BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 46, 3530—3533 (1973)

Application of the Mannich Reaction to 1-Azaazulan-2-one. Syntheses of Seven-Membered Analogues of Tryptophan and Related Compounds[1]

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(Received August 23, 1973)

Application of the Mannich reaction to 1-azaazulan-2-one (I) gave 3-dimethylamino-1-azaazulan-2-one (III) in a good yield. Tryptophan analogue and related compounds having this structure (I) were synthesized by the reactions of the quaternary base (VI) of III with potassium cyanide and diethyl acetylaminomalonate. Also, some other reactions of III and VI are reported.

Since 1954, the syntheses and reactions of 1-azaazulan-2-ones (2*H*-cyclohepta[*b*]pyrrol-2-ones) have been investigated,[2,3] and also synthetic studies of some physiologically interesting derivatives of them have been carried out.[4] However, the syntheses of physiologically more interesting 1-azaazulan-2-one derivatives whose structures are analogous to indolacetic acid and/or tryptophan have only been quoted by one of the authors (T.N.) in the monograph.[5] In this paper, we wish to describe the experimental details about the syntheses of seven-membered analogues of tryptophan and related compounds having 1-azaazulan-2-one (I) structure by the application of Mannich reaction.

(I) (Ia)

It is known that I is a tautomer of 2-hydroxy-1-azaazulane (Ia), though the keto-form (I) is predominant,[5] and the electron density is high at the 3-position[6] as in the case of azulene. In fact the electrophilic substitution reactions take place at its 3-position.[2a,d] Therefore, the Mannich reaction to I was expected to give good results. When the reaction was applied to I, 3-morpholinomethyl-1-azaazulan-2-one (II) and 3-dimethylamino-1-azaazulan-2-one (III) were obtained in good yields, respectively. However, fairly large amounts of bis[1-azaazulan-2-on-3-yl]methane (IV)[4a] were formed as a by-product when diluted acetic acid was employed as a solvent. The formation of the same type of bis-methylene compounds was observed in the cases of hydroxymethylation of I[4a] and the Mannich reactions of several azulene compounds.[7] Not as in the case of the Mannich reaction of pyrroles,[8] the order of the addition of the

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1) Taken from M. Sc. thesis of S. Nozoe (1956) and of A. Sato (1959) of Tohoku University.

2) a) T. Nozoe, S. Seto, S. Matsumura, and T. Terasawa, *Chem. Ind.* (London), **1954**, 1356, 1367. b) T. Nozoe, S. Seto, and S. Nozoe, *Proc. Japan Acad.*, **32**, 172 (1956). c) S. Seto and S. Nozoe, *ibid.*, **32**, 765 (1956). d) T. Toda, S. Seto, and T. Nozoe, This Bulletin, **41**, 2102 (1968).

3) N. Soma and G. Sunagawa, *Yakugaku Zasshi*, **82**, 418 (1962). N. Soma, *ibid.*, **82**, 892 (1962). K. Ogura, H. Sasaki, and S. Seto, This Bulletin, **38**, 306 (1965). H. Nakao, N. Soma, and G. Sunagawa, *Chem. Pharm. Bull.* (Tokyo), **13**, 828 (1965). M. Watatani, *ibid.*, **16**, 1503 (1968).

4) a) T. Toda, This Bulletin, **40**, 590 (1967). b) T. Nozoe, S. Seto, and T. Toda, *ibid.*, **41**, 208 (1968).

5) T. Nozoe and K. Kikuchi, "Dai Yuki Kagaku." Vol. 13, ed. M. Kotake, Asakura shoten, Tokyo (1960), pp. 569—572.

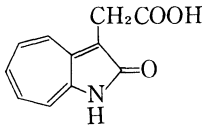
6) H. Kon, *Sci. Repts. Tohoku Univ.*, I, **38**, 67 (1954).

7) H. Arnold and K. Pahls, *Chem. Ber.*, **89**, 121 (1956); K. Hafner and W. Senf, *Ann. Chem.*, **656**, 34 (1962).

