Studies on Seven-Membered Heterocyclic Compounds Containing Nitrogen. XI. The Schmidt Reaction of 1-Benzyl-1-azacycloheptan-4-one, Menthone, and 2-Methyl-4,5,6,7-tetrahydrobenzo[*b*]thiazol-7-one[1]

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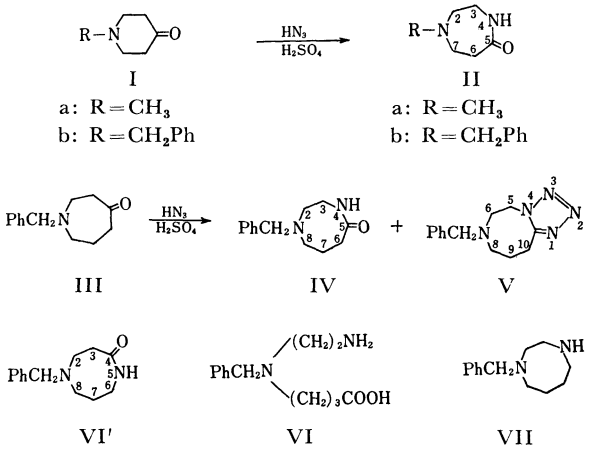
(Received June 17, 1970)

The Schmidt reaction of 1-benzyl-1-azacycloheptan-4-one afforded a mixture of 1-benzyl-1,4-diazacyclooctan-5-one (IV) and a tetrazole derivative (V). The treatment of menthone (VIII) was found to give a lactam (IX), plus a tetrazole derivative (X) as a minor product. 2-Methyl-4,5,6,7-tetrahydrobenzo[*b*]thiazol-7-one (XII) was subjected to the Schmidt reaction to give a lactam XIIIa; it did not afford a tetrazole derivative. The structures of these products were determined on the evidence of the NMR spectra.

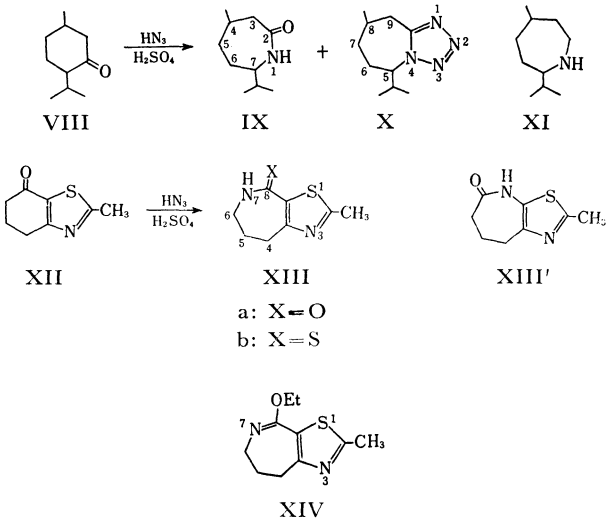
As a part of our investigation of the syntheses and reactions of seven-membered nitrogen heterocycles leading to azepine compounds, we studied the Schmidt reaction of the compounds named in the title. Dickermann and his co-workers[4] have reported that the Schmidt reaction of 1-methyl- and 1-benzylpiperid-4-one (Ia and b) gave the corresponding 1,4-diazacycloheptan-5-ones (IIa and b respectively) in reasonable yields.



Scheme 1

The treatment of 1-benzyl-1-azacycloheptan-4-one[5] (III) was found to give a mixture of 1-benzyl-1,4-diazacyclooctan-5-one (IV) and a tetrazole derivative (V) on the evidence of the NMR spectra. The main product, IV, gave a single spot on a paper chromatogram and showed the presence of an amido group in the IR spectrum. The assignment of the NMR signals (Table 1) was made by comparing them with those of 2-pyrrolidone[6] and the diazacycloheptanone, IIb. Deuterium exchange in the spectrum of IV caused the disappearance of the multiplet at τ 2.4 and the simultaneous collapse of the multiplet at 6.8 to a broad triplet. On the irradiation of the deuterium-exchanged solution at τ 8.45, the multiplet at 7.7 and the triplet at 7.43 collapsed to broad singlets, while the broad triplet at 6.8 remained unchanged. This observation eliminated the possibility of an isomeric structure (IV′) for IV, because if IV′ were present, the broad triplet at τ 6.8 due to the methylene protons adjacent to the lactam nitrogen in the structure IV′ would have collapsed to a singlet upon irradiation. The ring opening of the lactam IV with 5% sulfuric acid gave an amino acid (VI), and reduction with lithium aluminum hydride afforded 1-benzyl-1,4-diazacyclooctane (VII). The assignment of the NMR signals of the tetrazole derivative (V) is shown in Table 1. The lower chemical shift of the triplet at τ 5.50 indicated the presence of a methylene group adjacent to the tetrazole nitrogen. A reinvestigation of Dickermann's work gave no tetrazole derivative other than the lactam.

