forerun, boiling up to 72° (0.27 mm.), and 8.65 g. (46.8%) of crude adduct, b.p. 72–110° (0.17–0.3 mm.), which crystallized on standing. The gas chromatogram of the forerun indicated the presence of unchanged cyclohexenone and the dimer of 2,3-dimethylbutadiene. Redistillation of the forerun through an 18-in. spinning band column separated the diene dimer, 4-isopropenyl-1,2,4-trimethylcyclohexene, b.p. 110–112° (45 mm.), $n^{25}D$ 1.4784 (lit.[28] b.p. 85° (15 mm.), $n^{23}D$ 1.4804), which exhibits infrared absorption[14] at 1635 (C=C) and 895 cm.$^{-1}$ (C=CH_2) and only end absorption in the ultraviolet.[17] Recrystallization of the crude octalone from ethanol afforded 5.44 g. (29.4%) of the pure adduct, m.p. 61.5–62.5° (lit.[11] 62°), which exhibits infrared absorption[14] at 1712 cm.$^{-1}$ (C=O) and only end absorption in the ultraviolet.[17] In a comparable experiment in which only two equivalents of diene was employed, the yield of crude adduct was 31%. *Anal.* Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.82; H, 10.20.

Reaction of *trans*-Benzalacetone with 2-Ethoxy-1,3-butadiene.—A mixture of 177 g. (1.21 moles) of *trans*-benzalacetone, 118 g. (1.21 moles) of 2-ethoxybutadiene and a few crystals of 2,5-di-*t*-butylhydroquinone was heated to 180° in an autocalve for 48 hr. Distillation of the resulting mixture afforded 150 g. (51%) of crude adduct, b.p. 92–165° (0.68–0.85 mm.), which exhibits infrared absorption[14] at 1710 (C=O) and 1662 cm.$^{-1}$ (enol ether).[16] A solution of the adduct in a mixture of 200 ml. of ethanol, 100 ml. of concentrated hydrochloric acid and 50 ml. of water was refluxed for 2 hr., cooled, neutralized with dilute, aqueous sodium hydroxide and extracted with ether. After the ethereal solution had been dried over magnesium sulfate and concentrated, distillation of the residue afforded 64.5 g. of crude diketone, as a liquid, b.p. 150° (0.65 mm.). A solution of the crude product in an ether–hexane mixture deposited 41 g. (17% based on the starting benzalacetone) of ***trans*-4-acetyl-3-phenylcyclohexanone (XI)**, as white needles, m.p. 73.3–75°. Sublimation at 0.1–0.2 mm. afforded the pure diketone, m.p. 75–75.5°, which exhibits infrared absorption[14] at 1717 cm.$^{-1}$ (C=O) with a series of ultraviolet maxima[17] in the region 250–270 mμ with molecular extinction coefficients of less than 300.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.79; H, 7.38.

A series of fractional crystallizations of the mother liquors from hexane–benzene mixtures and, finally, from hexane separated a small amount of ***trans*-3-acetyl-4-phenylcyclohexane (XII)** as white needles, m.p. 107.5–109.5°. This diketone exhibits infrared absorption[19] at 1710 cm.$^{-1}$ with a shoulder at 1720 cm.$^{-1}$ (C=O) and a series of low intensity ultraviolet maxima[17] (ε 177 to 264) in the region 250–270 mμ.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.51; H, 7.41.

The Monoethylene Ketal of *trans*-4-Acetyl-3-phenylcyclohexanone (XIII).—A solution of 37 g. (0.171 mole) of the diketone, 12.4 g. (0.2 mole) of ethylene glycol and 0.1 g. of *p*-toluenesulfonic acid in 400 ml. of benzene was refluxed for 5 hr., the water (3 ml. or 98%) being separated as formed. After the benzene solution had been washed with aqueous sodium bicarbonate and concentrated, distillation of the residue afforded 43.49 g. (88%) of the monoketal as a colorless liquid, b.p. 135–140° (0.2–0.25 mm.), $n^{25}D$ 1.5321. The monoketal exhibits infrared absorption[14] at 1717 (C=O) and 1090 and 1127 cm.$^{-1}$ (ketal C–O) with a series of low intensity ultraviolet maxima[17] (ε 167 to 255) in the region 250–270 mμ.