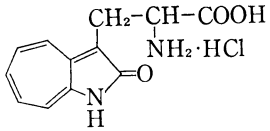
8) G. B. Bachman and L. K. Heisey, *J. Amer. Chem. Soc.*, **68**, 2498 (1946).

reagents did not cause any effect to the yields of II and III.

A catalytic hydrogenolysis of III afforded 3-methyl-1-azaazulan-2-one (V) and a treatment of III with methyl iodide gave its quaternary base (VI) respectively, in good yields. (1-Azaazulan-2-on-3-yl)acetonitrile (VII) and ethyl α-ethoxycarbonyl-β-(1-azaazulan-2-on-3-yl)propionate (VIII) were obtained by the reactions of VI with potassium cyanide and diethyl malonate, respectively. (1-Azaazulan-2-on-3-yl)acetic acid (IX), an indolacetic acid analogue, was obtained by the hydrolysis of VII. The hydrolysis of VIII and the following thermal decomposition of the free dicarboxylic acid (X) gave β-(1-azaazulan-2-on-3-yl)-propionic acid (XI).


(IX)

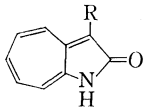
As we have reported[4a] an attempted synthesis of α-aminopropionic acid derivatives of I from the condensation products of 3-formyl-1-azaazulan-2-one with hippuric acid or nitromethane was unsuccussful. Under the modified conditions as in the case of gramine quaternary base,[9] the treatment of VI with acetoamido- and formamido-malonic acid diethyl esters afforded ethyl α-acetylamino-α-ethoxycarbonyl-β-[1-azaazulan-2-on-3-yl]propionate (XII) and ethyl α-ethoxycarbonyl-α-formylamino-β-[1-azaazulan-2-on-3-yl]propionate (XIII). α-Amino-β-[1-azaazulan-2-on-3-yl]propionic acid (XIV), a seven-membered analogue of tryptophan, was successfully obtained by the hydrolyses of XII and XIII. Application of the Schmidt reaction to ethyl α-acetyl-β-[1-azaazulan-2-on-3-yl]propionate (XV), which was synthesized from VI and acetoacetic ester, and hydrolysis of the obtained *N*-acetyl derivative (XVI) also gave XIV. The amino acid (XIV) shows red-violet colorations by the ninhydrin test.

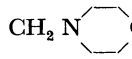
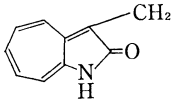

(XIV)

The reactions of quaternary base (VI) with other nucleophilic reagents, such as ethylmercaptan, diethyl nitromalonate, and methyl nitroacetate afforded [1-azaazulan-2-on-3-yl]methyl ethyl sulfide (XVII), ethyl α-ethoxycarbonyl-α-nitro-β-[1-azaazulan-2-on-3-yl]propionate (XVIII), and methyl α-nitro-β-[1-azaazulan-2-on-3-yl]propionate (XIX), respectively.

All the compounds obtained are listed in the table.

TABLE



Compound	R
I:	H
II:	
III:	CH_2NMe
IV:	
V:	Me
VI:	$CH_2\overset{\oplus}{N}(Me)_3\cdot\overset{\ominus}{I}$
VII:	CH_2CN
VIII:	$CH_2CH(COOEt)_2$
X:	$CH_2CH(COOH)_2$
XI:	CH_2CH_2COOH
XII:	$CH_2C(COOEt)_2$ NHAc
XIII:	$CH_2C(COOEt)_2$ NHCHO
XV:	$CH_2CHCOOEt$ COMe
XVI:	$CH_2CHCOOH$ NHAc
XVII:	CH_2SEt
XVIII:	$CH_2C(COOEt)_2$ NO_2
XIX:	$CH_2CHCOOMe$ NO_2

Experimental[10]

3-Morpholinomethyl-1-azaazulan-2-one (II). A mixture of 120 mg of I, 75 mg of morpholine, and 120 mg of 27% formalin was heated for 2 hr at 60 °C with stirring. After cooling, the reaction mixture was extracted with ethyl acetate and the combined organic layers were washed with water, dried over sodium sulfate and chromatographed on alumina. Alcohol elutes afforded 120 mg of orange yellow needles of II, mp 206—207 °C, from alcohol.

