BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 40 1954—1957 (1967)

Studies on Seven-Membered Heterocyclic Compounds Containing Nitrogen. VIII. Structural Considerations of Pyrazole and Thiazole Compounds Fused with a Hydrazepine Ring

Akira Yokoo and Shiro Morosawa

Department of Chemistry, Faculty of Science, Okayama University, Tsushima, Okayama

(Received February 22, 1967)

The alternative structure of III, 2-methyl-4,5,7,8-tetrahydro-6(*H*)-azepino[5,4-*d*]thiazole (IV) has been found by a study of the NMR spectrum of the corresponding 6-ethoxycarbonyl derivative (V). The structure of 1-ethoxycarbonyl-3-hydroxymethylene-1-azacycloheptan-4-one (VIII) has also been ascertained by a study of the NMR spectrum and also by its conversion into the methyl derivative (XI).

It has been reported that the pyrazole compound, hexahydro-1, 2, 5-triazaazulene (I),⁽¹⁾ and thiazole compound, 2-methyl-5, 6, 7, 8-tetrahydro-4(*H*)-azepino[4, 3-*d*]thiazole (III),⁽²⁾ have been synthesized; their structures have been postulated by estimating the bending vibrational spectrum of the methylene groups. On the basis of the structure, it was concluded that their precursors possessed the hydroxymethylene group and the bromine atom at the 3-position of the 1-azacycloheptan-4-one ring. In the present experiments, the alternative structure, 2-methyl-4, 5, 7, 8-tetrahydro-6(*H*)-azepino[5, 4-*d*]thiazole (IV), has been found, by a study of the NMR spectrum of the corresponding 6-ethoxycarbonyl derivative (V)⁽²⁾ to be preferable to III.

---

1) S. Morosawa, This Bulletin, **33**, 1108 (1960).
2) A. Yokoo and S. Morosawa, *ibid.*, **33**, 1118 (1960).

Figure 2 shows the NMR spectra of VIII, V, II, and I, together with those of two reference compounds, VII and VI.¹⁾ VIII shows a remarkable singlet absorption (overlapped with the quartet due to the methylene in the ethyl group) at 6.10 τ, caused by two protons at the 2-position, which could not be observed if the hydroxymethylene group were situated at the 5-position. At both 6.41 τ and 7.06 τ V shows absorptions caused by four protons. The former is derived from the combined protons of the two methylenes neighboring the nitrogen atom, and the latter, from those of the two methylenes neighboring the double bond. If the previously-proposed skeleton (III) is correct, we may expect that an absorption, assigned to the methylene protons between two methylene groups at the 4-position and the 6-position, will appear around 8.00—8.35 τ, as in the cases of compounds VII, VI, VIII, II, and I. However, V gave only a faint absorption in that region, probably suggesting the inclusion of an impurity. I itself indicated a rather broad singlet absorption at 5.65 τ, assigned to the methylene group of the 4-position and corresponding to the two bands, 6.10 τ of VIII and 5.74 τ, of II.

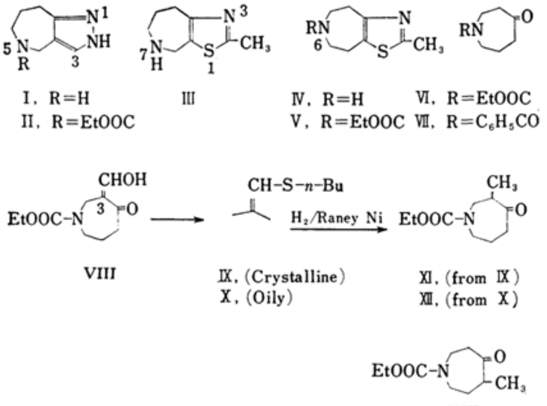

Fig. 1

From these considerations it can be concluded that, as may be seen in the formula of VIII, the hydroxymethylation had taken place at the 3-position of the seven-membered ring; hence, the pyrazole compounds derived from it had the I and II structures respectively. This judgment agrees with those already stated¹⁾ and with the chemical proofs to be described below, but it must be noticed that the thiazole compound, derived from the bromide of VI, has the alternative structure V. It may be assumed that, although the bromination of VI gave two isomeric bromides, 3- and 5-bromo compounds, only compound V was isolated from the 5-bromo compound.

