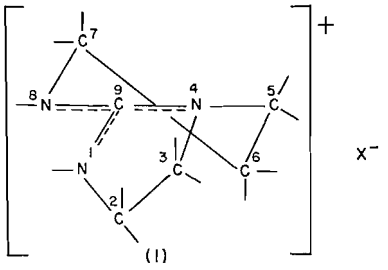
NITRATION OF BICYCLIC GUANIDINES[1]

A. F. McKay and M.-E. Kreling

ABSTRACT

The course of the nitration of a bicyclic guanidine system has been shown to depend on substitution at an adjacent carbon atom. The pyrimidine ring in 5-keto-2,3,6,7-tetrahydro-5(H)-thiazolo(3,2-*a*)pyrimidine is opened more rapidly by benzylamine and ethanolic hydrogen chloride than the pyrimidine ring in 5-keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidine. These effects are interpreted in terms of the resonance ion structure at the ring junctions.

The bicyclic guanidine, 2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidine,[2] has been converted into 1-nitro-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidinium nitrate by nitration in absolute nitric acid – acetic anhydride medium (1). Nitration of the 2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidinium ion is consistent with the presence of the guanidinium ion in its structure. The model of this bicyclic guanidinium ion may be represented diagrammatically by structure I. Atoms 1, 2, 3, 4, 5, 8, and 9 are



(I)

in the same plane, since the five-membered ring can be considered to be planar. A slight deviation of C atoms 2 or 3 from the plane of the ring would not contribute much to a relief of strain within this structure. A continuation of nitration studies on the 2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidine system has shown that an electronegative substituent such as oxygen or nitrogen on C_5 affects the nitration of the guanidine structure.

Nitration of 5-imino-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidinium chloride (II) in absolute nitric acid – acetic anhydride medium gave 5-nitrimino-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidinium nitrate (III). The failure of the guanidine structure to nitrate is explained by the electron displacements within structure II. There are two opposing electron attractive forces working on N_4; one involves its participation in the guanidinium ion and the other in the electron displacement indicated by the curved unbroken arrows in structure II. These opposing forces give the resonance ion structure more of an amidinium ion character than a guanidinium ion character and the amidinium ion does not nitrate. Thus nitration occurs only on the 5-imino nitrogen. The same explanation is given for the failure of 5-keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidine to nitrate.

5-Nitrimino-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidinium nitrate (III) is converted into 5-keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidinium nitrate (IV) on crystallization from ethanol. Because of this easy replacement of the nitrimino group, extreme care was required in the preparation of a pure sample of compound III.

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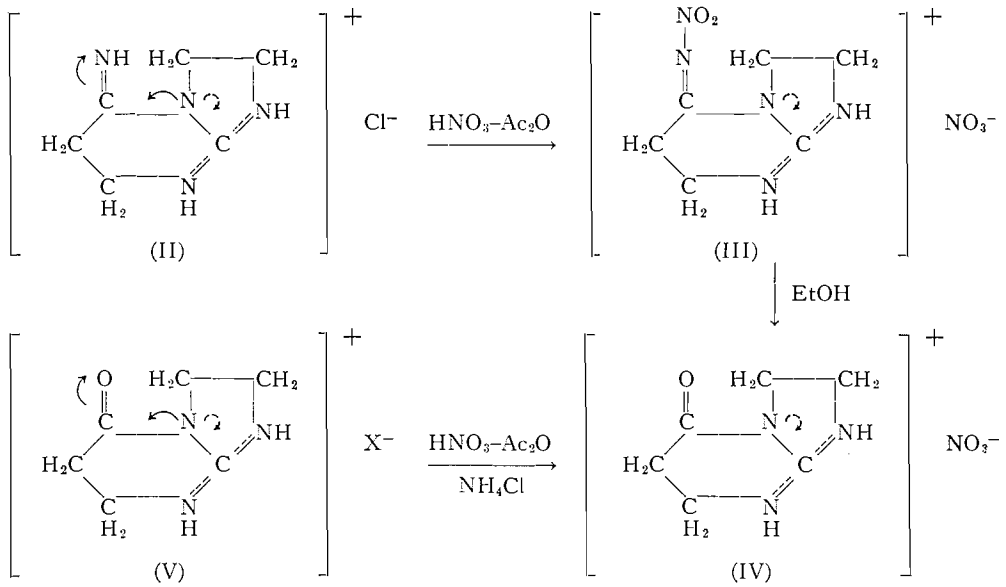
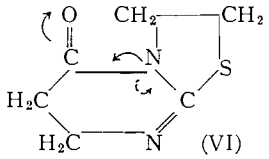
[2]*Named in accordance with the rules on nomenclature of fused ring systems given in The ring index, Am. Chem. Soc. 2nd ed., 1960. This compound was referred to as* Δ^8*-hexahydro-1,4,8-pyrimidazole in ref. 1.*