Found: C, 68.67; H, 6.25; N, 11.96%. Calcd for $C_{14}H_{16}O_2N_2$: C, 68.83; H, 6.60; N, 11.47%.

3-Dimethylaminomethyl-1-azaazulan-2-one (III). To a solution of 17 ml of acetic acid and 2.20 g of 40% dimethylamine, 200 mg of paraformaldehyde and 1.0 g of I were added. After it was heated for 12 hr at 40 °C, 30 ml of water was added to the solution and then brown precipitates (*ca.* 5%) formed was collected by filtration. The precipitates were recrystallized from ethyl acetate to give brown micro needles, mp>300 °C, which were identical with the authentic sample of IV[4a] by comparison of their IR spectra. The pH of the mother layer was adjusted *ca.* 10 with sodium carbonate, extracted with ethyl acetate, and the combined organic layers were washed with water. After dried over sodium sulfate, the extracts were chromatographed on alumina and alcohol elutes afforded orange red prisms of III; mp 149—150 °C, from ethyl acetate; yield 1.12 g.

Found: C, 71.26; H, 6.98; N, 13.85%. Calcd for $C_{12}H_{14}ON_2$: C, 71.35; H, 6.67; N, 13.85%.

When the reaction was carried out in the 60% aqueous acetic acid, *ca.* 30% of IV was obtained and the yield of III

9) H. R. Snyder and C. W. Smith, *ibid.*, **66**, 350 (1944); N. F. Albertson, S. Archer, and C. M. Suter, *ibid.*, **66**, 500 (1944).

10) All melting points are uncorrected.

was reduced.

3-Methyl-1-azaazulan-2-one (V). To a solution of 100 mg of III in 15 ml of methanol, 20 mg of 10% Pd-charcoal catalyst was added and then the reduction was carried out. After 13 ml of hydrogen was taken up, the catalyst was separated by filtration, and the methanol was removed by distillation. The residues were recrystallized from ethyl acetate to give orange yellow needles of V, mp 218—220 °C: yield, 95%.

Found: N, 8.85%. Calcd for $C_{10}H_9ON$: N, 8.80%.

3-Dimethylaminomethyl-1-azaazulan-2-one Methiodide (VI). Two hundred mg of III and 140 mg of methyl iodide in 2 ml of absolute alcohol were stirred for 2 hr at room temperature. The quaternary base of III was obtained as orange brown precipitates, mp 187—188 °C (dec.); yield, 300 mg.

Found: N, 8.54%. Calcd for $C_{13}H_{17}ON_2I$: N, 8.14%.

(1-Azaazulan-2-on-3-yl)acetonitrile (VII). A solution of 100 mg of potassium cyanide and 200 mg of VI in 60% alcohol was heated for 1 hr at 50 °C with stirring and then allowed to stand overnight at room temperature. After the alcohol was removed under reduced pressure, the obtained residue was washed well with water, dried in a desiccator, and recrystallized from ethyl acetate to give 80 mg of orange brown prisms of VII, mp 224—225 °C.

Found: C, 71.46; H, 4.10; N, 14.87%. Calcd for $C_{11}H_8ON_2$: C, 71.72; H, 4.38; N, 15.21%.

(1-Azaazulan-2-on-3-yl)acetic Acid (IX). One hundred mg of VII was refluxed for 4 hr in 2 ml of 20% potassium hydroxide solution, and then the solution was acidified with 6 M hydrochloric acid. The formed precipitates were collected by filtration, washed with water, dried in a desiccator and then recrystallized from alcohol to give 100 mg of IX, mp 236—237 °C (dec.).

