Pyrrolidinediols. 1-Substituted 3-Hydroxymethyl-4-hydroxypyrrolidines and Derivatives[1]

ERNST JAEGER AND JOHN H. BIEL

Research Laboratories, Aldrich Chemical Company, Milwaukee, Wisconsin

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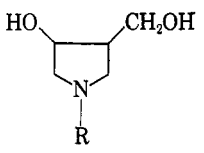
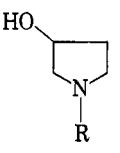
The preparation of a new type of pyrrolidinediol and derivatives by sodium borohydride reduction of 1-benzyl-3-carboethoxy-4-pyrrolidone and subsequent replacement reactions on the nitrogen and both alcoholic functions is described. An unusual reversal of a Dieckmann condensation was observed in the case of the pyrrolidine β-keto ester. The behavior of the corresponding piperidine compound is discussed.

The physiological activities of many derivatives of pyrrolidine alcohols have been reported in the literature.[2] Most of these were derived from monofunctional pyrrolidine alcohols and little work has been reported on the synthesis and use of dihydroxypyrrolidines.[3] The purpose of the present work was the preparation of the hitherto unknown amino alcohol I and its derivatives.



I



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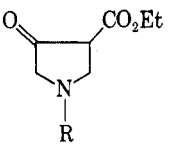
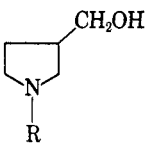


III



IV

The synthesis of 3-pyrrolidinols (II) by direct ring closure[4] or by decarboxylation of 1-substituted 3-carbethoxy-4-pyrrolidones (III)[5] is well known. 3-Hydroxymethylpyrrolidines (IV) were obtained by selective reduction of the keto function of III, subsequent dehydration, hydrogenation, and reduction of the ester.[6] By both routes, which use a cyclic β-keto ester III as starting material, one of the two original functional groups of the molecule is eliminated and a monohydroxy compound is obtained.

There is no report in the literature of an attempted one-step reduction of both the ester and the keto group of III with complex metal hydrides to obtain 1-substituted 3-hydroxymethyl-4-hydroxypyrrolidines (I), which would combine the primary and the secondary alcoholic functions of II and IV in one molecule.

Comparable examples for the reduction of cyclic β-keto esters with lithium aluminum hydride are reported in the alicyclic series.[7] Low yields of diols were obtained, together with large amounts of dehydration products. An attempted reduction of a heterocyclic β-keto ester system yielded no diol.[8]

The reduction of 1-acetyl-3-carbethoxy-4-pyrrolidone[9] with lithium aluminum hydride afforded low yields (6%) of 1-ethyl-3-hydroxymethyl-4-hydroxypyrrolidine.

Much better results were obtained by the lithium aluminum hydride reduction of V which was prepared according to the method of Plieninger.[10] Compound IX was obtained in 51% yield. To avoid dehydration, a two-step reaction was then investigated whereby V was first reduced by sodium borohydride to the hydroxy ester X, followed by lithium aluminum hydride reduction of X to IX.

Rather surprisingly, it was found that two steps were not necessary to obtain IX. A 5 molar excess of sodium borohydride was capable of reducing the β-keto ester V in methanol in one step to the diol IX in good yield (72%) without formation of low-boiling side products. The complete reduction of the β-keto ester with sodium borohydride was unexpected and is an example of an "abnormal" reduction in the pyrrolidine series.[11] (See Chart I.)

Sodium borohydride was originally considered incapable of reducing carboxylic esters. However, several cases have been reported in the literature of the reduction of esters with neighboring functional groups.[12] It was recently shown by Brown and Rapoport[13] that esters can generally be reduced by a large excess of sodium borohydride.

The selective reduction of V to obtain X could be achieved by using a 0.5 molar excess of sodium borohydride and working in a mixture of ethanol and ethyl acetate.

Several 1-substituted 3-hydroxymethyl-4-hydroxypyrrolidines were obtained from IX. Replacement of the N-benzyl group on the nitrogen by alkyl and aralkyl moieties could be effected by two different methods, as shown in Chart II. Method B was preferred, since it avoided the formation of quaternary ammonium salts which invariably occurs with the alkylation of secondary amines.

(1) Presented before the Division of Medicinal Chemistry, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964.

(2) (a) J. F. Cavalla, R. A. Selway, J. Wax, L. Scotti, and C. V. Winder, *J. Med. Pharm. Chem.*, **5**, 441 (1962); (b) R. E. Bowman, J. F. Cavalla, and J. Davoll, British Patent 821,436 (1962) [*Chem. Abstr.*, **56**, 2427 (1962)]; (c) C. W. Ryan and C. Ainsworth, *J. Org. Chem.*, **27**, 2901 (1962); (d) C. D. Lunsford, U. S. Patent 2,956,062 (1961) [*Chem. Abstr.*, **55**, 7434 (1961)]; (e) J. H. Biel, U. S. Patent 3,091,570.

(3) (a) A. J. Hill and M. G. McKeon, *J. Am. Chem. Soc.*, **78**, 3548 (1954); (b) German Patent 805,522 (1952) [*Chem. Abstr.*, **46**, 1049 (1952)].

