Studies on Seven-Membered Heterocyclic Compounds Containing Nitrogen. V. 2, 3, 4, 5-Tetrahydro-1(H)-indolo[2, 3-c]azepine

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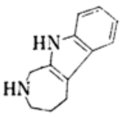
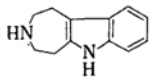
The initial purpose of the present investigation was to prepare 2, 3, 4, 5-tetrahydro-1(H)-indolo[2, 3-c]azepine (Ia) or 1, 2, 4, 5-tetrahydro-3(H)-indolo[3, 2-d]azepine (Ib) which suggests a possibility of dehydrogenation into 2, 3-benzo-1, 7-diazazulene (IIa) or 2, 3-benzo-1, 6-diazazulene (IIb). As similar compounds of this type, 4-ethyl-5, 6, 7, 12-tetrahydro-2-methylindolo[3,2-d] [1]-benzazepine (III)[1], 6,7-dihydro-1-methyl-2, 3-benzindolo[2′ : 3′-4 : 5]-azepine (IV)[2] and 1, 2, 3, 4, 5, 10-hexahydro-7-hydroxy-3-methylazep[4, 5-b]indole (V)[3] have been known. These are, however, compounds of *N*-alkyl or condensed type of phenyl and seven-membered ring, and it may be impossible to bring them into an azulene system by dehydrogenation. After several attempts the author synthesized 2-ethoxycarbonyl-2, 3, 4, 5-tetrahydro-1(H)-indolo[2, 3-c]azepine (XXII), 2-ethoxycarbonyl-7-methoxy-2, 3, 4, 5-tetrahydro-1(H)-indolo[2, 3-c]azepine (XXIII) (as picrate only) and Ia (as picrate only), each of which was assumed to have an angular structure as written from spectral data.



(Ia)



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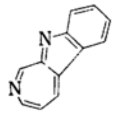
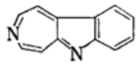


(IIa)



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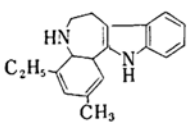
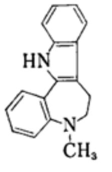
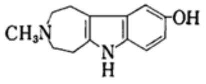


(III)



(IV)



(V)

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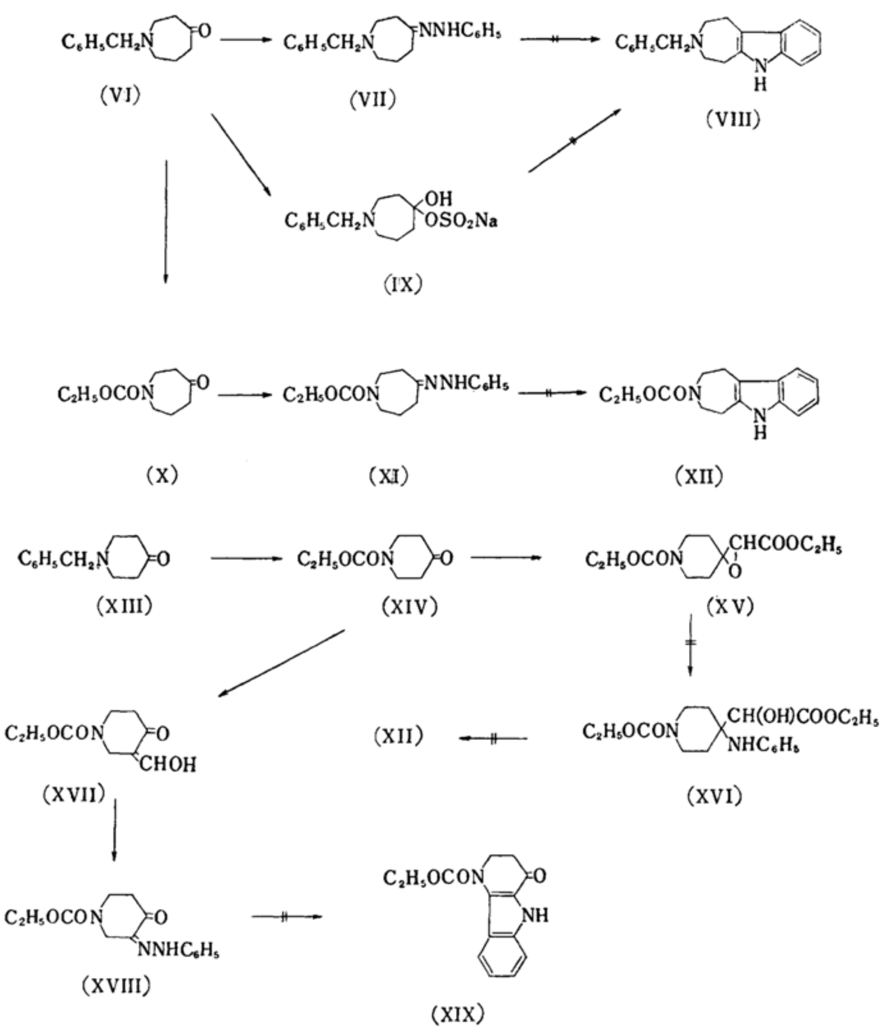
[1] H. B. MacPhillamy et al., *J. Am. Chem. Soc.*, **80**, 2172 (1958).