Found: C, 65.42; H, 4.74; N, 6.68%. Calcd for $C_{11}H_9O_3N$: C, 65.02; H, 4.46; N, 6.89%.

Ethyl α-Ethoxycarbonyl-β-(1-azaazulan-2-on-3-yl)propionate (VIII). A solution of 113 mg of VI and 53 mg of diethyl malonate in 5 ml of absolute alcohol was added drop by drop into the sodium ethoxide solution which was prepared from 15 mg of sodium and 1 ml of absolute alcohol with stirring and heated for 2 hr at 60 °C. After it was allowed to stand overnight at room temperature, the alcohol was removed under reduced pressure. The residue was acidified with 1M sulfuric acid, extracted with ethyl acetate and then the combined organic layers were washed with water and dried over sodium sulfate. The solution was chromatographed on alumina and ethyl acetate eluates gave 70 mg of orange scales of VIII, mp 119—120 °C, from ethyl acetate.

Found: N, 4.52%. Calcd for $C_{17}H_{19}O_5N$: N, 4.41%.

β-(1-Azaazulan-2-on-3-yl)propionic Acid (XI). Thirty mg of VIII was heated in 5 ml of 30% potassium hydroxide for 5 hr at 100 °C, and after cooling the resulted solution was acidified with 6M hydrochloric acid to form yellow micro needles of X, mp 188—189 °C (dec.) from alcohol; yield, 20 mg. The dibasic acid (X) was heated at 190 °C to decompose with carbon dioxide evolution. After recrystallization of the residues from alcohol, 18 mg of yellow needles of XI, mp 214—216 °C (dec.), was obtained.

Found: N, 6.15%. Calcd for $C_{12}H_{11}O_3N$: N, 6.45%.

Ethyl α-Acetamido-α-ethoxycarbonyl-β-(1-azaazulan-2-on-3-yl)-propionate (XII). A solution of 200 mg of diethyl acetamidomalonate[11] and 350 mg of VI in 20 ml of absolute alcohol was added to sodium ethoxide solution prepared from 2 ml of absolute alcohol and 20 mg of sodium and heated for 4 hr at 60 °C. After it was allowed to stand overnight at room temperature, the alcohol was removed under reduced pressure. The residues were washed with water and dried in a desiccator to give 200 mg of orange prisms of XII, mp 173—174 °C from ethyl acetate.

Found: C, 60.42; H, 5.97; N, 7.35%. Calcd for $C_{19}H_{22}O_6N_2$: C, 60.95; H, 5.92; N, 7.48%.

Ethyl α-Ethoxycarbonyl-α-formamido-β-(1-azaazulan-2-on-3-yl)-propionate (XIII). A solution of 350 mg of VI and 220 mg of diethyl formamidomalonate[11] in 20 ml of absolute alcohol was added to sodium ethoxide solution prepared from 25 mg of sodium and 2 ml of adsolute alcohol. The reaction mixture was treated as the case of XII to give 280 mg of orange prisms of XIII, mp 181—182 °C from ethyl acetate.

Found: C, 60.30; H, 5.41; N, 7.83%. Calcd for $C_{18}H_{20}O_6N_2$: C, 59.99; H, 5.85; N, 7.77%.

α-Amino-β-(1-azaazulan-2-on-3-yl)propionic Acid Hydrochloride (XIV). Three hundred mg of XII in 3 ml of conc. hydrochloric acid was heated for 4 hr at 100 °C, and then concentrated under reduced pressure to give yellow residues. Recrystallization of the residues from alcohol gave 200 mg of yellow needles of XIV, mp 260—261 °C (dec.). This compound showed red-violet color by ninhydrin reagent.

Found: C, 53.88; H, 4.80; N, 10.13%. Calcd for $C_{12}H_{12}O_3N_2HCl$: C, 53.64; H, 4.87; N, 10.43%.

