***N*-Benzoyl-*N*-methyl-1-adamantanamine-4α,6α-diol Diformate (6).**—A mixture of 3.01 g of *N*-benzoyl-*N*-methyl-1-adamantanamine-4α,6α-diol (**5**), 20 ml of dimethylformamide, and 5.5 g of triphenylphosphine under nitrogen was stirred in an ice bath and treated dropwise with bromine until an orange color persisted. After 1 hr, the mixture was diluted with water and extracted with methylene chloride; the extract was washed with 5% sodium bicarbonate solution and dried (Na_2SO_4). The solvent was removed and the residue was recrystallized from acetone–water: yield 1.20 g; mp 142–144°; ir (Nujol) 1730 (formate), 1630 cm^{-1} (amide); nmr ($CDCl_3$) δ 7.96 (s, 2, HC=O), 7.25 (s, 5, C_6H_5), 5.08 (m, 2, CHO–), 2.79 (s, 3, NCH_3).

Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.31; H, 6.64; N, 4.56.

Hydrolysis to *N*-Benzoyl-*N*-methyl-1-adamantanamine-4α,6α-diol (5).—A sample of the diformate ester **6** was converted to the free diol by warming in methanol and 10% aqueous sodium hydroxide solution. This product was identical in all respects with compound **5**.

4-(*N*-Benzoyl-*N*-methyl-1-aminoadamantoxymethylene)dimethylimmonium Iodide (2b).—When iodine was substituted in place of bromine in the above reaction with **1**, the product isolated was the iodide salt **2b**: mp 150° dec; ir (Nujol) 1695 (CH=N), 1640 cm^{-1} (amide).

Anal. Calcd for $C_{21}H_{29}N_2O_2I$: C, 53.85; H, 6.24; N, 5.98; I, 27.10. Found: C, 53.82; H, 6.22; N, 5.82; I, 27.00.

***N*-Benzoyl-*N*-methyl-4ϵ-bromo-1-adamantanamine (4).**—The compound **2a**, 5.59 g, was heated in an oil bath at 200–205° for 15 min. The mixture was cooled, treated with 25 ml of water, and extracted with methylene chloride; the extract was washed with water and dried (Na_2SO_4); the extract residue was chromatographed over 200 g of Florisil by the gradient elution method with 4 l. of solvent SSB containing increasing proportions of acetone from 0 to 25%; cuts of 70 ml each were collected. Residues from fractions 15–20 contained the C_4-bromo product **4**. Tlc of this material on a silica gel microplate developed ten times with 10% acetone in Skellysolve B showed this to be a mixture of 4α- and 4β-bromo compounds. A sample recrystallized from ether–pentane melted at 96–99°.

Anal. Calcd for $C_{18}H_{22}NOBr$: C, 62.07; H, 6.37; N, 4.02; Br, 22.95. Found: C, 62.38; H, 6.36; N, 4.19; Br, 22.81.

Reaction of 4-(4′-Hydroxy)cyclohexylcyclohexanone (7) with Triphenylphosphine Diiodide.—Triphenylphosphine (5.80 g, 0.022 mol) and 4-(4′-hydroxy)cyclohexylcyclohexanone (**7**)[8] (3.92 g, 0.020 mol) were dissolved in dimethylformamide (55 ml). Iodine crystals (5.06 g, 0.020 mol) were added to the solution over a period of 20 min at room temperature. After stirring at room temperature for 5 hr, the solution was light yellow. Methanol (5 drops) was added, causing most of the color to disappear. The solution was poured into water (300 ml) and the resulting cloudy mixture was extracted with ether (five 60-ml portions). The ether solution was washed with 5% $NaHCO_3$ solution (100 ml) and with water, then dried over $MgSO_4$. The dry ether solution was concentrated under reduced pressure, giving a mixture of liquid and crystals. This mixture was lixiviated with Skellysolve B (four times) and the solution was concentrated under reduced pressure. The residue was passed through silica gel (300 g) in 1:1 ethyl acetate–Skellysolve B, separating the products (fractions 1 and 2) from triphenylphosphine oxide. The presence of a formate ester (**9**) in the product mixture (fraction 2) was suggested by spectral evidence (a signal at δ 8.00 in the nmr and a band at 1720 cm^{-1} in the ir spectrum). Hydrolysis (5 ml of 5% $NaHCO_3$ plus 50 ml of CH_3OH) of the product mixture (fractions 1 and 2, reflux for 20 min) caused disappearance of one product (on tlc) and appearance of starting keto alcohol **7**, some of which crystallized and was recovered. The remaining product mixture was chromatographed on silica gel (300 g, 3.5 cm column) packed with 20% ethyl acetate in Skellysolve B. Elution with the same solvent (335-ml fractions) gave fraction 1, crystalline triphenylphosphine, identified by ir spectrum; fraction 2, triphenylphosphine and an olefinic component, δ 7.3 and 5.65, respectively, in the nmr spectrum; fraction 3, olefinic component plus 4-(4′-iodo)cyclohexylcyclohexanone; fraction 4, 4-(4′-iodo)cyclohexylcyclohexanone (**8**), δ 4.84 in the nmr for ICH, 0.551 g of viscous oil.

