Chemistry of Heterocyclic Compounds, Vol. 40, No. 9, 2004

THE USE OF 4-(BROMOMETHYLENE)-5,5-DIMETHYL-1,3-DIOXOLAN-2-ONE AS "MASKED" α-BROMO-α'-HYDROXY KETONE IN THE SYNTHESIS OF HETEROCYCLIC SYSTEMS

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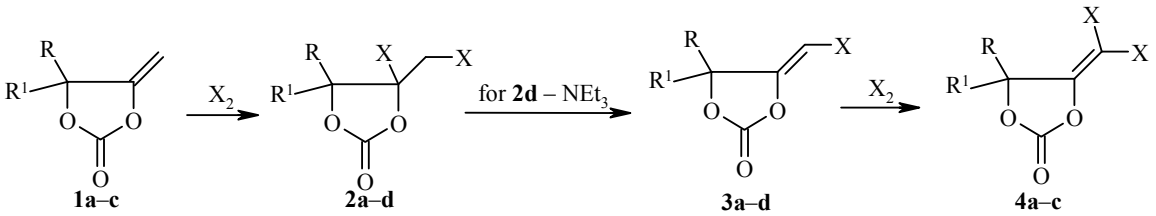
4-(Bromomethylene)-5,5-dimethyl-1,3-dioxolan-2-one was obtained on the basis of the readily obtainable 4-methylene-5,5-dimethyl-1,3-dioxolan-2-one. It forms 2-imidazo[1,2-a]pyridin-2-yl-2-propanol with 2-aminopyridine, 11a-hydroxy-1,1-dimethyl-3-oxo-1,5,11,11a-tetrahydro[1,3]oxazolo-[3,4-a]pyrido[1,2-d]-10-pyrazinium bromide with 2-(aminomethyl)pyridine, and the corresponding derivative of 4-hydroxyoxazolidin-2-one with 2-(3,4-dimethoxyphenyl)ethylamine. The last product was converted by intramolecular amidoalkylation without isolation into 10b-(bromomethyl)-8,9-dimethoxy-1,1-dimethyl-1,5,6,10b-tetrahydro[1,3]oxazolo[3,4-a]isoquinolin-3-one.

Keywords: 4-bromo-4-(bromomethyl)-5,5-dimethyl-1,3-dioxolan-2-one, 11a-hydroxy-1,1-dimethyl-3-oxo-1,5,11,11a-tetrahydro[1,3]oxazolo[3,4-*a*]pyrido[1,2-*d*]-10-pyrazinium bromide, 4-(bromomethylene)-5,5-dimethyl-1,3-dioxolan-2-one, 10b-(bromomethyl)-8,9-dimethoxy-1,1-dimethyl-1,5,6,10b-tetrahydro-[1,3]oxazolo[4,3-*a*]isoquinolin-3-one, 2-imidazo[1,2-*a*]pyridin-2-yl-2-propanol, intramolecular amido-alkylation.

The dioxolanones **2** and **3** can be regarded as "masked" precursors of the α-halo-α'-hydroxy ketone Hal–CH_2–CO–$C(RR^1)$–OH. In cases where the corresponding α-ketones do not exhibit the required regioselectivity it is possible to achieve the required direction of reaction by using compounds **2** and **3**.

It is known that the readily obtainable 4-methylene-1,3-dioxolan-2-ones (**1a-c**), prepared from propargyl alcohols and CO_2, can add Cl_2 [1]. Here the dioxolanones **3** or **4** are obtained. The compositions and yields of the products depend on the reaction conditions. Thus, in methylene chloride the dioxolanone **3a** was obtained with a 91% yield after 2 h at -50°C, and the dioxolanone **4a** was obtained with a 79% yield after 3 h at -30°C.



1a–c **2a–d** **3a–d** **4a–c**

1-4 a R + R^1 = $(CH_2)_5$, X = Cl; **b** R = R^1 = Me, X = Cl; **c** R = Me, R^1 = Et, X = Cl;
2, **3 d** R = R^1 = Me, X = Br

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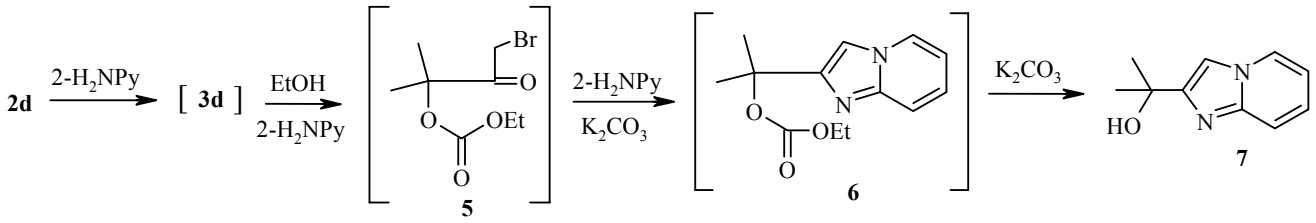
 0009-3122/04/4009-1124

The dioxolanones **2a-c** were not characterized by the authors of [1] since these substances are evidently unstable. On the other hand, the dioxolanone **2d** that we synthesized with a yield of 57% is completely stable under certain conditions (see the experimental section). By analogy with the dehydrobromination of 4-bromo-4-(bromomethyl)oxazolidin-2-ones [2] triethylamine in dry benzene was used to convert **2d** into the unsaturated dioxolanone **3d** with a yield of 90%. It should be noted that pyridine is not suitable for this purpose.