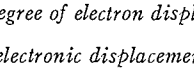
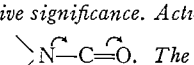
When 5-keto-2,3,6,7-tetrahydro-5(H)-thiazolo(3,2-*a*)pyrimidine (VI) was treated with an ethanolic solution of hydrogen chloride, a quantitative yield of 2-(β-carbethoxyethylamino)-2-thiazoline was obtained. Similarly benzylamine opened the pyrimidine ring of VI to give 2-(β-(N-benzylcarbamyl)-ethylamino)-2-thiazoline (2). Both ethanolic hydrogen chloride and benzylamine failed to open the pyrimidine ring of 5-keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidine (V) under similar conditions. The greater resistance of the pyrimidine ring to opening in V than in VI is due to the relative ease of electron displacements towards the carbonyl oxygen atom in these two systems. In V the opposing electron attractive force to the electron displacement indicated by the solid arrows[3] is greater than the opposing electron attractive force in VI. This is probably the main factor contributing to relative ease of opening the pyrimidine ring in these compounds although the slight difference in the conformations of the two ring systems also may make some contribution.



EXPERIMENTAL[4]

5-Keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-a)pyrimidine

2-(β-Carboxyethylamino)-Δ²-1,3-diazacyclopentene (m.p. 209–211° C with decomp.) was prepared in 73.2% yield and the acid was esterified with ethanolic hydrogen chloride as previously described (3). On evaporation of the ethanolic solution 2-(β-carbethoxyethylamino)-Δ²-1,3-diazacyclopentene hydrochloride was obtained as a viscous oil.

[3]*The solid and broken arrows in the graphic formulas are used only for differentiation in discussion and they have no quantitative significance. Actually the degree of electron displacement in the*  *system is greater than in*  . *The effects of electronic displacements and resonance on the chemical reactivity of the bicyclic guanidines are under investigation.*

[4]*All melting points are uncorrected. Analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.*

The above ester hydrochloride (10.3 g, 0.0465 mole) in absolute methanol (200 ml) was passed through a column of IRA-400 resin in the hydroxyl form. The resin column had been previously washed with absolute methanol. After the resin had been washed with absolute methanol (150 ml), the eluate and washings were evaporated to dryness *in vacuo*. The white crystalline residue weighed 6 g (92.8% yield). It melted at 141° C, resolidified, and melted at 148–149° C. This melting point was not changed by crystallization from absolute ethanol – ether (1:2) solution. Anal. Calc. for $C_6H_9N_3O$: C, 51.78; H, 6.52; N, 30.20%. Found: C, 51.53; H, 6.31; N, 30.34%.

The picrate (m.p. 248–249° C) of 5-keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*) pyrimidine was prepared in 95% yield from ethanol solution. Anal. Calc. for $C_{12}H_{12}N_6O_8$: C, 39.14; H, 3.29; N, 22.82%. Found: C, 38.93; H, 3.41; N, 22.75%.

5-Keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-a)pyrimidinium Nitrate

5-Keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidine (0.695 g, 0.005 mole) was added to a nitration medium consisting of 98% nitric acid (2.33 ml, 0.05 mole), acetic anhydride (4.72 ml, 0.05 mole) and ammonium chloride (0.6 g, 0.011 mole). After the reaction mixture was stirred at 32° C for 2 hours, it was poured into cold absolute ether (75 ml). The ether was decanted from the oil, which was washed twice with fresh portions of absolute ether. After the oil was triturated with absolute ethanol, crystals (m.p. 129.5–131° C) separated from the oil, yield 0.57 g (56.4%). One crystallization from absolute ethanol raised the melting point to 132–133° C. Anal. Calc. for $C_6H_{10}N_4O_4$: C, 35.65; H, 4.99; N, 27.71%. Found: C, 35.56; H, 4.88; N, 27.38%.

The picrate (m.p. 247–249° C), which was prepared from absolute ethanol solution in 91.8% yield, did not depress the melting point of a known sample of 5-keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidine picrate (m.p. 248–249° C).

5-Imino-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-a)pyrimidine

2-Methylmercapto-2-imidazolinium iodide (14.64 g, 0.06 mole) and β-aminopropionitrile (4.2 g, 0.06 mole) in absolute ethanol (15 ml) were refluxed for 7 hours. Crystals (m.p. 192–198° C) separated from the solution on cooling, yield 7.43 g (46.5%). Several crystallizations from absolute ethanol raised the melting point to 201–203° C. Anal. Calc. for $C_6H_{11}IN_4$: C, 27.08; H, 4.17; N, 21.06; I, 47.69%. Found: C, 27.26; H, 4.08; N, 20.86; I, 47.43%.

Decreasing the reflux period in the above reaction in individual runs to 2 and 5.5 hours lowered the yields of 5-imino-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidinium iodide to 37.6 and 41% respectively.

