SYNTHESIS AND CARDIOTONIC ACTIVITY OF 3,9-DIOXOPYRROLO[1,2-a]INDOLE DERIVATIVES

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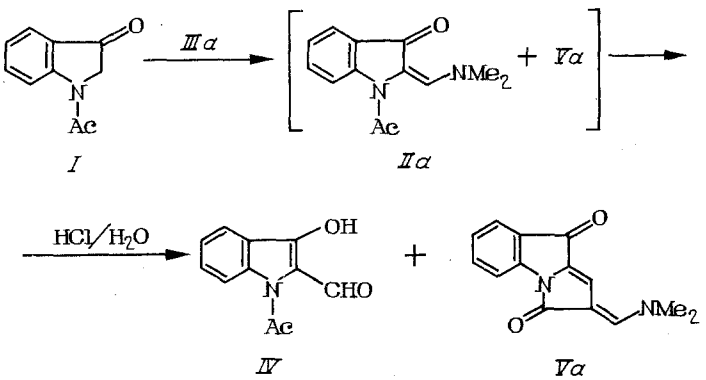
UDC 615.31:547.745.755

Amide acetals react easily with compounds containing active methylene groups to form the corresponding enamines [2, 9]. We have recently used 1-acetylindolinone-3 (I) as the active methylene component, and found that this results in the formation of 2-dialkylaminomethyleneindolinone-3 derivatives, such as compound II, which are suitable compounds for the synthesis of functionally substituted indoles [3-5].

Studies of the interaction of the diethylacetal of dimethylformamide (IIIa) with indolinone-3 (I) showed [3] that the reaction forms IIa, which is hydrolyzed in acid conditions to 1-acetyl-2-formyl-3-oxyindole (IV). We have demonstrated [6] that the reaction of the acetal of IIIa with indolinone-3 (I) produces, apart from the major condensation product IIa, 2-dimethylaminomethylene-3,9-dioxopyrrolo[1,2-a]indole (Va) (with a yield of 2%), which is presumably the product of an unexpected side reaction occurring while IIa and IIIa interact. The structure of the tricyclic compound Va was demonstrated using IR, PMR, and mass spectrometry. The IR spectrum of Va contained absorption bands at 1650 cm^{-1}, corresponding to an aromatic carbonyl group, and at 1620 cm^{-1}, corresponding to an enaminoamide carbonyl group. The PMR spectrum of this compound contained, apart from signals from aromatic protons and N-methyl groups, a singlet at 7.74 ppm from a vinyl proton, and a singlet at 7.40 ppm typical of the 1-H proton of a tricyclic group. The PMR spectra of 2-substituted 3-amino-9-oxopyrrolo[1,2-a]indoles have been published [5], where the signal from the analogous proton was located in the 7.04-7.34 ppm region. The most intense peak in the mass spectrum of Va corresponded to a molecular ion of $M^+ = 240$.



The pyrrolo[1,2-a] system is of great interest; this class of derivative includes the antitumor antibiotic mitomycin [14] and many compounds with significant antitumor [10], antibacterial [12], hypoglycemic [13], and antiallergic [5] activities.

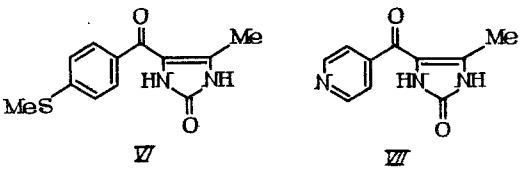
The literature does not contain any reports on the cardiotonic activity of pyrrolo[1,2-a]indoles.

However, analysis of the structures of many compounds with cardiotonic activity shows that the presence of oppositely directed dipoles is a very characteristic element, as is the common planar topography of these molecules [8]. Consideration of the formulas of such compounds as enoximone (VI) and piroximone (VII) suggests that they can have these characteristics when they interact with the complementary elements of their receptor structures. On the other hand, the structures of compounds Va and Vb, synthesized here, and of their primary amine transamination products (such as VIII) have some similarity with the above structures: the bond between the benzene and the five-member ring creates a "stabilized form" with oppositely directed

All-Union Scientific-Research Institute of the Chemicopharmaceutical Industry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 27, No. 11, pp. 21-26, November, 1993. Original article submitted November 25, 1992.

