[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

# Heterocyclic Compounds. VII. 5,5-Dimethyl-4-phenyl-2-(3-pyridyl)-pyrroline[1]

BY MILTON C. KLOETZEL, FRANCIS L. CHUBB AND JACK L. PINKUS

RECEIVED MAY 22, 1958

High pressure catalytic hydrogenation of 4-methyl-4-nitro-3-phenyl-1-(3-pyridyl)-1-pentanone (I) yields primarily 5,5-dimethyl-4-phenyl-2-(3-pyridyl)-$\Delta^1$-pyrroline (II), together with a small quantity of a more highly hydrogenated secondary amine (III or IV). The structures ascribed to these hydrogenation products are supported by chemical and spectral evidence.

In continuing our study of the synthetic utility of nitro ketone reductions[2,3] we have turned our attention to 4-methyl-4-nitro-3-phenyl-1-(3-pyridyl)-1-pentanone (I),[4] reduction of which might be expected to afford products containing the pyridylpyrrole nucleus characteristic of the nicotine series of alkaloids.

The major product (54–61% yield) from high pressure hydrogenation of I in methanol at 100° over Raney nickel appears to be the myosmine derivative II. The chemical and physical properties of II are generally those characteristic of a $\Delta^1$-pyrroline as would be expected, on the basis of recent studies,[3,5-8] for a pyrroline resulting from reductive cyclization of a $\gamma$-nitro ketone.

The infrared absorption spectrum of the free base II shows a strong band at 6.21 $\mu$ which probably is associated with the imino group conjugated with the aromatic pyridine nucleus (compare for example the spectra of 2-(3-pyridyl)-$\Delta^2$-thiazoline[9] and myosmine,[6,7] which have this structural feature, with the spectra[7] of metanicotine and nicotyrine which have a carbon–carbon unsaturation conjugated with the pyridine ring). In other respects also, the spectra of II and myosmine are strikingly similar. Thus the bands at 3.32, 6.21, 6.31, 6.39, 7.09 and 7.48 $\mu$ in the spectrum of II appear to be equivalent in relative position and intensity to those at 3.37, 6.15–6.17, 6.26–6.28, 6.36–6.38, 7.07 and 7.45 $\mu$, respectively, in the spectrum of myosmine.

Moreover, the changes in the spectrum of II effected by protonation of both basic nitrogen atoms are comparable to those described by Witkop[6] for myosmine. The dihydrochloride of II shows broad ammonium absorption at 3.75–4.31 $\mu$; immonium bands at 5.27 $\mu$ (pyrroline) and 4.77 and 5.05 $\mu$ (pyridine); and the hypsochromic shift of the conjugated C=N band of pyrroline to 6.03 $\mu$.[10]

The absence of a reactive secondary amino group in II was confirmed when Zerewitinoff determinations[5] at 25° in anisole and in *n*-butyl ether failed to detect significant active hydrogen.[11] However, in contrast to the behavior of both 2-phenyl-$\Delta^1$-pyrroline and 2,4-diphenyl-$\Delta^1$-pyrroline,[3] pyrroline II added one mole of methylmagnesium iodide readily at 25°. Evidently the imino group is activated by conjugation with the pyridine nucleus.

The absence of a reactive secondary amino group in II was further substantiated by the failure of this pyrroline to react with phenyl isothiocyanate or with acylating agents (acetic and phthalic anhydrides) under anhydrous conditions. Even myosmine has been reported[12] to undergo N-benzoylation under anhydrous conditions, a reaction which must involve tautomerization of the base. Nor could pyrroline II be benzoylated in the presence of aqueous base. Since 2-phenyl-$\Delta^1$-pyrroline, 2,4-diphenyl-$\Delta^1$-pyrroline[3] and myosmine[12,13] all undergo benzoylation with concomitant hydrolytic cleavage of the pyrroline ring, the unusual stability of that ring in 5,5-dimethyl-4-phenyl-2-(3-pyridyl)-$\Delta^1$-pyrroline (II) is attributed tentatively to the presence of a unique structural feature: namely, the geminal methyl groups on the 5-carbon atom. The association of geminal substitution with extraordinary ring stability or facile ring formation has been noted frequently.[14]

High pressure hydrogenation of I gave, in addition to II, small quantities (6–11%) of a second base which liberated one equivalent of methane upon treatment with methylmagnesium iodide at 25° but added no Grignard reagent even at 100°. The base gave a dipicrate and also reacted readily with phenyl isothiocyanate to produce a phenylthiourea. Analytical data for these two crystalline derivatives indicate that this second base contains 6 more atoms of hydrogen per molecule than does pyrroline II.