The Schmidt reaction of a carbocyclic six-membered ketone, menthone (VIII), afforded a lactam (IX), plus a tetrazole derivative (X) as a minor product. The NMR signals at τ 6.97 [CH(7) adjacent to the seven-membered ring nitrogen] for the lactam and at 5.65 for the tetrazole, and also the possible mode of formation, led to the assignment of the structure IX



Scheme 2

1) Presented in part at the Local Meeting of the Chemical Society of Japan, Okayama, October, 1967.

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4) S. C. Dickermann and G. Lindwall, *J. Org. Chem.*, **14**, 530 (1949); S. C. Dickermann and A. J. Beozzi, *ibid.*, **19**, 1855 (1954).

5) A. Yokoo and S. Morosawa, This Bulletin, **29**, 631 (1956).

6) Frank A. Bovey, "NMR Data Table for Organic Compounds," Vol. 1, John Wiley & Sons, New York (1967), p. 70.

Table 1. Assignment of NMR signals

Series of compounds 1[b,d] 2[c,d] 3[e]	τ Values[a] for					
	CH_2(2)(6)	CH_2(3)(5) CH (7)(5) CH_2(6)	NH(4) NH(1) NH(7)	CH_2(6)(10) CH_2(3)(9)	CH_2(7)(9) CH_2(5,6)(6,7) CH_2(5)	CH_2(8)(8) CH (4)(8) CH_2(4)
2-Pyrrolidone[f,g]	—	6.63 t	—	7.77 t	—	—
IIb[h]	7.34 bs	6.68 bq	2.25 bm	7.40 m	7.34 bs	—
IV[g]	7.43 bt	6.80 m	2.40 bm	7.70 m	8.45 m	7.43 bt
V[h]	7.40 m	5.50 t	—	7.00 bt	8.25 m	7.40 m
IX[g]	—	6.97 bqn	—	7.82 bd	8.35 m	8.35 m
X[g]	—	5.65 bqn	—	6.95 m	8.00 m	7.62 m
XIIIa[h]	—	6.54 bq	2.35 m	—	7.80 m	6.81 t
XIIIb[h]	—	6.45 bq	0.80 m	—	7.85 m	6.82 t

a) TMS as an internal standard. Suffixes: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet. b) Compounds, IIb, IV, and V. c) Compounds, IX and X. d) Figures in the former parentheses are for the compounds of the lactam type. e) Compounds, XIIIa and b. f) Values are from Ref. 6. g) In CCl_4. h) In $CDCl_3$.

and X for these products. The assignment of the signals is shown in Table 1. The treatment of IX with lithium aluminum hydride yielded the azacycloheptane (XI). The tetrazoles V and X were not formed from IV and IX under the same conditions as in the reaction of III or VIII. Therefore, the lactam can not be an intermediate of the tetrazole formation under these conditions.

2-Methyl-4,5,6,7-tetrahydrobenzo[*b*]thiazol-7-one (XII), which had been prepared according to the literature,[7] was subjected to the Schmidt reaction to give a lactam (XIIIa) in a 68% yield, but not a tetrazole derivative. It showed amido absorption in the IR spectrum. The assignment of the NMR signals is given in Table 1. On deuterium exchange, the multiplet at τ 2.35 disappeared and the broad quartet at 6.54 simultaneously became a more complex multiplet, while the other signals remained unchanged. This fact, as well as the lower chemical shift of the quartet at τ 6.54, indicated the presence of a methylene group adjacent to the lactam nitrogen, supporting the idea of the structure XIIIa for the reaction product. The alternative isomeric form (XIII') was eliminated on the grounds that such a compound would give the signal of CH_2(6) at about τ 7.7—7.8 (*cf.* the signals of 2-pyrrolidone, IV, and IX in Table 1) and that the deuterium exchange could not affect any signals of the compound. The complexity of the signal of CH_2(6) at τ 6.54 after deuterium exchange can be explained in terms of the unequivalency of the methylene hydrogens. The carbonyl group in XIIIa resisted reduction with lithium aluminum hydride even when refluxed for 15 hr in tetrahydrofuran. However, treatment with phosphorus pentasulfide gave the thio lactam, XIIIb, the structure of which was confirmed by a study of the NMR spectrum (for the assignment, see Table 1). The deuterium exchange caused the disappearance of the broad multiplet at τ 0.8, with a simultaneous change in the broad quartet at 6.45 to a more complicated multiplet, as in the case of XIIIa.

