Reactions of 1-Azaazulan-2-one and Its 3-Substituted Derivatives[1]

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Chemical properties of 1-azaazulan-2-one (I) and its 3-substituted derivatives such as 3-acetyl, 3-cycloheptatrienyl and 3-ethoxycarbonyl were investigated. It was shown that the electrophilic substitution reactions take place at the 3-position, replacement of the substituents occuring in some cases by the reactions with cationoid reagents. The Beckmann rearrangement, Curtius rearrangement, Hofmann degradation reaction, Stevens-McFadyen reaction, *etc.* of these compounds are described.

Since 1-azaazulan-2-one (I) (cyclohepta[*b*]pyrrol-2-one) and its 3-ethoxycarbonyl derivative (II) were synthesized,[2,3] new synthetic methods,[4] and some electrophilic and nucleophilic substitution reactions[2,3,5] of I and its derivatives have been investigated. However, the chemical properties of 3-substituted derivatives of I have not been published, except for its 3-formyl (III)[6] and 3-dimethylamino[7] derivatives. In some cases[2,8] abnormal reactions are known to take place on the seven-membered ring moiety of an azulene skeleton during the reactions of functional groups on the five-membered ring moiety. We have thus prepared 3-acetyl and 3-cycloheptatrienyl derivatives of I by means of cationoid reactions of I and investigated their chemical properties.

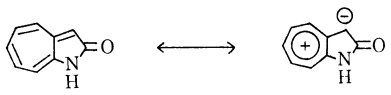
The reaction of I and 7-tropyl ethyl ether in the presence of a small amount of hydrochloric acid gave 3-(cycloheptatrien-7-yl)-1-azaazulan-2-one (IV). When IV was treated with mineral acids, bromine and *p*-tolyldiazonium chloride, compound (I), 3-bromo-1-azaazulan-2-one isolated as its *N*-acetate, and 3-(*p*-tolylazo)-1-azaazulan-2-one (VI) were obtained, respectively.

The Vilsmeyer reaction of I by means of dimethylacetamide afforded 3-acetyl-1-azaazulan-2-one (VII).[4a] The reaction of VII with iodine and pyridine gave 3*N*-pyridiniummethylcarbonyl-1-azaazulan-2-one and subsequent base treatment afforded 3-carboxy-1-azaazulan-2-one (VIII).[3] However, VIII could not be obtained by the usual iodoform reaction of VII. The catalytic reduction and Clemensen reduction of VII gave only resinous substances.[9]

Although VII gave the corresponding oxime (IX) and hydrazone (X), large excess hydrazine was necessary for the formation of X. When an equivalent amount of hydrazine was used, sparingly soluble azine derivative (XI) was formed as the sole product. In the Beckmann rearrangement of IX, the use of sulfuric acid caused only elimination of the substituent at the 3-position to give I, but the rearrangement proceeded smoothly and gave *N*-acetyl-3-acetylamino-1-azaazulan-2-one (XII)[3] when acetic anhydride was employed. The Wolff-Kishner reduction of X with potassium hydroxide in ethylene glycol gave only resinous substances, but with sodium ethoxide in absolute alcohol or potassium hydroxide in alcohol, it afforded *ca.* 40% of VII.

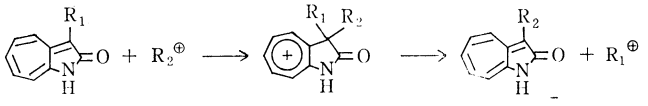
Treatment of 3-ethoxycarbonyl-1-azaazulan-2-one (II) with ammonia and hydrazine gave the corresponding 3-carbamoyl (XIII) and 3-hydrazidocarbonyl (XIV) derivatives, respectively. Reaction of XIII with bromine in methanol and subsequent acetylation gave XII. Diazotization of XIV afforded an unstable azidocarbonyl derivative (XV) which shows a strong characteristic absorption band at 2120 cm^{-1}.[10] Although XV could not be isolated in the pure state, heating in acetic anhydride caused the Curtius rearrangement to give 3-acetamido derivative (XII). The Stevens-McFadyen degradation of XIV by the reaction with tosyl chloride gave the expected 3-formyl derivative (III) in a good yield.

The electron density of I is high at the 3-position with a contribution of canonical formula such as Ia.[2,11] Thus, electrophilic substitution reactions of I proceed readily to give IV and VII in good yields.



I Ia

If substituents at the 3-position of I can be eliminated as stable cations such as tropylium ion, the exchange reaction of substituents takes place by attack of the second electrophilic reagents as shown below. This is the case of the reactions of IV with other electrophiles. The elimination reaction of acetyl oxime group of IX may be explained analogously.



In the case of the Hofmann and Curtius reactions of XIII and XV, an intramolecular reaction takes place between the electron rich center (C_3) and the electron deficient center (nitrogen) and the rearrangements proceed smoothly. Analogous elimination reactions at the 3-position of azulenes[12] and azaazulanes[5] have been observed.