The presence of a strong band at 6.12 $\mu$ in the infrared absorption spectrum of this base suggests that it too is a pyrroline, conceivably of structure

(1) Abstracted from portions of the Ph.D. dissertations of Francis L. Chubb and Jack L. Pinkus.

(2) M. C. Kloetzel, THIS JOURNAL, **69**, 2271 (1947).

(3) M. C. Kloetzel, J. L. Pinkus and R. M. Washburn, *ibid.*, **79**, 4222 (1957).

(4) M. C. Kloetzel and F. L. Chubb, *ibid.*, **79**, 4226 (1957).

(5) P. M. Maginnity and J. B. Cloke, *ibid.*, **73**, 49 (1951).

(6) B. Witkop, *ibid.*, **76**, 5597 (1954).

(7) C. R. Eddy and A. Eisner, *Anal. Chem.*, **26**, 1428 (1954).

(8) M. L. Stein and A. Burger, THIS JOURNAL, **79**, 154 (1957).

(9) W. Otting and F. Drawert, *Ber.*, **88**, 1469 (1955).

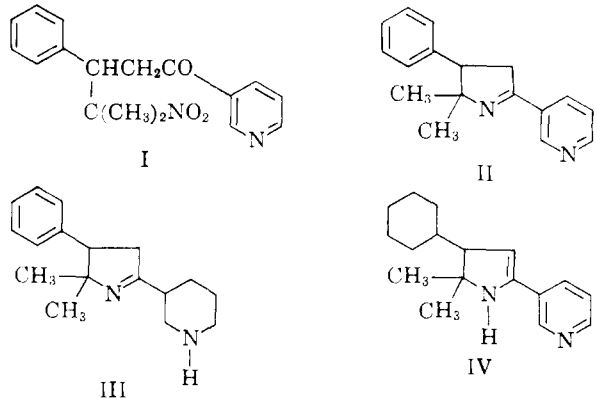
(10) The 6.03 $\mu$ band showed a shoulder on the longer wave length side which may be attributable to the hypsochromic shift of protonated pyridine.[8]

(11) A Zerewitinoff determination at 100° in *n*-butyl ether indicated the presence of 0.26 mole of active hydrogen. One interpretation of this observation suggests that II is capable of tautomerization to a $\Delta^2$- or $\Delta^3$-pyrroline. In this connection it is of interest that the infrared spectrum of II shows a very weak band at 2.91 $\mu$, in the region of N–H absorption. Myosmine likewise shows trace absorption at 2.92 $\mu$.[7]

(12) P. G. Haines, A. Eisner and C. F. Woodward, THIS JOURNAL, **67**, 1258 (1945).

(13) E. Späth, A. Wenusch and E. Zajic, *Ber.*, **69**, 393 (1936).

(14) W. H. Perkin and J. F. Thorpe, *J. Chem. Soc.*, **75**, 61 (1899); R. M. Beesley, C. K. Ingold and S. F. Thorpe, *ibid.*, **107**, 1080 (1915); C. K. Ingold, *ibid.*, **119**, 305 (1921); E. H. Farmer and J. Kracovski, *ibid.*, **131**, 680 (1927); M. T. Bogert and D. Davidson, THIS JOURNAL, **56**, 185 (1934); R. A. Barnes and B. D. Beitchman, *ibid.*, **76**, 5430 (1954); R. F. Brown and N. M. van Gulick, *J. Org. Chem.*, **21**, 1046 (1956); W. Kloetzer, H. Bretschneider, H. Deutscher, W. Sachsenmaier and M. Sander, XVIth International Congress of Pure and Applied Chemistry, Paris, July, 1957, Summary of Papers, Vol. 2, Division of Organic Chemistry, p. 312.



III or IV. Although this band falls within the range of absorption attributable to C=C and C=N stretching vibrations of the pyridine ring,[15] such absorption generally occurs at somewhat lower frequencies; moreover, it is unlikely that a band of such intensity at 6.12 $\mu$ results solely from the aromatic nucleus (compare, for example, the spectra nicotine,[6,7] nornicotine[7] and dihydrometanicotine[7]). Clearly this band cannot be attributed to the C=N linkage of a conjugated $\Delta^1$-pyrroline,[16] since the aforementioned chemical behavior of this base demonstrates the presence of a *sec*-amino group in either the 6-membered ring (III) or the 5-numbered ring (IV).[17]

