The duration of the soporific activity of hexenal (50 mg/kg intravenously) in the control group was 15 (12.4-17.6) min, and after previous administration of compounds VII or VIII in a dose of 15 mg/kg, and mexamine in a dose of 10 mg/kg subcutaneously, this increased to 20 (14.7-25.3), 30 (25.1-34.9), and 37 (30-44) min, respectively.

The toxicity of VIII approaches that of mexamine, while VII is less toxic. On intravenous injection the LD_{50} in white mice for compounds VII and VIII, and for mexamine is 217.5, 122.5, and 102.5 mg/kg, respectively.

The investigation we have carried out indicates that as regards the pharmacological effect, the activity, and the toxicity, compound VIII is close to mexamine. In addition to that compound VIII shows a strong sympathomimetic effect which is neutralized by phentolamine. Shift of the cyclic group of ethylenedioxytryptamine to the 5,6-position of the indole nucleus leads to a decrease in activity and toxicity.

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SYNTHESIS OF COMPLEX AZABICYCLO[3.3.1]NONANE ESTERS AND THEIR PSYCHOTROPIC ACTIVITY

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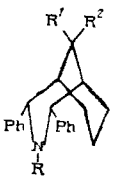
As a continuation of our earlier research on new physiologically active substances among the 3-azabicyclo [3.3.1]nonane series, we synthesized isomer 2,4-diphenyl-9-ethynyl-3-azabicyclo [3.3.1]nonane-9-ol acetic and benzoin esters (I, II), established their structure,* and investigated their psychotropic activity.



I: R = H, R^1 = C≡CH, R^2 = OH;
II: R = H, R^1 = OH, R^2 = C≡CH;
III. R = Ac, R^1 = C≡CH; R^2 = OAc;
IV: R = Ac, R^1 = OAc; R^2 = C≡CH;
V: R = COPh, R^1 = OH; R^2 = C≡CH;
VI: R = COPh, R^1 = C≡CH; R^2 = OCOPh.

O, N-diacetyl-2,4-diphenyl-9-ethynyl-3-azabicyclo[3.3.1]nonane-9-ols (III, IV) were obtained by reacting isomer acetylene alcohols of I and II with Ac_2O. The reaction products were white crystalline substances soluble in organic solvents and insoluble in water.

O, N-dibenzoyl-2,4-diphenyl-9-ethynyl-3-azabicyclo[3.3.1]nonane-9-ol (VI) and N-benzoyl-2,4-diphenyl-9-ethynyl-3-azabicyclo[3.3.1]nonane-9-ol (V) were formed by the benzoyl chloride acylation of isomer acetylene alcohols of I and II. In both cases the resultant products were white powdered water-insoluble substances that were poorly soluble in organic solvents. The structure of the synthesized compounds III-VI was confirmed by IR spectroscopy and element analysis as shown in the table.

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TABLE 1. Physical and Chemical Characteristics of III-VI Series Complex Esters of 2,4-Diphenyl-9-ethynyl-3-azabicyclo[3.3.1]nonane-9-ol

Compound	Yield, %	mp., °C	Found, %			Empirical formula	Calculated, %			IR-spectra, ν cm^{-1}				
			C	H	N		C	H	N	C—O—C	C=O	C≡C	N—C=	≡C—H
III	80	211—2	77,85	6,95	3,63	$C_{28}H_{27}NO_3$	77,80	6,70	3,50	1240	1745	2145		
IV	69	163—4	77,65	6,65	3,69	$C_{28}H_{27}NO_3$	77,80	6,70	3,50	1240	1745	2125		
V	81	235—6	83,11	6,90	3,35	$C_{29}H_{27}NO_2$	82,66	6,41	3,32	1260			1630	3280
VI	88	224—5	82,05	6,03	2,72	$C_{36}H_{31}NO_3$	82,29	5,91	2,67	1280	1735		1640	3290

EXPERIMENTAL – CHEMICAL

The IR-spectra of the synthesized compounds were recorded on a UR-20 spectrometer in KBR pellets.

