NOTES

Studies of Seven-membered Heterocyclic Compounds Containing Nitrogen. IX. The Synthesis of 5-Ethoxycarbonyl-1-azacycloheptan-4-one and Its Derivatives

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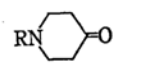
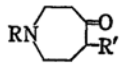
As an extension of our previous study[1] of the synthesis of the seven-membered ring ketone containing nitrogen through the reaction of 1-benzyl-1-azacyclohexan-4-one (I) with nitrosomethylurethane, the ring expansion of I and 1-ethoxycarbonyl-1-azacyclohexan-4-one (II) has been carried out using ethyl diazoacetate.

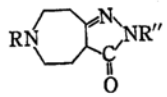
The ring expansion of I was examined first, using zinc chloride as a catalyst, according to the method of Eistert *et al.*,[2] the product, 1-benzyl-5-ethoxycarbonyl-1-azacycloheptan-4-one (III), was isolated as a hydrochloride. The yield of the reaction was 20%. This was improved to 34% by the use of boron trifluoride etherate as a catalyst, according to the method developed by Tal and Warnhoff.[3] In neither case, however, was it possible to isolate the free base (III) by the direct distillation of the reaction mixture, but III liberated from its hydrochloride was safely distilled. The decarboxylation of III by refluxing it with hydrochloric acid yielded the hydrochloride of 1-benzyl-1-azacycloheptan-4-one (V), which was found, by a mixed-melting-point determination and by a comparison of IR spectra, to be identical with an authentic sample.[1] The ring expansion of II, using boron trifluoride etherate, furnished 1, 5-diethoxycarbonyl-1-azacycloheptan - 4 - one (IV). IV was also derived from III by hydrogenolysis and subsequent ethoxycarbonylation.



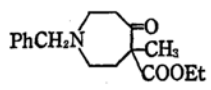
(I) R=$PhCH_2$
(II) R=COOEt



(III) R=$PhCH_2$, R′=COOEt
(IV) R=R′=COOEt
(V) R=$PhCH_2$, R′=H
(VI) R=H, R′=COOEt
(XIV) R=COOEt, R′=CH_3



(VII) R=$PhCH_2$, R″=H
(VIII) R=$PhCH_2$, R″=Ph
(IX) R=COOEt, R″=H
(X) R=COOEt, R″=Ph
(XI) R=R″=H
(XII) R=H, R″=Ph



(XIII)

III and IV gave the corresponding derivatives (VII—X) of a type of pyrazole or pyrazolone when treated with hydrazine or phenylhydrazine, while they gave normal 2, 4-dinitrophenylhydrazones. Debenzylation by the hydrogenolysis of VII in the presence of hydrochloric acid gave a hydrochloride of compound XI. A similar compound (XII) was obtained by the hydrogenolysis of VIII. XII was also derived from VI.

The methylation of III afforded 1-benzyl-5-ethoxycarbonyl-5-methyl-1-azacycloheptan-4-one (XIII). XIII was converted into 1-ethoxycarbonyl-5-methyl-1-azacycloheptan-4-one (XIV) by decarboxylation and debenzylation, followed by ethoxycarbonylation.

Experimental

Procedure for Ring Expansion of I and II. Into a solution of 0.28 mol of I or II in dry ether, maintained at −50——60°C, these were vigorously stirred, drop by drop, a solution of 0.26 mol of a freshly-distilled boron trifluoride etherate in 50 cc of dry ether and a solution of 0.85 mol of ethyl diazoacetate in 100 cc of dry ether were added. The addition of the two solutions was started simultaneously; it took 30 min for the addition of the former solution, and 100 min for the latter. After the reaction mixture had been stirred for an additional 30 min at the same temperature, the stirring was continued until the temperature of the mixture reached room temperature. The mixture was then shaken with a 20% aqueous potassium carbonate solution, and the ether layer was separated. The water layer was extracted with ether. The organic layer

1) S. Morosawa, This Bulletin, **31**, 418 (1958).
2) B. Eistert, F. Haupter, and K. Schank, *Ann.*, **665**, 55 (1963).
3) W. T. Tal and E. W. Warnhoff, *Can. J. Chem.*, **42**, 1333 (1964).

was dried over anhydrous potassium carbonate, and then treated in either of the ways shown below. (I): Dry hydrogen chloride was passed through to the organic layer, thus depositing a hydrochloride of III. This was recrystallized from ethanol. (II): After the solvent had been removed from the organic layer, IV was distilled under reduced pressure. The following results were obtained: III·HCl, yield, 34%, mp 164.5°C (dec.). Found: C, 61.68; H, 7.13; N, 4.55%. Calcd for $C_{16}H_{21}O_3N$·HCl: C, 61.63; H, 7.11; N, 4.49%; III, bp 160—162°C/0.4 mmHg. Found: C, 69.65; H, 7.50; N, 5.02%. Calcd for $C_{16}H_{21}O_3N$: C, 69.78; H, 7.68; N, 5.08%; Hydrochloride of 2, 4-dinitrophenylhydrazone, mp 179°C (dec.); IV, yield, 30.5%, bp 133—135°C/0.15 mmHg. Found: C, 56.33; H, 7.87; N, 5.45%. Calcd for $C_{12}H_{19}O_5N$: C, 56.02; H, 7.44; N, 5.42%; 2, 4-dinitrophenylhydrazone, mp 119.5°C.