Registry No.—DMF, 68-12-2; **2a**, 32653-72-8; **2b**, 32653-73-9; **3**, 32653-74-0; **4α**, 32653-75-1; **4β**, 32653-76-2; **6**, 32653-77-3; **8**, 32670-59-0.

Transannular Reactions of Heptamethylenimine Derivatives

ROY A. JOHNSON

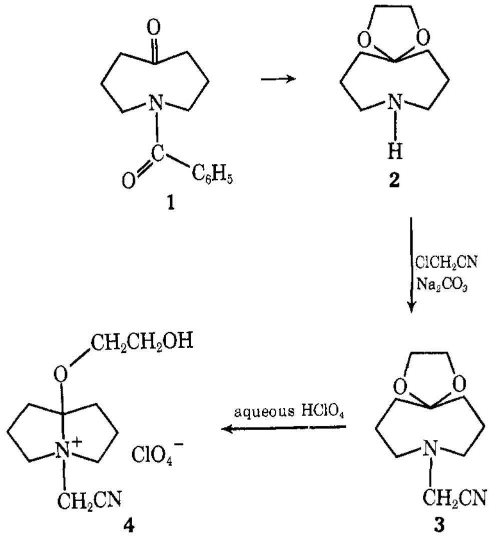
Research Laboratories, The Upjohn Company,
Kalamazoo, Michigan 49001

Received June 9, 1971

Microbial oxygenation of *N*-benzoylheptamethylenimine has provided a source of the 5-oxo derivative **1**, which can be modified to molecules that undergo transannular reactions.[1] Described below are two additional, unusual transannular reactions encountered in work with compounds derived from **1**.

Interception of Ketal Hydrolysis by Transannular Amine.—A large variety of nucleophiles other than water participate in reactions with acetals and ketals. Under anhydrous conditions, the acid-catalyzed exchange with alcohols is well known,[2] while other reports have demonstrated reaction with hydride,[3] Grignard reagents,[3b,4] imide nitrogen,[5] and amine nitrogen.[6] Participation of oxygen[7] and sulfur[8] in the hydrolysis of acetals has also been observed.

With the exception of the unusual example cited above, amine ketals generally form stable acid salts[9] under anhydrous conditions. We have hydrolyzed several amine ketals with no apparent anomalies.[1] However, when the amine ketal **3**, prepared from **1** *via* **2**



