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ACETALS OF ACID LACTAMS AND AMIDES. 75.* THE SYNTHESIS AND LOCAL ANESTHETIC ACTIVITY OF 2-METHYL-3-BENZOYL-5-HYDROXY-BENZOFURAN DERIVATIVES

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Substituted 5-hydroxybenzofurans prepared by the Neniceska reaction include a series of compounds with considerable local anesthetic activity [2-4].

We have recently demonstrated [5] that tertiary enaminoketone-1-benzoyl-2-dimethylaminopropene-1 [6] interacts with benzoquinone to form 2-methyl-3-benzoyl-5-hydroxybenzofuran. Studies of the reactions of the diethylacetal of N,N-dimethylacetamide (compound I) with a variety of substituted acetophenones (IIa-f), which are reported here, showed that this condensation provides a preparative approach to the synthesis of a large group of substituted tertiary enaminoketones (IIIa-f), which can be used in the Neniceska reaction to produce new polysubstituted derivatives of 2-methyl-3-benzoyl-5-hydroxybenzofurans (IVa-f). Given that compounds of this type, with a methyl group in position 2 of the benzofuran ring, have not previously received detailed biological study, the aims of the present work were to develop methods for the synthesis of compounds IVa-f, to use these to produce a series of aminomethyl derivatives using the Mannich reaction, and to study the local anesthetic properties of the resulting compounds.

The optimum conditions for obtaining enaminoketones (IIIa-f) consist of heating substituted acetophenones (II) with excess acetal (I) with distillation of the resulting alcohol under vacuum; good yields of tertiary enaminoketones (IIIa-f) were obtained. The structures of compounds IIIa-f were determined by elemental analysis, infrared, mass, and, in some cases (see Chemical Methods), ^{1}H-NMR spectroscopy. Infrared spectra contained absorption bands characteristic for the enaminoketone structure $-\overset{|}{N}-\overset{|}{C}=CHCOAr$ in the region 1530-1620 cm^{-1} [7]; mass spectra contained molecular ion peaks along with high-intensity (M^+-OH) peaks, demonstrating the presence of the enaminocarbonyl fragment. The resulting enaminocarbonyl compounds (IIIa-f) were suitable for carrying out benzofuran synthesis by the Neniceska reaction. Interaction of enamines (IIIa-e) with benzoquinone in acetic acid at room temperature produced 3-aroyl-5-hydroxybenzofurans (IVa-f) at satisfactory yield. The most intense molecular ion and fragment peaks in the mass spectra of these compounds corresponded to splitting of the benzoyl substituent in position. 3 — $ArC\equiv O^+$. The infrared spectra contained absorption bands at 1580-1620 cm^{-1} (diarylketone) and 3190-3270 cm^{-1} (OH). It is important to note that the Neniceska reaction was typical in this case in that it produced various products. Although side products were not here isolated and characterized, mass spectroscopic data of products obtained in these reactions (before purification) indicated that the major products consisted of compounds IV, with benzodifuran derivatives additionally being formed. Thus the mass spectrum of crude products obtained by reaction of benzoquinone with enaminoketones (IIIc-e) contained molecular peaks corresponding to benzofurans (IVc-e) with *m/z* values of 282, 213, and 312 respectively, along with peaks corresponding to 2,6-dimethyl-3,7-diaroyl[1,2-b; 4,5-b']benzodifuran (VI), with *m/z* values of 454, 514, and 514 respectively.

The preparation of similar tricyclic compounds using the Neniceska reaction has been described in [8, 9].

*See [1] for communication 74.