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.69; H, 7.86.

The Ethylene Ketal of *trans*-4-Keto-2-phenylcyclohexanecarboxylic Acid (XIV).—To a solution of 10.15 g. (0.039 mole) of the monoketal XIII in 200 ml. of dioxane was added, dropwise and with stirring, 21.5 g. (0.15 mole) of a 5.25% solution of sodium hypochlorite in water. After the mixture had been stirred for 2 hr. with no external heating, it was heated to 60° for 1 hr. and then cooled. After the reaction mixture had been made distinctly basic by the addition of aqueous sodium hydroxide and diluted with water, it was extracted with ether. The ethereal extract was washed with aqueous sodium hydroxide, dried over magnesium sulfate and concentrated to leave 6.62 g. (65% recovery) of the crude, unchanged diketone monoketal, $n^{25}D$ 1.5220. The combined aqueous, alkaline solutions were acidified and extracted with ether. After the ethereal extract had been dried and concentrated, several recrystallizations of the residue from ethyl acetate–hexane mixtures afforded 1.68 g. (16.5%) of the crude keto acid ethylene ketal as white plates melting in the range 120–130°. An additional recrystallization afforded the pure ketal, m.p. 129.5–130.5°. The product exhibits infrared absorption[14] at 2950 (broad, associated OH), at 1710 (carboxyl C=O) and at 1093 and 1128 cm.$^{-1}$ (ketal C–O) with a series of low intensity (ε 94 to 210) ultraviolet maxima[17] in the region 240–270 mμ.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.66; H, 6.88.

A solution of 0.49 g. (0.00187 mole) of the keto acid ethylene ketal in a mixture of 5 ml. of ethanol, 4 ml. of concentrated hydrochloric acid and 4 ml. of water was refluxed for 70 min. and then diluted with water and made alkaline by the addition of aqueous sodium hydroxide. After the resulting mixture had been extracted with ether and then acidified, an additional extraction with ether separated the crude ***trans*-4-keto-2-phenylcyclohexanecarboxylic acid** which crystallized from an ethyl acetate–hexane mixture as white needles, m.p. 144.5–145.5°, yield 0.096 g. (24%). The product was shown to be identical with the sample previously described both by a mixed melting point determination and by comparison of the infrared spectra of the two samples.

CAMBRIDGE 39, MASS.

(28) E. H. Farmer and R. C. Pitkethly, *J. Chem. Soc.*, 11 (1938).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

1-Hydroxypyrrolizidine and Related Compounds

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A new method for preparation of certain pyrrolizidine derivatives is described. 1-Oxo-3H-1,2-dihydropyrrolo[1,2-a]-pyrrole (Ia) is reduced with sodium borohydride to the corresponding alcohol which is reduced further with hydrogen and rhodium-on-alumina catalyst to 1-hydroxypyrrolizidine or is reduced in one step to 1-hydroxypyrrolizidine with hydrogen and rhodium catalyst. It was converted to 1-chloropyrrolizidine which was reduced with Raney nickel to pyrrolizidine. The hydroxypyrrolizidine was resolved.

The alkanolamine moieties of Senecio alkaloids, the substituted pyrrolizidine bases, have been subjected to intensive study in the last two decades.[1] Synthetic methods leading to the preparation of the pyrrolizidine nucleus may be divided as follows: the methods involving (a) intramolecular alkylation of an amino group,[2] (b) intramolecular cyclodehydration of an amino alcohol,[3] (c) ring

(1) F. L. Warren in "Progress in the Chemistry of Organic Natural Products," Vol. XII, Springer, Wien, 1955, p. 198; N. J. Leonard, in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. I, Academic Press, Inc., New York, N. Y., 1950, p. 107.