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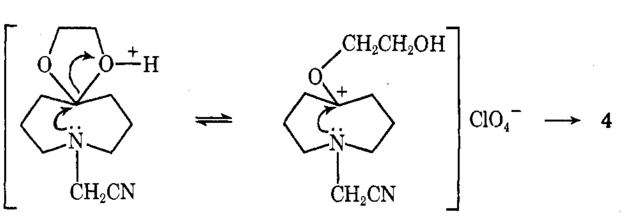
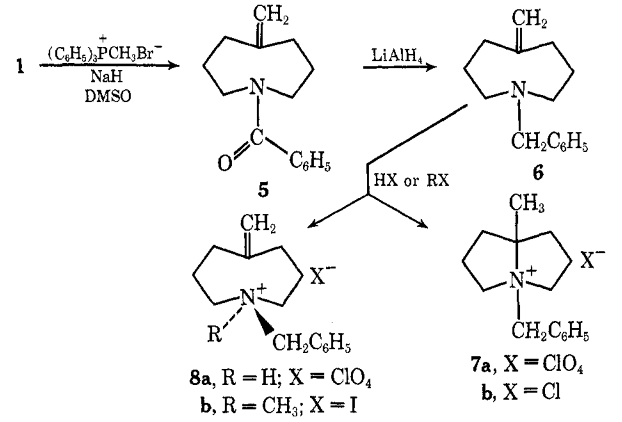
by a known procedure,[10] was allowed to react with aqueous (70%) perchloric acid in ethanol at temperatures of 10–30°, a water-soluble salt **4** was obtained after 15 min. The infrared spectrum (see Experimental Section) of the salt shows the presence of a hydroxyl group, and the nmr spectrum shows that the ethylene glycol moiety remains in the molecule. A structure fitting these requirements, and those of the elemental analysis, is the one that results from interception by the amine nitrogen of an intermediate ion during the hydrolysis of the ketal.

It seems probable that the reduced basicity[11] of the cyanomethyl-substituted amine **3** allows protonation of a ketal oxygen to compete with protonation of the nitrogen. The proximity of the nitrogen to the potential ketal carbonium ion permits the nitrogen to intercept the hydrolysis either by attack as the carbonium ion forms or in a concerted attack on the carbon as the oxonium ion forms and the C–O bond breaks. The latter pathway may be expected to accelerate the rate of the hydrolysis reaction.



Transannular Enamine.—We were curious as to whether an enamine could conveniently be prepared from intermediate **1** and would undergo transannular reaction. To this end, a Wittig reaction of **1** with methyltriphenylphosphonium bromide was carried out. The resulting methylene amide **5** was reduced with lithium aluminum hydride, giving the transannularly disposed enamine **6**.



Several experiments show that **6** may react as either a transannular enamine or as a typical amine. Thus, from reaction with 70% aqueous perchloric acid, there was obtained a crystalline salt having the properties of structure **7a** and a residual mixture containing **7a** and tertiary amine perchlorate, **8a**. Reaction of **6** with either benzoyl chloride or acetyl chloride in dioxane resulted in formation of crystalline salt **7b** in yields of 78 and 69%, respectively. Formation of this salt undoubtedly resulted from the presence of hydrogen chloride in the reaction, even though efforts were made to maintain anhydrous conditions. Finally, reaction of **6** with methyl iodide resulted in isolation of salt **8b** in low yield.

A few related transannular enamine reactions have been reported previously. Transannular cyclization of nitrogen to a styrenelike olefinic bond has been studied,[12] as has been cyclization to the olefinic bond of unsaturated lactams.[13] More recently, cyclization to an exocyclic methylene group has been noted.[14]

Experimental Section

1,4-Dioxa-9-azaspiro[4.7]dodec-9-ylacetonitrile (3).—A solution of 1,4-dioxa-9-azaspiro[4.7]dodecane (**2**)[1] (10.215 g, 0.0597 mol) in benzene (25 ml) was added slowly to a stirred mixture of chloroacetonitrile (6.0 g, 0.0795 mol) in benzene (125 ml) and anhydrous sodium carbonate (4.0 g). During the course of addition (15 min), the mixture was warmed to near the reflux temperature and then was heated to reflux with stirring for 18 hr, giving a light yellow solution over a brown and white precipitate. The precipitate was dissolved in dilute aqueous sodium bicarbonate solution. The benzene layer was washed twice with water and dried over magnesium sulfate. Concentration of the benzene under reduced pressure gave an oil which crystallized upon cooling. The crystalline material dissolved in hot Skellysolve B, leaving a small amount of gummy, yellow residue and giving a colorless solution. Cooling gave colorless crystals (8.960 g), mp 77–78°. A second crop, mp 75–77° (1.726 g, total 10.686 g, 0.0508 mol, 85%), was obtained from the concentrated filtrate. Recrystallization from Skellysolve B gave colorless needles, mp 78–79°, $\nu_{C\equiv N}$ 2220 cm^{-1} in Nujol.