There is no $[M]^+$ peak in the mass spectrum of the dioxolanone **2d**, but there is an M - 81 (M - HBr) peak coinciding with $[M]^+$ of the dioxolanone **3d**, and in addition there is a peak for M - 81 - 44 (M – HBr - CO_2). The mass spectrum of the dioxolanone **3d** is identical with the mass spectrum of the dioxolanone **2d**. The structure of all the synthesized substances, including the dioxolanones **2d** and **3d**, was also confirmed by data from the IR and ^{1}H NMR spectra (Tables 1 and 2).

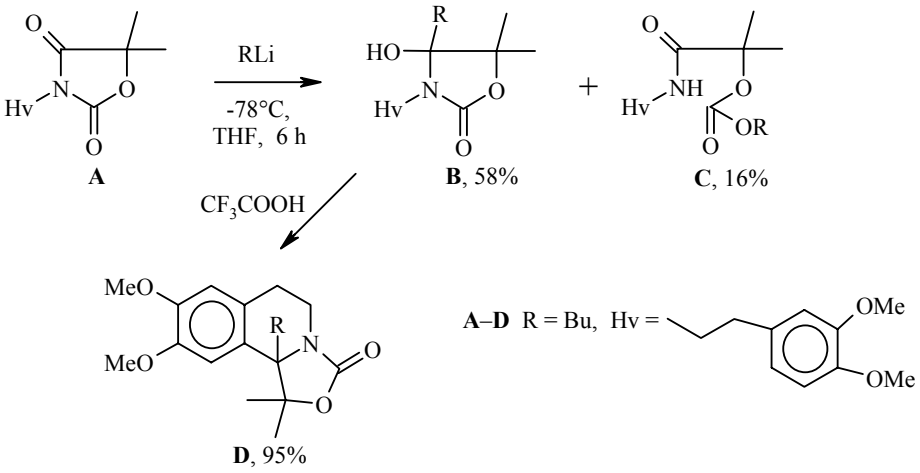
The dioxolanone **2d** reacts with 2-aminopyridine in the presence of calcined K_2CO_3 in anhydrous ethanol with the formation of the imidazolopyridine **7**. The yield in this reaction amounts to 74%; the use of 95% ethanol reduces the yield to 6-8%. In our proposed method the yield is no lower on average than during the direct reaction of α-bromo ketones with 2-aminopyridines [3].



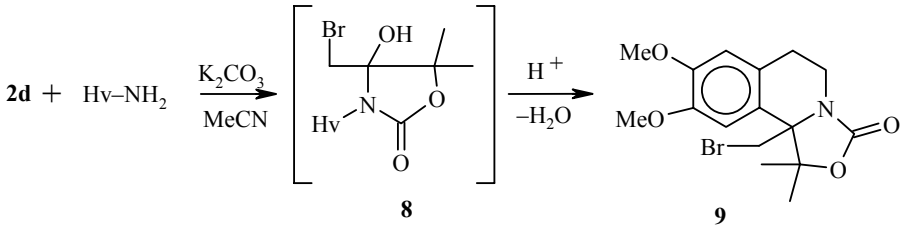
In our opinion the reaction takes place through a stage involving the formation of the dioxolanone **3d** and the linear unsymmetrical carbonates **5** and **6**. Opening of the dioxolanones **1**, related to the dioxolanones **2d** and **3d**, by alcohols in the presence of bases was described in [4]. It is also known that at 60°C in the absence of a solvent the dioxolanones **1** react with 2-aminopyridine and are converted after 115 h into 3-(2-pyridyl)oxazolidinones [5].

The mass spectrum of the imidazopyridine **7** contains $[M]^+$, $[M - 15]^+$ (M - Me), and [M - 15 - 18] (M - Me - H_2O) peaks.

One of the standard methods for the synthesis of oxazoloisoquinolines of type **D** is reaction of the corresponding oxazolidine-2,4-dione **A** with a suitable organolithium compound; the obtained oxazolidinone **B** is then treated with trifluoroacetic acid [6]. The first stage of the process is complicated by the formation of **C** as impurity.



This approach cannot be applied to oxazoloisoquinoline **9** of type **D** examined below, where R = CH_2Br. By analogy with our previous work [7] we used the reaction presented below for the synthesis of compound **9**.

