was measured upon introduction and 0.5, 1, 3, 6, and 25 h after introduction of the substances, which were used at a dose of 10 mg/kg. Five to six rats were used to study each dose. Recordings were made on a physiograph (DMP-4B, Harko Bio-systems, USA).

The compounds were introduced into the stomach in a volume of 5 ml/kg as aqueous suspensions prepared with Tween-80 (0.05 ml of 6% Tween per 5 ml of material).

The acute toxicity was studied on both sexes of white mice weighing 19-23 g by intraperitoneal injection. Each dose was studied with 6 mice, and the mice were observed for 10 days after treatment. Acute toxicity was obtained by the Litchfield-Wilcoxon method.

LITERATURE CITED

1. G. Ya. Dubur, Z. Ya. Ogle, and Ya. R. Uldrikis, Khim. Geterotsikl. Soedin., 1642-1645 (1974).
2. V. V. Kastron, G. Ya. Dubur, R. O. Vitolin', et al., Khim.-farm. Zh., No. 11, 42-49 (1982).
3. V. V. Kastron, R. O. Vitolin', G. Ya. Dubur, et al., Inventor's Certificate 706410 (USSR). Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki, No. 48 (1979).
4. E. Kusano, J. Asano, and K. Takeda, Arzneim. Forsch., 32, 1575-1580 (1982).
5. B. Loev and K. M. Snader, J. Org. Chem., 30, 1914-1916 (1965).
6. M. Schramm, G. Thomas, and R. Towart, et al., Arzneim. Forsch., 33, 1268-1272 (1983).

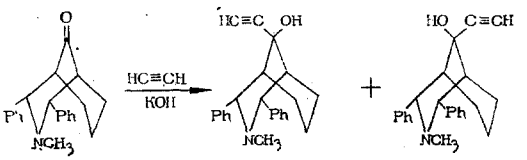
SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF ACETYLENE DERIVATIVES OF AZABICYCLONONANE

S. A. Baisalbaeva, T. T. Omarov, E. T. Nikitina, and G. G. Kazakova

UDC 615.281:547.518].012.1

Acetylene-containing compounds with a variety of biological activities including antimicrobial are widely known since they are often more active, less toxic, and more easily assimilated by the organism than the olefinic compounds [5]. The decreased toxicity and strong adsorption and metabolism of some drugs apparently is connected with the presence of the triple bond in these molecules.

In a synthesis program conducted with the aim of obtaining preparations with high activity and low toxicity, we carried out the synthesis of acetylenic alcohols, their acetates, and diacetylene derivatives.



I II III

The isomeric acetylenic derivatives were synthesized in a Favorskii reaction by the interaction of 2,4-diphenyl-3-methyl-3-azabicylo[3,3,1]-nonan-9-one (I) with acetylene in the presence of potassium hydroxide in liquid ammonia.

The isomeric 2,4-diphenyl-3-methyl-9-ethynyl-3-azabicyclo[3,3,1]nonan-9-ols (II and III) were stable and usually crystalline substances, easily soluble in organic solvents (ethanol, acetone, benzene, dioxane) and insoluble in water.

The 2,4-diphenyl-3-methyl-9-ethynyl-3-azabicyclo[3,3,1]nonan-9-yl acetates (IV and V) were prepared by the interaction of the isomeric acetylenic alcohols I and II with acetic anhydride; the reaction products were crystalline materials, soluble in organic solvents and insoluble in water.

Institute of Chemical Science and Institute of Microbiology and Virology of the Academy of Sciences of the Kazakh SSR, Alma-Ata.

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 19, No. 5, pp. 550-552, May, 1985. Original article submitted June 12, 1984.