Anal. Calcd for $C_{11}H_{18}N_2O_2$ (210.27): C, 62.83; H, 8.63; N, 13.32. Found: C, 62.44, 63.24; H, 8.35, 9.02; N, 13.80, 13.74.

4-Cyanomethylhexahydro-7a-(β-hydroxy)ethoxy-1*H*-pyrrolizinium Perchlorate (4).—Aqueous 70% perchloric acid (5 drops) was added to a solution of **3** (0.105 g, 0.000500 mol) in absolute ethanol (2.0 ml), which was kept cold on an ice bath. An oily precipitate formed, which solidified. Ether (6.0 ml) was added to the mixture, which was kept at room temperature overnight. The solid, mp 160–170° (0.122 g, 0.000393 mol, 78%) was collected by filtration and washed with ethanol (3.0 ml). Two recrystallizations from ethanol gave colorless crystals: mp 184–186°; ν_{OH} 3540 cm^{-1} in Nujol; nmr (DMF-d_7) δ 4.83 (s, NCH_2CN), 4.59 (OH), 3.91 (m, 8 H, N^+CH_2–, $-OCH_2$–), 2.42 (m, 8 H, CCH_2C).

Anal. Calcd for $C_{11}H_{19}N_2O_6Cl$ (310.74): C, 42.51; H, 6.16; N, 9.02. Found: C, 42.85; H, 6.26; N, 9.13.

At temperatures lower than 10°, a solid precipitated immediately upon addition of the perchloric acid to **3**. The solids obtained in this way varied from having weak hydroxyl absorption to strong absorption at 3350 cm^{-1} and exhibited wide melting point ranges, probably the result of varying degres of ketal hydrolysis at the lower temperatures.

1-Benzoyl-5-methyleneheptamethylenimine (5).—Sodium hydride (0.0700 mol) was washed with pentane (three 50-ml portions), the flask was flushed with nitrogen until the hydride was dry, and dimethyl sulfoxide (100 ml) was added. The mixture was stirred and heated to 75–80°. After 15–20 min at this temperature, bubbling stopped and a clear, yellowish solution was obtained. The solution was cooled on an ice bath and methyltriphenylphosphonium bromide (25.0 g, 0.070 mol) was added, giving a yellow-orange solution. After 10 min, a solution of 1-benzoylhexahydro-5(2*H*)-azocinone (**1**)[1] (12.35 g, 0.0534 mol) in dimethyl sulfoxide (50 ml) was added, causing the resulting solution to bcome warm. The solution was stirred at room temperature for 16 hr and poured into water (80 ml). The aqueous solution was extracted with pentane (five 75-ml portions).

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The pentane solution was washed with 1:1 dimethyl sulfoxide–water (two 50-ml portions) and with 50% aqueous sodium chloride. The pentane solution was dried over magnesium sulfate and concentrated to a colorless oil, which crystallized when kept in the refrigerator overnight. Recrystallization from cold Skellysolve B gave 5.05 g (0.022 mol, 41%) of crystals, mp 36–37°. Two recrystallizations from cold Skellysolve B gave colorless crystals: mp 36–37°; $\nu_{C=O}$ 1625, $\nu_{C=C}$ 1600, 1575, 1495, $\nu_{=CH_2}$ 880, ν_{Ph} 780, 730, 700 cm^{-1} in Nujol; nmr ($CDCl_3$) δ 7.33 (s, 5 H, C_6H_5), 4.86 (s, 2 H, $=CH_2$), 3.8–3.15 (m, 4 H, NCH_2), 2.45–1.50 (m, 8 H, $-CH_2-$).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.10; H, 8.32; N, 6.51.

