Claisen Rearrangement of Allyloxypyridines

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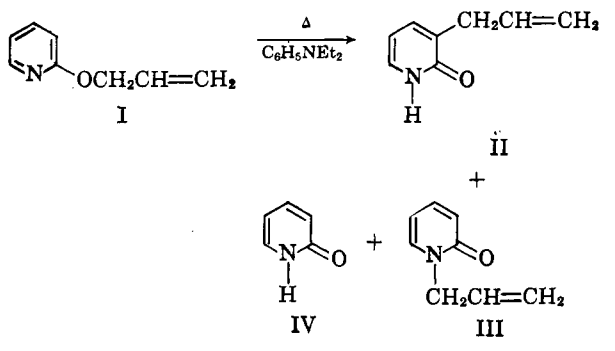
The Claisen rearrangement[1] has not been applied previously to allyloxypyridines. Indeed, of the necessary starting materials, only the 2-allyloxypyridine[2] has been reported.

The rearrangement of 2-allyloxypyridine was carried out under a variety of conditions. In each case a mixture of products was obtained consisting of unchanged starting material I, the expected 3-allyl-2-pyridone (II), N-allylpyridone (III), 2-pyridone (IV), and resin.



The best conditions found (but probably not optimum) for the preparation of the 3-allyl-2-pyridone are those described in the Experimental section using diethylaniline as solvent. Similar products were obtained when the diethylaniline was omitted but more tar was formed. Heating above 250° gave mostly resins. No reaction occurred at reflux temperature. The structure of the 3-allyl-2-pyridone was established by analysis, infrared, ultraviolet, and nuclear magnetic resonance spectra. The products III and IV are known and their infrared spectra were compared with those of authentic samples.

4-Allyloxypyridine was readily prepared by the action of sodium allyloxide on 4-bromopyridine. One attempt to rearrange this under the same conditions that worked for the 2-isomer gave largely polymer and no identifiable product.

Several attempts were made to prepare 3-allyloxypyridine from sodium allyloxide and 3-bromopyridine. When conditions were drastic enough to replace this inactive bromine, polymerization took place and only traces of the desired product were isolated. A small yield of this ether was obtained by the reaction of the sodium salt of 3-hydroxy pyridine with allyl bromide; but, as expected from the analogous work of Shapiro, *et al.*,[3] attack was mostly on the nitrogen.

(1) D. S. Tarbell, *Org. Reactions*, **2**, 1 (1944).

(2) B. I. Mikhant'ev, E. I. Fedorov, A. I. Kucherova, and V. P. Potapova, *Zh. Obshch. Khim.*, **29**, 1874 (1959); *Chem. Abstr.*, **74**, 8808e (1960).

(3) S. L. Shapiro, K. Weinberg, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 5140 (1959).

Experimental[4]

Rearrangement of 2-Allyloxypyridine. Preparation of 3-Allyl-2-pyridone (II).—A mixture of 27.0 g. (0.2 mole) of 2-allyloxypyridine and 29.8 g. (0.2 mole) of diethylaniline was heated in an autoclave at 250° for 8 hr. On standing at room temperature for several days the viscous solution deposited crystals which were collected, washed with pentane, and dried giving 4.27 g. of solid, m.p. 116–124°. The filtrate was shaken with pentane and water leaving an insoluble gum. Sublimation of this gum followed by crystallization from isopropyl alcohol gave 0.2 g. more of the same solid. The aqueous solution was separated and allowed to evaporate, giving a mixture of crystals and oil. Washing the crystals with benzene removed the oil, giving 2.1 g. of crystals which proved to be the same as those found in the first crystallization. The total yield of crude 3-allyl-2-pyridone was 6.6 g. (24.4%). Recrystallization from isopropyl alcohol gave 4.33 g. (16%) of pure product, m.p. 126.5–127.5°. The infrared spectrum (Nujol mull) showed major bands at 3260, 3125, 3080, 2600, 1659, 1612, 1566, and 775 cm.$^{-1}$. The ultraviolet spectrum showed bands (in ethanol) at 230 (6960) and 299 mμ (ε 6730); (in 0.01 *N* ethanolic KOH) at 233 (8020) and 299 mμ (ε 6510).

The n.m.r. spectrum[5] showed the allyl group bands between 190 and 365, the hydrogens at the 4- and 6-positions as a doublet at 440 and the hydrogen at the 5-position as a triplet centered at 375 c.p.s. (J = 7) relative to internal tetramethylsilane.

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36; O, 11.84. Found: C, 71.12; H, 6.58; N, 10.09; O, 12.17.[6]

Other runs (with and without the diethylaniline) were worked up by distillation but sharp separations were not obtained. Starting material I distilled followed by N-allyl-2-pyridone (III)[2] and then some crystalline solid. By heating the latter fractions, b.p. 112–132° (0.1 mm.), with water and cooling, a solid was obtained which, after recrystallization from isopropyl alcohol, yielded 10–15% of 3-allyl-2-pyridone (II). The aqueous solution was found to contain considerable 2-pyridone (IV). A large amount of undistillable resin remained.