[2] J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, **1958**, 3377.

[3] J. Harley-Mason and A. H. Jackson, ibid., **1955**, 374.



First of all the author attempted cyclization of phenylhydrazone (VII) and of its hydrochloride of 1-benzyl-1-azacycloheptan-4-one (VI)[4] under the condition of Fischer indole synthesis and under other similar conditions. They have shown a considerable resistance in the cyclizations and were recovered unchanged. In some cases, only a slight indole-like odor and a positive pine-splinter test were observed. Phenylhydrazone (XI) of 1-ethoxycarbonyl-1-azacycloheptan-4-one (X)[5] was also not cyclized with hydrogen chloride in ethanol. An application of the carbazole synthesis to bisulfite compound (IX)[6] of VI resulted in the recovery of VII.

Martynov's method[7], which has obtained 2, 3-pentamethyleneindole in good yield from cyclohexanone via glycidic acid derivative, was applied to 1-ethoxycarbonyl-1-azacyclohexan-4-one (XIV), but the addition reaction of glycidic acid derivative (XV) with aniline failed.

Mühlstädt and Treibs[8] have synthesized 1-keto-2, 3, 4, 5-tetrahydroheptiadole from monophenylhydrazone of cycloheptane-1, 2-dione, and Kent[9] has also obtained 1-keto-1, 2, 3, 4-tetrahydrocarbazole from cyclohexane-1, 2-dione monophenylhydrazone. As a preliminary experiment 1-ethoxycarbonyl-1-azacyclohexane-3, 4-dione monophenylhydrazone (XVIII) derived from XIV was treated under the above conditions, but no expected compound was obtained.

Campbell and McCall[10] have obtained some tetrahydrocarbazoles by heating 2-chlorocyclohexanone with arylamines. In a similar manner, a bromoketone (XXa or XXb)*, which

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[4] S. Morosawa, This Bulletin, 31, 418 (1958).

[5] S. Morosawa, ibid., 33, 1108 (1960).

[6] S. Morosawa, ibid., 33, 575 (1960).