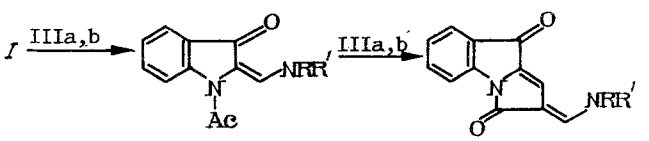
0091-150X/93/2711-0748$12.50 © 1994 Plenum Publishing Corporation

carbonyl groups, and the vinyl-like enamine fragment creates an electronic configuration in the pyrrole ring which is similar to those typical of the imidazole ring. Also, the tricyclic structure of the compounds studied here is nearly planar.



Thus, we developed a new preparative method for the synthesis of 2-dialkylaminomethylene-3,9-dioxopyrrolo-[1,2-a]indoles [7], and studied their transamination reactions and the cardiotonic activity of the derivatives of this heterocyclic system.

The starting compound was the easily available (more so than compound IIa) 1-acetyl-2-piperidinomethyleneindolinone-3 (IIb) [3]. Heating of enaminoketone IIb in the presence of excess IIIa acetal produced tricyclic compound Va with a yield of 73%. The reaction carried out in the presence of the acetal of IIIb produced piperidinomethylene derivative Vb with a yield of 70%. In addition, conditions for preparing Va and Vb by reaction with N-acetylindolinone-3 (I) with the corresponding acetals of IIIa and IIIb without removal of the intermediate enaminoketones IIa and IIb were determined experimentally. The spectral characteristics of compounds Va and Vb were similar.

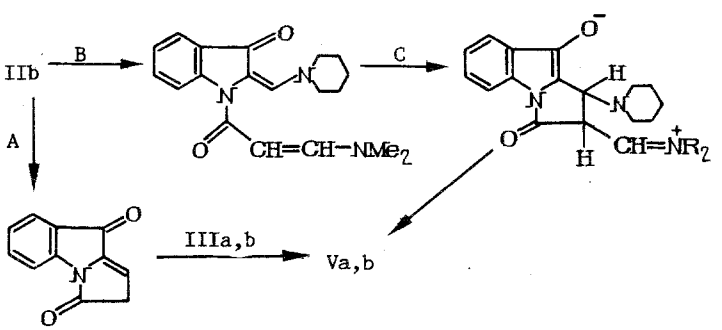


IIa,b

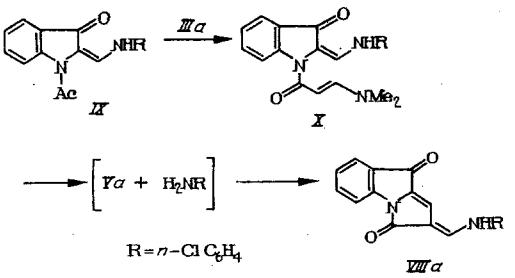
Va,b

a: R=R′=Me, b : R+R′=$(CH_2)_5$

We also established the pathway of this unexpected reaction. Two variants (A and B) can be proposed for the formation of pyrroloindoles Va and Vb.



In the first possibility (pathway A), cyclization occurs at the initial stage, while in the second (pathway B), cyclization occurs at a later stage (step C). It should be noted that in both the first and second pathways, cyclization is based on reactions (A, B, C) which are unknown for amide acetals and enamines. Evidence that the B—C pathway is the correct choice was obtained by studying the reaction of the IIIa acetal with 1-acetyl-2-n-chlorophenylaminomethyleneindolinone-3 (IX) [3]. Heating of IX and IIIa in benzene produced the bis-enamino derivative 1-β-dimethylaminoacryloyl-2-n-chlorophenylaminomethyleneindolinone-3 (X) (yield 57%), which was characterized. Boiling of a solution of X in xylene resulted in cyclization, with formation of a mixture (as shown by TLC analysis) of pyrroloindole Va and 2-(n-chlorophenylaminomethylene)-3,9-dioxopyrrolo[1,2-a]indole VIIIa (the yield of the latter was 17%).