XIV was also obtained by the same acid hydrolysis of XIII and XVI in quantitative yields.

Ethyl α-Acetyl-β-(1-azaazulan-2-on-3-yl)propionate (XV). To a solution of 350 mg of VI and 130 mg of ethyl acetoacetate in 5 ml of absolute alcohol, a sodium ethoxide solution prepared from 20 mg of sodium and 2 ml of absolute alcohol was added and heated at 60 °C for 5 hr. After it was allowed to stand overnight at room temperature, 180 mg of orange prisms of XV, mp 147—148 °C from ethyl acetate, was obtained by the same treatment as the case of the preparation of XII.

Found: C, 67.16; H, 5.77; N, 4.96%. Calcd for $C_{16}H_{17}O_4N$: C, 66.88; H, 5.96; N, 4.88%.

Ethyl α-Acetylamino-β-(1-azaazulan-2-on-3-yl)propionate (XVI). A solution of 300 mg of XV in 10 ml of chroloform and conc. sulfuric acid was heated at 40 °C, and to this solution 80 mg of sodium azide was added with stirring. The reaction mixtures were stirred for one and half hr and then poured into crushed ice. The chloroform layer was washed with water, dried over sodium sulfate and removed under reduced pressure to give 150 mg of yellow micro needles of XVI, mp 179—180 °C from ethyl acetate–alcohol.

Found: C, 63.74; H, 5.83; N, 9.09%. Calcd for $C_{16}H_{18}O_4N_2$: C, 63.56; H, 6.00; N, 9.27%.

S-(1-Azaazulan-2-on-3-yl)methyl Ethyl Sulfide (XVII). A solution of 200 mg of VI and 50 mg of ethylmercaptan in 3 ml of dioxane and 0.5 ml of 2 M sodium hydroxide was heated at 60 °C for 1 hr and allowed to stand overnight at room temperature. After the solvent was removed under reduced pressure, the formed residues were acidified with 6 M hydrochloric acid, washed with water, and dried in a desiccator to give 80 mg of orange scales of XVII, mp 172—173 °C from ethyl acetate.

Found: C, 66.03; H, 5.78; N, 6.18%. Calcd for $C_{12}H_{13}ONS$: C, 65.72; H, 5.98; N, 6.38%.

Ethyl α-Ethoxycarbonyl-α-nitro-β-(1-azaazulan-2-on-3-yl)-propionate (XVIII). A solution of 200 mg of VI and 120 mg of diethyl nitromalonate in 5 ml of absolute alcohol was added to a sodium ethoxide solution prepared from 15 mg of sodium and 1 ml of absolute alcohol, and then heated at 60 °C for 4 hr. After it was allowed to stand overnight at

11) Prepared by the method of following paper: S. Tatsuoka, T. Kinoshita, and R. Nakamori, *Yakugaku Zasshi*, **71**, 702 (1951).

room temperature, the alcohol was removed and the obtained residues were washed with water. Recrystallization of the residues from ethyl acetate gave 100 mg of yellow needles of XVIII, mp 158—159 °C.

Found: C, 56.83; H, 4.81; N, 7.67%. Calcd for $C_{17}H_{18}O_7N_2$: C, 56.35; H, 5.01; N, 7.73%.

Methyl α-Nitro-β-(1-azaazulan-2-on-3-yl)propionate (XIX). A solution of 350 mg of VI and 12 mg of methyl nitroacetate in 5 ml of absolute methanol was added to a sodium methoxide solution prepared from 100 mg of sodium methoxide and 1 ml of absolute methanol. After the reaction mixture was treated as above, 180 mg of yellow needles of XIX, mp 186—187 °C from methanol, was obtained.

Found: C, 57.05; H, 4.37; N, 9.70%. Calcd for $C_{13}H_{12}O_5N_2$: C, 56.52; H, 4.38; N, 10.14%.

This research was supported by a grant from the Ministry of Education and from Sankyo Co. to whom the authors' thanks are due.