4-Allyloxypyridine.—Sodium allyloxide was prepared by dissolving 18.4 g. (0.8 g.-atom) of sodium in 240 ml. of dry allyl alcohol. To this was added 63.2 g. (0.4 mole, of 4-bromopyridine, and the mixture was heated under reflux for 6 hr. The mixture was poured into ice–water, acidified with hydrochloric acid, and extracted with ether. The aqueous solution was treated with sodium hydroxide giving a light yellow oil which was extracted with ether. The extracts were washed with saturated sodium chloride solution and dried over sodium sulfate. After filtration and removal of the solvent the product was distilled, giving 45.9 g. (83%) of colorless liquid, b.p. 104° (11 mm.), n^{25}D 1.5224. The infrared spectrum showed major bands at 3040, 1590, 1575, 1500, 1215, 1020, and 815 cm.$^{-1}$. The n.m.r. spectrum[5] showed the allyl group bands between 265 and 385, the four ring hydrogens as an AB pattern (doublet of doublets) at 407 and 505 c.p.s. (J = 6) relative to internal tetramethylsilane.

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36; O, 11.84; equiv. wt., 135.16. Found: C, 71.33; H, 6.89; N, 1.10; O, 12.64[7]; equiv. wt., 137.

Picrate.—This was prepared from 4-allyloxypyridine with ethanolic picric acid and was recrystallized from absolute ethanol giving yellow crystals, m.p. 109–110°.

Anal. Calcd. for $C_{14}H_{12}N_4O_8$: C,46.16; H, 3.32; N, 15.38. Found: C, 46.48; H, 3.34; N, 15.27.

3-Allyloxypyridine.—To a solution of 19.0 g. (0.2 mole) of 3-hydroxypyridine in 120 ml. of dry dimethylformamide was added portionwise with cooling and stirring 10.5 g. (0.22 mole) of sodium hydride (51.5% in mineral oil). Then 29.0 g. (0.2 mole) of allylbromide was slowly added with vigorous stirring and cooling at 0–10°. After stirring at 0–13° for 1.5 hr. and standing overnight the mixture was poured into ice–water, made basic, and extracted with ether. The ether solution was washed with saturated sodium chloride solution, dried over potassium carbonate,

(4) Melting points were taken with a Thomas–Hoover capillary melting point apparatus using a partial immersion thermometer. Calibration with standard samples showed that no correction was necessary within an accuracy of ±1°. Except as noted, analyses and spectra are by our Department of Physical and Analytical Chemistry.

(5) This n.m.r. spectrum was determined in deuterated chloroform solution with a Varian A-60 spectrometer.

(6) This analysis was by Clark Microanalytical Laboratory.

(7) This analysis was by Huffman Microanalytical Laboratories.

and distilled. After removing the solvent and a small forerun, 1.5 g. liquid was obtained, b.p. 96° (12 mm.). The infrared spectrum showed major bands at 3065, 3040, 1585, 1575, 1485, 1230, 1185, 1046, 1015, 1010, 800, and 700 cm.$^{-1}$.

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36; O, 11.84. Found: C, 70.77; H, 6.80; N, 10.05; O, 12.74.[7]

Picrate.—This was prepared from 3-allyloxypyridine with ethanolic picric acid, and the solution was diluted with water. It was recrystallized from absolute ethanol giving yellow crystals, m.p. 56–58°.

Anal. Calcd. for $C_{14}H_{12}N_4O_8$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.31; H, 3.29; N, 15.20.

Steroidal Heterocycles. VIII.[1] Metal–Ammonia Reduction of Δ^4-Steroidal [3,2-*c*] Pyrazoles

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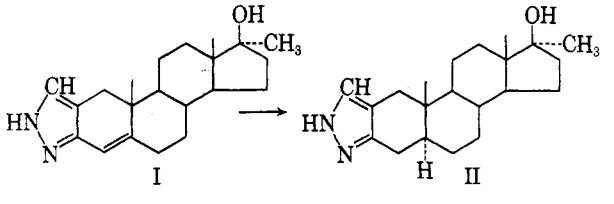
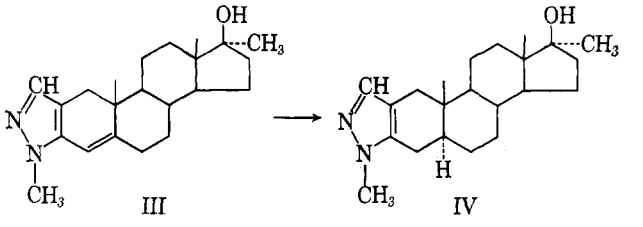
In our investigations of steroidal pyrazoles an alternate route to 5α-steroidal [3,2-*c*]pyrazoles[2] was desired. Since Δ^4-steroidal [3,2-*c*]pyrazoles were readily available,[2] reduction of these compounds to the corresponding 5α-derivatives appeared attractive. Catalytic hydrogenation has been shown to afford primarily the 5β-isomers.[3] Metal–ammonia reduction was then considered, since the product, if the pyrazole ring remained intact, might be expected to be the 5α-isomer by analogy with the reduction of steroidal Δ^4-3-ones[4] and other conjugated systems.[5]

Treatment of 17β-hydroxy-17α-methylandrost-4-eno-[3,2-*c*]pyrazole (I)[2a] with sodium or lithium in liquid ammonia–tetrahydrofuran–ethanol afforded 17β-hydroxy-17α-methylandrostano[3,2-*c*]pyrazole (II),[2a] the saturated A/B-*trans* compound, in 62 to 76% yield.



