RESEARCH ON UNSATURATED AZOLE DERIVATIVES.

IX.* TRANSFORMATIONS OF 2-ETHYLNYLBENZIMIDAZOLES IN REACTIONS WITH ALIPHATIC KETONES

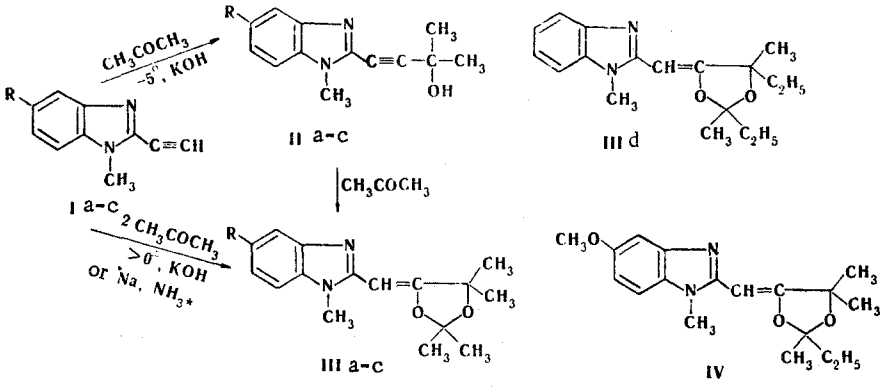
I. I. Popov, A. A. Zubenko, and A. M. Simonov

UDC 547.785.5

The reaction of 1-methyl-5-R-2-ethynylbenzimidazoles with aliphatic ketones leads to either 4-(1-methyl-5-R-2-benzimidazolyl)methylene-1,3-dioxolanes (ether, KOH, 5°C; or NH_3, Na, excess ketone) or to alkynylcarbinols (ether, KOH, −5°C, 1 mole of ketone). In contrast to 2-ethynylbenzimidazoles, 1-methyl-3-ethynylindazole is readily hydrated and does not form 1,3-dioxolanes.

Compounds that display soporific and general tranquilizing activity are known in the series of ethynylcarbinols that contain a pyridine ring [2, 3]. Up until recently, ethynylcarbinols were unknown in the series of benzimidazole derivatives [4]. In the present research we examined the possibility of the synthesis of 2-benzimidazolylethynylcarbinols by the Favorskii reaction in order to study their biological activity.

1-Methyl-2-ethynylbenzimidazoles (Ia-c) react with an equimolar amount of acetone in ether (−5°C, KOH) to give the corresponding carbinols (IIa-c) in good yields. Better yields and purer products are obtained in the reaction of acetone with the sodium salts of Ia-c in liquid ammonia. However, the reaction of Ia-c with ketones may take a different direction even when there is a slight change in the conditions. We established that the final products in the reaction of equimolar amounts of Ia-c and acetone at above 0°C are not the expected ethynylcarbinols IIa-c but rather 4-(2-benzimidazolyl)methylene-1,3-dioxolanes IIIa-c (see [4]). The reaction of Ia-c in ether (−5°C, KOH) or of the sodium salts of Ia-c in liquid ammonia with 2 moles of acetone leads to the formation of dioxolanes IIIa-c.



I-III a R=H; b R=CH_3; c R=OCH_3

However, a similar sample of Ia forms dioxolane IIId with methyl ethyl ketone. The IR spectra of IIIa contains the absorption band of an exocyclic —CH=C< bond (1680 cm^{-1}); resonance signals of four magnetically equivalent methyl groups (s, 1.5 ppm), an NCH_3 group (s, 3.6 ppm), and of the proton attached to the exocyclic double bond (s, 5.2 ppm) are observed in the PMR spectrum ($CDCl_3$).

We also accomplished the synthesis of dioxolanes IIIa-c by reaction of ethynylcarbinols IIa-c with acetone (ether, KOH, 12-20°C). Under these conditions the reaction is complete

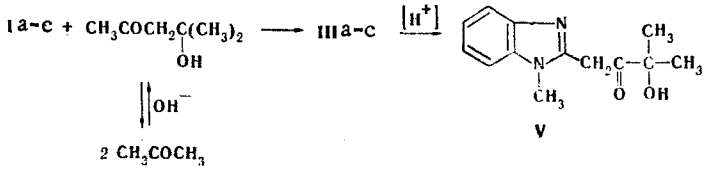
*See [1] for communication VIII.

