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1-R-3,3-DIALKYL-6,7-ETHYLENEDIOXY-3,4-DIHYDROISOQUINOLINES

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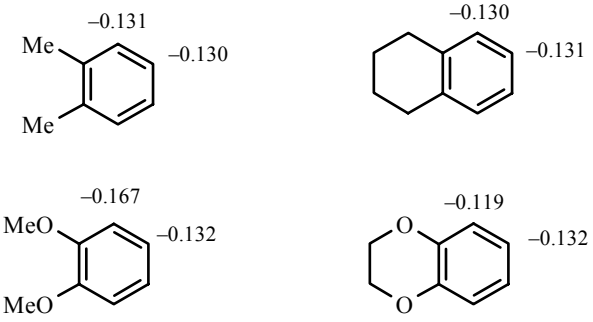
A three component "one-pot" condensation of 1,2-ethylenedioxybenzene and RCN nitriles with isobutylene oxide, isobutyraldehyde, or cyclohexanecarboxaldehyde in the presence of conc. H_2SO_4 gives 1-R-3,3-dialkyl-6,7-ethylenedioxy-3,4-dihydroisoquinolines.

Keywords: α-alkylaldehydes, 2,2-dimethyloxirane, isoquinoline, nitriles, 1,2-ethylenedioxybenzene, alkylation.

In recent years, so called "tandem" or "domino" reactions have been all the more widely used in the synthesis of heterocyclic compounds [1, 2] These reactions generally occur in a single reaction vessel but differ in simplicity and technical features. Nucleophilic [3, 4], electrophilic [5], and radical-photochemical [6,7] variants of the [2C+2C+2N] type are known.

We have previously studied a three component "tandem" alkylation-cyclization reaction of veratrole, isobutylene oxide, and nitriles which gave 1-R-6,7-(or 1-R-5,8-)dimethoxy-3,3-dimethyl-3,4-dihydro-isoquinolines [8, 9]. In the present work we have investigated the behaviour of 1,4-benzodioxane as an analog of veratrole [10] in this reaction with the aim of preparing substituted 6,7-ethylenedioxy-3,4-dihydroisoquinolines since 1,4-benzodioxanes show a variety of biological activity according to [11, 12]. In addition, it was of interest to compare the results of analogous reactions of two pairs of arenes chosen on the grounds of similarity, i.e. *ortho*-xylene and tetralin and also veratrole and 1,4-benzodioxane.

It is known that an electrophilic attack is directed to the position of greatest electron density. Consideration of the distribution of electronic charge in the molecules of the indicated arenes (using the AM1 program and Hyperchem 5.0 package) shows that there is virtually no difference in the charges on the arene carbons in the case of *ortho*-xylene and tetralin and the direction of initial attack should be determined by steric factors. At the same time the difference in charge distribution for veratrole and 1,4-benzodioxane is significantly different such that the preferred position of attack in veratrole is the carbon atom ortho to the alkoxy group



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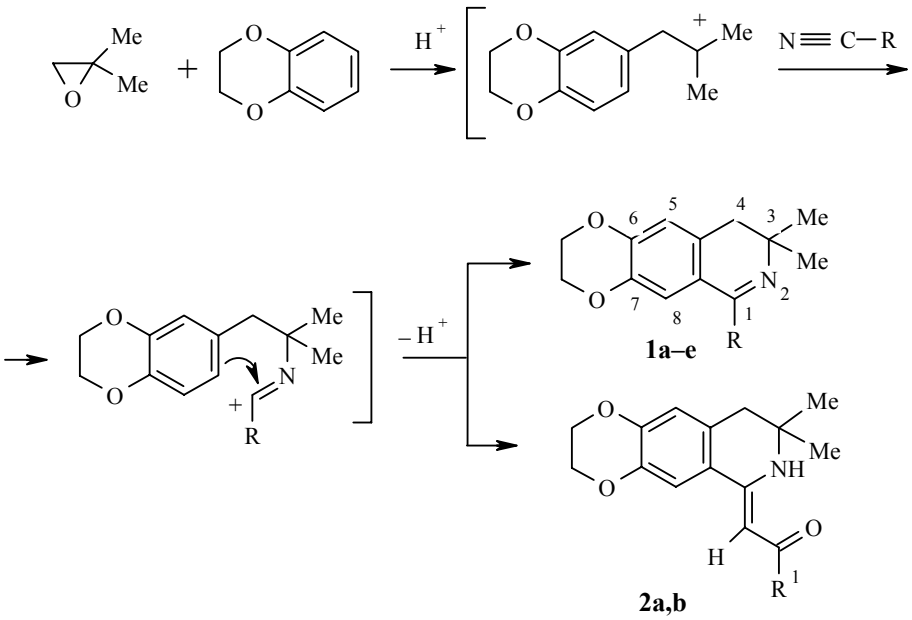
However, for veratrole the observed attack is at position 4 and leads to formation of 6,7-dimethoxy-3,4-dihydroisoquinolines [5, 13].