(2) V. Prelog and S. Heimbach, *Ber.*, **72B**, 1101 (1939).

(3) F. Šorm and J. Brandejs, *Coll. Czech. Chem. Commun.*, **12**, 444 (1947).

closure by means of a Dieckmann condensation[4] and (d) reduction of bicyclic lactams.[5] Substituted pyrrolidines, prepared from the corresponding substituted pyrroles, have been converted to pyrrolizidines by method c or d.[6]

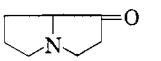
During the study now underway to determine the absolute configuration of the C_7-atom of the pyrrolizidine moiety from Senecio alkaloids, a source of 1-hydroxypyrrolizidine was desired. It was surprising to find that this pyrrolizidine derivative had never been synthesized. A necine with the empirical formula $C_7H_{13}NO$, properties undescribed and referred to as hydroxypyrrolizidine, has appeared in a paper by Corcilius.[7] It was obtained as a degradation product of fuchsisenecionine, an alkaloid from *Senecio fuchsii*.

The synthesis of 1-hydroxypyrrolizidine has now been successfully undertaken. The readily available 1-oxo-3H-1,2-dihydropyrrolo[1,2-a]pyrrole (Ia) was used as starting material. This product was first prepared by Clemo and Ramage[8] by a Hoesch reaction on 1-β-cyanoethylpyrrole. In a later paper Clemo and Melrose[4b] described unsuc-

Ia, R = H
b, R = $COCO_2Et$

II

IIIa, X = Cl
b, X = OH
c, X = H



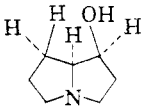
IV

cessful attempts to reduce the ketone Ia with hydrogen and platinum oxide or palladized charcoal as catalyst. More drastic reducing agents also failed to give pyrrolizidine derivatives.

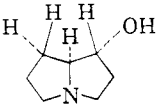
In our experiments rhodium-on-alumina as catalyst[9,10] was used and proved to be very effective for the reduction. This route to 1-hydroxypyrrolizidine apparently represents a general method by which substituted pyrroles may be converted to substituted hydroxypyrrolizidines.

The ketone Ia was reduced directly to 1-hydroxypyrrolizidine (IIIb), or stepwise with sodium borohydride to 1-hydroxy-3H-1,2-dihydropyrrole[1,2-a]pyrrole (II) followed by catalytic reduction to 1-hydroxypyrrolizidine.

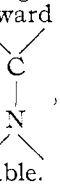
Reduction of the ketone Ia was stereospecific; it was possible to isolate only one hydroxypyrrolizidine which probably has structure VI. Stereospecificity by catalytic reduction was also observed in the conversion of desoxyretronecine to retronecanol,[11] isoheliotridene to heliotridane[12] and retronecine



V



VI

to platynecine.[11] Since the rings in the pyrrolizidine molecule are inclined upward from the plane of the paper along the axis  , formula VI is thermodynamically more stable. The repulsive interactions are in this case between H:H atoms, while in structure V the repulsive interactions are between H:OH groups.[13]

The resolution of 1-hydroxypyrrolizidine was effected through the acid tartrate salt. The less soluble tartrate gave 1-hydroxypyrrolizidine with a specific rotation of $[\alpha]D$ +1.7° in chloroform and $[\alpha]D$ 0° in ethanol.

When 1-hydroxypyrrolizidine was treated with thionyl chloride it was converted to 1-chloropyrrolizidine which upon reduction with hydrogen and Raney nickel gave pyrrolizidine. This is a more satisfactory method for obtaining pyrrolizidine than any hitherto reported.

An Oppenauer oxidation[14] of 1-hydroxypyrrolizidine afforded 1-oxopyrrolizidine (IV), an unstable amino ketone.

