CHEMISTRY

1962

SovietRxiv

Abstract

Full Text

CHEMISTRY

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SYNTHESIS AND PROPERTIES OF 1-DIMETHYLAMINO-3-METHYLAZETIDIN-2-ONE

(Presented by Academician A. E. Arbuzov, 20 IX 1961)

As is known, the β-lactam ring is formed in the interaction of ketenes with azomethines (^1), from β-amino acids and their derivatives under the influence of dehydrating agents (^2) or Grignard reagent (^3, ^4), in the reaction of azomethines with esters of α-bromo-substituted carboxylic acids in the presence of zinc (^5), by the interaction of phenyl isocyanate with diazomethane (^6), of chloracetylated aminomalonic ester with triethylamine (^7), or by the action of alkali-metal amides in liquid ammonia on amides of 5-halo-substituted carboxylic acids (^8). The β-lactam ring is a constituent of penicillin ((^9), ch. XV, p. 441), and synthetic azetidin-2-ones are of interest as pharmacologically active substances (^10). In addition, upon opening of the β-lactam ring one may expect the formation of a polyamide fiber-forming polymer of the poly-β-alanine type.

In the interaction of methacrylic acid anhydride or acid chloride with unsymmetrical dimethylhydrazine, we observed the formation of the hitherto unknown 1-dimethylamino-3-methylazetidin-2-one (I). Along with this compound, its isomer, dimethylhydrazide of methacrylic acid (II), also not described in the literature, is formed.

Having the same composition, $C_6H_{12}ON_2$, these compounds differ in their crystalline structure, melting point, and also in chemical behavior. Thus, I does not show a C=C double bond, adding no bromine at all. The IR spectrum of this compound in the solid state shows an absorption band at about 1578 cm^{-1}, corresponding to stretching vibrations of the C=O group. Absorption bands corresponding to the NH group in the region from 3100 to 3400 cm^{-1} are absent from the IR spectrum of I. By contrast, compound II reacts with bromine. In its IR spectrum absorption bands are found at about 1622 cm^{-1} and 915 cm^{-1}, corresponding to stretching vibrations of the C=C bond of the vinyl and isopropenyl groups, respectively. There is also an absorption band of the stretching vibrations of the C=O group at about 1664 cm^{-1} and, both in the solid state and in the melt, an absorption band at 3216 cm^{-1}, corresponding to an NH group bound by hydrogen bonds.

In a solution of II in CCl_4, an absorption band appears at about 3441 cm^{-1},

characteristic of free NH groups. This indicates that the molecules of II are associated by intermolecular hydrogen bonds. Association of molecules of II is also detected in the determination of molecular weight by the cryoscopic method. Its value increases with increasing concentration of II in solution.

It is known that in the β-lactam ring the C–N bond is cleaved under the influence of Raney nickel ((^9), ch. XXVI, p. 983), which also acts on the N–N bond (^11). To prove the structures of I and II chemically, we subjected these compounds to hydrogenolysis with Raney nickel. When I and II are heated with Raney nickel in aqueous dioxane, dimethylamine is evolved and isobutyric acid amide III is formed according to the scheme:

$$\text{(I)} \xrightarrow[(-\mathrm{NH(CH_3)_2})]{\text{Ni Raney}} \mathrm{CH_3{-}CH(CH_3){-}CONH_2} \quad \text{(III)}$$

$$\mathrm{CH_2{=}C(CH_3){-}CO{-}NH{-}N(CH_3)_2} \xrightarrow[(-\mathrm{NH(CH_3)_2})]{\text{Ni Raney}} \mathrm{CH_3{-}CH(CH_3){-}CONH_2}$$

$$\mathrm{CH_3{-}CH(CH_3){-}COCl + 2NH_3} \xrightarrow[-\mathrm{NH_4Cl}]{} \mathrm{CH_3{-}CH(CH_3){-}CONH_2}$$

The identification was completed by the counter-synthesis of III from isobutyric acid chloride and ammonia. From I and II crystalline iodomethylates of identical composition were also obtained.

On the basis of the fact that I is not formed on heating from II, we assume that the formation of these compounds proceeds by different mechanisms: II is formed by a nucleophilic-substitution mechanism, according to the scheme:

$$\mathrm{CH_2{=}C(CH_3){-}C(=O){-}O{-}C(=O){-}C(CH_3){=}CH_2 + H_2N{-}N(CH_3)_2}$$
$$\longrightarrow [\mathrm{CH_2{=}C(CH_3){-}C(=O)\cdots H{-}N(H){-}N(CH_3)_2}] + \mathrm{{}^{-}O{-}C(=O){-}C(CH_3){=}CH_2}$$
$$\longrightarrow \mathrm{CH_2{=}C(CH_3){-}CO{-}NH{-}N(CH_3)_2 + CH_2{=}C(CH_3){-}COOH} \quad \text{(II)}$$

In the formation of I, however, apparently the addition of dimethylhydrazine to the double bond of methacrylic anhydride first takes place, followed by closure of the β-lactam ring:

$$\mathrm{CH_2{=}C(CH_3){-}C(=O){-}O{-}C(=O){-}C(CH_3){=}CH_2 + H_2N{-}N(CH_3)_2}$$
$$\longrightarrow \mathrm{H{-}N{:}{-}N(CH_3)_2 \cdots CH_2{-}C(CH_3){-}C(=O){-}O{-}CO{-}C(CH_3){=}CH_2}$$
$$\longrightarrow \begin{bmatrix} \mathrm{CH_2{-}CH(CH_3)} \\ | \quad | \\ \mathrm{HN{-}C(=O)} \\ | \\ \mathrm{N(CH_3)_2} \end{bmatrix} + \mathrm{{}^{-}O{-}CO{-}C(CH_3){=}CH_2}$$
$$\longrightarrow \text{(I)} + \mathrm{CH_2{=}C(CH_3){-}COOH}$$

Thus, the study of this reaction opens up the possibility of obtaining β-lactams with various substituents in the 1 and 3 positions of the ring.

