Rearrangement Products of 9-Acetoxy- and 9-Hydroxy-2,5,9-trimethyl-6,7-benzomorphans

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Received September 27, 1965

Pyrolysis of 9-acetoxy-2,5,9-trimethyl-6,7-benzomorphan perchlorate (I) at 185° has given a mixture of 1,2,3,4-tetrahydro-1,4,4-trimethyl-9H-indeno[2,1-*b*]pyridine (Va, isolated as the perchlorate V) and 1,2,4a,9a-tetrahydro-1,4,4a-trimethyl-9H-indeno[2,1-*b*]pyridine perchlorate (IV). The structures of IV, V, and Va were assigned by nmr, ultraviolet, infrared, and mass spectral data, and from nmr, ultraviolet, and infrared analysis of their hydrogenation products (VI and VIII). Hofmann elimination products VII and IX provided confirmatory information. The yields and proportion of IV and V were dependent upon reaction time, short periods favoring IV. Thionyl chloride treatment of base II at room temperature or below gave the 9-methylene compound III (40%) and the base corresponding to IV (4%), but no Va. Neither III nor IV (after isolation) could be converted to V or Va.

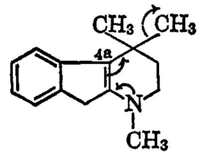
In 1957 it was reported[2] that the pyrolysis of α-9-acetoxy-2,5,9-trimethyl-6,7-benzomorphan[3] at 325° gave a 38% yield of the 9-methylene compound III. When, however, the perchlorate I (mp 163–165°) was heated at 185°, acetic acid was lost and an entirely different but isomeric product, suspected to be an indeno derivative, was isolated as the perchlorate salt. The pyrolysis of I has been reinvestigated, and the results are reported in this communication.

As I melted, acetic acid was evolved rapidly. After 5 min, a mixture of IV (70% yield) and V (11%)[4] could be isolated (see Scheme I). After 25 min, V was the principal product (70%), and only a 10% yield of IV was obtained. Nmr, ultraviolet, and infrared spectra provided the principal evidence for the structures of IV, V, and Va; mass spectral data were complementary.

Thus, Va shows a single peak integrating for six protons at 1.3 ppm [$>C(CH_3)_2$] and unsplit indeno methylene absorption (two protons)[5] at 3.3 ppm. Olefinic proton absorption was absent. Perchlorate V in chloroform absorbed strongly (infrared) at 5.85 μ ($>C=N^+<$). This band was shifted to 6.3 μ (conjugated $>C=C<$) in Va.[6] The ultraviolet spectrum of Va (or V) in alcohol was characteristic of that of an indene,[7] while V in alcohol containing a trace of perchloric acid displayed only phenyl absorption. One molar equivalent of platinum-catalyzed hydrogen was absorbed rapidly by V to give VIII, whose benzylic methylene group (as the free base) is a multiplet centered at 3.5 ppm and whose *gem*-dimethyl signals are at 0.5 and 1.1 ppm. The marked diamagnetic shift for one of these methyls is attributable to "benzene ring-current" effects.[8] A Dreiding model of the base VIII indicates that one of the C-methyls is in a position favorable for this. Treatment of the methiodide corresponding to VIII with hot aqueous alkali gave the 3-substituted indene (IX), presumably *via* IXa.[9] The *gem*-dimethyls of IX are (as in Va) equivalent as shown by a single peak at 1.4 ppm (six protons). The six N-methyl protons are at 2.2 ppm. The doublet (J = 1.9 cps) at 3.3 ppm (two protons) is due to the indeno methylene group, and the triplet (J = 1.9 cps) at 6.2 ppm integrates for a single (olefinic) proton.

Regarding the constitution of IV, the corresponding base showed one olefinic proton as a multiplet centered at 5.4 ppm, an N-methyl at 2.5 ppm, an unsplit C-methyl at 1.54 ppm, and a three-proton doublet at 1.62 and 1.58 ppm (J = 2.0 cps) indicative of the 4-methyl split by the olefinic hydrogen. Compound IV absorbed 1 molar equiv of platinum-catalyzed hydrogen very slowly to give the oily perchlorate of VI. The base VI, purified *via* its picrate, showed a doublet (J = 3.6 cps) at 0.8 ppm (4-methyl) and a singlet at 1.25 ppm (4a-methyl). Other features of its nmr spectrum were consistent with the structure VI. Likewise, the nmr signals (see Experimental Section) and ultraviolet maxima of the Hofmann degradation product of the methiodide of VI were consistent with structure VII.