Experiments designed to produce a tertiary alcohol from the ketone Ia by condensation with methylmagnesium iodide failed; a polymeric product resulted which was not characterized.

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Experimental

1-Hydroxy-3H-1,2-dihydropyrrolo[1,2-a]pyrrole.—A solution of 0.8 g. of 1-oxo-3H-1,2-dihydropyrrolo[1,2-a]pyrrole[4b] in 5 ml. of methanol was added in four to five portions with stirring to a suspension of 0.7 g. of sodium borohydride in 10 ml. of methanol. Stirring was continued for half an hour and the reaction mixture was then allowed to stand for 8 hours. After addition of 25 ml. of water, followed by addition of 15 g. of anhydrous potassium carbonate, the mixture was extracted with two 30-ml. portions of ether. The residual colorless oil weighing 0.5 g. (61.7%) was dried in a desiccator for two hours and then purified by distillation *in vacuo*, b.p. 50° at 2 mm. This compound begins to decompose upon standing in the air for a few hours, but remains essentially unchanged for 3 weeks in a vacuum desiccator.

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.10; H, 7.17; N, 11.32.

(4) (a) G. R. Clemo and T. P. Metcalfe, *J. Chem. Soc.*, 606 (1936); (b) G. R. Clemo and T. A. Melrose, *ibid.*, 424 (1942); (c) R. Adams and N. J. Leonard, THIS JOURNAL, **66**, 257 (1944).

(5) F. Galinovsky and A. Reichard, *Ber.*, **77B**, 138 (1944); N. J. Leonard, L. R. Hruda and F. W. Long, THIS JOURNAL, **69**, 690 (1947); N. J. Leonard and G. L. Shoemaker, *ibid.*, **71**, 1760 (1949); N. J. Leonard and D. L. Felley, *ibid.*, **71**, 1758 (1949).

(6) For a review of the preparation of pyrrolizidine and derivatives see: R. C. Elderfield, "Heterocyclic Compounds," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 396; Houben-Weyl, "Methoden der Organischen Chemie," Band XI/2, p. 582, Georg Thieme Verlag, Stuttgart, 1958, p. 582.

(7) F. Corcilius, *Planta Med.*, **3**, 147 (1955); the author has indicated in correspondence that the formula of the necine, published as $C_7H_{13}NO$, should be $C_7H_{13}NO_2$.

(8) G. R. Clemo and G. R. Ramage, *J. Chem. Soc.*, 49 (1931).

(9) Available from the Baker Chemical Co.

(10) C. G. Overberger, L. C. Palmer, B. S. Marks and N. R. Byrd, THIS JOURNAL, **77**, 4100 (1955).

(11) R. Adams and E. F. Rogers, *ibid.*, **63**, 537 (1941).

(12) R. Adams and J. E. Mahan, *ibid.*, **65**, 2009 (1943).

(13) D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).

(14) R. Adams and K. E. Hamlin, Jr., THIS JOURNAL, **64**, 2597 (1942).

1-Hydroxypyrrolizidine. (A) Reduction of 1-Oxo-3H-1,2-dihydropyrrolo[1,2-a]pyrrole.—A solution of 12 g. of 1-oxo-3H-1,2-dihydropyrrolo[1,2-a]pyrrole in 100 ml. of acetic acid was reduced over 2 g. of 5% rhodium-on-alumina catalyst at room temperature and 42 p.s.i. Absorption of the theoretical amount of hydrogen was completed in 2 hours. The catalyst was removed by filtration and the dark-brown liquid was concentrated under reduced pressure on a steam-bath. The residue was distilled under reduced pressure to give 8 g. (64%) of colorless oil, b.p. 90–91° at 1.5 mm.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.14; H, 10.14; N, 11.18.

The picrate was formed in 95% ethanol solution, m.p. 244–245° dec.

Anal. Calcd. for $C_7H_{13}NO \cdot C_6H_3N_3O_7$: C, 43.82; H, 4.49; N, 15.73. Found: C, 44.10; H, 4.42; N, 16.01.