The study has shown that a three component condensation of benzo-1,4-dioxane, isobutylene oxide, and the nitriles RCN in the presence of H_2SO_4 gives modest yields of the linearly annelated 1-R-6,7-ethylenedioxy-3,3-dimethyl-3,4-dihydroisoquinoline products **1a-e, 2a,b** (Scheme 1, Tables 1 and 2) as in the tetralin reaction [14].

Scheme 1



1 a R = Me, **b** R = Et, **c** R = Ph, **d** R = SMe, **e** R = SCH_2Ph; **2 a** R^1 = OEt, **b** R^1 = NH_2

TABLE 1. Physicochemical Parameters for Compounds **1-3**

Compound	Empirical formula	Found, % / Calculated, %			mp, ºC (solvent)	Yield, % (method)
		C	H	N		
1a	$C_{14}H_{17}NO_2$	72.66 / 72.70	7.53 / 7.41	5.98 / 6.06	97-98 (hexane–CH_2Cl_2)	44 (A), 38 (B)
1b	$C_{15}H_{19}NO_2\times$ $\times C_6H_3N_3O_7$	53.33 / 53.17	4.76 / 4.67	11.95 / 11.81	208-209 (ethanol)	65 (A), 64 (B)
1c	$C_{19}H_{19}NO_2$	77.84 / 77.79	6.49 / 6.53	4.70 / 4.77	139-141 (MeOH + H_2O)	68 (A), 60 (B)
1d	$C_{14}H_{17}NO_2S$	63.80 / 63.85	6.70 / 6.51	5.45 / 5.32	82-83 (MeOH)	35 (A), 31 (B)
1e	$C_{20}H_{21}NO_2S$	70.73 / 70.76	6.28 / 6.24	4.05 / 4.13	97-99 (MeOH)	37 (A), 29 (B)
2a	$C_{17}H_{21}NO_4$	67.17 / 67.31	7.00 / 6.98	4.50 / 4.62	123-124 (ethyl acetate)	72 (A), 69 (B)
2b	$C_{15}H_{18}N_2O_3$	65.71 / 65.68	6.59 / 6.61	10.37 / 10.21	212-214 (MeOH)	28 (A), 23 (B)
3	$C_{20}H_{25}NO_4$	70.09 / 69.95	7.46 / 7.34	4.00 / 4.08	126-128.5 (ethyl acetate)	58