0091-150X/85/1905-0322$09.50

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TABLE 1. Physicochemical Constants and Antimicrobial Activity of Acetylenic Derivatives of 2,4-Diphenyl-3-methyl-3-azabicyclo[3,3,1]nonan-9-one

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %			Minimum effective concentration, μg/ml							
			C	H	N		C	H	N	Staph. aureus	Streptococcus	Bac. anthracoides	Bact. caratovorum	Corinebacterium	E. coli	Mycobact. rubrum	Microsporum lanosum
I	72	160-162	82,56	7,64	4,67	$C_{21}H_{23}NO$	82,62	7,54	4,58	—	—	—	1,52	0,5	13,7	13,7	—
II	85	170-171	83,22	7,64	4,48	$C_{23}H_{25}NO$	83,38	7,55	4,23	1,56	100	3,1	4,6	0,5	200	—	200
III	15	138-139	83,61	7,59	4,54	$C_{23}H_{25}NO$	83,38	7,55	4,23	25	—	—	—	—	200	—	200
IV	72	137-138	78,87	7,86	3,87	$C_{23}H_{27}NO_2$	79,08	7,74	4,01	—	—	2,46	0,27	0,27	—	0,09	—
V	80	169-170	78,91	7,92	3,85	$C_{23}H_{27}NO_2$	79,08	7,74	4,01	66,6	—	66,6	66,6	0,82	—	22,2	—
VI	60	270-271	83,50	7,12	4,31	$C_{46}H_{48}N_2O_2$	83,64	7,27	4,24	66,6	—	—	66,6	66,6	—	—	—

The diacetylenic derivative, 1,4-bis(2,4-diphenyl-3-methyl-3-azabicyclo[3,3,1]nonyl-9 diacetylene (VI), was obtained by dimerization of compound III by the method of Eglinton [6] in dry pyridine in the presence of cupric acetate. The reaction product (VI) was a high-melting, crystalline substance, soluble in organic solvents and insoluble in water.

The steric configuration of the synthesized compounds was established on the basis of IR and PMR spectral data.

The IR spectra of compounds II and III showed intense absorption bands for ν_{OH} in the 3350-3500 cm^{-1} region, ν_{CH} in the 3290-3300 cm^{-1} region and ν_{C-O} in the 1040-1068 cm^{-1} region. Isomer III with the lowest absorption band for the C–O bond was assigned the axial orientation of the hydroxyl group [1]. The doublet absorption band for the O–H bond indicated the equatorial hydroxyl group in isomer II.

In the PMR spectra of the isomeric acetylenic alcohols II and III, signals for the N-methyl protons were observed in the 1.95 and 1.98 ppm regions, signals for the C_O–H protons in the 4.13 (d) and 4.05 (d) ppm regions and the ≡C–H protons at 2.56 and 2.81 ppm, respectively.

PMR spectral data indicate different degrees of protonation of the amino-alcohols in hydrochloric acid, which allowed deduction of the orientation of the methyl group on the nitrogen atom [4].

The IR spectra of the acetates IV and V show intense absorption bands for $\nu_{C=O}$ in the 1740-1745 cm^{-1} region and for ν_{C-O} in the 1243-1245 cm^{-1} region.

The characteristics of the synthesized compounds are presented in Table 1.

EXPERIMENTAL CHEMISTRY

IR spectra were recorded on an UR-20 spectrometer in KBr pellets and in $CHCl_3$ solution (C = 0.01 M/liter). PMR spectra were obtained on a BS487-C (ChSSR) instrument, with hexamethyldisilane as internal standard.

2,4-Diphenyl-3-methyl-3-azabicyclo[3,3,1]nonan-9-one (I). To a solution of 14.55 g (0.05 mole) of 2,4-diphenyl-3-azabicyclo[3,3,1]nonan-9-one [3] in 100 ml of dioxane was added 3 g (0.05 mole) of 80% formic acid and 4.7 g (0.05 mole) of 35% formalin solution and the mixture was heated in a boiling water bath until complete cessation of CO_2 evolution. The reaction mixture was cooled, the resulting crystals were filtered off, the solvent was evaporated from the filtrate and the remaining aqueous layer was extracted with ether. The extract was dried with potassium carbonate and the solvent was evaporated to give crystals which were collected and recrystallized from acetone to give 11.2 g (72.5%) of I, mp 160-162°C.