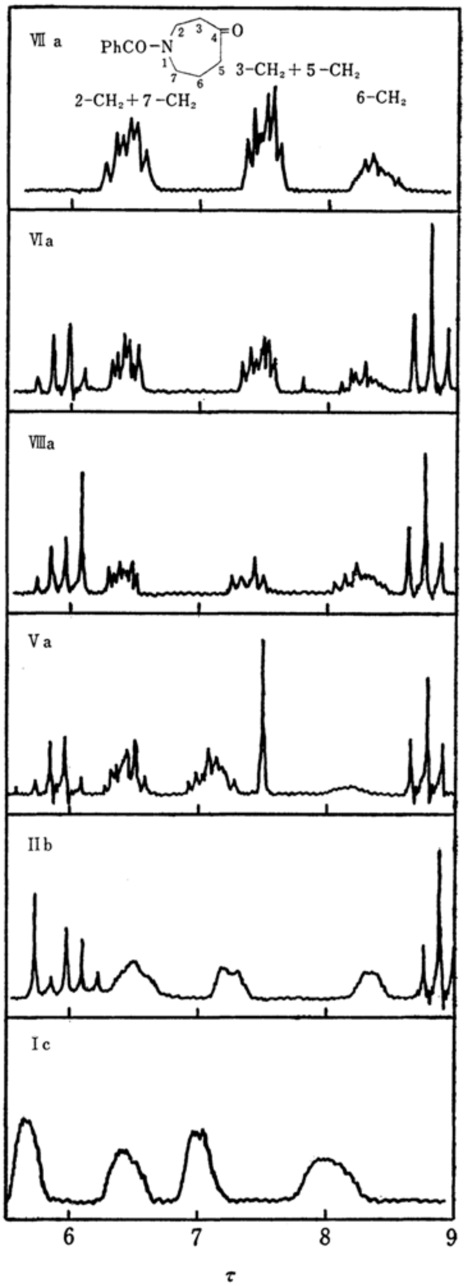

Fig. 2. The relative situations of the bands in 5.5—9 τ are indicated. Measured in a: carbon tetrachloride, b: carbon disulfide, c: trifluoroacetic acid.

In order to verify the situation of the hydroxymethylene group chemically, 1-ethoxycarbonyl-3-methyl-1-azacycloheptan-4-one (XI) was prepared from VIII by the method of Ireland *et al.*,³⁾ as is shown in Fig. 1. It was proved, by a study of the IR spectrum, that XI is not identical with the isomeric methyl ketone (XIII), in which the methyl group is undoubtedly located at the

---

3) R. E. Ireland and J. A. Marshall, *Chem.* & *Ind.*, **1960**, 1534.