3-Acetyl-9-acetyloxy-2,4-diphenyl-9-ethynyl-3-azabicyclo[3.3.1]nonane (endo-isomer IV). A 1-g portion of 2,4-diphenyl-9-ethynyl-3-azabicyclo[3.3.1]nonane-9-ol in 5 ml of Ac_2O was heated on a boiling water bath for 6 h. The mixture was then evaporated on a water bath under a water jet vacuum and the resultant white precipitate was washed with benzene. After recrystallization from acetone the yield of IV was 0.69 g.

3-Acetyl-9-acetyloxy-2,4-diphenyl-9-ethynyl-3-azabicyclo[3.3.1]nonane (exo-isomer III). A yield of 0.8 g of this compound was obtained in a similar manner as above from 1 g of the isomer acetylene alcohol of compound I.

N-benzoyl-2,4-diphenyl-9-ethynyl-3-azabicyclo[3.3.1]nonane-9-ol (endo-isomer V). A 3.07-g portion (0.01 mole) of 2,4-diphenyl-9-ethynyl-3-azabicyclo[3.3.1]nonane-9-ol and 0.7 g (0.005 mole) of PhCOCl in 15 ml of anhydrous xylene were heated for 4 h at 80°C. Then an additional 0.005 mole of PhCOCl was added to the mixture which was heated for 4 more hours. After the mixture was cooled, 15 ml of anhydrous ester was added to the reaction mixture which was then left overnight. The resultant precipitate was filtered off and recrystallized from benzene. The yield was 2.5 g of compound V.

O, N-dibenzoyl-2-4-diphenyl-9-ethynyl-3-azabicyclo[3.3.1]nonane-9-ol (exo-isomer VI). A 3.07 g portion of the isomer acetylene alcohol of I, 1.4 g (0.01 mole) of PHCOCL, and 30 ml of anhydrous xylene were heated for 4 h. An additional 0.01 mole of PhCOCl was added to the mixture which was then heated for 4 more hours. After the solution was cooled, 30 ml of anhydrous ether were added to the mixture which was then left overnight. The resultant precipitate was filtered off and recrystallized from benzene. The yield was 2.69 g of compound VI.

EXPERIMENTAL – BIOLOGICAL

All of the substances were administered in equivalent volumes of starch mucilage (0.1 ml per 10 g of mass).

The tested substances have a low toxicity and have a depressant action on the CNS. The substances caused no deaths in the mice even at a dose of 1000 mg/kg, with the exception of compound V whose LD_{50} was 900 mg/kg. Within the dose range of 200-1,000 mg/kg all of the compounds restrict motor activity without side reactions or disturbances of corneal or aural reflexes, and reduce rectal temperature by 1-4°C, dependent upon dosage. The depressant action which is the most pronounced effect exhibited by compounds III and IV was also manifested at a dose of 100 mg/kg in the form of an average 1°C drop in temperature (30th minute of the experiment), a threefold reduction in the number of visits made to the "open field" areas, and a 4.5-fold reduction in the visits made to the check point passages. This was a reflection of the animals' motor and orientational activity. Moreover, compound III completely suppressed the vertical component of motor activity whereas compound VI restricted that activity by 6.6 times. Both substances potentiated the action of hexenal by a 1.5-2.5-fold increase in the duration of the hexenal-induced side reaction in mice, and by the complete suppression of the previously induced dark room avoidance conditional reflex in the case of the rats. In spite of the depressant effect, none of the substances at a dose of 100 mg/kg affected the animals' clustering urge nor their ability to hold on to a rotating rod or grasp an immobile vertical rod. Furthermore, the substances did not exhibit any anticonvulsive effects and did not the alter the defense reflex time in the "hot plate" test nor did the substances alter the animals' responses to caudal stimulation or change that response as affected by amidopyrine.

The data we obtained indicate that the tested compounds, particularly compounds III and VI, exhibit elements of tranquilizing activity.