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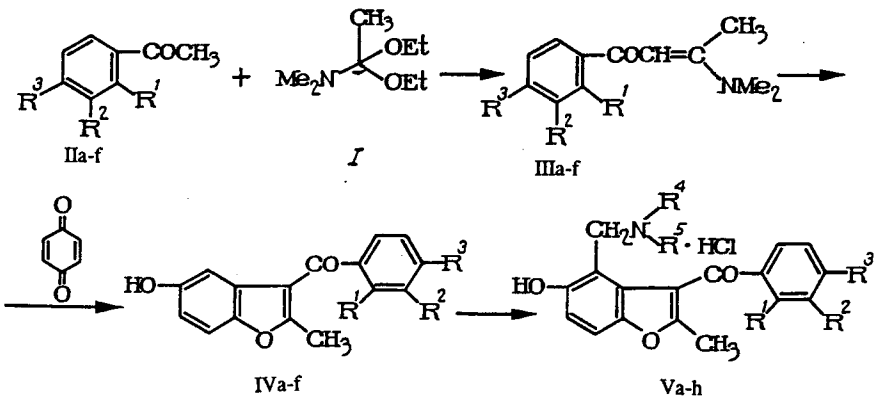
Scheme 1



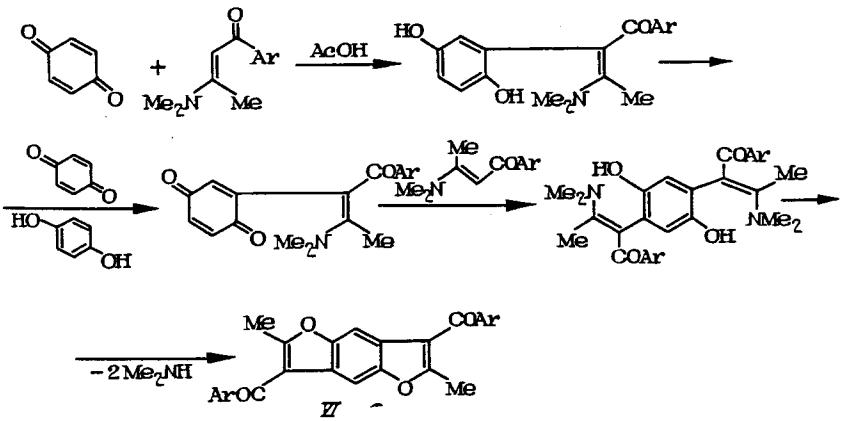
IIa-f I IIIa-f IVa-f Va-h

$R^1 = R^2 = H$, $R^3 = Br$ (IIa, IIIa, IVa, Va); $R^1 = R^2 = H$, $R^3 = F$ (IIb, IIIb, IVb, Vb); $R^1 = R^2 = H$, $R^3 = OCH_3$ (IIc, IIIc, IVc, Vc); $R^1 = R^3 = OCH_3$, $R^2 = H$ (IId, IIId, IVd, Vd,e); $R^1 = H$, $R^2 = R^3 = OCH_3$ (IIe, IIIe, IVe, Vf,g); $R^1 = R^2 = R^3 = OCH_3$ (IIf, IIIf, IVf, Vh); $R^4 = R^5 = CH_3$(Va,b,c,d,h); $R^4 = R^5 = (CH2)_5$ (Vc); $R^4 = R^5 = C_2H_5$ (Ve,g).

We have previously discussed the mechanism of the Neniceska reaction and the overall scheme used for preparation of benzofurans of the type represented by compound IV in detail [10]. The possibility of forming benzofurans of type VI is associated with the need for oxidative-reductive processes, which are required for indole synthesis by the Neniceska reaction [8, 9] but not participating in benzofuran synthesis.

The most logical scheme, used for preparation of compound VI, appears to be the following:

Scheme 2



The final stage in the chemical part of this study was the preparation of aminomethyl derivatives Va-h, which were synthesized from compounds IVa-f using the Mannich reaction. Aminomethylation occurred exclusively at position 4 of the benzofuran ring, as shown by the fact that the ^{1}H-NMR spectra of the resulting derivatives contained two doublet signals from protons in positions 6 and 7 of the condensed benzene ring at ~7.0-7.1 and 7.5-7.6 ppm.