Rostov State University, Rostov-on-Don 344006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1535-1538, November, 1978. Original article submitted December 7, 1977.

0009-3122/78/1411-1249$07.50

in 20-25 min and leads to dioxolanes IIIa-c in good yields. The use of methyl ethyl ketone and other aliphatic ketones in this reaction opens up a pathway to the synthesis of unsymmetrically constructed dioxolanes of the IV type.

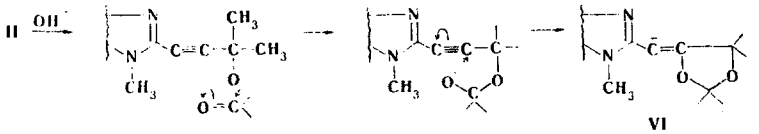
We also established that the reaction of Ia-c with diacetone alcohol both under the conditions of the Favorskii reaction and in liquid ammonia in the presence of sodium metal leads to the formation of dioxolanes IIIa-c. Diacetone alcohol is evidently cleaved under these conditions via reverse aldol condensation to give two molecules of acetone (see [4]), which then forms dioxolanes with Ia-c.



V

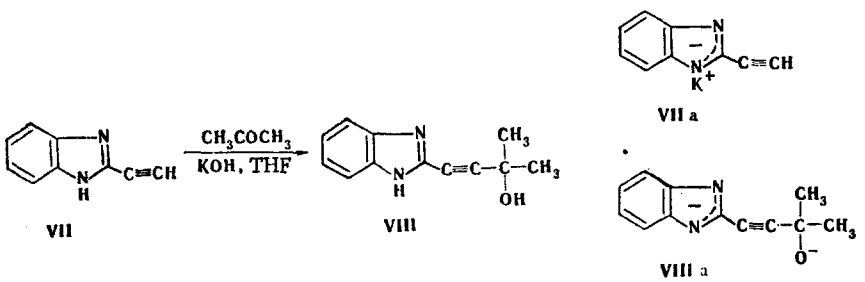
As expected, hydrolysis of dioxolane IIIa with dilute hydrochloric acid leads to acyloin V; the IR spectrum of V contains absorption bands at 1710 (C=O), 3590 (OH stretching vibrations), and 3150-3450 cm^{-1} (associated OH).

The possibility of the cycloaddition of ketones to IIa-c to give dioxolanes III and IV is evidently due to the high electrophilicity of the benzimidazolyl grouping and its ability to effectively stabilize anion VI, which is formed in the final step of the reaction (see [6, 7]).



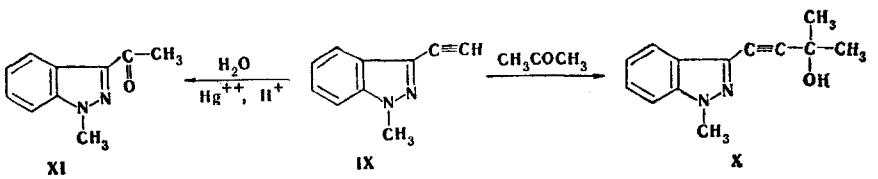
VI

In contrast to Ia-c, 2-ethynylbenzimidazole (VII) does not undergo reaction with acetone under the usual conditions of the Favorskii reaction (ether, KOH, 0-4°C), evidently because of the insolubility of VII in ether. Ethynylcarbinol VIII was obtained by the reaction of VII with acetone in tetrahydrofuran (THF) solution; however, prolonged heating is required for completion of the reaction because of the formation of slightly soluble salt VIIa, which is precipitated when powdered potassium hydroxide is added to a solution of acetylene VII in THF. The reaction of VII with acetone stops at the step involving the formation of ethynylcarbinol VIII; cycloaddition of a second molecule of acetone to it does not occur, apparently because of the considerable decrease in the electrophilicity of the benzimidazolyl ring and the acetylenic group in dianion VIIIa.



VII VIII VII a VIII a

It should be noted that, in contrast to 1-methyl-2-ethynylbenzimidazoles Ia-c, the previously synthesized [8] 1-methyl-3-ethynylindazole (IX), like phenylacetylene [9], does not form dioxolanes with excess acetone in the presence of bases in ether or in liquid ammonia. The reaction of IX with acetone in both cases leads to the formation of ethynylcarbonol X. As expected, acetylene IX, in contrast to 2-ethynylbenzimidazoles [10], readily undergoes hydration under the conditions of the Kucherov reaction to give ketone XI.