Additional confirmation of the structures of IV and Va is seen in their mass spectra. Both isomers exhibit intense parent peaks at m/e 213. In the case of Va, the base peak is at P − 15, as expected for structure Va since two methyl groups are attached to the same carbon atom (4), which is also allylic. In addition, the nitrogen atom facilitates methyl loss. In IV, on the other hand, the latter cleavage is not available although the methyl group on C-4a is both benzylic and allylic. Thus, the P − 15 peak is less than 10% as intense as in the former case.



Va

Dehydration of II with thionyl chloride at 5–25° produced a 40% yield of the 9-methylene compound (III)[2] along with three other products as reported for similar

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

[3] E. L. May, H. Kugita, and J. H. Ager, *ibid.*, **26**, 1621 (1961).

[4] A gradual increase of V and corresponding decrease of IV was observed in probes taken at 5-min intervals. These were analyzed in a Warner-Chilcott 1600 Series gas chromatograph (6-ft coiled glass column, 5% S.E. 30 on Chromosorb G, column temperature 170°) after treatment with NH_4OH, shaking the bases into ether, and injecting in acetone solution.

[5] H. Dressler and R. J. Kurland, *ibid.*, **29**, 175 (1964).

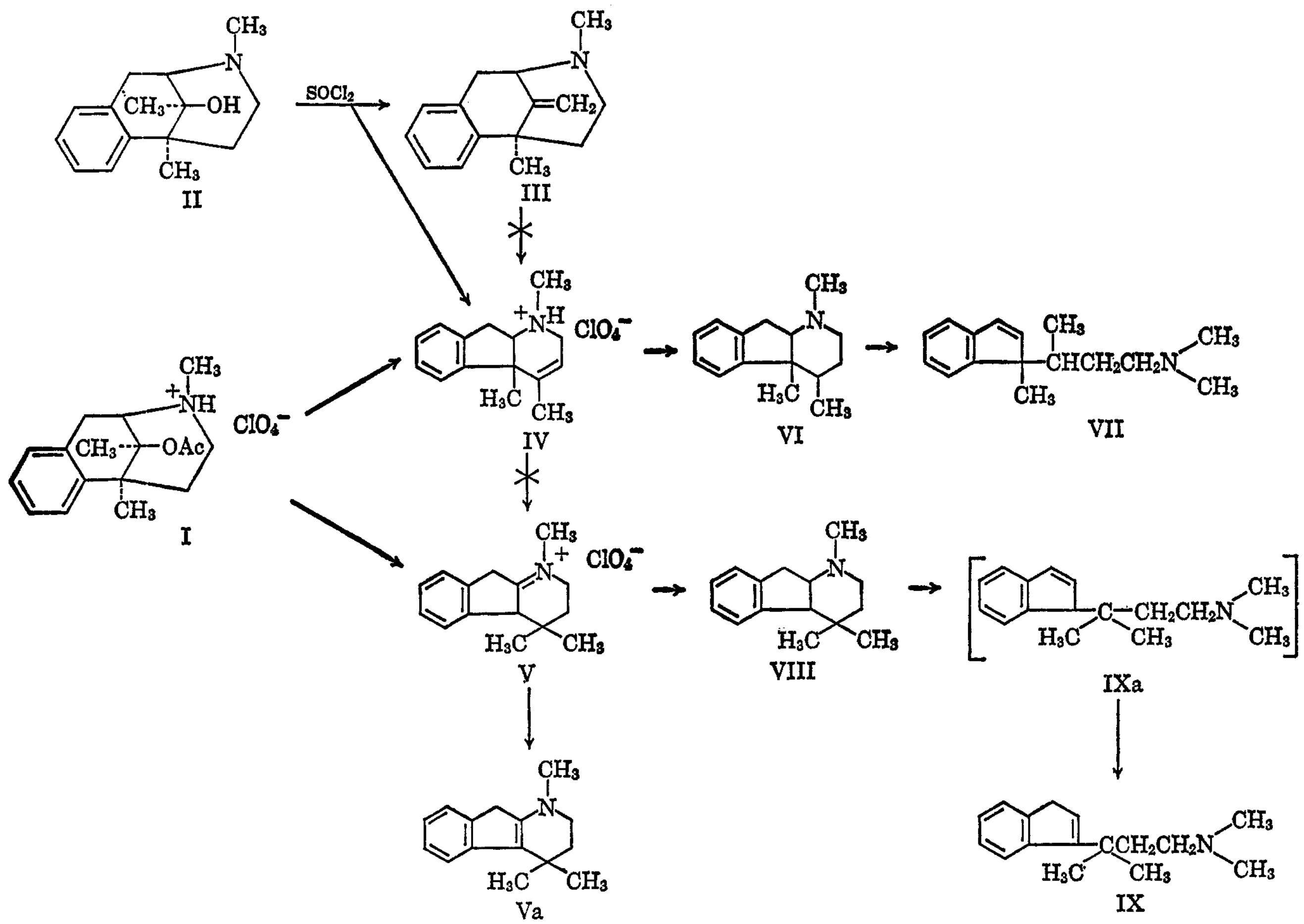
[6] See N. J. Leonard and F. P. Hauck, *J. Am. Chem. Soc.*, **79**, 5279 (1957), for a leading reference regarding this shift.