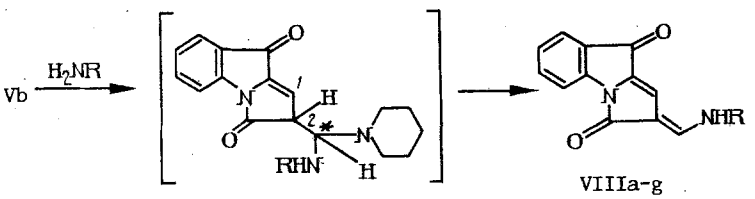


The tricyclic compound VIIIa was also obtained by reverse synthesis from Va and Vb by transamination reactions with n-chloroaniline, with a yield of 86%.

The structure of bis-enamino derivative X was confirmed by its PMR spectrum, which contained, apart from signals from aromatic protons and N-methyl group protons, two doublets, at 5.33 and 7.76 ppm, corresponding to the two vinyl protons of the dimethylaminoacryloyl substituent, as well as two broad singlets, at 7.79 and 9.00 ppm, corresponding to signals from the methylene proton and the NH group in the $=CHNHC_6H_4Cl$ fragment respectively.

A new reaction was observed, i.e., condensation of the amide acetal with the methyl group of the N-acetyl substituent of enaminoindolinones, followed by cyclization of the intermediate bis-enamino derivatives, which leads to the formation of new derivatives of the extensively studied pyrrolo[1,2-a]indole system, namely 2-dialkylaminomethylene-3,9-dioxopyrrolo[1,2-a]indoles Va and Vb. However, these cannot be prepared by any of the standard methods [11]. The synthesis of derivatives of 3,9-dioxo-1,2,3,9,9a-pentahydropyrrolo[1,2-a]indole was described in [1]; this is the compound with the closest structure to compounds such as Va and Vb. These derivatives cannot be used to synthesize enamines at position 2 of the tricyclic ring. At the same time, the presence of the functional enamine group in Va and Vb allows new compounds of this type to be prepared using the well-known enamine transamination reaction [2].

The transamination of Va and the synthesis of enamine VIIIa were mentioned above. The transamination of pyrroloindoles V was studied in more detail using the more available derivative Vb, which yielded a series of enamines VIIIa-VIIIg.



XIa-g VIIIa-g

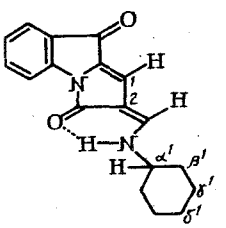
R=ClC_6H_4(a), $(CH_2)_2NHAc$(b), cyclohexyl (c); $(Me)_2$ (d), $CH_2C_6H_3(OMe)_2$-3,4 (e), $(CH_2)_2Ph$ (f), CH_2Ph (g).

It is interesting to note that transamination of Vb with cyclohexylamine by method 1 produces 2-cyclohexylaminomethylene-3,9-dioxopyrrolo[1,2-a]indole VIIIb, while use of method 2 initially produces the intermediate product formed by attachment of cyclohexylamine to the double exocyclic bond of the molecule, i.e., compound XIc.

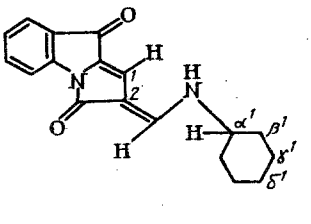
TLC analysis showed that recrystallization of XIc forms a mixture of the initial and final substances, i.e., compounds Vb and VIIIc, with equal splitting of the piperidine and cyclohexylamine molecules. The mother liquor resulting from recrystallization of technical grade XIc produced pure 2-(cyclohexylaminopiperidono)methyl-3,9-dioxo-2,3-dihydropyrrolo[1,2-a]indole (XIc) with a yield of 35%; however, our PMR spectral data indicated that this contained 3-5% contamination with VIIIc.