On the reaction of XIIIa with triethyloxonium fluoroborate,[8] the ethoxy compound XIV was obtained in a 78% yield.

Experimental

Elementary analyses were carried out using a Yanagimoto C.H.N. Corder, MT-1. The NMR spectra were recorded by means of a Hitachi High-resolution NMR Spectrometer, R-20A, and the IR spectra, by means of a Nihon-Bunko IR-S Spectrophotometer. Each analytical sample gave a single spot on a paper chromatogram (Toyo Roshi No. 51) developed with 3% aqueous ammonium chloride or 5 N acetic acid / 1-butanol (29 : 71 v/v) and examined under ultraviolet light at 365 and 254 mμ in turn.

1-Benzyl-1,4-diazacyclooctan-5-one (IV) and 7-Benzyl-5,6,7-8,9,10-hexahydrotetrazolo[4,5-d][1,4]diazocine (V). To a stirred solution of 9.6 g (0.04 mol) of III hydrochloride in 34 m*l* of concentrated sulfuric acid were added, in small portions, 4.2 g (0.065 mol) of sodium azide over a period of 6 hr at room temperature. After having been stirred for an additional 22 hr at the same temperature, for 9 hr at 30°C, and for 6 hr at 50—55°C, the reaction mixture was poured onto 50 g of ice and made alkaline with a saturated solution of sodium hydroxide under ice cooling. The sodium sulfate was filtered off, and the filtrate was extracted with ether and chloroform successively. The combined and dried (over anhydrous potassium carbonate) extract was evaporated, and the residue was distilled *in vacuo* to give two kinds of oily products. The first fraction (IV) amounted to 5.3 g (64%) (colorless; bp 155—156°C/0.14 mmHg, R_f=0.6).

Found: C, 71.64; H, 8.16; N, 13.20%. Calcd for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.84%.

The second fraction (V), 0.4 g (7%), was a viscous, light yellow oil, bp 177—180°C/0.1 mmHg, R_f=0.4.

Found: C, 63.96; H, 6.63; N, 28.41%. Calcd for $C_{13}H_{17}N_5$: C, 64.17; H, 7.04; N, 28.78%.

4-Methyl-7-isopropyl-1-azacycloheptan-2-one (IX) and 5-Isopropyl-8-methyl-5,6,7,8-tetrahydro-9H-tetrazolo[4,5-a]azepine (X). To a stirred, ice-cooled solution of 20 g (0.13 mol) of VIII in 50 m*l* of concentrated sulfuric acid were added 18 g (0.28 mol) of sodium azide over a period of 18 hr. The reaction mixture was stirred for an additional 50 hr at room temperature and then poured onto 100 g of ice and made alkaline

7) G. Lehmann, B. Luecke, H. Schick, and G. Hilgetag (Deut. Akad. Wiss., Berlin), *Z. Chem.*, **7** (11), 422 (1967); *Chem. Abstr.*, **68**, 39529h (1968).

8) V. G. Granik and R. G. Glushkov., *Khim.-Farm. Zh.*, **1**, 21 (1967); *Chem. Abstr.*, **68**, 12942a (1968).

with a saturated solution of sodium hydroxide. The sodium sulfate thus formed was filtered off, and the filtrate was extracted with ether. The ether layer was dried over anhydrous potassium carbonate and evaporated to give a mixture of an oil and crystals. The mixture was dissolved in ethanol, and water was added. The solid was collected and recrystallized from dilute ethanol to give 10.6 g (70%) of IX as white needles, mp 118—119°C.

Found: C, 71.08; H, 11.00; N, 7.92%. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28%.

The original filtrate was concentrated, and the residue was distilled *in vacuo* to give 4.3 g (16%) of X as a colorless oil, bp 142—143°C/0.20 mmHg.

Found: C, 61.99; H, 9.28; N, 29.11%. Calcd for $C_{10}H_{18}N_4$: C, 61.82; H, 9.29; N, 28.84%.