[7] T. L. Yarboro, C. Karr, and P. A. Estep, *J. Chem. Eng. Data*, **6**, 421 (1961).

[8] J. A. Pople, *J. Chem. Phys.*, **24**, 1111 (1956); C. E. Johnson, Jr., and F. A. Bovey, *ibid.*, **29**, 1012 (1958); S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).

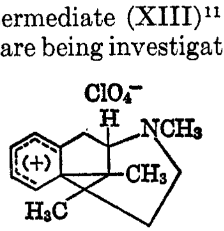
[9] Structure IXa which would result from loss of a proton at position 9 (probably the most acidic of the hydrogens in VIII available for β elimination) would be expected to undergo rearrangement to IX; see A. M. Weidler, B. Mathiasson, and G. Bergson, *Arkiv Kemi*, **21**, 187 (1963).

SCHEME I



series.[10] The perchlorate of one of these products (4% yield) proved to be IV; no Va could be detected.

When the perchlorate of III was heated at 184° it exploded and no products could be detected by thin layer or gas chromatography. Furthermore, under various conditions which simulated the pyrolysis experiments of I, compound IV could not be converted to V but underwent gradual destruction despite the observed change in ratio of IV to V with pyrolysis time.[4] The question of mechanism and the possibility of a phenonium ion intermediate (XIII)[11] in the formation of IV and V from I are being investigated.[12]



XIII

Experimental Section[13]

Pyrolysis of α-9-Acetoxy-2,5,9-trimethyl-6,7-benzomorphan Perchlorate. A. 1,2,4a,9a-Tetrahydro-1,4,4a-trimethyl-9H-indeno[2,1-*b*]pyridine Perchlorate (IV).—Compound I (0.5 g) was heated at 184° (aniline vapor bath) for 5 min (rapid evolution of acetic acid). Treatment of the resultant oil with methanol at −10°, warming to room temperature, and seeding gave 0.33 g (70%) of IV, mp 165–170°. Repeated recrystallization from ethanol-ethyl acetate (Norit A) gave prisms, mp 192–193°, retention time of the base[4] *ca.* 5 min.

Anal. Calcd for $C_{15}H_{20}ClNO_4$: C, 57.4; H, 6.4; N, 4.5. Found: C, 57.6; H, 6.3; N, 4.4.

B. 2,3,4,4a-Tetrahydro-1,4,4-trimethyl-9H-indeno[2,1-*b*]-pyridine Perchlorate (V).—The filtrate from the 0.33 g of V, on evaporation to dryness *in vacuo*, yielded an oil which crystallized from acetone. Repeated recrystallization from ethanol gave 0.05 g (10%) of V: mp 190–191; $\lambda_{max}^{CHCl_3}$ 5.85 μ ($>C{=}\overset{+}{N}<$); λ_{max}^{EtOH} 232, 305 mμ (ε 4000, 6000). When a trace of perchloric acid was added to the alcoholic solution of the perchlorate (to prevent dissociation), only phenyl absorption was observed in the ultraviolet.

Anal. Calcd for $C_{15}H_{20}ClNO_4$: C, 57.4; H, 6.4; N, 4.5. Found: C, 57.4; H, 6.5; N, 4.3.

The **base Va** was prepared by trituration of 0.4 g of V in 25 ml of 12% NH_4OH and quickly extracting with four 10-ml portions of ether. The dried extracts were evaporated to dryness *in vacuo* to give an oil which rapidly crystallized to a waxy solid (0.27 g), mp 66–68°, giving light gray needles from petroleum ether (bp 30–60°), mp 68–70°, which rapidly deteriorate even at −10°: retention time[4] 8 min; λ_{max}^{EtOH} 233, 305 mμ (ε 8784, 9310); $\lambda_{max}^{CHCl_3}$ 6.3 μ.

Anal. Calcd for $C_{15}H_{19}N$: C, 84.5; H, 9.0; N, 6.6. Found: C, 84.3; H, 9.2; N, 6.3.