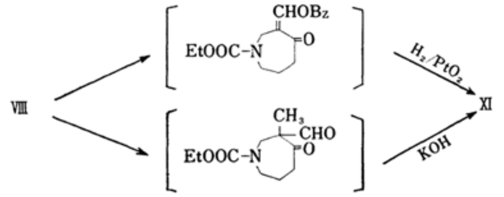

Fig. 3

5-position, judging from the route of synthesis. The intermediate thioether appeared in two forms; one was crystalline, mp 85—86°C (IX), and the other was oily, bp 219—221°C/0.7 mmHg (X). IX and X gave 2, 4-dinitrophenylhydrazones with mp of 117—119°C and of 169—170°C respectively. X contained a small amount of IX even after redistillation. IX and X indicated the same analytical values, but their IR spectra differed. The alternative methyl ketone of bp 138—140°C/1.5 mmHg (XII), obtained by the reduction of X, gave an IR spectrum almost identical with that of XI, although the bands in the 900—1050 cm^{-1} region differed slightly. Though 2, 4-dinitrophenylhydrazone of XII was quite identical with that of XI in IR spectra and the mixed melting point, it could not be verified whether the hydrazone resulted from the IX which contaminated X or not. An attempt was made to synthesize XI starting from VIII by the methods[4,5] shown in Fig. 3, but the yields were so poor that no pure product could be obtained. The product, however, was found to be identical in IR spectra and in mixed melting point with 2, 4-dinitrophenylhydrazone of XI.

Experimental

1-Benzoyl-1-azacycloheptan-4-one (VII). To a mixture of 5.0 g of 1-azacycloheptan-4-one hydrochloride,[6] 10 cc of water and 9.3 g of benzoyl chloride were added drop by drop, to a solution of 6.3 g of sodium hydroxide in 25 cc of water under stirring and cooling in ice water. After it had been stirred for an additional hour, the reaction mixture was extracted twice with benzene and the water layer was further extracted with benzene after salting out. The combined benzene solution was washed with a saturated solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was then removed and the residue was vacuum-distilled to afford 7.0 g (96.5% yield) of a colorless oil (bp 180°C/0.22 mmHg).

Found: C, 71.19; H, 7.16; N, 6.21%. Calcd for $C_{13}H_{15}O_2N$: C, 71.41; H, 6.95; N, 6.45%.

1-Ethoxycarbonyl-3-*n*-butylthiomethylene-1-azacycloheptan-4-one (IX and X). A solution of 10.0 g of VIII, 8.0 g of *n*-butylmercaptan, and 0.50 g of *p*-toluenesulfonic acid in 300 cc of benzene was so heated as to distil about 150 cc of the solvent over a 20 hr period. The reaction mixture was washed with a solution of sodium hydroxide and then with water, and dried over anhydrous magnesium sulfate. The benzene was removed, and the residue was allowed to stand for 2 days to form crystals. These were then separated by filtration and washed with ether. The filtrate was concentrated and allowed to stand for 2 days to give the same crystals. This procedure was repeated twice more to separate the crystalline product as completely as possible. The crystals were then combined and recrystallized three times from methanol to afford 4.42 g (33.0% yield) of colorless crystals with a melting point of 85—86°C (IX).

Found: C, 58.90; H, 8.25; N, 5.27%. Calcd for $C_{14}H_{23}O_3NS$: C, 58.92; H, 8.12; N, 4.92%.

2, 4-Dinitrophenylhydrazone of IX formed as tan crystals with a melting point of 117—119°C (from methanol).

Found: C, 52.15; H, 5.68; N, 15.36%. Calcd for $C_{20}H_{27}O_6N_5S$: C, 51.71; H, 5.63; N, 15.08%.

The filtrate of IX gave, on evaporation, an oily matter. This was taken up in ether, washed successively with a solution of sodium hydroxide and water, and dried over anhydrous magnesium sulfate. The ether was then removed and the residue was distilled *in vacuo* to give 2.74 g (20.3% yield) of an oil with a bp of 219—221°C/0.7 mmHg (X); this oil was isomeric with IX judging from the analytical values. (Found: C, 58.84; H, 8.23; N, 4.81%.)

2, 4-Dinitrophenylhydrazone of X was formed as red crystals with a melting point of 169—170°C; this also was isomeric with that of IX. (Found: C, 51.54; H, 6.20; N, 15.35%).

1-Ethoxycarbonyl-3-methyl-1-azacycloheptan-4-one (XI). (a) A suspension of W-2 Raney Ni, prepared from 85 g of the alloy, in 70 cc of absolute alcohol was shaken thoroughly in a hydrogen atmosphere. To this 4.4 g of IX were added, and the mixture was stirred for 5 hr. The nickel was then separated, and the solvent was removed under reduced pressure. A gel-like substance which formed on the adition of ether to the residue was filtered off, and the ethereal solution, after the removal of ether, gave 2.62 g (85.3% yield) of an oil with a boiling point of 132—134°C/0.7 mmHg on vacuum distillation.

