A SIDE CONDENSATION REACTION OF 5-ACETOXY-3-CHLOROPENTAN-2-ONE WITH THIOFORMAMIDE INVOLVED IN THE SYNTHESIS OF VITAMIN B_1

M. M. Litvak[1]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 32, No. 11, pp. 33 – 35, November, 1998.

Original article submitted May 28, 1998.

The commercial two-component synthesis of vitamin B_1 involves 4-methyl-5-(β-acetoxyethyl)thiazole (IV), a semiproduct obtained by the condensation of thioformamide (I) with 5-acetoxy-3-chloropentan-2-one (II). This process has been studied mostly with a view to optimization of the reaction conditions and modification of halogenoketone II. No data were reported on the detailed composition of the reaction mass; the yield of the target product or its deacylated derivative upon the final stage of vacuum distillation usually did not exceed 70% [1, 2].

Nor was the mechanism of condensation of compounds I and II studied, although there is no doubt that it falls within the general scheme of thiazole synthesis according to Hantzsch [3, 4].

Below we report on refined results of investigation of the reaction mixture composition involved in the condensation of compounds I and II. The condensation product was found to represent a mixture of acetoxyethylthiazole (IV) and a tricyclic "dithiazole" (VI).

The main stages of the work were as follows. Chloroketone II (100% purity) and thioformamide I, formed in a reaction of formamide with P_4S_{10}, were condensed for 1.5 – 2 h at 70 – 72°C until complete consumption of II in the mixture, as was evidenced by the gas chromatography (GC) data. Then the reaction mass was dissolved in water and the resulting acid solution was quantitatively neutralized with 6.05 N NaOH. Special preliminary experiments showed that neutralization of the reaction mass upon the complete conversion of 1 mole P_4S_{10} in formamide requires exactly 6 mole NaOH. The remainder of the NaOH is spent for the neutralization of HCl (whose amount agrees well with the theoretical value corresponding to the complete conversion of compound II), thus excluding other (possible, in principle) conversions of II retaining the covalently bound chlorine atoms.

The neutral condensation products were exhaustively extracted from the aqueous solution with toluene. Then the solvents were completely removed in vacuum at a temperature not exceeding 80°C. The resulting product had the form of a transparent yellow-orange liquid. Although the product yield calculated for pure compound IV was nearly quantitative (98.6%), the content of compound IV determined by GC using the absolute calibration technique amounted to only 62%. This was indicative of a considerable amount of side products. We failed to separate IV under mild conditions (selective extraction, chromatography), leaving side products intact for analysis, while attempts at separating IV by vacuum distillation at 4 – 5 Torr with heating of the product to 180°C was accompanied by polymerization of the residue.

In order to elucidate the composition and nature of the products resulting from the condensation of I and II, we have studied the ^{1}H NMR spectra of the mixture (containing 61.9% IV) and of the residue obtained upon vacuum distillation of IV. The spectra, measured on a high-resolution spectrometer (250 MHz) with a small signal integration error, have proved to be very informative (Figs. 1 and 2).

The ^{1}H NMR spectrum of the condensation products (Fig. 1) is remarkably simple. The chemical shifts of signals *a* – *e* and their multiplicity agree completely with the proposed structure of 4-methyl-5-(β-acetoxyethyl)thiazole (IV). The singlet signals at δ = 8.60, 2.42, and 2.06 ppm are assigned to the N=CH–, H_3C–C=, and CH_3CO fragments, respectively. The two triplets with δ = 4.24 and 3.10 ppm and

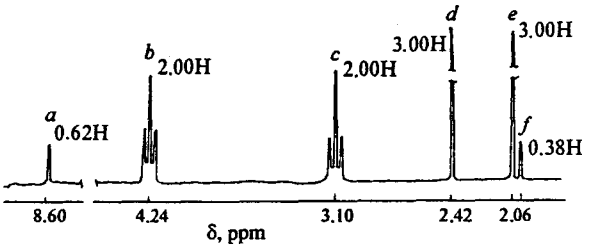


Fig. 1. ^{1}H NMR spectrum of a mixture of compounds IV and VI: (*a*) =CH (only in IV); (*b*) CH_2O; (*c*) =C–CH_2; (*d*) =C–CH_3; (*e*) OAc; (*f*) CH (only in VI).

[1] Belgorod State University, Belgorod, Russia.