Experimental part

Interaction of methacrylic anhydride (MAA) with dimethylhydrazine (DMH). a) Into a round-bottomed flask equipped with a stirrer, a reflux condenser, and a dropping funnel, 0.1 g of DMH was placed, and over the course of one hour, with stirring, 0.2 g of MAA was added dropwise. The reaction mixture was then heated for 6 h on a water bath at 90°. After heating was complete, the contents of the flask were distilled in vacuo. After distillation of the methacrylic acid (MA) formed and of the unreacted MAA and DMH, there remained a crystalline precipitate with m.p. 234°. Recrystallized from dimethylformamide, 1-dimethylamino-3-methylazetidin-2-one (I) was obtained in 23% of the theoretical yield, with m.p. 237–238°.

b) Into a round-bottomed flask, 0.2 g of MAA was placed, and to it, over the course of 45 min, with cooling by melting ice, 0.2 g of DMH was added dropwise. Stirring was continued for another 2.5 h, after which the syrupy mass was subjected to vacuum distillation. A fraction boiling at 110–112° at 10 mm was collected (yield 70% of theoretical). The product crystallizing in the receiver was purified by recrystallization from heptane. Dimethylhydrazide of methacrylic acid was obtained in the form of shiny, long (3 cm) needles with m.p. 71–71.5° (30% yield). I remains in the flask, with m.p. 235°.

Interaction of methacryloyl chloride (MCh) with DMH. Into a flask, 0.05 g of MCh in ether solution was placed, and to it, over the course of 40 min, with external cooling, ···

cooled with ice, 0.1 g of DMG was added. The mixture was stirred for another 1.5 h, after which the precipitate that formed was filtered off. On recrystallization from dimethylformamide, I was obtained in 30% of the theoretical yield, m.p. 234–236°. From the filtrate, after evaporation of the solvent, II was obtained in low yield, m.p. 69.5–70°. It was not possible to purify these compounds from an admixture of hydrochloride DMG by recrystallization.

I has m.p. 237–238°, is soluble in water, alcohol, and boiling dimethylformamide, and does not absorb bromine. Molecular weight (cryoscopically in water) 120; 130. Calculated for $C_6H_{12}N_2O$: 128.

Found, %: C 56.31, 56.30; H 9.38, 9.34; N 21.89, 21.87
$C_6H_{12}N_2O$. Calculated, %: C 56.25; H 9.38; N 21.88

II has m.p. 71–71.5°, is soluble in water, acetone, alcohol, benzene, chloroform, dimethylformamide, and ether, and absorbs bromine. Molecular weight (cryoscopically in benzene) 148; 183. Calculated for $C_6H_{12}N_2O$: 128.

Found, %: C 56.16, 55.94; H 9.30, 9.22; N 21.30, 21.31

$C_6H_{12}N_2O$. Calculated, %: C 56.25; H 9.38; N 21.88

Hydrogenolysis with Raney nickel. a) 0.6 g of I was heated in a flask with a reflux condenser in 30 ml of 50% aqueous dioxane with 5 g of moist Raney nickel for 2.5 h on a water bath at 70–80°. After completion of the reaction, the Raney nickel was filtered off on a glass filter and washed with dioxane. After removal of the solvent from the filtrate, a white crystalline precipitate of isobutyric acid amide III remained. After recrystallization from benzene, shiny plate-like crystals with m.p. 123–124° were obtained. A mixed sample with an authentic specimen of III showed no depression of the melting point.

b) From II, on hydrogenolysis under the conditions of a), a sample of III with m.p. 127–127.5° was obtained. A mixed sample with an authentic specimen of III showed no depression of the melting point.

Preparation of isobutyric acid amide (III). Isobutyric acid acid chloride (XIK) was obtained according to ([12], p. 128; [13], p. 262) with b.p. 92–93° (literature data: 92° ([12], p. 128; [13], p. 262)). III was obtained according to ([12], p. 293) by adding 0.2 g of XIK to 0.4 g of aqueous ammonia with cooling; m.p. 129–129.5° (literature data: 128–129°; ([9]), ch. XXVI, p. 983); 127.5° ([11])).

Preparation of methyl iodides of I and II. As a result of the interaction of I with an excess of methyl iodide in absolute alcohol, on standing, the methyl iodide of substance I precipitated. Recrystallization from absolute alcohol gave colorless needles with m.p. 246–247° (decomp.).

Found, %: C 31.64, 31.81; H 6.02, 5.91; N 10.53, 10.59; J 46.72, 46.44
$C_7H_{15}N_2OJ$. Calculated, %: C 31.11; H 5.56; N 10.37; J 47.03

The methyl iodide of substance II is formed on standing of a solution of II in excess methyl iodide, separating as a crystalline precipitate. Reprecipitated from a chloroform solution into benzene, it has m.p. 143–143.5°.

Found, %: C 31.85, 31.88; H 6.00, 5.92; N 10.25, 10.32; J 46.78, 46.53
$C_7H_{15}N_2OJ$. Calculated, %: C 31.11; H 5.56; N 10.37; J 47.03

The IR spectra of I and II were recorded on an IKS-14 instrument by N. A. Sharonova, to whom we express our gratitude.

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Received
15 IX 1961

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Note: Figure translations are in progress. See original paper for figures.