The picrate (m.p. 228–231° C) was formed from aqueous solution. Recrystallization from water–ethanol (1:1) solution raised the melting point to 248–249° C. This picrate was shown by analysis and a mixed melting point determination to be identical with the picrate (m.p. 248–249° C) from 5-keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*) pyrimidine. Thus the imino group of the original compound was hydrolyzed to a keto group during the formation of the picrate in aqueous solution.

A sample of 5-imino-2,3,6,7-tetrahydro-1(H),5(H)-imidazo-(1,2-*a*)pyrimidinium iodide (9.1 g, 0.034 mole) in absolute methanol (180 ml) was passed through a column of IRA-400 resin (Cl^- form) which had been washed thoroughly with absolute methanol. The column was washed with absolute methanol (150 ml) and the eluate was taken to dryness *in vacuo* under nitrogen. The hydrochloride salt was obtained in 98.9% (5.90 g) yield. One crystallization from absolute methanol – ether (1:1) gave crystals melting at 193–194° C. Anal. Calc. for $C_6H_{11}ClN_4$: C, 41.27; H, 6.35; Cl, 20.30; N, 32.09%. Found: C, 41.42; H, 6.36; Cl, 20.44; N, 31.89%.

An ethanolic solution of a sample of 5-imino-2,3,6,7-tetrahydro-1(H),5(H)-imidazo (1,2-*a*)pyrimidinium chloride on treatment with ethanolic picric acid gave a dipicrate (m.p. 218–220° C) in 77% yield. Anal. Calc. for $C_{18}H_{16}N_{10}O_{14}$: C, 36.25; H, 2.74; N, 23.49%. Found: C, 36.50; H, 2.96; N, 23.38%.

5-Nitrimino-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-a)pyrimidinium Nitrate

5-Imino-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidinium chloride (0.75 g, 0.0043 mole) was added to a nitration medium of 98% nitric acid (2.0 ml, 0.043 mole), acetic anhydride (4.06 ml, 0.043 mole), and ammonium chloride (0.3 g, 0.0056 mole) at 0° C. The temperature was raised to 32° C and the stirred solution was maintained at this temperature for 2.5 hours. When the solution was poured into cold absolute ether (75 ml) a sticky crystalline mass separated. The ether solution was decanted from the solid, which was washed with absolute ether (3×50 cc) by decantation. The solid was triturated with absolute ethanol (50 cc) and the crystals were recovered by filtration. After this process was repeated, the crystals were dried *in vacuo* at room temperature. The crystals melted at 152.5–153° C with decomposition, yield 0.45 g (42.6%). Anal. Calc. for $C_6H_{10}N_6O_5$: C, 29.27; H, 4.10; N, 34.13%. Found: C, 29.27; H, 4.32; N, 34.47%.

After a sample of the 5-nitrimino-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidinium nitrate was refluxed in ethanol for 1.5 hours, the crystals obtained on cooling the solution melted at 131–133° C. These crystals did not depress the melting point of a known sample of 5-keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidine nitrate (m.p. 132–133° C). The infrared spectra of these two samples were also identical.

Attempts to Open the Pyrimidine Ring of 5-Keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo-(1,2-a)pyrimidine

(*A*) *With Benzylamine*

5-Keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidine (0.556 g, 0.004 mole) and benzylamine (0.43 g, 0.004 mole) in absolute ethanol (7 ml) were allowed to stand at room temperature for 17 hours. The solution was concentrated to 3 ml *in vacuo* and ether was added. The crystals (m.p. 141° C and 148–149° C) on admixture with the starting material gave no depression in melting point, yield 0.506 g (91%).

A similar experiment in which the reactants in ethanolic solution were refluxed for 3.5 hours gave an 81% recovery of starting material.

(*B*) *With Ethanolic Hydrogen Chloride*

A solution of 5-keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidine (0.278 g, 0.002 mole) in ethanolic hydrogen chloride (10 ml of absolute ethanol containing 79 mg, 0.0022 mole of hydrogen chloride) was refluxed for 2.5 hours. The cooled solution was divided into two equal parts. One part on treatment with ethanolic picric acid solution gave 5-keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidine picrate (m.p. 248–249° C) in 98% (0.36 g) yield. This picrate did not depress the melting point of a known sample of 5-keto-2,3,6,7-tetrahydro-1(H),5(H)-imidazo(1,2-*a*)pyrimidine picrate (m.p. 248–249° C).

The second portion on standing in the cold gave crystals melting at 251.5–252.5° C, yield 120 mg (68.4%). The melting point of this sample of 5-keto-2,3,6,7-tetrahydro-1(H), 5(H)-imidazo(1,2-*a*)pyrimidinium chloride was not changed by crystallization from ethanol–ether solution. Anal. Calc. for $C_6H_{10}ClN_3O$: C, 41.04; H, 5.74; Cl, 20.19; N, 23.93%. Found: C, 41.18; H, 5.91; Cl, 20.00; N, 23.34%.

REFERENCES

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3. A. F. McKay and W. G. Hatton. J. Am. Chem. Soc. **78**, 1618 (1956).