N-Benzyl-N-(2-aminoethyl)-4-aminobutanoic Acid (VI). A solution of 3.0 g of IV in 60 m*l* of 5% sulfuric acid was refluxed for 10 hr. After cooling, the solution was adjusted to pH 7.0—7.2 with a 5% barium hydroxide solution. The excess barium hydroxide was removed by saturating the the solution with carbon dioxide, followed by filtration. The filtrate was evaporated to dryness under reduced pressure, and the residue was dissolved in a small amount of methanol (*ca.* 5 m*l*); ether was then added in small portions until precipitation began. The separation of the precipitate and two recrystallizations from methanol gave 1.3 g (58%) of VI as white prisms, mp 173°C (decomp.). The drying of an aliquot of the prisms at 70°C for 2 hr gave the analytical sample.

Found: C, 65.86; H, 8.52; N, 11.82%. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85%.

Picrate: VI combined with two molecules of picric acid to form yellow plates, mp 183°C (from ethanol). The analytical sample was dried at 70°C for 2 hr.

Found: C, 44.10; H, 4.17; N, 16.10%. Calcd for $C_{13}H_{20}N_2O_2 \cdot 2C_6H_3N_3O_7$: C, 43.83; H, 3.83; N, 16.36%.

2-Methyl-8-oxo-4,5,6,7-tetrahydro-8H-thiazolo[5,4-c]azepine (XIIIa). To a stirred solution of 3 g (0.018 mol) of XII in 15 m*l* of concentrated sulfuric acid, maintained at 0—5°C, were carefully added 2.5 g (0.038 mol) of sodium azide. After the mixture had been stirred for 10 hr, 100 m*l* of ice-cold water were added. The mixture was adjusted to pH 5 by adding a saturated solution of sodium hydroxide, and then it was repeatedly extracted with chloroform. The combined chloroform solution was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residual solid was recrystallized from a mixture of acetone and chloroform to afford 2.1 g (67.5%) of XIIIa as colorless crystals, mp 174—175°C, which sublimed at 120°C/0.2 mmHg.

Found: C, 52.69; H, 5.54; N, 15.15%. Calcd for $C_8H_{10}N_2OS$: C, 52.72; H, 5.53; N, 15.37%.

2-Methyl-8-thioxo-4,5,6,7-tetrahydro-8H-thiazolo[5,4-c]azepine (XIIIb). A mixture of 1 g (0.0051 mol) of XIIIa, 1.4 g (0.0061 mol) of phosphorus pentasulfide, and 15 m*l* of pyridine was heated under reflux for 1 hr. The reaction mixture was treated with a small amount of water, evaporated to dryness under reduced pressure, and sublimed at 160°C/0.2 mmHg to give 0.9 g (83%) of XIIIb as light yellow crystals, mp 176—178°C.

Found: C, 48.34; H, 4.79; N, 14.20%. Calcd for $C_8H_{10}N_2S_2$: C, 48.45; H, 5.08; N, 14.13%.

2-Methyl-8-ethoxy-5,6-dihydro-4H-thiazolo[5,4-c]azepine (XIV). To a stirred solution of triethyloxonium fluoroborate[9] (freshly prepared from 5 m*l* of borontrifluoride etherate, 15 m*l* of dry ether, and 5 m*l* of epichlorohydrin), was added a solution of 1 g (0.0055 mol) of XIIIa in 20 m*l* of dichloromethane at room temperature. The mixture was stirred for 30 hr and then made alkaline by adding an aqueous solution of potassium carbonate. Extraction with dichloromethane, followed by the evaporation of the solvent and vacuum distillation, gave 0.9 g (78%) of XIV as a colorless oil, bp 94—95°C/0.22 mmHg.

Found: C, 57.88; H, 7.12; N, 12.17%. Calcd for $C_{10}H_{14}N_2OS$: C, 57.11; H, 6.71; N, 13.32%.

The *picrate* formed as yellow crystals, mp 149—150°C (from ethanol).

Found: C, 43.56; H, 3.76; N, 15.79%. Calcd for $C_{10}H_{14}N_2OS \cdot C_6H_3N_3O_7$: C, 43.73; H, 3.90; N, 15.94%.

The authors wish to thank Dr. S. Morosawa and Dr. H. Yamamoto for their valuable advice and encouragement.

9) L. A. Paquette, *J. Amer. Chem. Soc.*, **86**, 4096 (1964).