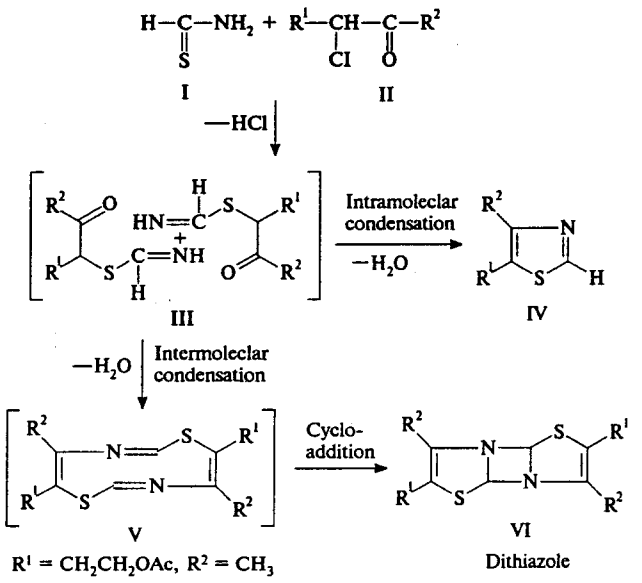
J = 7 Hz belong to the acetoxy substituent, the high-field component being due to the =C–CH_2 group. The only "excess" signal is the singlet at δ = 2.05 ppm. The ratio of the integral intensities of components *b* : *c* : *d* : *e* (2 : 2 : 3 : 3) agrees quite well with that expected for compound IV, but the intensity of the weak-field component *a* appears significantly "understated." Assuming that singlet *a* is related only to the acetoxyethylthiazole fragment, while the *b* – *e* components are due to like protons representing the whole mixture of compounds, we calculated the weight fraction of compound IV in this mixture and obtained 61.5%, which virtually coincided with the results of GC analysis (62%).

It was noted that, if the integral intensities of peaks *b* and *c* were taken equal to 2H and those of *d* and *e* – to 3H, the total intensity of signals *a* and *e* would correspond exactly to one proton.

Since the weak-field signal *a* is assigned to the -N=CH–S group (a thioformamide fragment), the side process is apparently related to a transformation of this group, probably into N–CH–S, shifting the H signal to higher field.

Additional information concerning the nature of the condensation products was obtained from the ^{1}H NMR spectrum of the residue obtained upon the vacuum distillation of IV (Fig. 2). The spectrum exhibits considerable variation. A shift of the signals *c* and *d* (corresponding to the fragments =C–CH_2 and =C–CH_3, respectively) to stronger field and a complicated multiplicity pattern of all signals are indicative of a polymerization of the product under the fractionation conditions used (10 – 15 Torr, 180°C). Note that acetoxyethylthiazole exhibits no transformations under these conditions.

Proceeding from general notions of the condensation of I and II, the experimental data presented above can be interpreted using the following scheme:



Thioamide I in the enolized form condenses with chloroketone II to form an intermediate compound III [1], which

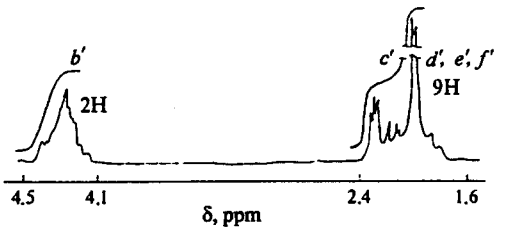


Fig. 2. ^{1}H NMR spectrum of a polymerized residue obtained upon the vacuum distillation of IV: (*b'*) CH_2O; (*c'*) C–CH_2; (*d'* – *f'*) C–CH_3, OAc, CH.

either rapidly converts into the thiazole derivative IV (intramoleclar cyclization) or (as we believe) yields a highly reactive imine V (intermoleclar condensation). The latter compound is capable of intramoleclar cycloaddition [5] to form a tricyclic "dithiazole" (VI), appearing as a side product to target compound IV.

The proposed intermediate compounds III and V are missing from the final condensation product, as evidenced by a lower (than might be expected) integral intensity of the lowest-field singlet (assigned to only the N=CH group of IV) in the ^{1}H NMR spectrum. The formation of intermediate VI agrees well with the experimental data. Indeed, because the molecular weight of compound VI is exactly twice that of IV, the complete conversion of compound II by only the two pathways indicated above leads to a virtually quantitative yield of the mixture of IV and VI (as calculated for the pure product IV). The proposed structure of VI is also consistent with the pattern of complete superposition of the ^{1}H NMR signals due to the chloroketone fragments of IV and VI. The singlet *e* at δ = 2.05 ppm is due to two identical protons ≡CH [6] appearing upon transformation of the S–CH_2=N group of thioformamide. The integral intensity of CH also agrees well with the value calculated for VI with an allowance for its content (38.1%) in the mixture. As noted above, fractionation of the mixture of IV and VI in vacuum at 180°C leads to the polymerization of product VI, leaving IV unchanged.

Thus, we have established for the first time that the commercially significant process of the condensation of compounds I and II leading to the target acetoxyethylthiazole III (a semiproduct in vitamin B_1 synthesis) is accompanied by the formation of a side product VI. A scheme is proposed that explains the formation of compounds IV and VI via the same intermediate III by the mechanism involving intra- and intermoleclar condensation.

As expected from the proposed scheme, dilution of the reagents with an inert solvent increases the yield of IV up to 85 – 89%, albeit at the expense of markedly decreased reaction rate, which has to be compensated by increasing the process temperature (typically to 80°C). It is interesting to note that the condensation of I and II at + 20 ... 24°C without solvent and using a double dilution with ethyl acetate led after interaction over several days to the formation of compound IV at nearly the same yields of 83 and 87%, respec-

tively. This result is apparently explained by a decrease in the number of active collisions of intermediate III.