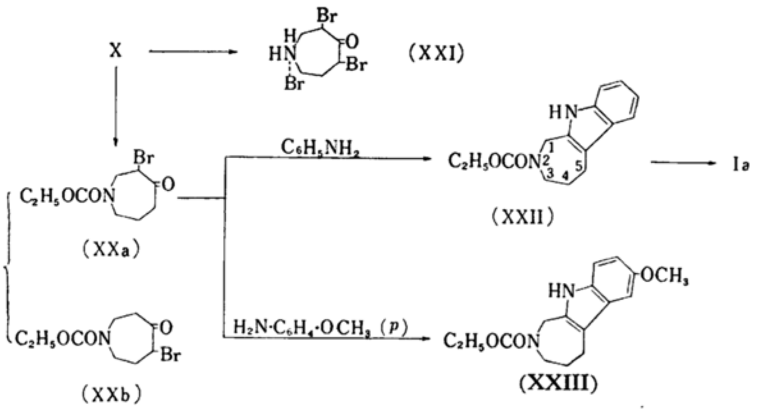
[7] V. F. Martynov, *Chem. Abstr.*, 49, 3124 (1955).

[8] M. Mühlstädt and W. Treibs, *Ann.*, 608, 38 (1957).

[9] A. Kent, *J. Chem. Soc.*, 1935, 976.

[10] N. Campbell and E. B. McCall, ibid., 1950, 2870.

* Situation of bromine atom is now under investigation by degradative method.



derived from X by NBS bromination, with aniline and *p*-anisidine gave rise to the desired compounds, XXII and XXIII (as picrate) respectively. The elimination of ethoxycarbonyl groupe of XXII gave Ia as a picrate. According to the same procedure of the formation of 3, 5, 7-tribromotropone[11], X was brominated in glacial acetic acid with bromine. But it resulted in elimination of the ethoxycarbonyl group, yielding 3, 5-dibromo-1-azacycloheptan-4-one hydrobromide (XXI). Ultraviolet absorption spectrum of XXII is given in Fig. 1, being compared with that of indole.

In the NBS bromination of X two kinds of bromide, 3-bromo (XXa) and 5-bromo (XXb) derivatives were expected. But only one kind of bromide was obtained. Sprague[12] has reported that NBS bromination of tetrahydro-1, 3-thiapyrone yielded 2-bromo compound exclusively. Similarly one might assume in the 1-azacycloheptan-4-one ring that activated 3-position by neighboring carbonyl, though weak, would be further affected more by the inductive effect of the nitrogen atom than 5-position, making the bromine attack on the position to give 3-bromo compound. Consequently XXII and XXIII may be assumed to be angular structures as shown. This accorded with the spectral data as follows:

The picrate of I indicated four bands near the region due to the hydrogen bending vibration of methylene at 1495, 1486, 1466 and 1430 cm^{-1}. The band at 1495 cm^{-1} was due to stretching vibration of the double bond in benzene ring and the other three to 3-, 1-(overlapping with 4-) and 5-methylene in the seven-membered ring as mentioned in the foregoing paper[5]. XXII, on the other hand, gave a broad absorption band in the region owing to overlapping of the above three bands with that arising

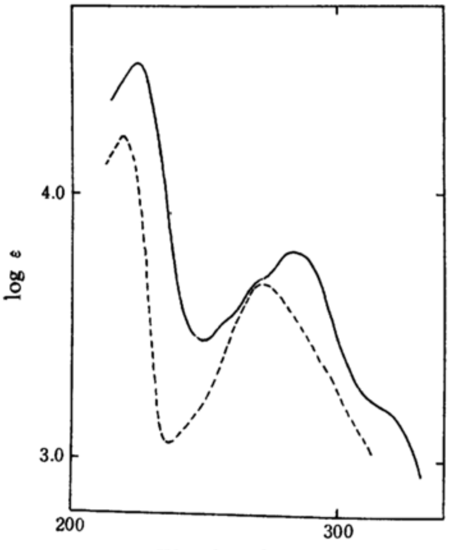


Fig. 1. (in methanol).
—— XXII ; ---- indole.