Found: C, 59.97; H, 8.68; N, 6.75%. Calcd for $C_{10}H_{17}O_3N$: C, 60.28; H, 8.60; N, 7.03%.

2, 4 - Dinitrophenylhydrazone formed as yellow crystals with a melting point of 177—179°C (from ethanol).

Found: C, 50.35; H, 5.47; N, 18.10%. Calcd for $C_{16}H_{21}O_6N_5$: C, 50.65; H, 5.58; N, 18.46%.

(b) A solution of 3.6 g of VIII, 2.5 g of pyridine, and 3.4 g of benzoyl chloride in 50 cc of benzene was left to stand for one day. The solution was then heated, at 60°C for 4 hr and washed successively with water, 4 N hydrochloric acid, water again, a 5% solution of sodium hydroxide, and a saturated solution of sodium chloride. The benzene solution was dried over anhydrous magnesium sulfate and evaporated under reduced pressure on a water bath to give 5.03 g of a colorless, viscous residue. This was dissolved in 100 cc of absolute alcohol and shaken in a hydrogen atmosphere with 0.32 g of PtO_2 at a normal temperature and under

---

4) B. D. Astill and V. Boekelheide, *J. Am. Chem. Soc.*, **77**, 4079 (1955).

5) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, **1949**, 1855.

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

normal pressure. After the absorption of the hydrogen had been completed, the catalyst was separated and the solvent was removed. The residue was dissolved in 20 cc of ether, washed with a saturated solution of potassium carbonate, and dried over anhydrous potassium carbonate. The ether was removed; vacuum distillation of the residue then gave 1.15 g (34.2% yield) of a colorless oil with a boiling point of 135—139°C/0.7 mmHg. (Found: C, 59.50; H, 7.96; N, 6.52%.)

2, 4-Dinitrophenylhydrazone had a melting point of 175—177°C. (Found: C, 51.24; H, 5.97; N, 18.71%.)

(c) A mixture of 6.0 g of VIII, 3.18 g of anhydrous potassium carbonate (calcined and ground before use), 3.3 g of methyl iodide, and 36 cc of acetone (dried over anhydrous potassium carbonate) was heated under reflux for 24 hr. The acetone solution was then separated from any solid in the mixture and concentrated. To the residue a 6 cc portion of a 10% methanolic solution of potassium hydroxide was added, and the mixture was heated on a water bath for 1 hr. The methanol was then removed, and water was added. The oil liberated was taken up in benzene and dried over anhydrous potassium carbonate. The benzene was removed, and the residue was distilled *in vacuo* to yield 1.3 g of a colorless liquid with a boiling point of 133—142°C/0.4 mmHg. Repeated distillation gave 1.0 g (22.9% yield) of a colorless liquid with a boiling point of 130—132°C/0.3 mmHg. (Found: N, 6.58%.) The oil gave **2, 4-dinitrophenylhydrazone** with a melting point of 178—179°C; the melting point was undepressed on admixture with that described in (a). (Found: C, 50.36; H, 4.97; N, 19.00%.)

Reduction of X. In the same procedure as was used in the case of IX, 3.4 g of X gave two oily fractions, 0.18 g with a boiling point of 130—138°C/1.5 mmHg and 0.86 g with a boiling point of 138—140°C/1.5 mmHg (XII). XII (0.1 g) afforded 0.12 g of yellow 2, 4-dinitrophenylhydrazone with a melting point of 176—178°C, a substance proved identical with the above oil (XI) by a mixed melting point determination and by IR measurements.

The authors wish to express their hearty thanks to Professors Yoshio Kitahara and Ichiro Murata, of Tohoku University, for affording facilities for measuring the NMR spectra.