All the compounds obtained are listed in the following table.

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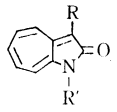
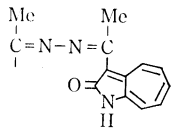
TABLE



	R	R′
III:	CHO	H
IV:		H
V:	Br	Ac
VI:	p-$MeC_6H_4N_2$–	H
VII:	Ac	H
VIII:	COOH	H
IX:	MeC=NOH	H
X:	MeC=NNH_2	H
XI:		H
XII:	NHAc	Ac
XIII:	$CONH_2$	H
XIV:	$CONHNH_2$	H
XV:	CON_3	H

Experimental[13]

3-(Cycloheptatrien-7-yl)-1-azaazulan-2-one (IV). To a solution of 1.45 g of I in 30 ml of ethanol and 20 ml of benzene containing a few drops of concd. hydrochloric acid was added 2.95 g of tropyl ethyl ether with stirring and the reaction mixture was allowed to stand at room temperature for 3 hr. The precipitates formed were collected by filtration to give 2.10 g of orange scales of IV, mp 213—215 °C from dioxane.

Found: C, 81.68; H, 5.57; N, 5.95%. Calcd for $C_{16}H_{13}ON$: C, 82.21; H, 5.83; N, 5.79%.

Acetate of IV. A solution of 470 mg of IV in 10 ml of acetic anhydride was heated at 120 °C for 3 hr, and the solvent was removed under reduced pressure. The residue was recrystallized from cyclohexane to give 360 mg of orange yellow needles, mp 132—133 °C.

Found: N, 4.75%. Calcd for $C_{18}H_{15}O_2N$: N, 5.05%.

Bromination of IV. A solution of 235 mg of IV and 180 mg of bromine in 5 ml of acetic acid was stirred for one hr. After the solvent had been removed under reduced pressure, the residue was heated with 1 ml of acetic anhydride for 1 hr. Excess acetic anhydride was removed and the residue was recrystallized from ethyl acetate to give 200 mg of orange yellow needles, mp 245—247 °C which was identical with the authentic sample of *N*-acetyl-3-bromo-1-azaazulan-2-one.[3]

Azo-coupling Reaction of IV. p-Tolyldiazonium chloride prepared from 110 mg of p-toluidine was added with stirring to a solution of 235 mg of IV in 5 ml of dioxane cooled in an ice bath. After 3 hr, the precipitates formed were collected by filtration and recrystallized from cyclohexane–acetone to give 200 mg of 3-(p-tolylazo)-1-azaazulan-2-one, mp 153—154 °C which was identical with the authentic sample of the azo compound.[3]

3-Acetyl-1-azaazulan-2-one (VII). To a solution of 500 mg of I in 3 ml of dimethylacetamide cooled in an ice bath was added 1.0 g of phosphorus oxychloride with stirring. The reaction mixture was allowed to stand for 4 days at room temperature, and was then poured into crushed ice containing 1.0 g of sodium acetate and extracted with chloroform. The combined chloroform layer was washed with saturated sodium bicarbonate, water, dried over sodium sulfate, and then concentrated. The residue was chromatographed on alumina. Benzene–ether (1: 1) elutes afforded 380 mg of yellow needles of VII, mp 297—299 °C from cyclohexane–acetone.

1-Azaazulan-2-on-3-carboxylic Acid (VIII). A solution of 500 mg of VII and 800 mg of iodine in 5 ml of pyridine was stirred for 24 hr. To this was added 20 ml of 10% of sodium hydroxide and heated for 4 hr on a water bath. The solution was then acidified with 1 M hydrochloric acid to give precipitates. Recrystallization of the precipitates from methanol gave 260 mg of VIII, mp 200—202 °C (decomp.), which was identical with the authentic sample.[3]

Oxime of VII (IX). An equivalent of VII, two equivalents of hydroxylamine and of sodium acetate in alcohol were refluxed for 5 hr. After the alcohol had been removed, the residue was washed with water and recrystallized from alcohol to give the oxime in a quantitative yield, mp 241 °C (decomp.).

Found: C, 62.84; H, 5.24; N, 13.53%. Calcd for $C_{11}H_{10}O_2N_2 \cdot 1/2H_2O$: C, 62.55; H, 5.25; N, 13.26%.

Beckmann Rearrangement of IX. a) A solution of 290 mg of IX in 9 M sulfuric acid was heated on a water bath for 2.5 hr. After being cooled the reaction mixture was poured onto crushed ice, and the resulting precipitates were collected by filtration. Recrystallization from alcohol gave 157 mg of I.

b) A solution of 700 mg of IX in 10 ml of acetic anhydride was heated under reflux for 4 hr, and excess acetic anhydride was removed under reduced pressure. The residues were recrystallized from alcohol to give 420 mg of XII, mp 265—267 °C.