(4) C. D. Lunsford, J. W. Ward, A. J. Pallotta, T. W. Tusing, E. K. Rose, and R. S. Murphey, *J. Med. Pharm. Chem.*, **1**, 73 (1959).

(5) (a) See ref. 2c; (b) R. Kuhn and G. Osswald, *Chem. Ber.*, **89**, 1423 (1956); (c) N. J. Leonard, F. E. Fischer, E. Barthel, Jr., J. Figueras, Jr., and W. C. Wildman, *J. Am. Chem. Soc.*, **73**, 2371 (1951); (d) E. A. Prill and S. M. McElvain, *ibid.*, **55**, 1233 (1933).

(6) Y.-H. Wu and R. F. Feldkamp, *J. Org. Chem.*, **26**, 1519 (1961).

(7) (a) E. Buchta and H. Bayer, *Ann. Chem.*, **573**, 227 (1951); (b) A. S. Dreiding and J. A. Hartman, *J. Am. Chem. Soc.*, **75**, 939 (1953).

(8) R. Adams, S. Miyano, and M. D. Nair, *ibid.*, **83**, 3323 (1961).

(9) Prepared as described by Y.-H. Wu, W. G. Lobeck, Jr., and R. F. Feldkamp, *J. Med. Pharm. Chem.*, **5**, 762 (1962).

(10) H. Plieninger and S. Leonhäuser, *Chem. Ber.*, **92**, 1579 (1959).

(11) Compare N. J. Leonard, K. Conrow, and R. W. Fulmer, *J. Org. Chem.*, **22**, 1445 (1957).

(12) For references see (a) E. Schenker, *Angew. Chem.*, **73**, 81 (1961); (b) J. E. G. Barnett and P. W. Kent, *J. Chem. Soc.*, 2743 (1963).

(13) M. S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963).

CHART I

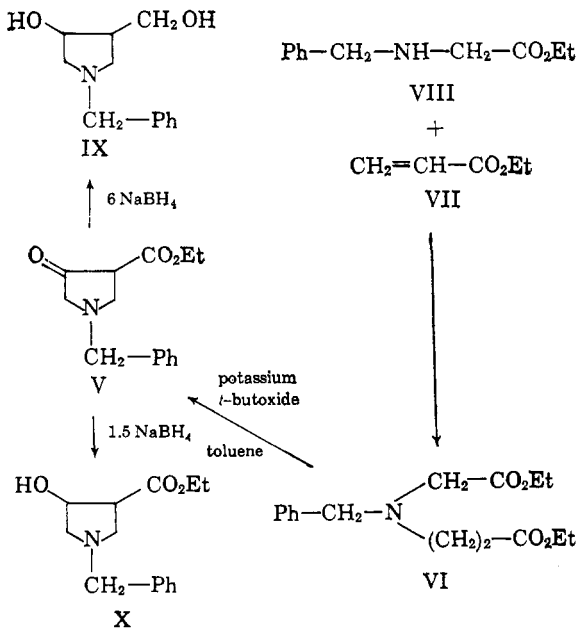
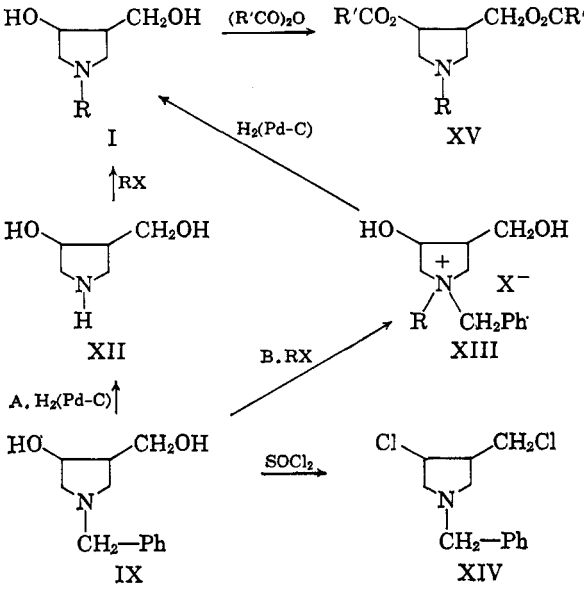


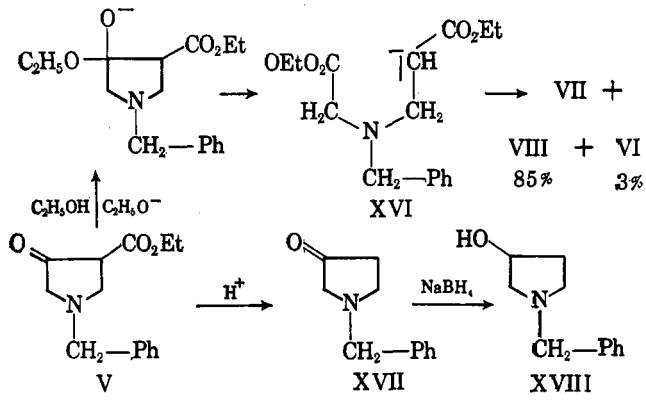
CHART II



Both alcoholic functions of the 1-substituted 3-hydroxymethyl-4-hydroxypyrrolidines undergo halogenation and esterification without appreciable dehydrohalogenation or dehydration, as is shown in several examples. Thus, 1-benzyl-3-chloromethyl-4-chloropyrrolidine (XIV) was obtained as a stable compound by treatment of IX with thionyl chloride. Esterification of I with acetic or propionic anhydride yielded diesters XV of the pyrrolidinediols.

