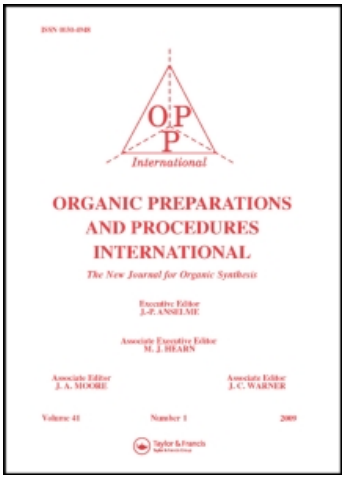

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OXIDATION OF AMINO ALCOHOLS TO AMINO KETONES

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obtain a colorless, crystalline solid, salicylaldehyde hydrazone (II). The solid was collected, washed with a small portion of cold (0°) absolute ethanol, and air dried. The combined mother liquor and ethanol washing was concentrated to a volume of approximately 65 ml and chilled to -20°. A second crop of colorless, crystalline product was obtained. The two samples were combined to provide 4.3 g (64%) of salicylaldehyde hydrazone (II), mp 96-97°, lit.[2] 96°. IR ($CHCl_3$): 3400, 3100, 2990, 2910, 1620, 1570, 1490, 1390, 1265, 1150, 1030, 940, 900 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.48 (bs, 2H, =N-NH_2), 7.12 (m, 4H, aryl), 7.95 (s, 1H, -CH=N-), 11.14 (bs, 1H, -OH).

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OXIDATION OF AMINO ALCOHOLS TO AMINO KETONES

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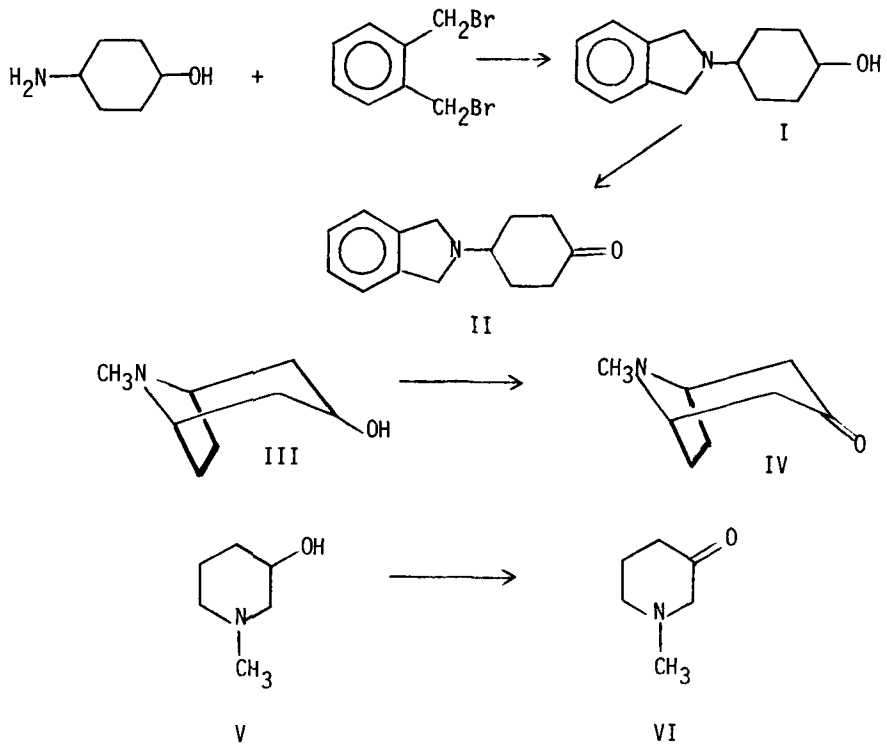
The oxidation of amino alcohols to amino ketones is experimentally difficult since the bidentate functionality of the amino ketones frequently forms strong complexes with the metal cation of the oxidizing agent complicating the isolation; moreover, the amino ketone may be oxidized further

resulting in carbon bond cleavage.[1] Since cyclic amino alcohols are conveniently prepared by the catalytic hydrogenation of available phenols,[2] a successful oxidation procedure would enhance the availability of many cyclic aminoketones.

A recent modification[3] of the Jones oxidation by chromic oxide[4] in which the isolation of aminoketones is facilitated, circumvents these problems. The successful conversion of three amino alcohols to their corresponding amino ketones by this modified procedure indicates the scope of the reaction. The β- and γ-aminoketones (IV and II, respectively) were isolated in good yields and purity. The α-aminoketone (VI) was obtained conveniently and in excellent purity, albeit in lower yield (40%) as expected, since the C-C bond of the α-aminoketone function is very sensitive to oxidation.