TABLE 1. Properties of Compounds

Compound	Yield, %	mp, °C	Atomic formula
IIIa	71,6	118-20**	$C_{12}H_{14}BrNO$
IIIb	67,5	77-8	$C_{12}H_{14}FNO$
IIIc	68,2	138-9	$C_{13}H_{17}NO_2$
IIId	64,6	79-80	$C_{14}H_{19}NO_3$
IIIe	84,1	102-3	$C_{14}H_{19}NO_3$
IIIf	76,9	85-7	$C_{15}H_{21}NO_4$
IVa	39,2	187-8***	$C_{16}H_{11}BrO_3$
IVb	42	191-2	$C_{16}H_{11}FO_3$
IVc	32,5	169-70	$C_{17}H_{14}O_4$
IVd	32,5	204-6	$C_{18}H_{16}O_5$
IVe	40,7	180-2	$C_{18}H_{16}O_5$
IVf	36	171-3	$C_{19}H_{18}O_6$
Va	73,1	230-2*4	$C_{19}H_{19}BrClNO_3$
Vb	65,9	207-9	$C_{19}H_{19}FClNO_3$
Vc	54,4	184-6	$C_{22}H_{26}ClNO_4$
Vd*	55,9	196-7	$C_{21}H_{24}ClNO_5$
Ve	60,6	204-5	$C_{23}H_{28}ClNO_5$
Vf	58,5	190-1	$C_{21}H_{24}ClNO_5$
Vg	62,6	174-5	$C_{23}H_{28}ClNO_5$
Vh	80,7	221-4	$C_{22}H_{26}ClNO_6$

*Prepared as the monohydrate.

**Recrystallized from i-C_3H_7OH (IIIa-f).

***Recrystallized from CH_3COOH (IVa-f).

*4Recrystallized from C_2H_5OH (Va-h).

TABLE 2. The Local Anesthetic Activity and Acute Toxicity of Compounds Va-h

Compound	Specific activity (Regney index)*	Relative activity R	LD_{50}, mg/kg (i.v.)	Relative toxicity R^1	Therapeutic index
Va	628 ± 117	26,1	49,5 (27,9-87,6)	2,1	12,43
Vb	148 ± 41	6,2	27,1 (16,1-39,3)	3,8	1,63
Vc	102 ± 31	4,2	29,8 (16,8-52,8)	3,5	1,20
Vd	164 ± 41	6,8	22,2 (11,0-44,7)	4,7	1,45
Ve	304 ± 102	12,7	19,0 (16,0-25,3)	5,5	2,31
Vf	291 ± 71	12,1	17,7 (11,4-19,4)	5,9	2,05
Vg	349 ± 62	14,5	15,7 (12,9-22,6)	6,6	2,20
Vh	193 ± 48	8,0	15,9 (14,0-19,4)	6,6	1,21
Benzofurocaine	24 ± 4	1,0	104,5 (94,2-116,0)	1,0	1,0
Marcaine	267 ± 65	11,1	10,2 (9,3-11,2)	10, 2	1,1
Lidocaine	64,5 ± 11,5	2,7	35,0 (27,8-42,2)	3,0	0,9

*Eight experiments were carried out with each compound.

EXPERIMENTAL (CHEMICAL)

Infrared spectra were recorded on a Perkin-Elmer 456 spectrophotomer (USA) using samples prepared as a paste in Vaseline oil; mass spectra were recorded on a Varian MAT-112 (70 eV) spectrometer by direct sample injection into the ion source; NMR spectra were recorded on a Varian XL-200 spectrometer (USA). The internal standard for measurement of chemical shift was ^{1}H-TMS. Spectra were determined in DMSO-d_6 solutions.

The results of elemental analysis agreed with calculated values.

The properties of the compounds synthesized here are shown in Table 1.

1-(4-Bromobenzoyl)-2-dimethylaminopropene-1 (IIIa). A mixture of 10 g (50 mmole) of 4-bromoacetophenone and 13.1 ml (75 mmole) of the diethylacetal of N,N-dimethylacetamide was mixed at 110°C (in an oil bath) for 5 h with distillation of the resulting alcohol. The alcohol residue and the excess acetamide diethylacetal were evaporated *in vacuo*. Crystals forming on cooling of the reaction were washed onto filter paper using ether and dried. The yield was 9.6 g (71.6%) of compound IIIa, with a melting temperature of 118-120°C (i-C^3H_2OH).

The ^{1}H-NMR spectrum was (δ, ppm): 2.58 (s, 3H, CH_3); 3.07 (s, 6H, $N(CH_3)_2$); 5.62 (s, 1H, =CH); 7.70 (4H, A_2B_2-system of aromatic protons).