An attempt to effect C-alkylation of V in the 3-position by the use of sodium ethoxide and alkyl halides in order to obtain 1-benzyl-3-alkyl-3-carbethoxy-4-pyrrolidones and the corresponding 3-substituted pyrrolidinediols was not successful. Rather unexpectedly, ethyl N-benzylglycinate (VIII) was isolated in 78% yield. An investigation of the properties of the five-membered β-keto ester V showed that prolonged heating with ethanol was capable of opening the pyrrolidine ring, giving VIII in 86% and VI in 3% yields, as well as partially polymerized ethyl acrylate,

CHART III

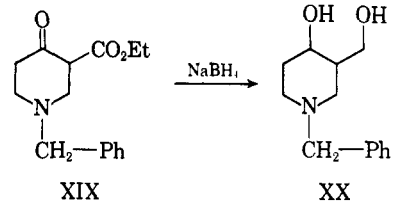


indicating that an unusual reversal of the Dieckmann condensation had occurred. The suggested mechanism is an autocatalyzed attack of an ethoxide anion on the keto form of V, followed by ring opening to the intermediate anion XVI, which cleaves to yield ethyl acrylate (VII) and ethyl N-benzylglycinate (VIII) (see Chart III). Anion XVI stabilizes only in very small amounts to form the diester VI, which is not the main intermediate in the reaction. This was shown by the fact that the diester VI did not cleave under comparable conditions to yield VII and VIII.

The structure of V was confirmed by decarboxylation to 1-benzyl-3-pyrrolidone (XVII) in 78% yield, which reduced with sodium borohydride to yield 1-benzyl-3-pyrrolidino (XVIII), which was identical with the compound obtained by the cyclization of 1,4-dibromo-2-butanol with benzylamine.[4] A comparison of n.m.r. values of the free base V and the protonated compound showed a downfield shift in the cation of 4- and not of 3-protons, which proved the Dieckmann condensation product to have structure V and not the structure of a 1-benzyl-2-carbethoxy-3-pyrrolidone.

The corresponding 6-membered β-keto ester 1-benzyl-3-carbethoxy-4-piperidone (XIX) did not undergo a similar reversal of the Dieckmann condensation. This compound was stable in boiling ethanol. The difference between V and XIX can be explained by the fact that, from the infrared spectra, V appears to be almost pure keto form, whereas XIX is enolized to a large extent. Compound XIX shows a pair of absorption bands at higher frequency (1730–1710 cm.$^{-1}$) associated with the keto tautomer and a strong pair of bands at lower frequency (1650–1610 cm.$^{-1}$) due to the chelated enol. Compound V, however, shows only two bands at higher frequency and almost no absorption at the lower frequency.[14]

The one-step conversion of a heterocyclic β-keto ester to the corresponding diol is independent of the



(14) Compare the results and discussions of S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkit, *Tetrahedron*, **19**, 1625 (1963); S. J. Rhoads and A. W. Decora, *ibid.*, **19**, 1645 (1963).

degree of enolization of the starting material. This was shown by the fact that the six-membered compound XIX could also be reduced under the same conditions as applied for the reduction of V, to yield 1-benzyl-3-hydroxymethyl-4-hydroxypiperidine (XX).

All reactions described were carried out with freshly prepared β-keto esters. Compound V, especially, undergoes rapid decomposition within a few days with the formation of acid- and base-insoluble materials, even if refrigerated.

Experimental[15]

Ethyl N-Benzyl-N-(β-carbethoxyethyl)glycinate (VI).—A mixture of 483 g. (2.5 moles) of ethyl N-benzylglycinate, 275 g. (2.75 moles) of ethyl acrylate, and 3 ml. of "Triton B" catalyst[16] was refluxed for 24 hr. Unchanged starting materials were removed by distillation through a 6-in. column. The residue was distilled without column at 150–160° (0.3 mm.) to provide 300 g. (40.8%) of product, which was purified by redistillation, b.p. 135° (0.04 mm.), $n^{25}D$ 1.4910.

Anal. Calcd. for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.78; O, 21.82. Found: C, 65.66; H, 7.97; N, 4.60; O, 21.99.