4-(2'-Isoindoline)cyclohexanol (I).- To 10.4 g (as a 50% aqueous solution from Fluka Chemical Co.) of 4-aminocyclohexanol was added 3.5 g (0.088 mol) of sodium hydroxide. Enough water was then added to dissolve any amino alcohol which had precipitated. A solution of 11.5 g (0.043 mol) of α,α'-dibromo-o-xylene in 100 ml of chloroform was added in one portion and the two-phase mixture was stirred rapidly overnight. The layers were separated and the chloroform layer was extracted twice with 30% ammonium hydroxide and once with water. The chloroform solution was dried ($MgSO_4$) and evaporated under reduced pressure to give 6.41 g (68%) of a crude mixture of cis- and trans-4-(-)-(2'-insoindoline)cyclohexanol (I), mp. 143-163° (acetone).

^1H NMR ($CDCl_3$): δ 7.02 (s, 4H), 3.86 (s, 4H), 3.5 (m, 1H). IR (KBR): ν_{max} 2916, 1135, 756 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45.

Found: C, 77.30; H, 8.70; N, 6.44.

Oxidation of 4-(2'-Isoindoline)cyclohexanol (I).- A solution of 2.17 g (10 mmol) of 4-(2'-isoindoline)cyclohexanol (I) in 25 ml of glacial acetic acid was further acidified with 0.53 ml of conc. H_2SO_4; then 3.75 ml of Jones reagent (prepared by diluting a solution of 13.36 g of CrO_3 in 11.5 ml of conc. H_2SO_4 to a volume of 50 ml with water) was slowly added with stirring. After 20 min, 2-propanol (5 ml) was added to destroy any excess oxidant. Water (75 ml), 8.75 g (30 mmol) of trisodium citrate dihydrate, and a piece of amalgamated mossy zinc of ∿ 3 g were added. The mixture was stirred for 20 min. The aqueous solution was extracted three times with 30 ml of chloroform each. The solution was dried ($MgSO_4$) and the chloroform evaporated to give 1.73 g (78%) of 4-(2'-isoindoline)cyclohexanone (II). An analytical sample of II (mp. 103-105.5°) was prepared by recrystallization from hexane and sublimation.

^{1}H NMR (DMSO-d_6) δ 7.05 (s, 4H), 3.91 (s, 4H), 1.75-2.85 (m, 10H). IR (Film): ν_{max} 1715, 767 cm^{-1}.

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51.

Found: C, 77.94; H, 7.78; N, 6.50.

Oxidation of Tropine (3-Tropanol, III).- To a solution of 20 g (0.14 m) of tropine in 100 ml of glacial acetic acid was added 13.0 g (0.14 mol) conc. sulfuric acid and 53 ml of Jones reagent. After 30 min, 100 ml of water, 125 g (0.42 mol) of trisodium citrate dihydrate and an ∿ 3 g piece of amalgated mossy zinc were added. The flask was flushed with argon and the mixture was allowed to stir for 15 min. About 25-50 ml of a saturated KOH solution was added and the mixture was filtered by suction. The filtrate was extracted with three 100 ml portions of chloroform. The combined chloroform extracts were dried and concentrated and the residue was distilled to give 13.7 g (70%) of tropanone (IV) as an oil, bp. 126-127°/44 mm, lit.[5] bp. 107-110°/23 mm, which solidified on standing. The solid, mp. 39-41°, lit.[5] mp. 39-43.8°, was identical with authentic tropanone (IR, NMR and TLC behavior on alumina).

Oxidation of 1-Methyl-3-hydroxypiperidine (V).- To a solution of 1-methyl-3-hydroxypiperidine (V) (Aldrich) (5 g, 43.5 mmol) in 110 ml glacial acetic acid, was added 2.4 ml of conc. H_2SO_4. Jones reagent (16.1 ml) was slowly added with cooling, and stirring was continued for 20 min. The excess oxidant was then destroyed with a saturated solution of 4.6 g of sodium bisulfite. Water (65 ml), a piece of amalgamated zinc (∿ 3 g), and 38.6 g of trisodium citrate dihydrate were added. Stirring was continued for 20 min. under argon. The solution was made basic with about 25-50 ml of 50% KOH, then saturated with solid KOH while being cooled in an ice-water bath, and extracted five times with 100 ml of ether. After removal of the solvent, the residue (3.11 g) was distilled to give 2.09 g (42%) of 1-meth-

yl-3-piperidone (VI), bp. 87-90°/38 mm; HCl salt, mp. 109-111°, lit.[6] mp. 110-111°.

^{1}H NMR ($DMSO_6$): δ 2.78 (s, 2H), 2.21 (s, 3H), 2.65-1.7 (m, 6H). IR (film): ν_{max} 2940, 2775, 1720, 1452, 1140 cm^{-1}.

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SOME 5,6- AND 2,5-DIHALONICOTINAMIDES

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(8/20/79)

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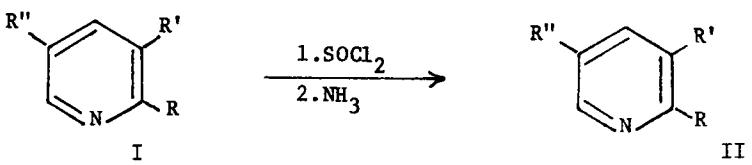
A number of dihalonicotinamides (IIa-f) have been prepared.



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