The structures of compounds VIIIc and XIc were studied by PMR spectroscopy. The PMR spectrum of the end product VIIIc (DMSO-d_6) showed signals from the cyclohexyl fragment as multiplets in the range 1.10-2.05 ppm (β^1, β^1-$2CH_2$,γ^1, γ^1-$2CH_2$, δ^1-CH_2) and at 3.54 ppm (α^1-CH); this differed from the situation with derivative Vb, whose spectrum contained signals from the piperidine ring: a broad singlet at 1.65 ppm (β, β-$2CH_2$, γ-CH_2) and a multiplet at 3.70 ppm (α, α-CH_2). The PMR spectrum of VIIIc showed signal doubling; this was clearest for the signals from the protons of the aminomethylene fragment —CHNH at 9.66 and 9.46 ppm (widening of the NH signals), at 8.03 ppm (doublet, $^3J_{CH,NH}$ = 14 Hz, CH), and at 7.78 ppm (doublet, $^3J_{CH,NH}$ = 10 Hz, CH), and a 1-CH signal at 7.04 and 7.33 ppm (singlets). This signal doubling results from the presence of enamine VIIIc in solution as a mixture of geometrical (1-CH and CH) cis- and trans-isomers whose relative contents were 60 and 40%, as indicated by the spectrum. The first value of each pair of chemical shifts relates to the predominant cis form.

The fact that the predominant isomer has a value of $^3J_{CH,NH}$ = 14 Hz (which is possible when the CH and NH bonds are in the trans position), and that the NH signal was seen at 9.66 ppm, suggests that the cis isomer contains an internal hydrogen bond of the "chelate" type, which makes the cis isomer more stable than the trans isomer.



cis-VIIIc



trans-VIIIc

Comparison of the chemical shifts of the 1-CH and CH protons in compounds Va and Vb with the analogous values for enamine VIIIc allowed us to determine the configurations of Va and Vb. The values of δ for 1-CH in compounds V were 7.40 ppm for compound Va and 7.45 ppm for compound Vb, while the values of δ for CH were 7.74 ppm in compound Va and 7.64 ppm in compound Vb, which is in quite good agreement with the analogous values for the trans isomer of compound VIIIc, i.e., Va and Vb are isomers with the 1-CH and CH groups in trans.

The PMR spectrum of the intermediate compound XIc contained signals from the piperidine ring protons (1.66, 3.45-3.65 ppm) and from the cyclohexylamino fragment (1.20-2.10, ~3.55 ppm). Since compound XIc has two asymmetrical centers, 2-C and C*, it can exist as two diasteroisomers. This was supported by the PMR spectra, in which the signals from the 2-C and C* protons were doubled: 5.40 and 5.37 ppm (2-CH, doublet, $^3J_{2\text{-}CH^*,CH}$ = 12.5 Hz), and 7.67 and 7.64 ppm (doublet, *CH). The first of each pair of δ values relates to the predominant isomer, which accounted for 85% of the total. It should be noted that the 1-CH signal was a narrow singlet at 8.54 ppm; this result is only possible when the nucleus of the tricyclic ring and the 2-CH*—CHRR^1 (R = piperidono, R^1 = cyclohexamino) fragment are located in mutually perpendicular planes, which is expected for such a sterically voluminous molecule.

EXPERIMENTAL (CHEMICAL)

IR spectra were taken on a Perkin—Elmer 457 spectrometer in Vaseline, and mass spectra were recorded on a Varian MAT-112 with direct injection of samples into the ion source. The ionizing electrode energy was 70 eV; the ionization chamber temperature was 180°C. PMR spectra were recorded using a Varian-X-linked-200 apparatus using TMS as the internal standard. Monitoring of reactions was carried out by TLC on Silufol UV-254 plates with a solvent system consisting of chloroform—methanol (10:1), and visualized under UV light. Elemental analysis and M^+ data agreed with expected values.