1-Benzyl-3-carboethoxy-4-pyrrolidone (V).—Potassium *t*-butoxide (112.1 g., 1.0 mole) was slurried in 1.5 l. of dry toluene. The mixture was cooled to 5° and 293 g. (1.0 mole) of ethyl N-benzyl-N-(β-carboethoxyethyl)glycinate was added slowly with stirring within 2 hr. The temperature was kept below 10°. Stirring was continued for 3 hr. The mixture was extracted with two 500-ml. portions of ice-cold water. The aqueous layer was extracted several times with ether, was made strongly acid with concentrated HCl, and was extracted again with ether to remove all side products. The aqueous acid solution was brought to pH 7.0 with potassium carbonate and the β-keto ester was extracted with ether until the last ether extract showed no $FeCl_3$ reaction. The ether solution was dried with anhydrous magnesium sulfate. After removal of ether, 142 g. (57.5%) of product remained as a slightly colored oil, $n^{25}D$ 1.5264. An infrared spectrum (film between NaCl plates) showed bands at 1759 (keto carbonyl) and 1720 $cm.^{-1}$ (ester carbonyl), but almost no absorption in the region of 1665–1600 $cm.^{-1}$.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66; O, 19.41. Found: C, 67.88; H, 6.94; N, 5.72; O, 19.54.

The hydrochloride was recrystallized from ethanol–ether; m.p. 127–129° dec.

Anal. Calcd. for $C_{14}H_{18}ClNO_3$: N, 4.93. Found: N, 4.77.

The n.m.r. spectrum of the free base showed a multiplet (area 5) with a center peak at τ 6.95 for the protons of the pyrrolidine ring. The n.m.r. spectrum of the hydrochloride showed a singlet at τ 6.52 and a multiplet (area 4) with a center peak at 5.78 for the same ring protons.

The phenylhydrazone was recrystallized from methanol; m.p. 104–105°.

Anal. Calcd. for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found: C, 71.20; H, 7.17; N, 12.45.

The semicarbazone was recrystallized from aqueous ethanol; m.p. 143–145°.

Anal. Calcd. for $C_{13}H_{14}N_4O_2$: C, 59.19; H, 6.62; N 18.41; O. 15.77. Found: C 59.16; H. 6.79; N, 18.33; O, 15.84.

1-Benzyl-3-hydroxymethyl-4-hydroxypyrrolidine (IX). A. By Lithium Aluminum Hydride Reduction of V.—To a well-stirred slurry of 38 g. (1.0 mole) of lithium aluminum hydride in 1.5 l. of dry tetrahydrofuran was added slowly a solution of 247.0 g. (1.0 mole) of 1-benzyl-3-carbethoxy-4-pyrrolidone (V) in 1 l. of dry tetrahydrofuran. The temperature of the reaction mixture was kept below 25° and stirring was continued overnight at room temperature. Saturated sodium sulfate solution (300 ml.) was added carefully. Dilution with tetrahydrofuran was necessary to keep the mixture stirrable. After filtration, the residue was extracted with 300 ml. of boiling tetrahydrofuran and filtered again. The combined filtrates were dried over anhydrous magnesium sulfate. After removal of the solvent a mixture of low-boiling reaction products was distilled through a 6-in. column at 120–160° (0.08 mm.). The residue was distilled without column to yield 106.5 g. (51.2%) of product, b.p. 160–170° (0.08 mm.). Redistillation of a portion of this material gave an analytical sample, b.p. 145–147° (0.01 mm.), $n^{25}D$ 1.5585.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76; O, 15.44. Found: C, 69.68; H, 8.37; N, 6.92; O, 15.54.

B. By Sodium Borohydride Reduction of V.—To a well-stirred solution of 123.5 g. (0.5 mole) of keto ester V in 1.0 l. of methanol was added 114 g. (3.0 moles) of sodium borohydride in portions within 0.5 hr. The temperature of the reaction mixture was kept below 25° and stirring was continued overnight. After removal of methanol *in vacuo*, the residue was dissolved in 500 ml. of water and left standing for 1 hr. The aqueous solution was extracted with three 250-ml. portions of chloroform, the chloroform was removed *in vacuo*, and the residue was dissolved in 400 ml. of 10% hydrochloric acid and again left standing for 1 hr. The solution was made strongly alkaline and extracted with chloroform. After drying over anhydrous magnesium sulfate and removal of solvent, 74.6 g. (72.1%) of IX could be distilled as a highly viscous, colorless oil, b.p. 150–160° (0.03 mm.). No low-boiling material was obtained. Redistillation gave an analytical sample, b.p. 147–148° (0.01 mm.), $n^{25}D$ 1.5583. The infrared spectrum showed a strong absorption at 3295 $cm.^{-1}$ (hydroxyl groups) and two bands at 745 and 698 $cm.^{-1}$ (monosubstituted benzene), but no carbonyl absorption. The product was identical with the diol obtained by method A.