These results may be of interest for refining the technology of vitamin B_1 production.

EXPERIMENTAL PART

The ^1H NMR spectra were recorded on a Bruker WM-250 spectrometer. The GC analyses were performed on an LKhM-8MD chromatograph (Russia) with a thermal conductivity detector, equipped with a 2-m column (i.d., 2.5 mm) filled with Chromaton N-AW sorbent (fraction 0.16 – 0.20 mm) impregnated with 5% XE-60. GC analysis conditions: carrier gas, helium; column temperature, 170°C; evaporator temperature, 200°C; detector temperature, 200°C; detector bridge current, 105 mA.

Synthesis of the mixture of 4-methyl-5-(β-acetoxyethyl)thiazole (IV) and "dithiazole" (VI). A suspension prepared from 8.70 g (19.57 mmole) of powdered P_4S_{10} and 17.30 g (96.86 mmole) of 100% 5-acetoxy-3-chloropentan-2-one (II) in a pear-shaped flask, equipped with mechanical stirrer, thermometer, and dropping funnel with pressure-leveling feedback, was placed in a water bath with the temperature adjusted to + 60°C. When the reaction mixture temperature reached 60°C, 9.5 ml (238.7 mmole) of 100% formamide was added to the suspension by uniformly dripping over 20 min. The mixture exhibited no spontaneous increase in temperature and acquired a light-brown color. After standing for 20 min, the reaction mixture was heated to 72°C and stirred at this temperature for 1.5 h. By the end of this period, the homogeneous mass acquired an orange color and got thick, while the initial 5-acetoxy-3-chloropentan-2-one (II) was completely missing as indicated by the GC data. To this mass was added 40 ml toluene and 20 ml water and the mixture was stirred until obtaining a two-phase system. The process was not accompanied by any significant heat evolution. The resulting acid solution (pH~1 of the bottom aqueous phase) at a temperature of about 25°C was neutralized on stirring with 6.05 N NaOH by consuming 36.0 ml (217.9 mmole) NaOH solution to reach the first stable value within the pH 7 – 8 range in the aqueous phase.

Then the reaction mass was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was extracted with toluene (2 × 40 ml). From the GC data, the ratio of the weight fractions of 4-methyl-5-(β-acetoxyethyl)thiazole in three sequential extracts was 92.3 : 7.4 : 0.3. The toluene extracts were combined and toluene was distilled off at a reduced pressure on a rotory evaporator. The compete elimination of toluene was reached by azeotropic distillation with $CHCl_3$ (2 × 30 ml), followed by treating in the rotory evaporator at a temperature of about 80°C and a pressure of 10 – 15 Torr to constant weight. This yielded 17.70 g (98.6%, as calculated for 5-acetoxy-3-chloropentan-2-one) of a mixture of compounds IV and VI in the form of a transparent yellow-orange liquid with a density of 1.206 g / ml; $C_8H_{11}NO_2S$.

The ^1H NMR spectrum of the product mixture IV + VI in $CDCl_3$ (δ, ppm): 8.60 (s, 0.62H, =CH for IV), 4.24 (t, 2H, J 6.82 Hz, CH_2O), 3.10 (t, 2H, J 6.82 Hz, =C–CH_2), 2.42 (s, 3H, =C–CH_3), 2.06 (s, 3H, OAc), 2.05 (s, 0.38H, CH). Content of compound IV: 61.5% (^1H NMR data).

The resulting mixture of compounds IV and VI (15.9 g) was fractionated by vacuum distillation at 4 – 5 Torr at a temperature not exceeding 180°C to obtain 9.48 g of compound III (92.6% purity by GC data) in the form of a light-yellow liquid (b.p., 110 – 114°C at 4 – 5 Torr). Yield of compound IV, 53.6% (calculated on the basis of the initial II). The remainder, comprising a thick red-orange liquid containing about 15% IV (GC and ^1H NMR data) and polymerized VI, was analyzed by ^1H NMR. The spectrum contained (besides clearly pronounced signals of residual IV) two groups of broadened signals with complicated multiplicity in the regions of δ = 4.5 – 4.1 ppm (CH_2O) and 2.4 – 1.6 ppm, having a ratio of integral intensities 1 : 4.5 and attributed to polymerized compound VI.

REFERENCES

1. V. M. Berezovskii, *The Chemistry of Vitamins* [in Russian], Moscow (1973).
2. L. O. Shnaidman, *Vitamin Production* [in Russian], Moscow (1973).
3. N. K. Kochetkov (Ed.), *General Organic Chemistry* [in Russian], Moscow (1985), Vol. 9, pp. 472 – 479.
4. B. G. Yasnitskii and E. B. Dol'berg, *Khim. Geterotsikl. Soedin.*, No. 7, 927 – 930 (1971).
5. N. K. Kochetkov (Ed.), *General Organic Chemistry* [in Russian], Moscow (1982), Vol. 3, pp. 518 – 533.
6. N. M. Sergeev, *NMR Spectroscopy* [in Russian], Moscow State Univ., Moscow (1981), p. 66.