Similar conditions were used to prepare compounds IIIb-f from acetophenones IIb-f.

2-Methyl-3-(4-bromobenzoyl)-5-hydroxybenzofuran (IVa). *p*-Benzoxynone (5.4 g, 50 mmole) in 20 ml of glacial acetic acid was added to a solution of 13.4 g (50 mmole) of enamine IIIa in 40 ml of glacial acetic acid with mixing at room temperature. The reaction was kept for 15-17 h at room temperature. The crystals precipitating during this time were collected by filtration and washed on a filter using 40 ml of 50% acetic acid and dried. The yield was 6.5 g (39.2%) of compound IVa, with a melting temperature of 187-188°C (CH_3COOH).

The ^{1}H-NMR spectrum (δ, ppm) was: 2.43 (s, 3H, 2-CH_3); 6.73-6.77 (m, 2H, 4-H and 6-H); 7.46 (d, 1H, 7-H, J = 9 Hz); 7.73 (4H, A_2B_2-system of phenyl protons); 9.29 (s, 1H, 5-OH).

Similar conditions were used to prepare benzofurans IVb-f from enamines IIIb-f.

2-Methyl-3-(4-bromobenzoyl)-4-dimethylaminomethyl-5-hudroxybenzofuran Hydrochloride (Va). A mixture of 3.3 g (10 mmole) of benzofuran IVa and 1.5 ml (11 mmole) of bisdimethylaminomethane in 20 ml of dioxane was boiled until the initial benzofuran was exhausted. The process was monitored by chromatography on Silufol UV-254 plates run in benzene–acetone (9:1). The reaction generally needed 7 h to go to completion. The solvent was removed by evaporation *in vacuo*. Water was added to the residue. Crystals were collected by filtration, washed on the filter paper with water, and dried. The dry residue was dissolved in absolute ether and supplemented with an ether solution of HCl to pH 1.0-2.0. The resulting precipitate was collected by filtration and washed with absolute ether. The yield was 3.1 g (73.7%) of compound Va, with a melting temperature of 230-232°C (i-C_3H_7OH).

The ^{1}H-NMR spectrum (δ, ppm) was: 2.15 (s, 3H, 2-CH_3); 2.74 (s, 6H, $N(CH_3)_2$); 4.45 (s, 2H, $-CH_2-$); 7.36 (2H, AB-system 6-H and 7-H); 7.81 (s, 4H, Ph); 9.51 (s, 1H, 5-OH); 10.52 (s, 1H, NH).

Similar conditions were used to prepare Mannich bases Vb,d,f,h from benzofurans IVb-f.

When other aminomethylating agents (bisdiethylaminomethane, dipiperidinomethane) were used, compounds Vc,e,g were prepared using the conditions described for the synthesis of compound Va.

EXPERIMENTAL (PHARMACOLOGICAL)

The local anesthetic activity of compounds Va-h was studied by dropping 0.05% solutions into the conjunctival sacs of male rabbits weighing 2-2.5 kg [11]. Activity was measured in terms of the Regnier index of anesthesia; the therapeutic indexes of compounds were also determined, i.e. the ratio of relative activity to relative toxicity (R/R^1). Acute toxicity was determined in mongrel white male mice weighing 18-20 g given a single intravenous dose as 0.1% aqueous solutions at rates of 10-60 mg/kg (Table 2).

Because of similarities in the chemical structure between compounds Va-h and benzofurocaine, their properties were compared with those of benzofurocaine, and also with those of marcaine and lidocaine. Results were analyzed statistically using Student's *t* criterion.

Compounds Va-h were found to have greater local anesthetic activity than benzofurocaine and lidocaine in terms of the index of anesthesia. The most active compound, Va, was also more active than marcaine.

Studies of the tolerance of compounds Va,e showed that subcutaneous or intramuscular dosage resulted in local irritation, with development of tissue hyperemia and edema. Thus, further studies of these compounds were not studied.

Thus, these studies have demonstrated the synthesis of a series of benzofuran derivatives with high local anesthetic activity, which shows that this class of compounds has potential for further investigation.

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