1-Benzyl-5-methyleneheptamethylenimine (6).—A solution of **5** (5.05 g, 0.0220 mol) in ether (50 ml) was added to a mixture of lithium aluminum hydride (3.5 g) and ether (200 ml). The mixture was heated at reflux temperature for 5 hr. Ethyl acetate and water were added to consume the excess hydride and the inorganic solids were collected by filtration. The ether filtrate was dried over magnesium sulfate and concentrated to an oil. The oil was transferred to a 10-ml distillation flask with ether and distilled, giving 3.687 g (0.0171 mol, 78%) of colorless oil: bp 78–80° (0.05 mm); λ_{max} in 95% ethanol 258 mμ (ε 508), 263 (362), 268 (254); $\nu_{=CH}$ 3060, 3020, $\nu_{C=C}$ 1630, 1595, 1490, ν_{Ph} 724, 700 cm^{-1} on the oil; nmr ($CDCl_3$) δ 7.29 (m, 5 H, C_6H_5), 4.76 (s, 2 H, $=CH_2$), 3.61 (s, 2 H, $NCH_2C_6H_5$).

Anal. Calcd for $C_{15}H_{21}N$: C, 83.66; H, 9.83; N, 6.51. Found: C, 84.14, 82.96; H, 10.53, 9.93; N, 5.44, 6.18.

4-Benzylhexahydro-7a-methyl-1*H*-pyrrolizinium Perchlorate (7a). Aqueous perchloric acid (70%, 20 drops) was added to a solution of **6** (0.42 g, 0.0195 mol) in absolute ethanol (5.0 ml). The solution was heated to reflux for 90 min. Addition of ether (25 ml) caused rapid separation of a first crop of 0.148 g of colorless crystals, mp 195–198°. Recrystallization from absolute ethanol gave colorless crystals: mp 215–216°; $\nu_{C=C}$ 1580, 1495, ν_{Ph} 770, 710 cm^{-1} in Nujol; nmr (DMF-d_7) δ 4.53 (s, $PhCH_2N$), 3.63 (m, $-CH_2NCH_2-$), 2.32, 2.26 (s, $-CH_2-$), 1.75 (s, $-CH_3$).

Anal. Calcd for $C_{15}H_{22}NO_4Cl$: C, 57.05; H, 7.02; N, 4.44. Found: C, 56.79; H, 7.10; N, 4.85.

The filtrate from the isolation of product above was kept in the freezer overnight. Colorless crystals, appearing to be a mixture of **7a** and **8a**, mp 60–80°, 140–145° (0.269 g), formed and were collected: $\nu_{=CH}$ 3140, $\nu_{C=C}$ 1630, 1575, 1492, ν_{Ph} 751, 697 cm^{-1} in Nujol. Two recrystallizations from ethanol–ether gave colorless crystals, softening at 90–100°, mp 140–145°. Recrystallization of 0.16 g from absolute ethanol, preceded by heating in refluxing ethanol for 1 hr, gave colorless crystals (0.03 g), partial softening at 140–150°, mp 190–205°.

4-Benzylhexahydro-7a-methyl-1*H*-pyrrolizinium Chloride (7b). A. From Attempted Benzoylation of 1-Benzyl-5-methyleneheptamethylenimine.—A solution of **6** (0.314 g, 0.00146 mol) in dioxane (reagent grade, 5.0 ml) was added to a solution of benzoyl chloride (0.218 g, 0.00156 mol) in dioxane (5.0 ml). Crystals began forming after 30 min at room temperature and were collected after 22 hr, giving 0.289 g (0.00115 mol, 78%) of product, mp 282–284° dec. Two recrystallizations from ethanol–ether, the last preceded by decolorization with activated charcoal, gave colorless crystals: mp 295–296 subl; $\nu_{C=C}$ 1600, 1580, 1495, ν_{Ph} 770, 720 cm^{-1} in Nujol; nmr $PhCH_2N$ (δ 4.68, singlet), $-CH_2-$ (2.35, 2.29, singlets), $-CH_3$ (1.82, singlet) in dimethylformamide-d_7 at 95°.

Anal. Calcd for $C_{15}H_{22}NCl$: C, 71.54; H, 8.81; N, 5.56. Found: C, 71.46; H, 8.99; N, 5.79.