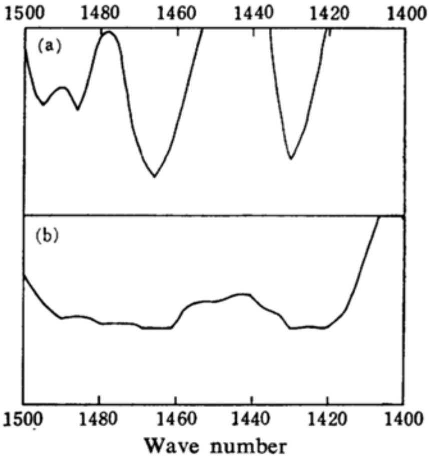


Fig. 2. (a) I picrate ; (b) XXII.

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[11] T. Nozoe, Y. Kitahara, T. Ando and S. Masamune, *Proc. Japan Acad.*, 27, 415 (1951).

[12] R. H. Sprague, *J. Am. Chem. Soc.*, 79, 2275 (1957).

from methyl and methylene in the ethoxycarbonyl group. Infrared absorption spectra of these two compounds are given in Fig. 2.

Experimental

1-Benzyl-1-azacycloheptan-4-one Phenylhydrazone (VII).—To a solution of 1 g. of recrystallized phenylhydrazine hydrochloride and 1.6 g. of anhydrous sodium acetate in 10 cc. of water was added 0.8 g. of VI. Ethanol was added to the mixture until a clear solution was obtained and heated on a water bath for 30 minutes. Crystals formed on cooling were recrystallized from diluted ethanol to give 1.1 g. (80%) of **VII hydrochloride** in light greenish yellow needles, m. p. 225°C (decomp.).

Found: N, 12.39. Calcd. for $C_{19}H_{23}N_2 \cdot HCl$: N, 12.74%.

The hydrochloride was mixed with an excessive diluted potassium carbonate solution and evaporated to dryness under reduced pressure. The residual mass was treated with benzene, and benzene was expelled to leave **free phenylhydrazone** as an oil which crystallized on standing. It was recrystallized from diluted ethanol in light yellow needles, m. p. 75°C.

Found: N, 14.98. Calcd. for $C_{19}H_{23}N_3$: N, 14.32%.

1-Ethoxycarbonyl-1-azacycloheptan-4-one Phenylhydrazone (XI).—A mixture of 1.6 cc. of phenylhydrazine, 1.6 cc. of glacial acetic acid and 0.8 g. of X was treated as above. Crude product 1.2 g. (100%), m. p. 130°C (decomp.), was recrystallized from diluted ethanol to give 0.9 g. of XI as yellow needles, m. p. 130°C (decomp.).

1-Ethoxycarbonyl-1-azacyclohexan-4-one (XIV).—According to the same procedure as that of the formation of X, 15 g. of 1-benzyl-1-azacyclohexan-4-one (XIII)[4] yielded 12.3 g. (90.8%) of XIV, boiling at 93~94°C/1 mmHg as a colorless oil.

Found: N, 8.12. Calcd. for $C_8H_{13}O_3N$: N, 8.18%.

2, 5-Diethoxycarbonyl-1-oxa-5-azaspiro (5, 2) octane (XV).—To a mixture of 3.5g. of XIV and 2.4g. of ethyl monochloroacetate was added a solution of 0.74 g. of metallic potassium in 25 cc. of tertiary butanol under stirring and ice-water cooling during 30 minutes in the nitrogen atmosphere. After an additional stirring for 1 hour the butanol was expelled under reduced pressure and the residue was dissolved in 15 cc. of water. The solution was adjusted to pH 2.0 with hydrochloric acid and extracted with ether. The ethereal solution was washed once with water and dried over anhydrous sodium sulfate. The ether was removed and the residue was distilled in vacuo to give 2.5 g. (47.7%) of a colorless viscous oil, b.p. 146~150°C/1.5 mmHg.

Found: N, 5.21. Calcd. for $C_{12}H_{19}O_5N$: N, 5.44%.