Eddy and Eisner[7] have observed absorption at 6.05–6.09 $\mu$ for certain nicotine derivatives containing a C=C linkage conjugated with a pyridine ring and absorption due to C=C stretching vibrations in phenyl-conjugated alkenes generally is near 6.15 $\mu$.[18] On the other hand, the C=N linkage in non-conjugated ring systems absorbs in the range of 5.91–6.10 $\mu$.[19,20] Thus available evidence does not permit an unequivocal choice between structures III and IV for our *sec*-amine. However, no instance of an authenticated secondary $\Delta^2$-pyrroline has yet been reported.[3,6] Moreover, the pyridine ring usually is reduced more readily than the benzene ring in compounds where both occur.[21,22] These observations lend a certain attractiveness to the view that our *sec*-amine is a hexahydro derivative of II and is best represented by structure III. Due to unavoidable interruption of this study, further investigation of this compound is not now contemplated.

**Acknowledgment.**—The authors are indebted to Parke, Davis and Co., Detroit, Mich., for generous financial aid which made part of this study possible, and to R. Bruce Scott, Research Department, Parke, Davis and Co., for his help in determining and interpreting infrared spectra during the initial stages of this investigation.

(15) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1954, p. 232.

(16) Witkop[6] observed a strong band at 6.15 $\mu$ in the spectrum of myosmine, which he attributed to this structural feature.

(17) J. W. Cornforth and A. J. Henry, *J. Chem. Soc.*, 597 (1952), have reported the catalytic isomerization of a conjugated pyrroline to an unconjugated $\Delta^2$-pyrroline. This observation suggests that a structure isomeric with IV but containing a $\Delta^3$-pyrroline ring also be considered for our *sec*-amine. This structure is considered unlikely, however, for any absorption at 6.12 $\mu$ attributable to the isolated alkene linkage would be expected to be weak (see ref. 15, p. 32).

(18) Reference 15, p. 31.

(19) Reference 15, p, 226.

(20) G. G. Evans, THIS JOURNAL, **73**, 5230 (1951).

(21) J. Overhoff and J. P. Wibaut, *Rec. trav. chim.*, **50**, 957 (1931).

(22) H. S. Mosher, "Heterocyclic Compounds," ed. by R. C. Elderfield, Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 407.

## Experimental[23]

**Hydrogenation of 4-Methyl-4-nitro-3-phenyl-1-(3-pyridyl)-1-pentanone (I).**—A rocking bomb was charged with 30 g. of nitro ketone I, 90 ml. of methanol and 4 g. of Raney nickel[24] and hydrogenation was continued for 0.5–2 hr. at 100° under a pressure of 1000 p.s.i. After filtration of catalyst and removal of solvent under reduced pressure, distillation of the residue yielded 20–21.5 g. of a yellow oil, b.p. 160–175° at 1 mm.

Treatment of this oil with 20 g. of picric acid in ethanol yielded 4.3–8 g. (6–11%) of the **dipicrate of III or IV**, which formed yellow plates, m.p. 213–214°.

*Anal.* Calcd. for $C_{29}H_{30}N_8O_{14}$: C, 48.74; H, 4.23; N, 15.68. Found: C, 48.68; H, 4.38; N, 15.89.

When an additional 20-g. portion of picric acid was added to the solution from which the aforementioned picrate was filtered, 38–43 g. (54–61%) of the **dipicrate of 5,5-dimethyl-4-phenyl-2-(3-pyridyl)-$\Delta^1$-pyrroline (II)** crystallized, m.p. 148–150°. Recrystallization from 95% ethanol yielded yellow needles, m.p. 149–150°.

*Anal.* Calcd. for $C_{29}H_{24}N_8O_{14}$: C, 49.16; H, 3.41; N, 15.82. Found: C, 49.04; H, 3.68; N, 15.38.

After standing for several months the picrate spontaneously changed to a more stable form, m.p. 178–180°, which also separated from 95% ethanol in yellow needles. Thereafter, the lower-melting form was never again obtained in this Laboratory.

*Anal.* Calcd. for $C_{29}H_{24}N_8O_{14}$: C, 49.16; H, 3.41. Found: C, 49.46; H, 3.58.

**5,5-Dimethyl-4-phenyl-2-(3-pyridyl)-$^1\Delta$-pyrroline (II).**—This pyrroline, liberated from its dipicrate through the use of lithium hydroxide solution, was obtained as a colorless liquid, b.p. 178° at 2 mm. The infrared absorption spectrum[25] of this compound showed maxima at 2.91(w), 3.22(m), 3.32(s), 6.21(s), 6.31(m), 6.39(m), 6.70(m), 6.87(m), 7.09(s), 7.26(m), 7.35(m) and 7.48(s)$\mu$.

