Some Substituted Pyrrolizidines

B. M. GOLDSCHMIDT[1,2]

Department of Chemistry, University of Wisconsin, Madison, Wisconsin

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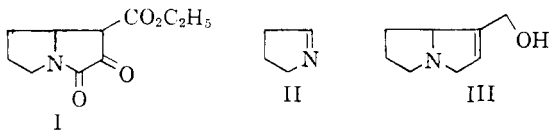
As part of an investigation of a general synthetic approach to the alkamine moiety of *Senecio* alkaloids[3] 1-carboethoxy-2,3-dioxopyrrolizidine (I) was prepared by allowing 1-pyrroline (II) to react with ethyl oxosuccinate. The analysis, infrared spectrum, and subsequent chemical transformations confirmed the structure of I; and recently Adams, Miyano, and Nair[4] synthesized I by the condensation of ethyl 2-pyrrolidylacetate with diethyl oxalate in the presence of sodium ethoxide.

It was envisaged that stepwise reduction and dehydration of I would produce *dl*-supinidine (III). Catalytic reduction of I gave in near quantitative yield 1-carboethoxy-2-hydroxy-3-oxopyrrolizidine (IV). Adams[4] and his co-workers also catalytically reduced I to IV.

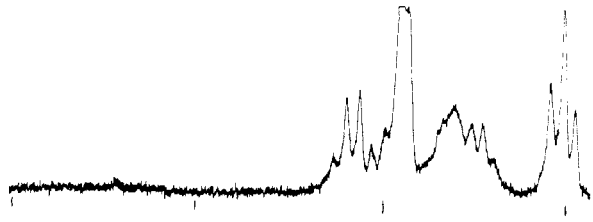


I II III

Attempts to dehyrate 1-carboethoxy-2-hydroxy-3-oxopyrrolizidine (IV) were unsuccessful. Upon treatment of IV with phosphorus oxychloride in pyridine an oil was obtained which was probably 1-carboethoxy - 2 - chloro - 3 - oxopyrrolizidine. Attempted pyrolytic dehydrations as well as acid- and iodine-catalyzed dehydrations of IV yielded starting material.

The lability of the hydroxy group in IV was increased by conversion to the tosylate (V), a transformation which was readily accomplished. The structure of V was confirmed by analysis, as well as infrared and ultraviolet spectra.

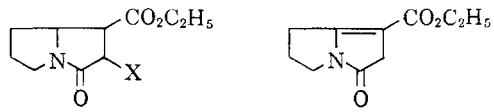
Treatment of V with one equivalent of potassium *t*-butoxide in *t*-butyl alcohol resulted in the facile elimination of *p*-toluenesulfonic acid and the formation of compound VI. Compound VI reacted instantly with bromine and precipitated manganese dioxide upon addition of a potassium permanganate solution. The required formula ($C_{10}H_{13}O_3N$) was indicated by analysis. With 10% palladium on charcoal as a catalyst, compound VI took up one mole of hydrogen. All these experiments and the method of preparation were consistent with the formulation of VI as 1-carboethoxy-3-oxopyrrolizid-1,2-ene. Nair and Adams[5] isolated VI after allowing 1-carboethoxy-2-hydroxy-3-oxopyrrolizidine (IV) to react with *p*-toluenesulfonyl chloride in pyridine. They firmly established the gross structure of VI as they reduced it to the known *dl*-isoretronecanol (1-hydroxymethylpyrrolizidine).[5]



−100 c.p.s. 0 c.p.s. 100 c.p.s. 200 c.p.s.

Fig. 1.—Nuclear magnetic resonance spectrum of 1-carboethoxy-3-oxopyrrolizid-1,8-ene (VI).