The picrolonate was prepared and recrystallized from 80% ethanol; prisms, m.p. 244–246° dec.

Anal. Calcd. for $C_7H_{13}NO \cdot C_{10}H_8N_4O_5$: C, 52.17; H, 5.14; N, 17.90. Found: C, 52.24; H, 5.31; N, 17.77.

The chloroaurate was formed by adding to an aqueous solution of 1-hydroxypyrrolizidine hydrochloride a 10% aqueous solution of gold chloride. After two recrystallizations from water the product was dried in air, m.p. 211–213° dec.

Anal. Calcd. for $C_7H_{13}NO \cdot HAuCl_4$: C, 18.00; H, 3.02; Au, 42.20. Found: C, 18.10; H, 2.99; Au, 42.45.

(B) **Reduction of 1-Hydroxy-3H-1,2-dihydropyrrolo[1,2-a]pyrrole.**—Reduction of 1.2 g. of 1-hydroxy-3H-1,2-dihydropyrrolo[1,2-a]pyrrole with 0.3 g. of rhodium-on-alumina catalyst and hydrogen at room temperature and atmospheric pressure gave 0.65 g. (52.8%) of 1-hydroxypyrrolizidine.

1-Oxo-2-ethoxalyl-3H-1,2-dihydropyrrolo[1,2-a]pyrrole.—To a cooled solution of 0.12 g. of sodium in 6 ml. of absolute ethanol was added 0.75 g. of ethyl oxalate. After stirring 10 minutes 0.6 g. of 1-oxo-3H-1,2-dihydropyrrolo[1,2-a]-pyrrole was introduced. No appreciable heat was evolved. The mixture was stirred for one hour during which time the color turned to orange-yellow. The reaction mixture was evaporated under reduced pressure to give the yellow sodium salt of the product. Acidification with acetic acid gave 0.95 g. (79.2%) of product which was purified by recrystallization from benzene and petroleum ether (b.p. 40–60°), m.p. 107–108°.

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 60.05; H, 4.98; N, 6.25.

1-Acetoxypyrrolizidine.—A mixture of 0.5 g. of 1-hydroxypyrrolizidine and 5 ml. of acetic anhydride was refluxed for one hour and the excess anhydride removed *in vacuo*. The picrate precipitated when an ethanol solution of picric acid was added to the residual oil. After purification from ethanol, it melted at 181–182°.

Anal. Calcd. for $C_9H_{15}NO_2 \cdot C_6H_3N_3O_7$: C, 45.23; H, 4.55; N, 14.07. Found: C, 45.47; H, 4.51; N, 13.96.

1-Chloropyrrolizidine.—A solution of 5.5 g. of 1-hydroxypyrrolizidine in 10 ml. of absolute ethanol was treated with adequate dry hydrogen chloride to form the salt, the ethanol evaporated and the oily residue heated for one hour with 12 ml. of thionyl chloride. The excess of thionyl chloride was evaporated *in vacuo* and the residue treated with 20 g. of ice. The filtrate from the precipitate was made strongly alkaline with aqueous *N* sodium hydroxide, the alkaline solution was extracted with chloroform, the organic solvent dried over potassium carbonate and evaporated *in vacuo*. The residue was dissolved in ether and filtered from insoluble material. Evaporation of ether gave 3.2 g. (47%) of product which distilled as a colorless oil, b.p. 84° at 20 mm., $n^{25}D$ 1.4903.

Anal. Calcd. for $C_7H_{12}ClN$: C, 57.73; H, 8.31; N, 9.62. Found: C, 57.48; H, 8.04; N, 9.47.

The picrate was prepared in ethanolic solution and was crystallized from 75% ethanol, m.p. 212–214° dec.

Anal. Calcd. for $C_7H_{12}ClN \cdot C_6H_3N_3O_7$: C, 41.66; H, 4.04; N, 14.95. Found: C, 41.74; H, 3.75; N, 15.30.