1-Benzyl-3-carboethoxy-4-hydroxypyrrolidine (X).—To a solution of 74.1 g. (0.3 mole) of keto ester V in a mixture of 300 ml. of ethanol and 300 ml. of ethyl acetate was added slowly in portions a slurry of 17.1 g. (0.45 mole) of sodium borohydride in 200 ml. of ethanol with stirring. The temperature was kept below 10°. After removal of solvents *in vacuo* the residue was dissolved in water and left standing for 1 hr. The oil which separated was extracted with chloroform and dried over anhydrous magnesium sulfate. After removal of solvent, 31.6 g. (42.3%) of hydroxy ester X could be distilled at 160–170° (0.3 mm.), which, on redistillation, boiled at 133–134° (0.02 mm.): $n^{25}D$ 1.5239; infrared absorption 3390 (hydroxyl group), 1718 (ester carbonyl), 738 and 696 $cm.^{-1}$ (monosubstituted benzene).

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62; O, 19.25. Found: C, 67.60; H, 7.71; N, 5.78; O, 19.30.

3-Hydroxymethyl-4-hydroxypyrrolidine (XII).—A solution of 41.4 g. (0.2 mole) of 1-benzyl-3-hydroxymethyl-4-hydroxypyrrolidine in 300 ml. of absolute ethanol was neutralized with an equivalent of ethanolic hydrogen chloride. The solution was shaken with 5 g. of 10% palladium on charcoal in hydrogen at 60 p.s.i. The theoretical amount of hydrogen was taken up in 24 hr. The solution was clarified by filtration and a solution of 11.2 g. (0.2 mole) of potassium hydroxide in 100 ml. of absolute ethanol was added. The precipitate of potassium chloride was removed by filtration. After removal of the solvent the residue was distilled *in vacuo* to yield 22.1 g. (94.3%) of a colorless viscous oil: b.p. 148–149° (0.03 mm.); $n^{25}D$ 1.5122; infrared absorption 3295 $cm.^{-1}$ (hydroxyl group), no absorption for monosubstituted benzene.

Anal. Calcd. for $C_5H_{11}NO_2$: N, 11.96; Found: N, 11.80.

Debenzylation of the free base of IX was carried out in a similar way, but gave a lower yield of XII (71.0%).

The secondary amine XII is soluble in polar solvents like ethanol, water, or dimethylformamide but, unlike IX, very slightly soluble in ether, methylene chloride, chloroform, and similar solvents.

The 1-Substituted 3-Hydroxymethyl-4-hydroxypyrrolidines. Method A. Example 1. 1-β-Phenethyl-3-hydroxymethyl-4-hydroxypyrrolidine (XXIV).—To a refluxing mixture of 11.7 g. (0.1 mole) of XII, 12.1 g. (0.12 mole) of triethylamine, and 100 ml. of ethanol was added dropwise within 1 hr. 18.5 g. (0.1 mole) of ethanol was added dropwise within 1 hr. 18.5 g. (0.1 mole) of β-phenylethyl bromide with stirring. Refluxing was continued for 8 hr. After removal of solvent the residue was treated with 10% potassium hydroxide solution and the product was extracted with ether and distilled after drying over anhydrous magnesium sulfate.

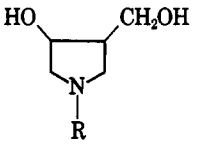
Example 2. 1-γ-Benzoylpropyl-3-hydroxymethyl-4-hydroxypyrrolidine Hydrochloride (XXV).—A mixture of 3.5 g. (0.03 mole) of XII, 5.5 g. (0.03 mole) of γ-chlorobutyrophenone, 4.2 g. (0.03 mole) of anhydrous potassium carbonate, 5.0 g. (0.03 mole) of potassium iodide, and 80 ml. of dimethylformamide was re-

(15) Melting points and boiling points are uncorrected. Analyses were performed by Dr. Alfred Bernhardt, Mikroanalytisches Laboratorium, Mülheim (Ruhr), Germany.

(16) J. L. Szabo and E. T. Stiller [*J. Am. Chem. Soc.*, **70**, 3667 (1948)] use Triton B (35% aqueous solution of benzyltrimethylammonium hydroxide) as a catalyst.

TABLE I

1-SUBSTITUTED 3-HYDROXYMETHYL-4-HYDROXYPYRROLIDINES



Compd.	R	Method	Yield,[a] %	B.p., °C. (mm.)	$n^{25}D$	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	% O Calcd.	% O Found
XXI	CH_3	A	16.2	105–106 (0.01)	1.4942	$C_6H_{13}NO_2$	54.94	54.87	9.99	9.96	10.68	10.70	24.40	24.61
XXI	CH_3	B	79.1	104–106 (0.01)	1.4943	$C_6H_{13}NO_2$	...	...	...	...	10.68	10.66	...	...
XXII	C_2H_5[b]	B	68.8	109–112 (0.03)	1.4897	$C_7H_{15}NO_2$	57.90	58.24	10.41	10.64	9.65	9.52	...	...
XXIII	n-C_4H_9	B	36.0	116–117 (0.01)	1.4862	$C_9H_{19}NO_2$	62.39	62.49	11.05	10.88	8.09	8.31	18.47	18.54
IX	$CH_2C_6H_5$	..	72.1	145–147 (0.01)	1.5585	$C_{12}H_{17}NO_2$	69.54	69.39	8.27	8.12	6.76	6.91	15.44	15.53
XXIV	$C_2H_4C_6H_5$	A	61.2	175 (0.04)[c]	...	$C_{13}H_{19}NO_2$	70.55	70.40	8.65	8.65	6.23	6.38	14.46	14.59
XXV	$(CH_2)_3COC_6H_5$	A	22.1	93–95[d] (...)	...	$C_{16}H_{22}NO_3Cl$	60.14	60.16	7.38	7.60	4.66	4.83	...	...