1-Ethoxycarbonyl-3-hydroxymethylene-1-azacyclohexan-4-one (XVII).—A solution of 12.3 g. of XIV and 10.6 g. of ethyl formate in 150 cc. of dry benzene was added with swirling to an ice cold suspension of crushed methanol-free sodium methoxide[13] (from 3.3 g. of sodium) in 150 cc. of dry benzene. The system was evacuated and filled with nitrogen, and allowed to stand at room temperature overnight. Precipitates were dissolved by adding 60 cc. of water. The benzene layer was separated and washed four times with each 10 cc. of 5% solution of sodium hydroxide. The water layer and the washings were united, washed once with ether and acidified with concentrated hydrochloric acid to deposit an orange oil. The oil was taken up in benzene and the water layer was concentrated under reduced pressure, and extracted further with benzene. Benzene extracts were united, washed five times with a small volume of saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After removal of benzene, the vacuum distillation gave 3.5 g. (24.5%) of a colorless viscous oil, boiling at 130~131°C/2 mmHg.

Found: N, 7.06. Calcd. for $C_9H_{13}O_4N$: N, 7.03%.

The oil gave a **monosemicarbazone**, m. p. 156.5°C (Found: N, 22.09%) and a **cyclic semicarbazone**, m. p. 128.5°C (Found: N, 23.28%).

1-Ethoxycarbonyl-1-azacyclohexan-3, 4-dione Monophenylhydrazone (XVIII).—To a mixture of 0.63 g. of redistilled aniline, 0.67 cc. of concentrated sulfuric acid and 5 cc. of water was added dropwise a solution of 0.47 g. of sodium nitrite in 1.8 cc. of water under stirring and ice-water cooling, followed by the addition of a saturated solution of 1.1 g. of anhydrous sodium acetate. Then a solution of 1 g. of XVII in 3 cc. of ether was added dropwise and the resultant mixture was stirred for 15 minutes while cold and for 30 minutes at room temperature. The orange crystals which separated were collected and recrystallized five times from methanol to give 0.6 g. (43.5%) of XVIII, m. p. 116~117°C.

Found: N, 15.07. Calcd. for $C_{14}H_{17}O_3N_3$: N, 15.26%.

3(or 5)-Bromo-1-ethoxycarbonyl-1-azacycloheptan-4-one (XXa or XXb).—A mixture of 7.4 g. of X, 0.3 g. of benozyl peroxide and 8 g. of NBS in 400 cc. of carbon tetrachloride was heated on a water bath, protected from moisture. As soon as the boiling took place, the mixture turned red and suddenly the color disappeared. After the boiling was further continued gently for 3 minutes the mixture was cooled under the tap and allowed to stand for 2 hours in a refrigerator. Succinimide was removed and washed with carbon tetrachloride. Carbon tetrachloride solutions were united, washed with 20 cc. of 20% sodium carbonate solution and then with water, and finally dried over anhydrous potassium carbonate. After removal of the solvent, residual oil was distilled in vacuo to yield 5.3 g. (50%) of a slightly colored oil, boiling at 140~145°C/1 mmHg.

Found: N, 5.85. Calcd. for $C_9H_{14}O_3NBr$: N, 5.31%.

A mixture of 0.1 g. of the above oil, 0.1 g. of 2,4-dinitrophenylhydrazine, 3 cc. of ethanol and 0.1 cc. of concentrated hydrochloric acid was boiled on a water bath for 2 minutes and let stand overnight. Crystals formed were recrystallized twice

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[13] W. S. Johnson and H. Posvic, *J. Am. Chem. Soc.*, **69**, 1361 (1947).

from methanol to yield yellow **2, 4-dinitrophenylhydrazone**, m. p. 149~152°C (decomp.).

Found: N, 15.86. Calcd. for $C_{15}H_{18}O_6N_5Br$: N, 15.75%.