The hydrochloride of VI was obtained by the hydrogenolysis of the hydrochloride of III in ethanol, using palladium as a catalyst. Yield, 81%, mp 133—134°C. Found: C, 49.03; H, 7.42; N, 6.44%. Calcd for $C_9H_{15}O_3N$·HCl: C, 48.75; H, 7.28; N, 6.32%; VI, bp 112—114°C/0.6 mmHg. Found: C, 58.01; H, 8.37; N, 7.39%. Calcd for $C_9H_{15}O_3N$: C, 58.36; H, 8.16; N, 7.55%.

The Preparation of VII—X. A mixture of III (1 equiv.), hydrazine hydrate (2 equiv.), and ether was warmed on a water bath for 15 min. In a similar method, each of the following mixtures was warmed for 1—3 hr; III·CHl (1 equiv.), hydrochloride of phenylhydrazine (1 equiv.), sodium acetate (2 equiv.), and water; IV (1 equiv.) and hydrazine hydrate (1 equiv.); IV (1 equiv.) and phenylhydrazine (1 equiv.). The following results were obtained: VII, yield, 95%, mp 220°C (dec.). Found: C, 69.61; H, 7.63; N, 17.03%. Calcd for $C_{14}H_{17}ON_3$: C, 69.20; H, 7.05; N, 17.29%; VIII, yield, 92%, mp 198°C (dec.). Found: C, 75.22; H, 6.61; N, 12.84%. Calcd for $C_{20}H_{21}ON_3$: C, 75.21; H, 6.63; N, 13.13%; IX, yield, 35%, mp 242—243°C (dec.). Found: C, 53.24; H, 6.65; N, 18.87%. Calcd for $C_{10}H_{15}O_3N_3$: C, 53.35; H, 6.72; N, 18.66%; X, yield, 76%, mp 144.5°C. Found: C, 63.93; H, 5.96; N, 13.58%. Calcd for $C_{16}H_{19}O_3N_3$: C, 63.77; H, 6.32; N, 13.95%.

XI and XII were prepared by the hydrogenolysis of VII and VIII in ethanol, (in the case of VII, the ethanol contained hydrochloric acid) by using palladium as a catalyst: XI·HCl, yield, 46%, mp 270°C (dec.). Found: C, 38.02; H, 6.54; N, 18.92%. Calcd for $C_7H_{11}ON_3$·2HCl: C, 37.71; H, 6.24; N, 18.58%. XII, yield, 41%, mp 203—204°C (dec.). Found: C, 63.34; H, 6.84; N, 16.70%. Calcd for $C_{13}H_{15}ON_3$·H_2O: C, 63.14; H, 6.93; N, 16.99%.

Preparation of XIII. To a solution of 1.2 g of metallic sodium in 20 cc of absolute ethanol, there was added a solution of 8 g of the hydrochloride of III in a small amount of absolute ethanol with stirring and ice-salt cooling. After 30 min of stirring, 3.7 g of methyl iodide was added, drop by drop, over a 10 min period, and then the stirring was continued for 2 more hours. After a large amount of water had been added to the reaction mixture, it was extracted with benzene. XIII was distilled under reduced pressure from the benzene layer; (yield 33%), colorless oil, bp 171—173°C/0.2 mmHg. Found: C, 70.69; H, 7.78; N, 4.48%. Calcd for $C_{17}H_{23}O_3N$: C, 70.95; H, 7.95; N, 4.83%.

Preparation of XIV. A mixture of 2.4 g of XIII and 70 cc of 4 N hydrochloric acid was refluxed for 2.5 hr, concentrated under reduced pressure, and made alkaline by adding solid potassium carbonate. The liberated oil was separated and hydrogenolized in 30 cc of water containing 0.1 cc of concentrated hydrochloric acid, in the presence of palladium chloride as a catalyst. After the removal of the catalyst, the solution was concentrated under reduced pressure. To the residue were added 7 cc of a 5% potassium hydroxide solution and 1.5 g of anhydrous potassium carbonate under ice-water cooling. Into the mixture was added 1.5 g of ethyl chloroformate under stirring. After 1 hr of stirring, XIV was extracted with ether. Colorless oil, bp 93—95°C/0.1 mmHg. Found: C, 60.17; H, 8.23; N, 6.51%. Calcd for $C_{10}H_{17}O_3N$: C, 60.35; H, 8.54; N, 7.03%. 2, 4-Dinitrophenylhydrazone, yellow plates (from ethanol), mp 145—146°C, Found: C, 50.54; H, 5.72; N, 18.46%. Calcd for $C_{16}H_{21}O_6N_5$: C, 50.65; H, 5.42; N, 18.46%.