[a] Based on purified products. [b] This compound was also obtained in 6% yield by lithium aluminum hydride reduction of 1-acetyl-3-carbethoxy-4-pyrrolidone. [c] The distilled product solidified on standing, m.p. 99–101°. [d] Melting point of hydrochloride, recrystallized from n-butanol–pentane.

fluxed with stirring for 16 hr. The mixture was poured into water. The crude oil which separated was dissolved in methylene chloride, dried over anhydrous magnesium sulfate, and converted to the hydrochloride.

Method B. 1-Methyl-3-hydroxymethyl-4-hydroxypyrrolidine (XXI).—To a solution of 6.2 g. (0.03 mole) of IX in 200 ml. of 2-propanol was added slowly with stirring a solution of 5.7 g. (0.06 mole) of methyl bromide in 50 ml. of 2-propanol. The mixture was refluxed for 6 hr., using a Dry Ice condenser. After removal of the solvent, the residue was treated with ether to remove starting materials. The ether-insoluble quaternary compound was dissolved in 100 ml. of 2-propanol and hydrogenated over 2 g. of 10% palladium on charcoal at 60 p.s.i. for 6 hr. The oily hydrobromide which remained after removal of the solvent was converted to the free base XXI, which was extracted from aqueous alkaline solution with chloroform, dried over anhydrous magnesium sulfate, and distilled.

The physical properties of the pyrrolidinediols obtained by the described methods are listed in Table I.

1-Benzyl-3-chloromethyl-4-chloropyrrolidine (XIV).—Dry hydrogen chloride was passed into a solution of 20.7 g. (0.1 mole) of IX in 50 ml. of chloroform to form the hydrochloride of IX, which separated as an oil. The mixture was refluxed and a solution of 47.5 g. (0.4 mole) of thionyl chloride in 50 ml. of chloroform was added slowly with stirring within 0.5 hr. Refluxing was continued for 1 hr. Solvent and excess thionyl chloride were removed *in vacuo*. The residue was dissolved in 50 ml. of water, extracted with isopropyl ether, and made basic with potassium carbonate. The oil which separated was extracted with ether and dried over anhydrous magnesium sulfate. After removal of the solvent, 15.0 g. (61.4%) of a colorless oil could be distilled at reduced pressure; b.p. 120–125° (0.08 mm.). Redistillation gave an analytical sample, b.p. 111–113° (0.03 mm.), $n^{20}D$ 1.5493.

Anal. Calcd. for $C_{12}H_{15}Cl_2N$: C, 58.98; H, 6.21; Cl, 29.06; N, 5.75. Found: C. 59.21; H, 6.25; Cl, 29.07; N, 5.92.

The hydrochloride had m.p. 122–124° (from ethanol–ether).

Anal. Calcd. for $C_{12}H_{16}Cl_3N$: C, 51.33; H, 5.75; Cl, 37.93; N, 4.99. Found: C, 51.38; H, 5.68; Cl, 37.88; N, 5.10.

Preparation of Diesters of the Pyrrolidinediols. 1-Benzyl-3-acetoxymethyl-4-acetoxypyrrolidine (XXVI). General Procedure.—A mixture of 10.35 g. (0.05 mole) of IX, 30 g. of acetic anhydride, and 100 ml. of pyridine was refluxed overnight. The pyridine was removed *in vacuo*, the residue was dissolved in 10% hydrochloric acid, and the solution was extracted with methylene chloride. The solvent was removed from the extract and the residue was treated with water and left standing overnight. The mixture was made alkaline with potassium carbonate and the pyrrolidine diester was extracted with methylene chloride and dried over anhydrous sodium sulfate. The solvent was removed and distillation of the residue *in vacuo* gave an oil, b.p. 145–160° (0.25 mm.). Purification from small amounts of dehydration product was carried out by chromatography on neutral alumina. The fraction which was free of any C=C absorption in the infrared spectrum was redistilled; 7.1 g. (48.6%) of XXVI was obtained, b.p. 142–144° (0.15 mm.), $n^{20}D$ 1.5098.

Anal. Calcd. for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.81; H, 7.29; N, 5.01.

1-Benzyl-3-propionoxymethyl-4-propionoxypyrrolidine (XXVII).—Using propionic anhydride in the above procedure gave the dipropionate of IX in 52.2% yield, b.p. 146–149° (0.02 mm.), $n^{25}D$ 1.4995.

Anal. Calcd. for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39; O, 20.04. Found: C, 67.61; H, 7.78; N, 4.49; O, 20.12.

1-(β-Phenethyl)-3-propionoxymethyl-4-propionoxypyrrolidine (XXVIII).—The dipropionate of XXIV was obtained in 55% yield, b.p. 154–155° (0.02 mm.), $n^{20}D$ 1.5002.