B. From Attempted Acetylation of 1-Benzyl-5-methyleneheptamethylenimine.—The above compound (**7b**) was obtained from addition of a solution of **6** (0.387 g, 0.0018 mol) in dioxane (dried over sodium, 5.0 ml) to a solution of acetyl chloride (0.153 g, 0.00195 mol) in dioxane (5.0 ml), giving, after 6 hr, 0.313 g (0.00125 mol, 69%) of product, mp 272–275° dec. The infrared spectrum in Nujol is identical with that of the above product.

1-Benzyl-1-methyl-5-methyleneheptamethyleniminium Iodide (8b).—Excess methyl iodide was added to a solution of **6** (0.143 g, 0.665 mol) in methanol (5 ml). After 3 days at room temperature, the now yellow solution was partially concentrated by evaporation on the steam bath. Ether was added to the solution, which became cloudy. Crystals slowly formed and, after cooling the mixture in the refrigerator, were collected, mp 187–189°. Two recrystallizations from methanol–ether gave colorless crystals of **8b**: mp 184–186°; nmr ($CDCl_3$) δ 7.7 (m, 5 H, $-C_6H_5$), 5.00 (s, 2 H, $=CH_2$ or $-NCH_2Ph$), 4.93 (s, 2 H, $=CH_2$ or NCH_2Ph), 3.66 (m, 4 H, $-NCH_2-$), 3.18 (s, 3 H, $-CH_3$), 2.35 (m, 8 H, $-CH_2-$).

Anal. Calcd for $C_{16}H_{24}NI$: C, 53.78; H, 6.77; N, 3.92. Found: C, 53.73; H, 6.75; N, 4.36.

Registry No.—**3**, 32674-93-4; **4**, 32674-94-5; **5**, 32674-95-6; **6**, 32674-96-7; **7a**, 32674-97-8; **7b**, 32670-60-3; **8a**, 32670-61-4; **8b**, 32653-78-4.

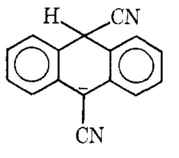
Reaction of Cyanide Ion with Aromatic Nitriles and Aromatic Heterocyclic Compounds in Dipolar Aprotic Solvents. Cyanide Exchange[1]

RICHARD B. CHAPAS, R. F. NYSTROM, AND H. R. SNYDER*

School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

Received May 11, 1971

The cyanation of electronegatively substituted aromatic compounds and of unsaturated hydrocarbons containing extended π systems by treatment with sodium cyanide and an oxidizing agent in aprotic solvents offers attractive synthetic possibilities.[2] The reaction has been considered to proceed *via* reversible addition of cyanide ion to the substrate to yield a carbanion (*e.g.*, **1**, from 9-cyanoanthracene) which is then converted to the cyanation product by the action of the oxidizing agent. A similar addition of cyanide ion to a heterocyclic aromatic system has been proposed by Happ and Janzen[3] to account for the esr spectrum observed when acridine is treated with cyanide ion in air-saturated dimethylformamide (DMF); the spectrum is that of the radical anion resulting from the action of oxygen on the carbanion **2**. These authors have also studied the esr spectrum of the radical anion formed by the attack of oxygen on the 9-cyanoanthracene adduct (**1**). In the present study, undertaken before the publication of the work of Happ and Janzen, the oxidizing agent (sodium anthraquinone-α-sulfonate, α-SAS) preferred for the conversion of 9-cyanoanthracene and cyanide ion to 9,10-dicyanoanthracene has been found highly effective for the conversion of acridine and sodium cyanide to 9-cyanoacridine. This result is in accord with the postulation of the similar intermediates **1** and **2**. Further evidence for intermediates such as **1** and **2** has been sought by the use of labeled cyanide ion in reactions with electronegatively substituted aromatic compounds. The use of labeled cyanide in the



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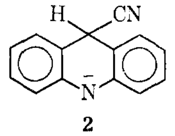

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[1] Grateful acknowledgment is made to the U. S. Army Research Office for partial support of this work [Grant DA-ARO(D)-G857].

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[3] E. H. Janzen and J. W. Happ, *ibid.*, **35**, 96 (1970).