*Anal.* Calcd. for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19; mol. wt., 250. Found: C, 81.70; H, 7.24; N, 11.34; mol. wt., 254, 256.[26]

Zerewitinoff determinations[5] in *n*-butyl ether showed addition of 1.04 moles of methylmagnesium iodide and evolution of 0.03 mole of methane at 25°; addition of 0.76 mole of Grignard reagent and evolution of 0.26 mole of methane at 100°. A similar determination in anisole showed no methane evolution at 25°.

**The dihydrochloride of II** separated as a solid when a solution of hydrogen chloride in anhydrous ether was added dropwise to a solution of the pyrroline in ether; colorless needles, m.p. 217–222° dec., after recrystallization from a mixture of isopropyl alcohol and ethyl acetate. The infrared spectrum[27] showed strong broad absorption at 3.75–4.31 $\mu$ and maxima at 2.87(m), 4.77(s), 5.05(m), 5.27(m), 6.03(s) and 6.22(s) $\mu$.

*Anal.* Calcd. for $C_{17}H_{20}Cl_2N_2$: C, 63.16; H, 6.24; N, 8.67. Found: C, 63.00; H, 6.30; N, 8.80.

**The methiodide of II** precipitated after the pyrroline was dissolved in excess methyl iodide. Recrystallization from absolute ethanol yielded yellow needles, m.p. 202–203°.

(23) Microanalyses are by William Schenck and Joseph Piric, both formerly of the University of Southern California, and by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles. Melting points are uncorrected.

(24) R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).

(25) Determined for a liquid film, employing a Perkin–Elmer model 13 double beam spectrophotometer with sodium chloride prism and silver chloride plates supporting the film.

(26) Kindly determined by W. M. Hazenberg, Laboratory for Organic Chemistry, The University, Groningen, The Netherlands, employing the Rast method in tetramethyl orthothiocarbonate.

(27) Kindly determined by Dr. M. Geller, Hughes Aircraft Co., Los Angeles, employing a Perkin–Elmer model 112U spectrophotometer with sodium chloride prism and silver chloride plates for supporting the Nujol mull.

*Anal.* Calcd. for $C_{18}H_{21}IN_2$: C, 55.11; H, 5.39. Found: C, 54.87; H, 5.60.

5,5-Dimethyl-4-phenyl-2-(3-pyridyl)-$\Delta^1$-pyrroline (II) did not react with phenyl isothiocyanate.

When II was heated with phthalic anhydride at 210° for 15 min., 91% of unchanged pyrroline was recovered as the dipicrate.

A mixture of 1 g. of II, 1 g. of benzoyl chloride and 10 ml. of 10% aqueous sodium hydroxide was shaken until all benzoyl chloride was decomposed. An ether extract of the reaction mixture yielded 88% of unchanged pyrroline as the dipicrate.

A solution of 856 mg. of pyrroline II in 1 ml. of acetic anhydride was heated to 100° under a nitrogen atmosphere for 7.5 hours. Water (5 ml.) was then added, heating was continued for 5 min. with vigorous stirring, and the reaction mixture was neutralized with 2.8 g. of potassium carbonate. An ether extract of this mixture yielded 70% of unchanged pyrroline in the form of its dipicrate.

**The Secondary Amine (III or IV).**—Decomposition of the dipicrate of III or IV with 20% aqueous lithium hydroxide and subsequent distillation of the product under reduced pressure gave the pure amine as a colorless oil, b.p. 160° at 2 mm. An infrared absorption spectrum[28] of this substance showed maxima at 2.98(m), 3.38(s), 6.12(s), 6.25(m), 6.70(m), 6.89(s), 7.34(m), 7.60(m), 8.44(m), 11.62(m), 12.92(s) and 14.20(s) $\mu$.

A Zerewitinoff determination on this substance in *n*-butyl ether at 25° resulted in liberation of 0.99 mole of methane and decomposition of 0.04 mole of additional Grignard reagent. At 100° the quantity of methane liberated was 1.01 moles and no additional methylmagnesium iodide was consumed.

Heat was liberated when equimolecular quantities of this amine and phenyl isothiocyanate were mixed. Crystallization of the resulting phenylthiourea from ethanol afforded colorless needles, m.p. 185–186°.

*Anal.* Calcd. for $C_{24}H_{29}N_3S$: C, 73.61; H, 7.46. Found: C, 73.48; H, 7.52.

(28) Kindly determined by R. Bruce Scott, Parke, Davis and Co., Detroit, Mich., with a liquid film of the amine, employing a Beckman IR-2T spectrophotometer equipped with a sodium chloride prism.