Anal. Calcd. for $C_{19}H_{27}NO_4$: N, 4.20. Found: N, 4.31.

Reversal of Dieckmann Condensation. Degradation of 1-Benzyl-3-carbethoxy-4-pyrrolidone.—A solution of 9.9 g. (0.04 mole) of freshly prepared keto ester V in 100 ml. of absolute ethanol was refluxed for 10 hr. No evolution of carbon dioxide was observed during the reaction. The solvent was removed *in vacuo*. The residue no longer gave the characteristic ferric chloride reaction of the starting material V. The infrared spectrum showed only one carbonyl absorption at 1720 cm.$^{-1}$; the band at 1759 cm.$^{-1}$ had disappeared. The material was subjected to fractional distillation and 6.6 g. (85.6%, calcd. for VIII) of an oil was collected, b.p. 90–93° (0.03 mm.), as well as 0.35 g. (3%, calcd. for VI) of a higher boiling material, b.p. 135° (0.04 mm.). The infrared spectra of both materials were identical with those of VIII and VI and showed the same retention times as VIII and VI on a silica gel gas chromatographic column.

The hydrochloride was prepared from the main fraction; m.p. 109–110° (from ethanol–ether).

Anal. Calcd. for $C_{11}H_{16}ClNO_2$: C, 57.52; H, 7.03; Cl, 15.48; N, 6.11; O, 13.96. Found: C, 57.65; H, 7.03; Cl, 15.33; N, 6.20; O, 13.97.

This hydrochloride showed no melting point depression with an authentic sample prepared from ethyl N-benzylglycinate. The infrared spectra of both hydrochlorides were superimposable.

A pure sample of VI was refluxed with absolute ethanol for 10 hr. Analysis by gas chromatography did not show any formation of VII and VIII, and VI could be recovered.

Attempted Degradation of 1-Benzyl-3-carbethoxy-4-piperidone.—A pure sample of XIX was refluxed for 24 hr. in absolute ethanol. The residue which remained after removal of the solvent was identical (infrared spectrum, ferric chloride test) with the starting material. No low-boiling amino esters were obtained on attempted distillation.

1-Benzyl-3-pyrrolidone (XVII).—A mixture of 50 g. of 1-benzyl-3-carboethoxy-4-pyrrolidone, 500 ml. of water, and 20 ml. of concentrated hydrochloric acid was refluxed for 2 hr. The resulting solution was made alkaline by the addition of potassium carbonate and was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, and the reaction product was distilled *in vacuo* to yield 27.7 g. (78.2%) of a colorless liquid, b.p. 77° (0.01 mm.), $n^{20}D$ 1.5362. The infrared spectrum showed one carbonyl absorption at 1745 cm.$^{-1}$ and two bands due to a monosubstituted benzene ring at 738 and 695 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99; O, 9.13. Found: C, 75.37; H, 7.55; N, 7.97; O, 9.22.

The hydrochloride was recrystallized from ethanol–ether; m.p. 194–195° dec.

Anal. Calcd. for $C_{11}H_{14}ClNO$: C, 62.42; H, 6.67; Cl, 16.73; N, 6.62. Found: C, 62.31; H, 6.70; Cl, 16.34; N, 6.58.

1-Benzyl-3-pyrrolidinol (XVIII).—1-Benzyl-3-pyrrolidone (8.75 g., 0.05 mole) was dissolved in 100 ml. of methanol and 5.7 g. (0.15 mole) of sodium borohydride was added with stirring. The mixture was stirred for 5 hr. at room temperature. The solvent was removed *in vacuo*, the residue was dissolved in water, and the product was extracted with chloroform and dried over anhydrous magnesium sulfate. After the solvent was removed the residual oil was distilled *in vacuo* to yield 8.2 g. (92.5%) of product, b.p. 110–112° (0.2 mm.), $n^{20}D$ 1.5475. The hydrochloride was recrystallized from *n*-butanol; m.p. 123–124°.

The product was identical with an authentic sample[4] prepared from 1,4-dibromo-2-butanol and benzylamine. The infrared spectra were superimposable and the hydrochlorides showed no melting point depression; reported b.p. 120–121° (0.4 mm.); $n^{25}D$ 1.5473.

1-Benzyl-3-hydroxymethyl-4-hydroxypiperidine (XX).—1-Benzyl-3-carboethoxy-4-piperidone (XIX) was prepared freshly from its commercially available hydrochloride.[17] The free keto ester showed absorption in the infrared spectrum at 1730 and 1710 cm.$^{-1}$ (keto tautomer) and two strong bands at 1648 and 1610 cm.$^{-1}$ (enol tautomer). Using a procedure similar to the one described for the reaction of V, 13.05 g. (0.05 mole) of XIX was reduced with 11.4 g. (0.3 mole) of sodium borohydride in 100 ml. of methanol. Compound XX (4.6 g., 41.7%) could be distilled as a highly viscous white oil, b.p. 142–146° (0.03 mm.). The product solidified on standing: m.p. 115–120°; infrared absorption 3305 (hydroxyl groups), 743, and 696 cm.$^{-1}$ (monosubstituted benzene), no carbonyl absorption.