TABLE 2. IR and ^{1}H NMR Data for Compounds **1-3**

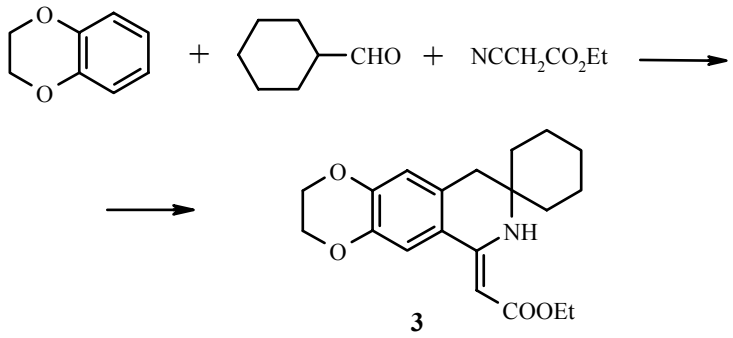
Com-pound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, pm (*J*, Hz)				
		3,3-$(CH_3)_2$, 6H (or 3,3-$(CH_2)_5$, 10H)	4-CH_2, 2H, s,	OCH_2CH_2O, 4H, m	H-5 (1H, s) and H-8 (1H, s)	1-R, NH
1a	1615, 1570, 1500, 1330, 1315, 1260, 1170, 1150, 1070, 935, 875	1.08, s	2.47	4.25	6.55, 6.90	2.19 (3H, s, CH_3)
1b	3100 (br), 1625, 1560, 1330, 1280, 1165, 1080, 1070, 920	1.41, s	2.88	4.28 (2H), 4.35 (2H)	6.77, 7.27	1.30 (3H, t, *J* = 7.5, CH_3); 2.99 (2H, q, *J* = 7.5, CH_2); 8.82 (2H, s, H_{arom})*
1c	1610, 1595, 1570, 1495, 1325, 1300, 1275, 1250, 1230, 1165, 1070, 1030	1.18, s	2.60	4.23	6.62, 6.65	7.37 (3H, m); 7.50 (2H, m)
1d	1570, 1500, 1330, 1315, 1260	1.10, s	2.49	4.17	6.54, 7.11	2.32 (1H, s, SCH_3)
1e	1585, 1560, 1490, 1330, 1300, 1260, 1245, 1170, 1130, 1070, 1035, 960, 895	1.15, s	2.65	4.50	6.75, 6.96	2.60 (1H, s, SCH_2); 7.22 (1H, t, *J* = 8, H-4'); 7.28 (2H, t, *J* = 8, H-3',5'); 7.39 (2H, d, *J* = 8, H-2',6')
2a	3260 (NH), 1640 (C=O), 1590, 1570, 1490, 1300, 1280, 1240, 1180, 1150, 1090, 1065, 1050, 1025, 960, 925, 900, 890	1.20, s	2.70	4.26	6.75, 7.19	1.19 (3H, t, *J* = 7.6, CH_3); 4.03 (2H, q, *J* = 7.6, OCH_2); 4.94 (1H, s, =CH); 8.90 (1H, s, NH)
2b	3440 (br., NH), 3300 (br., NH), 3170 (br., NH), 1625, 1605, 1570, 1290, 1260, 1240, 1100, 1070, 1025, 925, 890	1.18, s	2.60	4.20	6.55, 7.06	4.85 (2H, s, NH_2); 4.82 (1H, s, CH=); 9.45 (1H, s, NH)
3	3260 (NH), 1640 (C=O), 1590	1.35-1.58, m	2.64	4.18	6.56, 7.12	1.23 (3H, t, *J* = 7.6, CH_3); 4.09 (2H, q, *J* = 7.6, OCH_2); 4.94 (1H, s, =CH); 9.23 (1H, s, NH)

* Data give for the spectra of the picrate. The phenolic hydroxyl signal is not observed in the ^{1}H NMR spectrum due to proton exchange.

The reaction mechanism and possible intermediates have been previously discussed for veratrole [9]. Compounds **2a,b** are separated in the enamine form as shown by their ^{1}H NMR spectra. Thus the ^{1}H NMR spectra of compounds **2a,b** show olefine singlets at 4.94 and 4.82 ppm respectively as well as signals for the NH groups at 8.90 and 9.45 ppm.

As was shown in the studies [5, 13], isobutyraldehyde can be used in place of the isobutylene oxide and the authors favored the proposal that any α-branched aliphatic aldehyde can be used as the aldehyde. In fact, the replacement in this reaction of isobutylene oxide (method A) by isobutyraldehyde (method B) also gives the products **1a-e** and **2a,b** in comparable yields (Table 1). Use of cyclohexanecarboxaldehyde in the reaction with 1,4-benzodioxane and ethyl cyanoacetate gives ethyl (6,7-ethylenedioxy-3,3-pentamethylene-1,2,3,4-tetrahydroisoquinolyl-1-idene) acetate **3** (Scheme 2).

