with ether. The product was recrystallized from hot water; yield, 80%; m.p. 222°, $[\alpha]^{25}D$ +4° (*c* 2, methanol).

Anal. Calcd. for $C_{18}H_{18}N_2O_2 \cdot HCl$: C, 65.45; H, 5.78; N, 8.48. Found: C, 65.55; H, 5.83; N, 8.28.

Carbobenzoxy-L-tryptophan *p*-Nitrophenyl Ester.—Cbz-L-tryptophan (34 g.) was dissolved in ethyl acetate and *p*-nitrophenol (14 g.) was added. The solution was cooled to 0° and dicyclohexylcarbodiimide (20.5 g.) was added. After 2 hr. at room tem-

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