LOS ANGELES, CALIF.

---

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

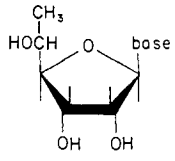
# Potential Anticancer Agents.[1] VIII. Synthesis of Nucleosides Derived from L-Talofuranose

BY ELMER J. REIST, LEON GOODMAN AND B. R. BAKER

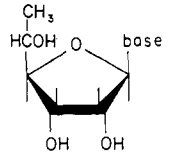
RECEIVED APRIL 24, 1958

The L-talose derivative methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-$\alpha$-L-talofuranoside (VI) has been synthesized by SN2 displacement of the tosylate III of methyl 6-deoxy-2,3-*O*-isopropylidene-$\beta$-D-allofuranoside, epimerization at $C_5$ having taken place. Further conversion to 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-6-deoxy-L-talofuranose (XI) followed by nucleoside formation gave 9-(6′-deoxy-$\alpha$-L-talofuranosyl)-adenine (XIII) and 2,6-diamino-9-(6′-deoxy-$\alpha$-L-talofuranosyl)-purine (XVI).

In a preceding paper[2] of this series, a biological rationale for the synthesis of 5′-C-methyl-D-ribonucleosides was discussed. There are two stereoisomeric 5′-C-methyl-D-ribonucleosides: namely, the 6′-deoxy-D-allofuranosides (I) and the 6′-deoxy-L-talofuranosides (II). The earlier paper[2]




I




II

described the synthesis of the allose nucleosides (I) and this paper describes the synthesis of 9-(6′-deoxy-$\alpha$-L-talofuranosyl)-adenine (XIII) and 2,6-diamino-9-(6′-deoxy-$\alpha$-L-talofuranosyl)-purine (XVI).

6-Deoxy-L-talose (epifucose) has been synthesized[3] by the epimerization of 6-deoxy-L-galactonolactone (fucose lactone) at $C_2$ in boiling pyridine followed by reduction with sodium amalgam. The epifucose was obtained as an oil and characterized by its phenylosazone and *p*-bromophenylosazone.

The availability of methyl 6-deoxy-2,3-*O*-isopropylidene-$\beta$-D-allofuranoside (IV) in three steps from L-rhammose[2,4] made this an attractive starting material for the synthesis of 6-deoxy-L-talose derivatives (such as VI) if the 5-*O*-tosylate III could be inverted in configuration by SN2 displacement. Secondly, the 6-deoxy-L-talose would thus be obtained in the furanose form necessary for conversion to the nuceosides; this is a distinct advantage over the method starting with the sequence L-fucose → 6-deoxy-L-talose[3] which, although requiring only three steps, would then require a number of steps to obtain the requisite furanose form by some, as yet, unknown and not easily predictable sequence.

Little work has been reported on the displacement of secondary tosylates of sugars beyond stating that they are more difficult to displace than primary tosylates.[5,6] In a simpler system, Phillips[7] reported that the tosylate of $\alpha$-methylphenethyl alcohol could be displaced by potassium acetate in alcohol to give the corresponding carbinyl acetate with Walden inversion. Since the 5-benzoate VI of methyl 2,3-*O*-isopropylidene-$\alpha$-L-talofuranoside would be more useful for further transformations to the blocked sugar XI suitable for nucleoside coupling, and since sugar benzoates frequently give higher yields in nucleoside coupling reactions than sugar acetates,[8,9] the direct displacement of the

(1) This program is under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan-Kettering Institute for Cancer Research. For the preceding paper in this series *cf.* C. D. Anderson, L. Goodman and B. R. Baker, THIS JOURNAL, **80**, 5247 (1958).

(2) E. J. Reist, L. Goodman, R. R. Spencer and B. R. Baker, *ibid.*, **80**, 3962 (1958).

(3) E. Votocek and J. Cervany, *Ber.*, **48**, 658 (1915).

(4) P. A. Levene and J. Compton, *J. Biol. Chem.*, **116**, 169 (1936).

(5) R. S. Tipson, *Adv. in Carbohydrate Chem.*, **8**, 167 (1953).

(6) J. M. Sugihara, *ibid.*, **8**, 26 (1953).

(7) H. Phillips, *J. Chem. Soc.*, **123**, 44 (1923).

(8) H. M. Kissman, C. Pidacks and B. R. Baker, THIS JOURNAL, **77**, 18 (1955).

(9) B. R. Baker, K. Hewson, H. J. Thomas and J. A. Johnson, Jr., *J. Org. Chem.*, **22**, 954 (1957).