XI IX X

TABLE 1. Yields and Constants of the Synthesized Compounds

Compound	mp, °C[a]	IR spectrum, cm^{-1}	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IIa	182	2245, 3600	72,8	6,5	13,1	$C_{13}H_{14}N_2O$	72,8	6,2	13,5	78
IIb	165	2250, 3610	73,5	6,9	12,0	$C_{14}H_{16}N_2O$	73,7	7,0	12,3	73
IIc	151	—	69,1	6,7	11,3	$C_{14}H_{16}N_2O_2$	68,8	6,5	11,5	82
IIIa	173	1680	70,7	7,7	10,1	$C_{16}H_{20}N_2O_2$	70,5	7,4	10,3	62
IIIb	177—179	1690	70,9	7,9	10,2	$C_{17}H_{22}N_2O_2$	71,3	7,6	9,8	50
IIIc	175—176	—	67,5	7,3	9,2	$C_{17}H_{22}N_2O_3$	67,7	7,3	9,3	80
IIId	178[c]	1685	54,2	5,3	13,2	$C_{18}H_{24}N_2O \cdot C_6H_3N_3O_7$	54,4	5,1	13,2	58
IV	173[c]	1688	52,6	4,7	12,6	$C_{18}H_{24}N_2O_3 \cdot C_6H_3N_3O_7$	52,6	4,7	12,8	60
V	133	1710, 3590	66,9	7,2	12,5	$C_{13}H_{16}N_2O_2$	67,3	6,9	12,1	65
VIII	200—202	3150—3450	72,4	5,9	14,4	$C_{12}H_{12}N_2O$	72,0	6,0	14,0	50
X	Oil	2240, 3620	72,8	6,1	13,0	$C_{13}H_{14}N_2O$	72,8	6,5	13,1	93
XI	88—90	1680	69,1	5,7	16,0	$C_{10}H_{10}N_2O$	68,9	5,7	16,1	86

a) The following solvents were used for recrystallization: ethyl acetate for IIa-c and V, methanol—water for IIIa, ethanol—water for IIIb and VIII, ethanol for IIIc, d and IV, and hexane for XI. b) These are the yields of IIa-c and IIIa-d by method A. c) This is the melting point of the picrate.

Tests of the hypotensive activity of the compounds obtained in this research, which were carried out in the Volgograd Medical Institute, showed the presence of a weak hypotensive effect in the case of dioxolane IIIa; ethynylcarbinol II does not display this effect.

EXPERIMENTAL

The IR spectra of solutions of the compounds in $CHCl_3$ were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Tesla BS 487C spectrometer with hexamethyldisiloxane as the standard.

1-(1-Methyl-5-R-2-benzimidazolyl)-3-methyl-1-butyn-3-ols (IIa-c, see Table 1). A) A solution of 3 mmole of anhydrous acetone in 2 ml of ether was added dropwise with vigorous stirring to a cooled (to −15°C) mixture of 3 mmole of 2-ethynylbenzimidazole (Ia-c) and 13 mmole of fused powered KOH in 5 ml of dry ether, and the mixture was stirred at −15°C for 1.5 h. It was then decomposed with 20 ml of water and extracted with chloroform. The extract was dried with sodium sulfate and filtered, and the solvent was removed. The residue was chromatographed on aluminum oxide (elution with chloroform).

B) A 0.003 g-atom sample of sodium metal was dissolved in 30 ml of liquid ammonia, and 3 mmole of the corresponding acetylene (Ia-c) was added. After 15 min, a solution of 3 mmole of dry acetone in 3 ml of ether was added, and the mixture was stirred until the ammonia evaporated. The residue was decomposed with water, and the aqueous mixture was extracted with chloroform. The yields of IIa-c were 80, 85, and 80%, respectively.

4-Methylene-(1-methyl-2-benzimidazolyl)-1,3-dioxolanes (IIIa-d, Table 1). A) A solution of 12-15 mmole of the corresponding ketone in 3 ml of ether was added dropwise with stirring to a mixture of 3 mmole of Ia-c and 13 mmole of anhydrous powdered KOH in 5 ml of dry ether, while maintaining the temperature of the reaction mixture at 12-20°C. The mixture was stirred for 5 h, after which it was decomposed with water and extracted with chloroform.