2-Dimethylaminomethylene-3,9-dioxopyrrolo[1,2-a]indole (Va). 1. 1-Acetyl-2-formyl-3-oxyindole (IV) was prepared from 56 g (320 mmoles) of N-acetylindolinone-3 (I) using conditions described in [3]. After filtration of IV, the mother liquor was extracted with chloroform and evaporated, which yielded 9.4 g of a mixture which TLC analysis showed to contain N-acetylindolinone-3 (I) and pyrrolo[1,2-a]indole (Va). This mixture (9.4 g) was loaded onto an SiO_2 column and eluted with chloroform, and the colorless zone was collected until TLC results showed the absence of N-acetylindolinone-3. The column was then eluted with dimethylformamide to yield 1.3 g of pure pyrroloindole Va. PMR spectrum, δ, ppm (DMSO-d_6): 3.41 (6H, s, NMe_2), 7.40 (1H, s, 1-CH), 7.74 (1H, s, CH), 7.12-7.20, 7.55-7.69 (4H, m, aromatic protons).

2. A solution of 0.5 g (1.9 mmoles) of N-acetyl-2-piperindomethyleneindolinone-3 (IIb) in 2 ml (12.5 mmoles) of the diethylacetal of dimethylformamide (IIIa) was boiled for 1 h. The reaction was cooled and the precipitate was collected by filtration and washed with methanol and ether. This yielded 0.34 g of pyrroloindole Va. The melting temperature of a mixed sample containing the products of this method and method 1 did not show any depression.

3. The acetal of IIIa (3.4 ml, 21.3 mmoles) was added to a suspension of 1 g (5.7 mmoles) of N-acetylindolinone-3 in 10 ml of benzene, and the mixture was boiled for 1 h with stirring. The benzene was evaporated in vacuo at a water bath temperature of 45°C. Benzene (2 ml) was added to the residue, along with 1.5 ml (9.4 mmoles) of the acetal of IIIa, and the mixture was boiled for 2 h. The reaction was cooled and the precipitate was collected by filtration and washed with benzene and ether. This yielded 0.25 g of pyrroloindole Va. The melting temperature of a mixed sample containing the products of this method and method 1 did not show any depression.

TABLE 1. Characteristics of 3,9-Dioxopyrrolo[1,2-a]indole Derivatives

Compound	Preparation method	Reaction time, h	Yield, %	Melting temperature, °C (solvent)	IR spectrum, ν_{max}, cm^{-1}	Elemental formula	Concentration increasing contraction amplitude by 50% (IC50), M
Va	1		1,7	270—2	1650, 1620	$C_{14}H_{12}N_2O_2$	$3 \cdot 10^{-5}$
	2		73	(MeOH)			
	3		18				-
Vb	1	9	31	234—5	1640, 1600	$C_{17}H_{16}N_2O_2$	Inactive at concn. of 0.1 mM to 0.3 mM
	2		70	(MeOH)			
	3		67				
VIIIa	1	0,5	86	318—20 dimethylformamide	1685, 1640, 1610, 3280	$C_{18}H_{11}ClN_2O_2$	Same
VIIIb	1	0,5	63	247—8 dimethylformamide	1690, 1630, 1600,	$C_{16}H_{15}N_3O_3$	» »
	2	20	94		3300, 3180		
VIIIc	1	0,5	78	212—5	1660, 1620, 3220	$C_{18}H_{18}N_2O_2$	» »
	2	5	19	isopropanol			
VIIId	1	0,5	67	196—7 isopropanol	1680, 1610, 3220	$C_{15}H_{14}N_2O$	» »
	2	5	64				
VIIIe	1	0,5	63	205—7 dimethylformamide	1650, 1620, 3220	$C_{22}H_{20}N_2O_4$	» »
VIIIf	1	1,5	53	195—7 isopropanol	1685, 1630, 1610, 3200	$C_{20}H_{16}N_2O_2$	$1,1 \cdot 10^{-4}$
	2	2	83				
VIIIg	1	1	85	220 (MeOH)	1650, 1620, 3220	$C_{19}H_{14}N_2O_2$	$4,3 \cdot 10^{-4}$

*IC50 for the milrinone was 3 μM.