3, 5-Dibromo-1-azacycloheptan-4-one Hydrobromide (XXI).—A solution of 3 g. of X and 15 g. of bromine dissolved in 5 cc. of glacial acetic acid was allowed to stand overnight. The solution was heated on a water bath for 50 hours and evaporated under reduced preseure. The residue was taken up in ethanol, which was evaporated to leave an oil with some crystals. To this was added a small amount of ethanol to bring the oil into solution and isopropyl ether was added in small portions until precipitation occurred. After standing overnight in a refrigerator, the crystals were collected and charcoaled in 200 cc. of ethanol. Charcoal was separated and the ethanolic solution was concentrated to a smaller volume under reduced pressure. The crystals which were deposited during the evaporation were collected and washed with ethanol to yield 0.8 g. of XXI. Another crop, 0.4 g. was obtained from the filtrate. Crude crystals were recrystallized together from a small amount of water to give 0.7 g. of XXI as slightly colored microneedles, m. p. 186°C (decomp.).

Found: C, 20.33; H, 2.89; N, 3.68. Calcd. for $C_6H_9ONBr_2 \cdot HBr$: C, 20.45; H, 2.84; N, 3.97%.

2-Ethoxycarbonyl-2, 3, 4, 5-tetrahydro-1(H)-indolo-[2, 3-c]azepine (XXII).—A mixture of 5.3 g. of XX and 10.6 g. of redistilled aniline was boiled in an oil bath for 3 hours. The reaction mixture was treated with diluted potassium carbonate solution and taken up in ether. Ether was removed and aniline was thoroughly driven off by distillation in an oil bath maintained at 180°C under diminished pressure (0.8 mmHg). The residual tarry oil was dissolved in 70 cc. of benzene and washed once with 5 cc. of 2 N hydrochloric acid, thrice with a small portion of saturated sodium chloride solution and dried over anhydrous potassium carbonate. To the residue left on evaporation of benzene were added ethanol and picric acid, boiled for a while and allowed to stand overnight. Crystals formed were collected, washed with ether and recrystallized from ethanol to yield 1.5 g. (15.3%) of **picrate** as tan needles (indol odor), m. p. 156°C.

Found: N, 14.46. Calcd. for $C_{15}H_{18}O_2N_2 \cdot C_6H_3O_7N_3$: N, 14.37%.

Free base, though in poor yield, was obtained by treating the picrate with a saturated sodium bicarbonate solution and extracting with benzene as extremely viscous yellow oil (indole odor), boiling at 216°C/0.4 mmHg. This did not crystallize on standing.

Found: N, 10.75. Calcd. for $C_{15}H_{18}O_2N_2$: N, 10.85%.

The free base again formed a **picrate** which was found to be the same as that mentioned above, giving no m. p. depression.

2-Ethoxycarbonyl-7-methoxy-2, 3, 4, 5-tetrahydro-1(H)-indolo[2, 3-c]azepine (XXIII) Picrate.—A mixture of 2.8 g. of XX and 3.3 g. of redistilled *p*-anisidine was treated as before and 0.5 g. (9.1%) of picrate (indole odor) was obtained as deep tan needles, m. p. 164.5°C.

Found: N, 13.66. Calcd. for $C_{16}H_{20}O_3N_2 \cdot C_6H_3O_7N_3$: N, 13.54%.

Free base was distilled in vacuo at 220~228°C/0.5 mmHg with decomposition, and for lack of the distillate it could not be studied further.

Deethoxycarbonylation of XXII.—The picrate of XXII, 1 g. was treated with a saturated sodium bicarbonate solution and taken up in benzene. The residual oil which was left on evaporation of benzene was dissolved in 8 cc. of glacial acetic acid and saturated with dry hydrogen bromide under cooling. After standing overnight the solution was boiled under reflux for 2 hours. Acetic acid was removed under reduced pressure and the residue was heated in ethanol with an excessive picric acid. Crystals deposited on standing were recrystallized twice from ethanol to give 0.2 g. of Ia picrate as tan yellow prisms, m. p. 254°C (decomp.).

Found: C, 51.80; H, 4.43; N, 16.65. Calcd. for $C_{12}H_{14}N_2 \cdot C_6H_3O_7N_3$: C, 52.05; H, 4.13; N, 16.86%.

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