B) The procedure was similar to that described for IIa-c in method B, except that a twofold to threefold excess of the ketone was used. The yields were 65, 66, 72, and 63%, respectively.

C) Dioxolanes IIIa-c were obtained by reaction of IIa-c with excess acetone under the conditions described in method A. The reaction was complete in 20-30 min. The yields of IIIa-c were 87, 84, and 80%, respectively.

Compound IV was obtained in 60% yield under these conditions by reaction of IIc with methyl ethyl ketone.

D) Compounds IIIa-c were obtained by reaction of Ia-c with excess diacetone alcohol under the conditions described in methods A and B. The yields were 55-65%.

1-(2-Benzimidazolyl)-3-methyl-1-butyn-3-ol (VIII, Table 1). A solution of 0.7 ml of dry acetone in 2 ml of tetrahydrofuran (THF) was added dropwise with stirring at 0°C to a mixture of 0.43 g (3 mmole) of 2-ethynylbenzimidazole (VII) and 0.67 g (12 mmole) of powdered KOH in 5 ml of dry THF, and the mixture was stirred at 0°C for 1 h and at room temperature for 8 h. The resulting viscous mass was treated with water, and the solvent was removed by vacuum distillation. The residue was neutralized with dilute HCl, and the precipitate was removed by filtration, dried, powdered thoroughly, and transferred to a chromatographic column (2 by 5 cm) containing aluminum oxide. Elution with chloroform gave starting acetylene VII, and subsequent elution with acetone gave pure reaction product.

2-Methyl-4-(1-methyl-2-benzimidazolyl)butan-3-on-2-ol (V, Table 1). A solution of 0.54 g (2 mmole) of dioxolane IIIa in 10 ml of 10% HCl was refluxed for 3 h, after which it was cooled and neutralized with sodium bicarbonate, and the precipitate was removed by filtration and dried at 70-80°C. It was then treated with ethyl acetate and crystallized from ethyl acetate.

1-(1-Methyl-3-indazolyl)-3-methyl-1-butyn-3-ol (X, Table 1). A 0.67-g (12 mmole) sample of powdered KOH was added to a solution of 0.47 g (3 mmole) of 1-methyl-3-ethynylindazole (IX) in 15 ml of dry ether, the mixture was cooled to 0°C, and a solution of 0.73 ml (10 mmole) of acetone in 5 ml of ether was added with stirring in the course of 15 min. After 1.5 h, the mixture was decomposed with water and extracted with ether. The extract was dried with Na_2SO_4 and chromatographed on Al_2O_3 (elution with ether).

1-Methyl-3-acetylindazole (XI, Table 1). Two drops of concentrated sulfuric acid and a catalytic amount of mercuric chloride were added to 5 ml of 70% methanol, the mixture was heated to 70°C, and 0.47 g (3 mmole) of 1-methyl-3-ethynylindazole was added with stirring. The mixture was stirred at 70°C for 5 h, after which it was diluted with water and neutralized with $NaHCO_3$. The precipitate was removed by filtration, dried, and chromatographed on aluminum oxide (elution with chloroform).

LITERATURE CITED

1. A. A. Zubenko, I. I. Popov, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 8, 1111 (1978).
2. D. Popa, F. Villani, and H. F. Ginsberg, J. Am. Chem. Soc., No. 76, 4446 (1954).
3. A. N. Kost, P. B. Terent'ev, and A. A. Shegolev, Zh. Obshch. Khim., 32, No. 8, 2606 (1962).
4. I. I. Popov, A. M. Simonov, and A. A. Zubenko, Khim. Geterotsikl. Soedin., No. 1, 140 (1975).
5. H. Walba, W. J. Murray, G. Knitson, and A. Diaz, J. Am. Chem. Soc., 88, 1692 (1966).
6. H. Meister, Chem. Ber., 98, 2862 (1965).
7. H. Meister, Liebigs Ann. Chem., 724, 128 (1969).
8. I. I. Popov, A. A. Zubenko, A. M. Simonov, B. A. Tertov, and P. P. Onishchenko, Khim. Geterotsikl. Soedin., No. 12, 1678 (1975).
9. A. E. Favorskii, Zh. Russk. Fiz. Khim. O-va, 37, 643 (1905).
10. A. A. Zubenko, I. I. Popov, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 11, 1544 (1974).