Pyrrolizidine.—A solution of 2.2 g. of 1-chloropyrrolizidine in 100 ml. of ethanol was reduced with 1 g. of Raney nickel and hydrogen at 45 p.s.i. The theoretical amount of hydrogen was consumed in 3 hours. The catalyst was removed, the ethanol evaporated and the residue distilled, b.p. 140–143° (lit.[15] b.p. 143°), yield 1.4 g. (83%).

The picrate crystallized from 90% ethanol in long needles, m.p. 254–255° dec. (lit.[15] m.p. 255–256°).

Anal. Calcd. for $C_7H_{13}N \cdot C_6H_3N_3O_7$: C, 45.88; H, 4.74; N, 16.47. Found: C, 45.57; H, 4.41; N, 16.45.

The picrolonate was crystallized from ethanol, m.p. 227–228° dec. (lit.[15] m.p. 227°).

Anal. Calcd. for $C_7H_{13}N \cdot C_{10}H_8N_4O_5$: C, 54.39; H, 5.64; N, 18.66. Found: C, 54.32; H, 5.54; N, 18.54.

1-Oxopyrrolizidine.—A mixture of 6 g. of 1-hydroxypyrrolizidine, 700 ml. of dry toluene, 200 g. of dry cyclohexanone and 1.5 g. of aluminum *t*-butoxide was refluxed for 6 hours and then allowed to remain overnight at room temperature. The reaction mixture was treated with two 30-ml. portions of 10% sulfuric acid. After extraction of the sulfuric acid with three 50-ml. portions of ether to remove any cyclohexanone it was made strongly alkaline with 40 ml. of 12 *N* aqueous sodium hydroxide and the reaction mixture extracted with four 70-ml. portions of ether. From the ether was obtained 2.3 g. (38%) of yellow oil, b.p. 110–115° (air-bath temperature) at 1.5 mm.

Anal. Calcd. for $C_7H_{11}NO$: C, 67.17; H, 8.86. Found: C, 66.88; H, 9.10.

The picrate was prepared in and crystallized from 96% ethanol; needles, m.p. 175–178°.

Anal. Calcd. for $C_7H_{11}NO \cdot C_6H_3N_3O_7$: C, 44.07; H, 3.98; N, 15.82. Found: C, 44.26; H, 3.84; N, 15.72.

Resolution of 1-Hydroxypyrrolizidine.—A solution of 3.7 g. of 1-hydroxypyrrolizidine and 4.4 g. of (+)-tartaric acid in 15 ml. of absolute ethanol was permitted to stand overnight in a refrigerator. The crystalline salt, which separated (3.6 g.), was three times recrystallized from absolute ethanol yielding 2.9 g. of white prisms, m.p. 115–117°; rotation: 0.0286 g. made up to 3 ml. with methanol at 26° gave $\alpha D + 0.26°$, *l* 2; $[\alpha]^{26}D + 13.6 \pm 0.5°$.

Anal. Calcd. for $C_7H_{13}NO \cdot C_4H_6O_6$: C, 47.62; H, 6.94; N, 5.06. Found: C, 47.75; H, 6.98; N, 5.00.

A solution of the crystalline acid tartarate in 50 ml. of ethanol was treated with 11.8 ml. of a 10% ethanolic potassium hydroxide solution. The crystalline precipitate was removed by suction, the ethanol evaporated and the residue distilled at 110–115° (air-bath temperature) and 0.08 mm.; rotation, 0.8439 g. made up to 5 ml. with chloroform at 27° gave $\alpha D + 0.56°$, *l* 2; $[\alpha]^{27}D + 1.7 \pm 0.1°$.

Anal. Found: N, 10.88.

The picrate was prepared in and recrystallized from absolute ethanol, m.p. 244–245° dec.

The chloroaurate was formed in the same manner as the racemic analog. After purification from water it melted at 205–206° dec.

Anal. Found: C, 18.24; H, 3.01.

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