When 0.5 g of I was heated at 184° for 25 min, the yield of V, isolated from methanol at −10°, was 70% and of IV, purified as the base on a Woelm aluminum oxide neutral grade I column

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[10] S. Saito and E. L. May, *J. Org. Chem.*, **27**, 1087 (1962); C. Chignell and E. L. May, *J. Med. Chem.*, **8**, 385 (1965); C. Chignell, J. H. Ager, and E. L. May, *ibid.*, p. 235; H. Kugita and M. Takeda, *Chem. Pharm. Bull.* (Tokyo), **12**, 1163 (1964).

[11] See L. Eberson and S. Winstein, *J. Am. Chem. Soc.*, **87**, 3506 (1965), and D. J. Cram, *ibid.*, **86**, 3767 (1964), as leading references.

[12] Infrared (in chloroform) and nmr (in deuteriochloroform) spectroscopic examination of the cooled melt (pale yellow glass), after the almost instantaneous expulsion of acetic acid, indicated only a mixture of IV and V. The SO_2–SbF_5–SO_3H solvent system of Olah and Pittman [*ibid.*, **87**, 309 (1965)] has not been used as yet.

[13] Melting points (capillary) are corrected. Microanalyses are by the Analytical Services Section of these institutes. Nmr spectra were determined in $CDCl_3$ with tetramethylsilane as internal reference (Varian A-60 Model). Accurate mass measurements were made relative to perfluorokerosene internal standard where C = 12.000.

(developing solvent benzene, elution solvent chloroform), was 11%.[4]

1,2,3,4,4a,9a-Hexahydro-1,4,4-trimethyl-9H-indeno[2,1-*b*]-pyridine Perchlorate (VIII).—Methanol (40 ml), 0.5 g of V, and 12.5 mg of platinum oxide absorbed 1 molar equiv of hydrogen in 15 min. The resultant VIII (0.5 g) melted at 59–64° to a glass which charred above 145°; needles from methanol.

Anal. Calcd for $C_{15}H_{22}ClNO_4$: C, 57.1; H, 7.0. Found: C, 57.1; H, 6.9.

The **methiodide**, prepared from an ethereal solution of the base (retention time 5 min),[4] crystallized from acetone–ethyl acetate as pale yellow prisms, mp 252–253°.

Anal. Calcd for $C_{16}H_{24}IN$: C, 53.8; H, 6.8. Found: C, 53.7; H, 7.0.

3-(1,1-Dimethyl-3-dimethylaminopropyl)indene (IX).—The above methiodide (0.2 g), 0.2 g of KOH, and 3 ml of water were refluxed for 4 hr. The resultant IX was isolated from ether and distilled at 100–110° (0.1 mm), giving 72 mg (57%) of IX: λ_{max}^{EtOH} 224, 246, 249, 263, 280, 290 mμ (ε 7872, 8409, 8766, 5093, 822).

Anal. Calcd for $C_{16}H_{23}N$: C, 83.8; H, 10.1. Found: C, 83.5; H, 10.3.

1,2,3,4,4a,9a-Hexahydro-1,4,4a-trimethyl-9H-indeno[2,1-*b*]-pyridine (VI) Methiodide.—Methanol (80 ml), 0.6 g of IV perchlorate, and 15 mg of platinum oxide absorbed 1 molar equiv of hydrogen during 48 hr to yield VI as its oily perchlorate. This was converted (*via* the base) in ethanol to the VI picrate (0.8 g, 94%), which recrystallized from acetone as yellow prisms, mp 234–235° dec. The methiodide of VI was prepared in ether solution from the base (which had been purified through the picrate). It crystallized from methanol as short needles, mp 282–284° dec.

Anal. Calcd for $C_{16}H_{24}IN$: C, 53.8; H, 6.8. Found: C, 53.5; H, 6.8.

1-(3-Dimethylamino-1-methylpropyl)-1-methylindene (VII).—To a suspension of 0.15 g of the methiodide corresponding to VI in 5 ml of water was added 0.1 *M* thallous hydroxide until precipitation ceased. The suspension was digested under reflux for 20 min and filtered. The filtrate was evaporated to dryness *in vacuo*. Distillation of the residue at 100° (0.2 mm) gave 66 mg (70%) of VII: λ_{max}^{EtOH} 259, 283, 294 mμ (ε 7084, 894, 371); δ = 1.0, 0.87 (*J* = 7 cps, equivalent to three protons), 1.23, 1.18 (*J* = 1.5 cps, also equivalent to three protons), and 2.1 ppm equivalent to six protons [$-N(CH_3)_2$].

