SYNTHESIS OF α-SULFUR-CONTAINING 2-IMIDAZOLINONE DERIVATIVES

S. I. Zav'yalov, O. M. Radul, and V. I. Gunar

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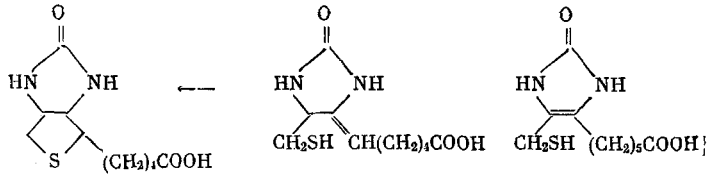
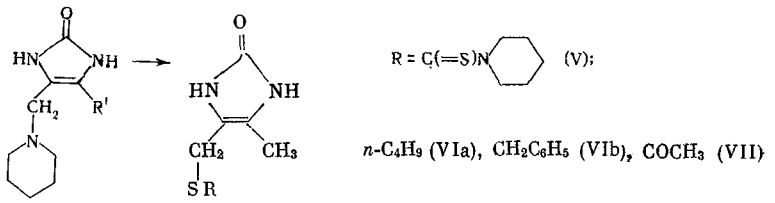
According to [1], vitamin H (biotin) (I) is formed in the living cell by the cyclization of the sulfur-containing bioprecursor (II), which contains a semicyclic double bond:



(I) (II) (III)

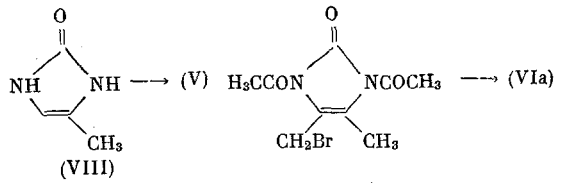
One of the routes for the synthesis of (II) could be the preparation of its structural isomer (III), which contains an endocyclic double bond, and the subsequent isomerization of (III) to (II). In the present paper, in order to effect the synthesis of (III), we studied methods for inserting the sulfur atom into the α-position of 2-imidazolinone derivatives.

The reaction of 4(5)-methyl-5(4)-piperidinomethyl-2-imidazolinone (IV) with CS_2, mercaptans or with excess CH_3COSH in refluxing alcohol, by analogy with the thiylation reactions of other types of Mannich bases [2], respectively gave 4(5)-S-thiocarbopiperididomethyl-, 4(5)-S-alkylmercaptomethyl-, and 4(5)-S-acetylmercaptomethyl-5(4)-methyl-2-imidazolinones (V), (VIa, b) and (VII) (Table 1):



R′ = CH_3 (IV)

The structure of (V) and (VIa) was proved by countersyntheses: by the reaction of $(CH_2O)_x$ and $C_5H_{10} \cdot NC(=S)SH \cdot HNC_5H_{10}$ with 4(5)-methyl-2-imidazolinone (VIII), and of n-C_4H_9SNa with 4(5)-methyl-5(4)-bromomethyl-2-imidazolinone (MB), while the structure of (VII) was proved by its conversion to the known N,N′-diacetyl derivative (by refluxing with $(CH_3CO)_2O$) [3]:



(VIII)

The reaction of (IV) with an equimolar amount of CH_3COSH gave a mixture of (VII) and sulfide (IX), the structure of which was proved by elemental analysis, molecular weight determination, desulfurization with Ni to 4,5-dimethyl-2-imidazolinone (X), and the NMR spectrum of the tetracetyl derivative (XI):

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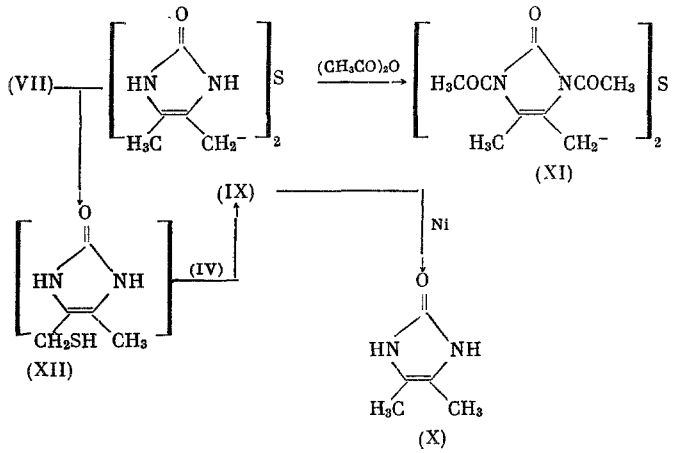
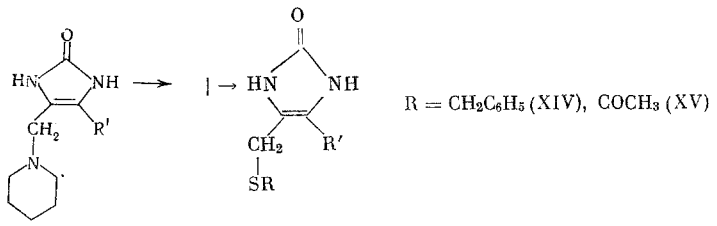