2-Piperidinomethylene-3,9-dioxopyrrolo[1,2-a]indole (Vb). 1. Piperidine (1 ml, 100 mmoles) was added to a solution of 0.55 g (23 mmoles) of pyrroloindole Va in 40 ml of methanol, and the mixture was boiled for 5 h, after which a further 1 ml (100 mmoles) of piperidine was added, and the mixture was then boiled for 4 h more. The reaction was cooled and the precipitate was collected by filtration and washed with methanol and ether. This yielded 0.2 g of pyrroloindole Vb. PMR spectrum, δ, ppm (DMSO-d_6): 1.65, 3.70 (10H, br.s, piperidine protons), 7.45 (1H, s, 1-CH), 7.64 (1H, s, CH), 7.12-7.20, 7.55-7.0 (4H, m, aromatic protons).

2. Pyrroloindole Vb was prepared from 0.8 g (3 mmoles) of enaminoketone IIb and 2.5 ml (12.5 mmoles) of the acetal of IIIb using conditions similar to those used for the synthesis of Va by method 2; the yield was 0.58 g. The melting temperature of a mixed sample containing the products of this method and method 1 did not show any depression.

3. Pyrroloindole Vb was prepared from 5 g (28.5 mmoles) of N-acetylindolinone-3 (I) and 9 ml (43 mmoles) of the acetal of IIIb, using conditions similar to those used for preparation of Va by method 3; the yield was 5.35 g. The melting temperature of a mixed sample containing the products of this method and method 1 did not show any depression.

2-(n-Chlorophenylaminomethylene)-3,9-dioxopyrrolo[1,2-a]indole (VIIIa). A mixture of 0.2 g (0.55 mmole) of 1-α-dimethylaminoacryloyl-2-n-chlorophenylaminomethyleneindolinone-3 and 5 ml of xylene was boiled for 45 min. A new precipitate formed in the resulting solution. The reaction was cooled and the precipitate was collected by filtration and was washed with xylene and ether. The yield was 0.15 g of a mixture of pyrroloindoles Va and VIIIa, as indicated by TLC analysis. This was mixed with chloroform which dissolved pyrroloindole Va. The insoluble pyrroloindole VIIIa was collected by filtration and washed with chloroform. The yield was 0.03 g (17%), the melting temperature was 318-320°C (decomposed, in a sealed capillary, from dimethylformamide). The melting temperature of a mixed sample containing the products of this method and the standard transamination method (method 1) did not show any depression.

General Methods for Preparing Transamination Products (VIIIa-VIIIg). 1. Mixtures of 11 mmoles of 2-piperindomethylene-3,9-dioxopyrrolo[1,2-a]indole (Vb), 14 mmoles of a primary amine in 10 ml of isopropanol, and 0.07 ml of acetic acid were boiled for 0.5-1.5 h. Reactions were cooled, precipitates were collected by filtration and washed with isopropanol and recrystallized to yield compounds VIIIa-VIIIg (Table 1).

2. Mixtures of 71 mmoles of 2-piperidinomethylene-3,9-dioxopyrrolo[1,2-a]indole (Vb, 90 mmoles of a primary amine in 50 ml of methanol (or absolute ethanol in the case of compound VIIIc) were kept at room temperature for 5-20 h. Precipitates were collected by filtration, washed with methanol and ether, and recrystallized to yield compounds VIIIb-VIIIf (Table 1).