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33; O, 14.46. Found: C, 70.45; H, 8.55; N, 6.10; O, 14.44.

(17) Aldrich Chemical Co., Milwaukee, Wis.

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Isolation and Structure of Fusaroskyrin[1]

SUMU MATSUEDA

Department of Chemistry, Faculty of Literature and Science, Hirosaki University, Hirosaki, Aomori, Japan

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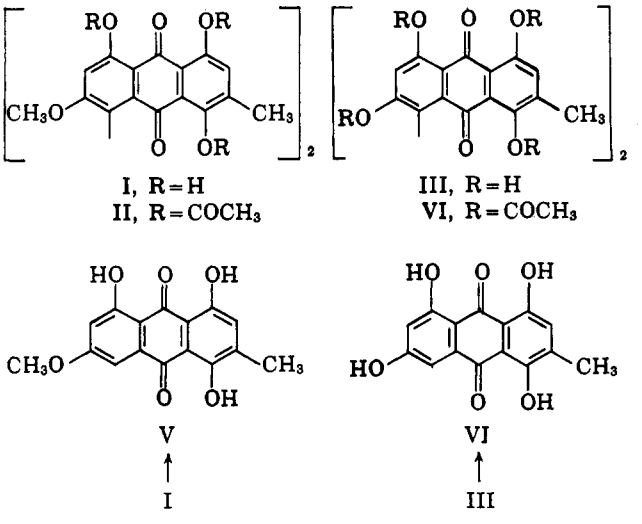
Fusaroskyrin, the main metabolic pigment of *Fusarium* species which is one of the organisms responsible for Purple Speck disease of soy beans, is obtained by acetone extraction of the dried mycelium, and has been purified by chromatography of its acetyl derivative on alumina. Fusaroskyrin gives erythroglaucin on sodium dithionite reduction. The structure of fusaroskyrin has been established as 1,1′-bi(4,5,8-trihydroxy-2-methoxy-7-methylanthraquinone).

In 1951, Shibata and Masumura demonstrated that *Fusarium* sp. is one of the pathogens which cause Purple Speck disease in Japanese soy beans.[2] *Cercosporina Kikuchii* Matsumoto et Tomoyasu, another pathogen of the same disease of soy beans, had been well known at that time.[3] However, Shibata and Masumura tried unsuccessfully to isolate this organism from soy beans infected with Purple Speck disease, but obtained only the *Fusarium* sp.. From the dried mycelium of the latter, they isolated palmitic, stearic, linoleic, and linolenic acids by ether extraction, while the crude pigments were obtained by extracting the residue with acetone.[4]

These mixed pigments have now been acetylated and the acetyl derivatives chromatographed on alumina. A pale yellow crystalline hexaacetate II, $C_{44}H_{34}O_{18}$, mol. wt. 830, and other acetates were thereby obtained. Alkaline deacetylation of II then gave the pure pigment, fusaroskyrin (I), $C_{32}H_{22}O_{12}$, as dark red crystals, m.p. >300°, mol. wt. 598. Fusaroskyrin gave a blue color with magnesium acetate[5]; it contained two C-methyl and two methoxyl groups as shown by Kuhn–Roth and Zeisel analyses, respectively. Demethylation of fusaroskyrin with hydroiodic acid yielded a red crystalline product III, m.p. >300°, $C_{28}H_4O_4(OH)_8(Me)_2$, which formed a yellow octaacetate IV, m.p. 295–297°.

Reduction of I, by lithium aluminum hydride or with sodium dithionite and alkali by the method of Raistrick and Howard,[6] gave erythroglaucin (V) (1,4,5-trihydroxy-7-methoxy-2-methylanthraquinone). Similarly, reduction of III gave catenarin (VI) (1,4,5,7-tetrahydroxy-2-methylanthraquinone). V and VI are the only products formed on reduction of



I and III, respectively. Ready cleavage by alkaline dithionite, yielding simple anthraquinones, is a typical property of 1,1′-bianthraquinones having hydroxyl or methoxyl groups in the positions *ortho* to the bond connecting the two moieties. Our findings thus suggest that I belongs to this class of compounds, a conclusion supported by the high melting point of I, and the molecular weight of 830 found for II. This in-

(1) A short communication of this work has been published by S. Fujise, S. Hishida, M. Shibata, and S. Matsueda [*Chem. Ind.* (London), 1754 (1961)].

(2) M. Shibata and M. Masumura, *Tohoku Seibutsu kenkyu*, **II**, 16 (1951).

(3) S. Kuyama and T. Tamura, *J. Am. Chem. Soc.*, **79**, 5725, 5726 (1951).

(4) Shibata and Masumura reported[2] that the yield of mixed pigments was 0.01% of dry fungus, and the yields of fatty acids were unknown.

(5) S. Shibata, *J. Pharm. Soc. Japan*, **61**, 320 (1941).

(6) B. H. Howard and H. Raistrick, *Biochem. J.*, **56**, 56 (1954).