The conversion of (IV) to (IX) can be depicted as a multistep process, which includes the intermediate steps of forming (VII), the aminolysis of (VII) to 4(5)-methyl-5(4)-mercaptomethyl-2-imidazolinone (XII), and the subsequent reaction of (XII) with (IV). This scheme is in agreement with the ability of (VII) to smoothly change to (IX) when heated with excess piperidine in refluxing alcohol. The use of excess CH_3 ·COSH in the reaction with (IV) excludes the formation of free piperidine and prevents the aminolysis of (VII) to (XII), thus assuring a high yield of (VII).

The thiylation methods that were worked out on the model example (IV) were also applied to 4(5)-piperidinomethyl-5(4)-(α-hydroxy-ε-carbethoxyamyl)-2-imidazolinone (XIII), which with $C_6H_5CH_2SH$ and CH_3COSH gave sulfur derivatives that were related to (III), and specifically the 4(5)-S-benzylmercaptomethyl- and 4(5)-S-acetylmercaptomethyl-5(4)-(α-hydroxy-ε-carbethoxyamyl)-2-imidazolinones (XIV) and (XV). The structure of the latter is in agreement with the elemental analysis data and the IR spectra (see Table 1):



R = $CH_2C_6H_5$ (XIV), $COCH_3$ (XV)

R′ = $CH(OH)(CH_2)_4COOC_2H_5$ (XIII)

EXPERIMENTAL METHOD

Preparation of (V), (VIa, b), (VII), (XIV) and (XV). A mixture of (IV) [3] or (XIII) [4] and the sulfur-containing reagent in either alcohol or n-propanol was refluxed for 2-8 h, and the reaction products were isolated in the following manner: evaporation and subsequent purification of the residue by preparative TLC [Al_2O_3 (III activity), acetone–water, 9:1)] [(V)], recrystallization [(VIa) and (XIV)] or washing the residue with ether [(XV)], and filtration of the obtained precipitate [(VIb) and (VII)]. The experimental conditions and characteristics of the reaction products are given in Table 1.

Reaction of (VIII) with $(CH_2O)_X$ and $C_5H_{10}NC(=S)SH \cdot HNC_5H_{10}$. With stirring, to 4.25 g of piperidine in 40 ml of alcohol was added 3.8 g of CS_2 in 25 ml of alcohol, after which the mixture was kept for 0.5 h, and then a finely pulverized mixture of 1.5 g of $(CH_2O)_X$ and 4.9 g of (VIII) [5] was added gradually. The mixture was refluxed for 8 h, cooled, and the precipitate was filtered. We obtained 8.2 g (60%) of (V).

Countersyntheses of (VIa). To 0.185 g of n-C_4H_9SH and 0.08 g of NaOH in 10 ml of alcohol was added a solution of 0.55 g of (MB) [3] in 15 ml of alcohol, after which the mixture was kept at ~20° for 48 h, filtered, and the filtrate was evaporated. The residue was recrystallized in succession from a 1:1 EA–heptane mixture and a 5:1 EA–alcohol mixture. We obtained 0.28 g (70%) of (VIa).

N-Acetylation of (VII). A mixture of 0.18 g of (VII) and 5 ml of $(CH_3CO)_2O$ was refluxed for 3 h, the filtrate was evaporated, and the residue was recrystallized from n-heptane. We obtained 0.07 g (27%) of the N, N′-diacetyl derivative, mp 78-80° [3].