1-β-Dimethylaminoacryloyl-2-n-chlorophenylaminomethyleneindolinone-3 (X). The diethyl acetal of dimethylformamide (IIIa) (15 ml) was added to a boiling suspension of 1.56 g (5 mmoles) of 1-acetyl-2-(n-chlorophenylaminomethylene)indolinone-3 (IX) [3] in 35 ml of benzene over 30 min with simultaneous distillation of the mixture of benzene and ethanol that is formed during the reaction. The reaction was then boiled for 10 min, which produced a precipitate from the boiling solution. The reaction was cooled, and the precipitate was collected by filtration and washed with benzene and ether. The yield was 1.05 g (57%) of X, which lacked a clear melting point (from a 1:1 mixture of methanol and dimethylformamide). The formula was $C_{20}H_{18}ClN_3O_2$.

IR spectrum, ν, cm^{-1}: 3090, 1650, 1615, 1600.

PMR spectrum ($CDCl_3$), δ, ppm: 3.04 (6H, br.s, NMe_2), 5.33 (1H, d, COCH), 7.76 (1H, d, $^3J_{CH,CH}$ = 12 Hz, $\underline{CH}NMe_2$), 7.79 (1H, br.s, $\underline{CH}NH$), 9.00 (1H, br.s, NH), 7.10-7.90 (8H, m, aromatic protons).

2-(Cyclohexylaminopiperidino)methyl-3,9-dioxo-2,3-dihydropyrrolo[1,2-a]indole (XIc). Reaction of 6 g (21 mmoles) of pyrroloindole Vb with 2.6 g (26 mmoles) of cyclohexylamine produced compound VIIIc in the conditions used for method 2.

The mother liquor was evaporated and the residue was mixed with ether. The resulting crystalline precipitate was collected by filtration and washed with ether. This yielded 3.6 g of technical grade IXc, which was recrystallized from 100 ml of isopropanol to yield 0.25 g of a mixture of Vb and VIIIc. The mother liquor was evaporated and the residue was mixed with ether; crystals were filtered and washed with ether. The yield was 2.9 g (35%) of pure XIc, which lacked a clear melting point. The elemental formula was $C_{23}H_{29}N_3O_2$.

EXPERIMENTAL (BIOLOGICAL)

The pharmacological activity of compounds was studied using isolated spontaneously contracting right atria from guinea pigs (180-200 g), by measuring the amplitude and frequency of contractions. Atria were placed in a 50-ml glass vessel (a "bath," a two-channel apparatus from Hugo Sacks Elektronik, Germany) in Krebs—Hanseleit solution oxygenated with carbogen (95% O_2, 5% CO_2). The strength and frequency of atrial contractions were recorded using a UC-2 isometric probe (USA). After 40-60 min from placing atria in the bath, when contractions had stabilized, compounds were added to the perfusate at increasing concentrations from 0.1 μM to 0.3 mM. The maximum increases in the contraction frequency and amplitude were measured 1, 5, 10, and 15 min after addition of each concentration of agents. Cardiotonic activity was expressed as the EC_{50} value (50% effective concentration) reflecting effects on the contraction amplitude. Agents were compared with the reference compound milrinone. Each compound was tested in 3-5 experiments.

Pharmacological studies were carried out with compounds Va, Vb, and VIIIa-VIIIg.

Compounds Vb and VIIIa-VIIId had no effect on atrial contraction. Compounds Va, VIIIf, and VIIIg had positive inotropic actions at concentrations of 10 μM and 1 mM, though they were less active than milrinone by an average of one order of magnitude (Table 1). The maximum inotropic effect of compound Va was greater than that of milrinone [i.e., the mean (three experiments) increases in the contraction amplitude at concentrations of Va of 10 and 100 μM were 18 and 130% respectively, compared with increases of 9.40 and 55% obtained with milrinone at 0.1, 1, and 10 μM].

Thus, a number of 3,9-dioxopyrrolo[1,2-a]indole derivatives containing substituents in the pyrrole ring side chain amino group had positive inotropic effects, though they were only moderate in intensity.

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