No reduction of the pyrazole ring or formation of the 5β isomer was detected; apparently only unchanged pyrazole I contaminated the crude product. Pyrazole II was recovered unchanged when treated under the same conditions.

Two factors may be responsible for the nonreduction of the pyrazole ring: (1) the "aromatic" pyrazole ring, which is more electronegative than the aryl ring (reduced under the conditions used[6]), is more resistant to electron addition, considered to be the initial step of the reductive process[7]; (2) metal salt formation may prevent reduction of the ring. The second possibility can not be the major factor since the N-methyl derivative of I, 17β-hydroxy-17α-methylandrost-4-eno[3,2-*c*]-2′-methylpyrazole (III),[2b] which has no acidic hydrogen, is reduced in 75% yield to the N-methyl derivative of II, 17β-hydroxy-17α-methylandrostano[3,2-*c*]-2′-methylpyrazole (IV)[2b] with lithium–ammonia–*t*-butyl alcohol (see Experimental). Pyrazole IV can be recovered in 75% yield when treated under the same conditions (thin layer chromatographic examination of the mother liquors show some decomposition products along with additional quantities of pyrazole IV).[8] Similar results have been obtained with pyrrole and 1-methylpyrrole.[9]



The 4,5-double bonds in pyrazoles I and III are probably reduced in a manner similar to the reduction of styrene-type double bonds.[10]

Experimental[11]

Reduction of 17β-Hydroxy-17α-methylandrost-4-eno[3,2-*c*]-pyrazole (I).—To a solution of 10.00 g. of 17β-hydroxy-17α-methylandrost-4-eno[3,2-*c*]pyrazole [m.p. 248.4–257.4°; $[\alpha]_D$ +134° (pyridine); λ_{max} 261 mμ (ϵ 10,600)[2a]] in 300 ml. of tetrahydrofuran (distilled from calcium hydride) and 300 ml. of liquid ammonia, was added 20 g. of sodium in portions during 5 min. with stirring at reflux. Two layers formed: a bronze colored upper layer and a gray opaque lower layer. The mixture was stirred at reflux for 1 hr. Ethanol (100 ml.) was added in 15 min. The mixture was stirred at reflux for an additional 6 hr. (upper bronze layer still present), then allowed to warm to room temperature overnight. The colorless mixture was concentrated under reduced pressure to about 200 ml. and then poured with stirring into 1500 ml. of ice–water. The mixture was filtered to yield light yellow crystals, m.p. 157–165°; partially resolidified, m.p. <215°; λ_{max} 223 mμ (ϵ 4600), 260 mμ (ϵ 130). Two recrystallizations from ethanol afforded 6.38 g. (63%) of fine colorless prisms (dried *in vacuo* at 120° for 20 hr.); m.p. 232–241°; $[\alpha]_D$ +34.9° (chloroform); λ_{max} 223 mμ (ϵ 4710).[2a]

(1) Paper VII: A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, D. K. Phillips, G. O. Potts, A. Arnold, A. L. Beyler, and R. O. Clinton, *J. Med. Chem.*, **6**, 1 (1963).

(2) (a) R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts, and A. Arnold, *J. Am. Chem. Soc.*, **81**, 1513 (1959); (b) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *ibid.*, **83**, 1478 (1961).

(3) (a) R. O. Clinton, R. L. Clarke, F. W. Stonner, D. K. Phillips, K. F. Jennings, and A. J. Manson, *Chem. Ind.*, 2099 (1961); (b) R. O. Clinton, R. L. Clarke, F. W. Stonner, A. J. Manson, K. F. Jennings, and D. K. Phillips, *J. Org. Chem.*, **27**, 2800 (1962).

(4) D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 903 (1954).

(5) D. H. R. Barton and C. H. Robinson, *ibid.*, 3045 (1954).

(6) H. L. Dryden, Jr., G. M. Webber, R. B. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961).

(7) A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950).

(8) 1-Arylpyrazoles are reduced with sodium and alcohol to 1-arylpyrazolines or ring-opened products [T. L. Jacobs, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 104–105]. In this case the aryl ring apparently increases the electrophilic character of the pyrazole enough to make it susceptible to electron attack.

(9) S. O'Brien and D. C. C. Smith, *J. Chem. Soc.*, 4609 (1960).

(10) Isolated double bonds are not reduced with metals and amines, except under forcing conditions. For a discussion of the factors influencing metal–amine reductions, see ref. 7 and A. J. Birch and H. Smith, *Quart. Rev.* (London), **12**, 17 (1958).

(11) All melting points are corrected. Optical rotations were determined as 1% solutions at 25°. Ultraviolet spectra were determined on a Cary spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as external standard.