The **hydrochloride** was prepared in ethereal solution, giving colorless needles from ethanol, mp 161–162°.

Anal. Calcd for $C_{16}H_{24}ClN$: C, 72.3; H, 9.1. Found: C, 72.35; H, 9.1.

Dehydration of II.—Thionyl chloride (25 ml) and 0.5 ml of pyridine were mixed and added cautiously with stirring to 2.6 g of II cooled to 0°. Reaction was vigorously exothermic. The solution was kept at 40° for 2 hr, concentrated to one-half volume *in vacuo*, poured onto 200 g of ice, and made basic with concentrated NH_4OH. The mixture was extracted with four 50-ml portions of ether. Evaporation of the dried ether extracts left an amber oil which could be resolved into two major and two minor fractions by vpc and tlc. Evaporative distillation of this oil at 140–160° (0.1 mm) gave 2.1 g of colorless distillate consisting of five products. It was acidified with ethereal HCl to give an oily hydrochloride of III[2] which crystallized from ethanol–ether in a yield of 0.8 g of needles, mp 254–255°.

Anal. Calcd for $C_{15}H_{20}ClN$: C, 72.1; H, 8.1. Found: C, 72.4; H, 7.8.

The mother liquors from the hydrochloride of III were basified with 12% NH_4OH and extracted four times with ether. The residue from the dried, evaporated extracts were dissolved in 5 ml of petroleum ether (bp 60–75°) and put onto a column containing 25 g of Woelm grade III alumina. Elution with 200 ml of petroleum ether gave an oil which yielded an unidentified perchlorate (48 mg), mp 184–195°; benzene (5%) in petroleum ether (100 ml) gave an oil whose perchlorate (0.15 g), mp 192–193° after recrystallization from methanol–ethyl acetate, was identical in all respects with the IV obtained from I. Further elution with 250 ml of 30:55 benzene–petroleum ether gave additional III isolated as the perchlorate[2] (0.43 g); the total yield of III perchlorate was 41%, mp 218–220° alone or in mixture with authentic material.

Acknowledgment.—We are indebted to Dr. H. M. Fales for determination and interpretation of the mass spectra and to Dr. Arthur Jacobson for valuable discussions.

The Wohl Reaction Applied to Some Benzoylated Aldononitriles

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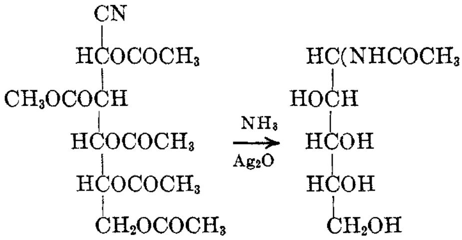
Received July 28, 1965

Hexa-*O*-benozyl-D-*glycero*-D-*gulo*-heptononitrile (III), hexa-*O*-benzoyl-D-*glycero*-L-*manno*-heptononitrile (IV), D-*glycero*-D-*galacto*-heptose oxime (V), and, from this last compound, hexa-*O*-benzoyl-D-*glycero*-D-*galacto*-heptononitrile (VI) were prepared; these nitriles were treated with methanolic ammonia. From III, 1,1-bis(benzamido)-1-deoxy-D-glucitol, *N*-benzoyl-β-D-glucopyranosylamine, and D-glucose were obtained. From IV, 1,1-bis(benzamido)-1-deoxy-D-galactitol, *N*-benzoyl-β-D-galactopyranosylamine, and D-galactose were obtained. From VI, 1,1-bis(benzamido)-1-deoxy-D-mannitol, *N*-benzoyl-β-D-mannopyranosylamine, and D-mannose were obtained.

The aldose degradation reaction *via* acylated aldononitriles was discovered by Wohl[1] in 1893. With the purpose of obtaining an aldose having one carbon atom less than the original one, Wohl prepared the oxime and, by acetylation and dehydration, obtained the acetylated aldononitrile. By eliminating the acetyl and cyano groups with aqueous ammonia and a trace of silver oxide, he expected to isolate the lower aldose.

He treated penta-*O*-acetyl-D-glucon准nitrile (I) in this way, but, instead of the D-arabinose expected, he obtained a nitrogen-containing substance which he called "arabinose diacetamide," now known as 1,1-bis(acetamido)-1-deoxy-D-arabinitol (II). The structure of this compound may be considered as deriving formally from the condensation of the free aldehyde group of a molecule of the D-arabinose originated in the reaction with two molecules of acetamide arising from



I II

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[1] A. Wohl, *Ber.*, **26**, 730 (1893).