Scheme 2



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Hence it has been shown that, in the three component synthesis of 3,4-dihydroisoquinolines, 1,4-benzodioxane behaves similarly to veratrole and gives linearly annelated products in reaction with both isobutylene oxide and isobutyraldehyde. It was also found that cyclohexanecarboxaldehyde can behave in this reaction as a two carbon synthon. This confirms the proposal by the authors of [5] regarding the general behaviour of α-branched aliphatic aldehydes in a three component synthesis.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument for suspensions in vaseline oil. ^{1}H NMR spectra were obtained at 30°C on a Bruker DRX-500 spectrometer (500 MHz) using DMSO-d_6 and HMDS internal standard (δ 0.05 ppm). The mass spectrum of compound **2a** (EI, 70 eV) was taken on a Finnigan MAT instrument. Monitoring of the reaction course and the purity of the products obtained was carried out by TLC on Silufol using the system chloroform-acetone (9: 1) and revealed using a 3% solution of chloranil in toluene.

6,7-Ethylenedioxy-1,3,3-trimethyl-3,4-dihydroisoquinoline (1a). A. A solution of 1,4-benzodioxane (6.8 g, 5 mmol), isobutylene oxide (3.6 g, 5 mmol), and acetonitrile (2.05 g, 5 mmol) was added dropwise over 30 min to conc. H_2SO_4 (30 ml), holding the temperature of the mixture to 20-30°C. The reaction product was stirred for 1 h, poured into water (300 ml), and extracted with toluene (2 × 30 ml). The aqueous layer was basified with ammonium carbonate and then aqueous ammonia to pH ~8, extracted with CH_2Cl_2 (3 × 50 ml), and the extracts dried using $MgSO_4$. Dichloromethane was distilled off and the residue was recrystallized to give compound **1a** (5.1 g, 44%).

B. Similarly using freshly distilled isobutyraldehyde (3.7 g, 5 mmol) in place of the isobutylene oxide to give compound **1a** (4.4 g, 38%).

Compounds 1b-e were prepared similarly from 1,4-benzodioxane, isobutylene oxide (or isobutyraldehyde), and the corresponding nitriles. The picrate of compound **1b** was prepared in ether and crystallized from ethanol. In the case of compounds **1c,d** the residue after distillation of the dichloromethane was triturated with methanol (4 ml) to the start of crystallization.

Ethyl (6,7-Ethylenedioxy-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolyl-1-idene) Acetate (2a). A solution of 1,4-benzodioxane (6.8 g, 5 mmol), isobutylene oxide (3.6 g, 5 mmol), and ethyl cyanoacetate (5.65 g, 5 mmol) in toluene (30 ml) was added dropwise over 30 min to conc. H_2SO_4 (20 ml), holding the temperature of the mixture to 20-30°C. The reaction product was stirred for 2 h at 20°C, poured into water (300 ml), and the organic layer was separated and washed with water (40 ml). The combined aqueous layers were washed with toluene (2 × 30 ml), basified with ammonium carbonate and then aqueous ammonia to pH ~8, and extracted with ethyl acetate. The extract was dried with $MgSO_4$, the major part of the ethyl acetate was distilled off, and after complete evaporation of the solvent yielded coarse crystals of compound **2a**. Mass spectrum, *m/z* (I_{rel}, %): 303 $[M]^+$ (48); 288 (23); 258 (15); 242 (100); 231 (30); 231 (30); 216 (34).

Amide of (6,7-Ethylenedioxy-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolyl-1-idene) Acetic Acid (2b). A mixture of 1,4-benzodioxane (6.8 g, 5 mmol), isobutylene oxide (3.6 g, 5 mmol), and toluene (15 ml) was added with vigorous stirring to a solution of cyanoacetamide (4.2 g, 5 mmol) dissolved in conc. H_2SO_4 (30 ml) with cooling on a water bath so that the temperature did not exceed 20°C. Further treatment resembled compound **2a**. After basification of the reaction mixture with ammonia the precipitated crystals were separated, washed with water, dried, and crystallized from methanol to give compound **2b** (1.53 g).

Ethyl (6,7-Ethylenedioxy-3,3-pentamethylene-1,2,3,4-tetrahydroisoquinolyl-1-idene) Acetate (3) was prepared similarly to compound **2a** from 1,4-benzodioxane (1.34 g, 1 mmol), cyclohexanecarboxaldehye (1.12 g, 1 mmol), and ethyl cyanoacetate (1.13 g, 1 mmol). Yield 1.9 g (58%).

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