Nair and Adams[5] considered compound VI to be 1-carboethoxy-3-oxopyrrolizid-1,2-ene, though they were unable to obtain *dl*-supinidine (III) by stepwise reduction of VI. On the basis of the following evidence, we have concluded that VI is the isomeric 1,8-ene. The ultraviolet spectrum of VI had two peaks, one at 288 mμ (ϵ 12,000) and the other at 218 mμ (ϵ 4600). If VI were the 1,2-ene, it would probably have only one peak of higher intensity in the 220-mμ region as fumarates and related compounds have.[6] A nuclear magnetic resonance spectrum[7] (Fig. 1) of VI showed the hydrogens of one ethyl ester and also methylene hydrogens, but no vinyl hydrogen was detected. The ratio of ethyl ester hydrogens to methylene hydrogens was that expected for VI, 5:8. This evidence allows us to conclude that VI is 1-carboethoxy-3-oxopyrrolizid-1,8-ene not the corresponding 1,2-ene as previously suggested.[5]



IV. X = OH
V. X = OTs

VI

Experimental[8]

1-Carboethoxy-2,3-dioxopyrrolizidine (I).—Ethyl oxosuccinate (22.1 g., 0.117 mole) was added to a solution of 1-pyrroline in ethanol–ethyl ether. (The maximum amount of 1-pyrroline was 0.250 mole; this is based on the amount of pyrrolidine used in the preparation of 1-pyrroline *via* N-

(1) Present address: State University of New York, Long Island Center, Oyster Bay, New York.

(2) The author is indebted to Professor E. E. van Tamelen for suggesting this problem and advising and encouraging the author throughout this work.

(3) (a) N. J. Leonard, "The Alkaloids Chemistry and Physiology," Vol. I, R. H. F. Manske and H. L. Holmes, ed., Academic Press, New York, 1950, p. 108. (b) N. J. Leonard, *ibid.*, Vol. VI, R. F. Manske, ed., 1960, p. 35.

(4) R. Adams, S. Miyano, and M. D. Nair, *J. Am. Chem. Soc.*, **83**, 3323 (1961).

(5) M. D. Nair and R. Adams, *J. Org. Chem.*, **26**, 3059 (1961).

(6) (a) H. Ley and H. Wingchen, *Ber.*, **67**, 501 (1934); (b) A. Smakula, *Angew. Chem.*, **47**, 657 (1934).

(7) The n.m.r. spectrum of VI was taken on a Varian Associates Instrument at 40 Mc. and 14,000 gauss with benzene as an internal reference and carbon tetrachloride as the solvent (20%).

(8) All melting points are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan.

chloropyrrolidine.[9] This solution was refluxed for 3.5 hr., cooled, and acidified with aqueous hydrochloric acid. The volume of solution was reduced to *ca.* 100 ml. by reduced pressure distillation. The solution was then extracted with three 100-ml. portions of benzene. The benzene extract was washed with three 30-ml. portions of water saturated with sodium chloride. The washings were discarded and the benzene solution dried over sodium sulfate. After the benzene was removed, 15.7 g. (64.0%) of crude solid I was obtained. The solid was dissolved in warm benzene and charcoal was added. This solution was warmed on a steam bath for 10–15 min.; Filter-Cel was added and the solution filtered. After removal of the benzene, the solid was recrystallized from ethyl ether-purified petroleum ether (b.p. 90–100°). The recrystallized white solid was sublimed, m.p. 123–125°.

Anal. Calcd. for $C_{10}H_{13}O_4N$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.92; H, 6.33; N, 6.71.

1-Carboethoxy-2-hydroxy-3-oxopyrrolizidine (IV).—Six grams (0.0285 mole) of sublimed I was dissolved in 50 ml. of 95% ethanol and placed in a hydrogenation bomb, and 3 g. of W-2 Raney nickel was added. At 100° and 2000 p.s.i. the theoretical amount of hydrogen was taken up in 4 hr. The solution was allowed to cool to room temperature and brought to atmospheric pressure. The solution was then filtered. After removal of the solvent the solid was recrystallized from ethyl acetate-purified petroleum ether (b.p. 60–68°) and sublimed, m.p. 128.2–132.1°.

Anal. Calcd. for $C_{10}H_{15}O_4N$: C, 56.32; H, 7.09; N, 6.57. Found: C, 56.24; H, 7.01; N, 6.54.

1-Carboethoxy-2-hydroxy-3-oxopyrrolizidine Tosylate (V).—A 0.153-g. (2.31 mmoles) sample of IV was dissolved in 10 ml. of anhydrous pyridine, and 1.11 g. (5.71 mmoles) of recrystallized *p*-toluenesulfonyl chloride was added. The solution was stored at 0° for 17 hr. and then poured onto crushed ice. Within 0.5 hr., a copious white precipitate formed. This was filtered, washed with water, and after being dried, 0.634 g. (67.8%) of V was obtained, recrystallized from ethyl acetate, m.p. 123.1–124.2°.