Found: C, 63.68; H, 4.45; N, 11.64%. Calcd for $C_{13}H_{12}O_3N_2$: C, 63.92; H, 4.95; N, 11.47%.

Hydrazone of VII (X). A solution of 1.13 g of VII and 12 equivalents of hydrazine hydrate and 0.5 ml of 6 M hydrochloric acid in 100 ml of alcohol was refluxed for 6 hr. The precipitates formed were collected by filtration. Recrystallization from alcohol containing hydrazine gave dark red needles of X, mp 270 °C; yield 986 mg.

Found: C, 65.76; H, 5.74; N, 20.23%. Calcd for $C_{11}H_{11}ON_3$: C, 65.67; H, 5.51; N, 20.88%.

When the reaction was carried out with 1.2 equivalent moles of hydrazine, the azine (XI) of VII was formed quantitatively. The azine is hard to purify and did not give good analysis.

Diacetate of XI. A solution of 242 mg of XI and 1 ml of acetic anhydride in 10 ml of pyridine was refluxed for 7 hr. The usual treatment gave 208 mg of diacetate of XI, mp 270 °C (decomp.); orange yellow needles from ethyl acetate.

Found: C, 68.09; H, 4.73; N, 11.99%. Calcd for $C_{26}H_{22}O_4N_4$: C, 68.71; H, 4.88; N, 12.33%.

Wolff-Kishner Reduction of X. A solution of 178 mg of X and 525 mg of potassium hydroxide in 200 ml of alcohol was refluxed for 8 hr. Alcohol was then removed under reduced pressure. The residue was washed with 1 M hydrochloric acid and water, and recrystallization from alcohol gave 124 mg of VII.

When the reaction was carried out with 2.4 equivalent moles of sodium ethoxide in absolute alcohol and treated as above, 40% of VII and 6.5% of XI were obtained together with some resinous substances. The reaction in boiling ethylene glycol gave only intractable resinous substances.

3-Carbamoyl-1-azaazulan-2-one (XIII). A solution of 500 mg of II in 10 ml of alcohol cooled in an ice bath was saturated with ammonia gas and allowed to stand for 6 hr at room temperature, and then heated on a water bath for 1 hr. After excess alcohol was removed, the residue obtained was recrystallized from cyclohexane–acetone to give yellow prisms of XIII, mp 186—187 °C; yield, 420 mg.

Found: C, 64.25; H, 4.71; N, 15.14%. Calcd for $C_{10}H_8O_2N_2$: C, 63.82; H, 4.29; N, 14.89%.

3-Hydrazinocarbonyl-1-azaazulan-2-one (XIV). A solution of 500 mg of II and 350 mg of hydrazine hydrate in 10 ml of alcohol was heated on a water bath for 1 hr and then concentrated. The residue formed was recrystallized from alcohol to give 450 mg of orange yellow needles of XIV, mp 198—200 °C.

Found: C, 59.03; H, 4.20; N, 20.55%. Calcd for $C_{10}H_9O_2N_3$: C, 59.10; H, 4.46; N, 20.68%.

Hofmann Degradation of XIII. A solution of 320 mg of XIII, 270 mg of bromine in 10 ml of absolute methanol containing 80 mg of sodium was refluxed for 1 hr, and excess reagents and the solvent were removed under reduced pressure. The residue was treated with 5 ml of boiling acetic anhydride for 3 hr, concentrated, and extracted with benzene. The combined benzene extracts were washed with water, dried over sodium sulfate and concentrated. The residue obtained was recrystallized from cyclohexane–acetone to give 270 mg of orange scales of XII, mp 265—267 °C, which was identical with the authentic sample of 1-acetyl-3-acetylamino-1-azaazulan-2-one.[3]

Curtius Rearrangement of XIV. A solution of 600 mg of XIV and 250 mg of sodium nitrate in 10 ml of dimethylformamide was stirred at room temperature. To this was added dropwise 2 ml of acetic acid and stirring was continued for 24 hr. Crystalline substances precipitated were collected by filtration, washed with water, and dried in a desiccator to give the acid azide (XV), mp 280—285 °C (decomp.); yield, 520 mg. ν_{KBr}: 2120, 1670, and 1590 cm^{-1}.

Five hundred mg of XV was heated under reflux for 5 hr in 5 ml of acetic anhydride, and acetic anhydride was removed under reduced pressure. The residue was recrystallized from acetone–cyclohexane to give 340 mg of XII, mp 263—265 °C.

Stevens-McFadyen Reaction of XIV. Five hundred mg of tosyl chloride was added in small portions with stirring to a solution of 500 mg of XIV in 5 ml of pyridine and 10 ml of dimethylformamide. The reaction was continued for 48 hr at room temperature. The precipitate formed was then collected by filtration and recrystallized from acetone–cyclohexane to give 360 mg of yellow needles, mp 283—285 °C, which was identical with the authentic sample of 3-formyl-1-azaazulan-2-one.[6]

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