TABLE 1

Starting compounds, M		Solvent, M	Reaction, time hours	Reaction product	Yield, %	Mp, °C (solvent)*	Found / Calculated, % C	H	N	S	Empirical formula	TLC (detection with I_2 or in UV) adsorbent	solvent	R_f	Infrared spectra† (KBr) ν, cm^{-1} OH	NH	CH	C=O C=C	C_6H_5 ring
(IV) 0,003	CS_2 0,003	Alcohol, 5	5	(V)	36	290 decomp.	48,68 / 48,70	6,57 / 6,33	15,33 / 15,52	23,87 / 26,65	$C_{11}H_{17}N_3OS$	Al_2O_3 (III activity)	EA–H_2O	0,38	—	—	—	—	—
(IV) 0,003	n-C_4H_9SH 0,003	Alcohol, 20	5	(VIa)	100	243–244 (benzene–EA–alcohol, 5 : 1 : 0.5)	53,57 / 53,96	7,95 / 8,05	13,72 / 14,00	16,08 / 16,06	$C_9H_{16}N_2OS$	Silufol	EA–alcohol, 3.5: 1.5	0,46	—	3020–3190	2860–2960	1655 1675 1710	
(IV) 0,003	$C_6H_5CH_2SH$ 0,003	Alcohol, 20	3	(VI6)	88	246–248 (alcohol)	61,87 / 61,50	6,06 / 6,01	12,21 / 12,10	13,72 / 13,65	$C_{12}H_{14}N_2OS$	"	The same	0,50	—	3030–3185	2835 2932 2964	1654 1657 1710	703 729 1495
(IV) 0,03	CH_3COSH 0,09	Alcohol, 50	12 (20°)	(VII)	59	232–233 (decompn.) (alcohol)	45,06 / 45,00	5,34 / 5,35	14,93 / 15,00	17,42 / 17,20	$C_7H_{12}N_2O_2S$	"	"	0,47	—	3050–3195	2842 2935	1651 1690 1710	—
(XIII) 0,004	$C_6H_5CH_2SH$ 0,004	Alcohol, 50	8	(XIV)	73	129–131 (EA–heptane 1 : 1)	60,39 / 60,28	7,01 / 6,92	7,52 / 7,40	8,80 / 8,47	$C_{19}H_{26}N_2O_4S$	"	"	0,59	3320–3385	3038–3160	2830–2990	1688 1692 1735	710 740 1458
(XIII) 0,002	CH_3COSH 0,006	n-Propanol, 50	2	(XVI)	60	150–151 (EA)	51,08 / 50,92	7,01 / 6,70	—	9,55 / 9,68	$C_{14}H_{22}N_2O_2S$	"	EA–alcohol 4 : 1	0,48	3575	2922–3195	2848–2880	1657–1670 1691 1734	—

*EA = ethyl acetate.

†The IR spectra were taken on a 2S-301 instrument.

Preparation of (IX). A mixture of 0.37 g of (VII) and 0.3 ml of piperidine in 25 ml of alcohol was refluxed for 3h, and the precipitate was filtered and washed in succession with hot alcohol, dilute HCl solution (1 : 1), water, alcohol and ether. We obtained 0.21 g (83%) of (IX), decomposition point above 280°. Found: C 46.93; H 5.48; S 13.09%. $C_{10}H_{14}O_2N_4S$. Calculated: C 47.10; H 5.50; S 12.50%. When (VIII) was heated with excess skeletal Ni in refluxing alcohol (10 h) we isolated (X), with decomposition point above 290° (from water) [5].

Tetraacetyl Derivative (IX)-(XI). A mixture of 1 g of (IX) and 35 ml of $(CH_3CO)_2O$ was refluxed until all of the precipitate had dissolved (6 h), after which the solution was evaporated and the residue was treated with ethyl acetate. We obtained 0.88 g (53%) of (XI), mp 119-120° (from 4 : 1 benzene–heptane), R_f 0.61 (Silufol, 1 : 1 benzene–ethyl acetate). Infrared spectrum (KBr, ν, cm^{-1}): 1750, 1730, 1720 (C=O). NMR spectrum* (δ, ppm): 2.23 (2-CH_3, here and subsequently a singlet), 2.51 (2-CH_3CO), 2,55 (2-CH_3CO), 3.95 (2-CH_2S). Found: C 50.93; H 5.12; N 13.07; S 7.44%; mol. wt. 420 (Rast). $C_{18}H_{22}O_6N_4S$. Calculated: H 5.24; N 13.26; S 7.95%; mol. wt. 422. Compound (VIII) was isolated in 89% yield when (XI) was heated with excess piperidine in refluxing alcohol (3 h).

CONCLUSIONS

1. A method was developed for the synthesis of α-sulfur-containing derivatives of 2-imidazolinone by the reaction of 4(5)-piperidino-methyl-2-imidazolinones with mercaptans, carbon disulfide and thioacetic acid.

2. 4(5)-Methyl-5(4)-S-acetylmercaptomethyl-2-imidazolinone was converted to bis[4(5)-methyl-2-imidazolinonyl-5(4)-methyl] sulfide under the influence of piperidine.

LITERATURE CITED

1. A. Lezius, E. Ringelmann, and F. Lynen, Biochim. Z., 336, 510 (1963).
2. N. Kreutzkamp, H. Y. Oei, and H. Peschel, Arch. Pharm., 304, 649 (1971).
3. N. A. Rodionova, M. P. Unanyan, G. V. Kondrat'eva, S. I. Zav'yalov, and V. V. Filippov, Izv. Akad. Nauk SSSR, Ser. Khim., 1970, 660.
4. S. I. Zav'yalov, O. M. Radul, and N. A. Rodionova, Izv. Akad. Nauk SSSR, Ser. Khim., 1972, 2025.
5. S. I. Zav'yalov, M. P. Unanyan, G. V. Kondrat'eva, and V. I. Filippov, Izv. Akad. Nauk SSSR, Ser. Khim., 1967, 1792.

*The NMR spectrum was taken on a DA-60-II instrument in pyridine, using HMDS as the internal standard.