The infrared spectrum of V in 10% chloroform solution had no absorption bands in the 3.0-μ region and had peaks at 5.80 and 6.24 μ. The ultraviolet spectrum in 95% ethanol had one peak at 226 mμ (ϵ 12,500).

Anal. Calcd. for $C_{17}H_{21}O_6NS$: C, 55.72; H, 5.50; Found: C, 55.63; H, 5.97.

1-Carboethoxy-3-oxopyrrolizid-1,8-ene (VI).—A 0.529-g. (1.43 mmoles) sample of V was placed in a flask and 50 ml. of anhydrous *t*-butyl alcohol was added. The solution was warmed on a steam bath for 5–10 min., and most of the tosylate dissolved. To this warmed stirred solution, 7.49 ml. of 0.193 *N* (1.43 mmole) of potassium *t*-butoxide in *t*-butyl alcohol was added. The solution became bright red as each drop of base was added, but the color then disappeared and only persisted after all the base had been addded. The solution was acidified with dilute hydrochloric acid and then extracted with benzene. The benzene was removed by reduced pressure distillation. The residue was chromatographed on a column packed with Florosil (60/100 mesh, Floridian Co., Tallahassee, Florida). The chromatographed material (over 90%) was sublimed, m.p. 88.9–90.0°.

Anal. Calcd. for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.61; H, 6.66; N, 6.55.

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(9) D. W. Fuhlage and C. A. VanderWerf, *J. Am. Chem. Soc.*, **80**, 6249 (1958).

Formylation of *t*-Butylamine and *t*-Octylamine[1,2]

JAMES MOFFAT, MARVIN V. NEWTON, AND GERALD J. PAPENMEIER

Department of Chemistry, University of Kansas City, Kansas City 10, Missouri

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During studies on isocyanides in these laboratories we have had occasion to prepare large quantities of formo-*t*-butylamide. Neither the formylation of *t*-butylamine by formic acid nor the Ritter reaction on isobutylene or *t*-butyl alcohol[3] is appealing as a routine preparation, the former because mixing the very volatile *t*-butylamine with formic acid is a troublesome and tedious procedure, and the latter because of the obvious hazards of working with hydrogen cyanide. We have found that *t*-butylamine can be formylated conveniently by refluxing and then distilling an equimolar mixture of ethyl formate and *t*-butylamine. The high rate of this reaction is in striking contrast with the negligible rate of acetylation of *t*-butylamine by methyl acetate[4] at 25°. Similarly *t*-octylamine (2,4,4-trimethyl-2-pentylamine) is formylated at approximately the same rate.

Experimental[5]

Equimolar quantities of ethyl formate and *t*-butylamine were refluxed in tared flasks, the excess reagents and ethanol were distilled on the water bath, and the residual formo-*t*-butylamide was weighed. The procedure was checked by distilling several batches. Typical yields for 4,16,32, and 48 hr. of reflux were 29.4, 66.8, 79.2, and 84.0%, respectively. Similarly, a mixture of 120 g. (1.0 mole) of *t*-octylamine and 150 g. (2.0 moles) of ethyl formate was refluxed 12 hr. and then distilled. The formo-*t*-octylamide was obtained in a yield of 98 g. (62%), b.p. 245–248°. This material is slightly amber in color and may be better purified by vacuum distillation.

(1) Abstracted from the M.S. theses of Marvin K. Newton and Gerald J. Papenmeier, University of Kansas City, 1960.

(2) The authors gratefully acknowledge support of this work by the National Science Foundation under Grant No. G10031.

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(5) A gift of *t*-octylamine from the Rohm & Haas Corporation is gratefully acknowledged. The other chemicals were purchased.

Bridged Polycyclic Compounds. XVIII. Addition of Dialkyl Azodicarboxylates to Norbornadiene[1]

STANLEY J. CRISTOL, EVAN L. ALLRED, AND DAVID L. WETZEL

Department of Chemistry, University of Colorado, Boulder, Colorado

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Recent reports have established that norbornadiene (I) exhibits unusual chemical reactivity as