2,4-Diphenyl-3-methyl-9-ethynyl-3-azabicyclo[3,3,1]nonan-9-ol (II, III). In a three-necked round-bottom flask fitted with a mechanical stirrer, addition funnel, and tube for introduction of acetylene was placed 3.92 g (0.07 mole) of powdered potassium hydroxide in 1.5 liters of liquid ammonia. The mixture was saturated with acetylene over a period of 2 h with energetic stirring and then a solution of 15.25 g (0.05 mole) of I in 250 ml of absolute tetrahydrofuran was added dropwise over 3 h. The reaction mixture was stirred for 3 h while continuing the acetylene flow. On the following day the reaction mixture was hydrolyzed with water. The aqueous layer was extracted many times with chloroform, which was dried over calcined sodium sulfate. The solvent was distilled to give a glassy residue, which was crystallized from benzene to give 12.83 g of II and III mixture. Fractional crystallization from benzene gave 10.85 g of isomer II and 1.82 g of isomer III.

2,4-Diphenyl-3-methyl-9-ethynyl-3-azabicyclo[3,3,1]nonan-9-yl Acetate (IV). Compound II (1 g) in 5 ml of acetic anhydride was heated for 4 h in a water bath. The solution was then concentrated in the water bath under aspirator vacuum and the white residue remaining was washed with benzene. Recrystalization from ethanol gave 0.72 g of IV.

2,4-Diphenyl-3-methyl-9-ethynyl-3-azabicyclo[3,3,1]nonan-9-yl Acetate (V) was obtained analogously from the isomeric alcohol III (1 g) to give 0.8 g of V.

1,4-Bis(2,4-diphenyl-3-methyl-3-azabicyclo[3,3,1]nonan-9-yl)diacetate (VI). A solution of 1 g (0.03 mole) of III in 50 ml of pyridine was heated with 6 g of cupric acetate for 4 h at 55-60°C and kept overnight. The pyridine was then removed under vacuum and the residue was added to 50 ml of 7% HCl. The precipitate was separated, washed with water and dilute NH_4OH. Crystallization from dioxane gave 0.71 g of VI.

EXPERIMENTAL BIOLOGY

The antimicrobial activity of the compounds was studied by serial dilution on liquid nutritive medium [2] with a spectrum of 3 to 8 strains of microorganisms. The activity of the compounds was evaluated as the minimum bacteriostatic concentration (in μg/kg); the results of the study are presented in Table 1.

Determination of the acute toxicity was carried out on white mice of both sexes (weight 18-22 g) on doses of 100 to 2500 mg/kg. Each dose of the preparation was studied in four mice. Observations on general condition and conduct of the animals was carried out over 30 days. Acute toxicity for the hydrochloride of I was 2500 mg/kg.

The hydrochloride of the starting material (I) showed a suitable spectrum of activity on the strains of microorganisms studied. It should be noted that the introduction of a substituent in position C-9 substantially changes the activity and leads to a sharply selective suppression of the growth of some microorganisms. The isomeric acetylenic alcohols II and III lead to high activity against *Staph. aureus* which is absent in I. The esters of the acetylenic alcohols IV and V give high selective activity against *Corinebacterium*. However, the introduction of a second acetylenic bond (compound VI) noticeably lowers the antimicrobial activity, but this material shows weak activity against paragrippa virus.

It should be noted that the series of isomeric acetylenic derivatives in the 3-azabicyclononane series do not show a significant dependence of the antimicrobial activity on the spacial arrangement of the hydroxyl and ethynyl groups. Presumably, this may be explained by peculiarities in the structure of the azabicyclononane skeleton, which contains piperidine as well as cyclohexane fragments, each of which is the basis of many compounds manifesting different biological activity.

LITERATURE CITED

1. S. I. Bakum and T. N. Dymova, Izv. Akad. Nauk SSSR, Ser. Khim., 1890-1893 (1970).
2. N. S. Egorov, Microbe Antagonists and Biological Methods of Determining Antibiotic Activity [in Russian], Moscow (1965), pp. 86-89.
3. V. Baliah and R. Jevamaran, Indian J. Chem., 9, 1020-1023 (1971).
4. J. B. Lambert and R. C. Keske, Tetrahedron Lett., 2023-2027 (1969).
5. T. F. Rutledge, Acetylenic Compounds, Vol. 1, New York (1968), pp. 134-136.
6. H. Stetter and P. Goebel, Chem. Ber., 95, 1039-1042 (1962).