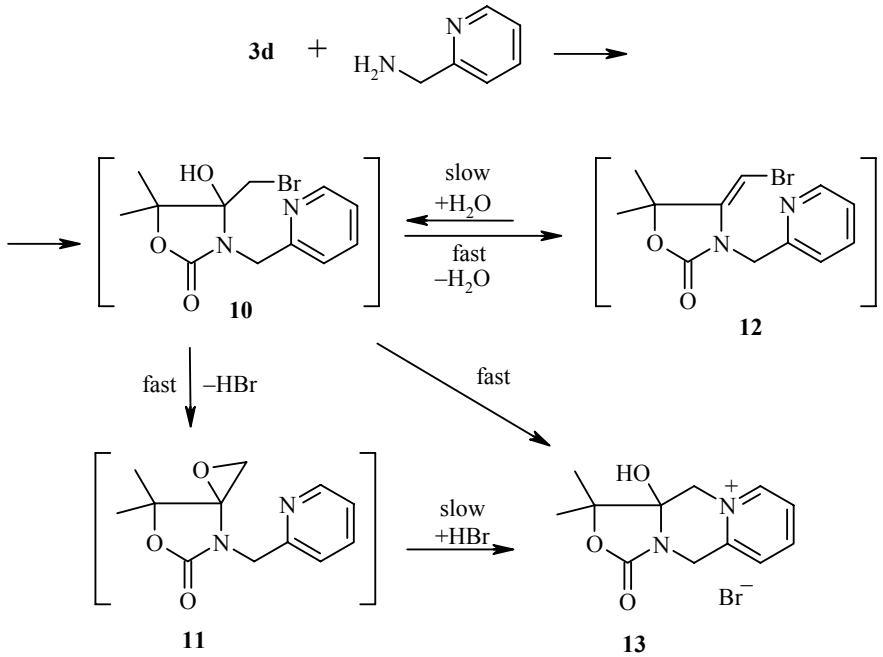


8 **9**

The intermediate not isolated oxazolidinone **8** is formed during the reaction of 2-(3,4-dimethoxyphenyl)ethylamine (homoveratrylamine, Hv–NH_2) with the dioxolanone **2d**.* When treated with 99.8% formic acid the oxazolidinone **8** gives the desired product **9** with a yield of 61%. The concentration of the substance **8** in the reaction mixture amounted to 0.12 g/ml. If the amount of the acid is reduced to a quarter, the yield of **9** decreases to 30%; we have observed this effect before [7]. In this case the process is complicated by side reactions.

In the mass spectrum of the oxazoloisoquinoline **9** there are $[M]^+$, [M - 81] (M - HBr), [M - 94] (M - CH_2Br), and [M - 94 - 44] (M - CH_2Br - CO_2) peaks.

An example of the use of the dioxolanone **3d** is the preparation of the salt **13** – a representative of the new heterocyclic system oxazolo[3,4-*a*]pyrido[1,2-*d*]-10-pyrazinium.



If a chloroform solution of 2-(aminomethyl)pyridine is added to a chloroform solution of the dioxolanone **3d**, the salt **13** separates out. To judge from TLC the mother solution contains several substances, presumably **11** and **12**, but no longer contains the initial 2-(aminomethyl)pyridine. The salt **13** begins to separate

* The reaction of amines with the related dioxolanones **1** was examined in [8].

out even at the moment the solutions are mixed, and it can therefore be supposed that the oxazolidinone **10** is unstable and immediately changes into compounds* **11**, **12**, and **13**, its concentration is low, and it cannot be seen on the TLC. We consider that compounds **11** and **12** are slowly transformed into the salt **13**, as shown in the scheme. If the salt is periodically removed from the mother solution, it is possible to observe the separation of new portions of the salt **13** from the solution. After 20 h at 50°C approximately 25% of the salt **13** has separated from the mother solution (total yield 48%). The best results were obtained with benzene as solvent, and the yield in this case amounted to 83%. From benzene practically all the salt separates immediately. Further

TABLE 1. The Constants and Yields of the Synthesized Compounds

Compound	mp, °C*	R_f (system)	IR spectrum, cm^{-1}	Mass spectrum, *m*/*z* (*I*, %)	Yield, %
2d	54-55.5	—	1816	288 $[M]^+$ absent, 207 (20.0), 163 (30.3), 137 (46.4), 135 (52.3), 123 (58.5), 121 (65.9)	57
3d	105-106.5	—	1828, 1688	207 $[M]^+$ (20.0), 163 (30.3), 137 (46.4), 135 (52.3), 123 (58.5), 121 (65.9)	90
7	120-121	0.22 (B)*[2]	3240	176 $[M]^+$ (23.5), 161 (100.0), 143 (13.0), 119 (18.1)	74
9	146-151	0.28 (A)	1740	370 $[M]^+$ (0.5), 289 (22.0), 176 (100.0), 232 (70.5)	61
13	129-144 (with dec.)	—	1748, 3424	234 $[M^+ - 1]$ (35.0), 216 (14.0), 173 (28.1), 157 (14.0), 148 (13.2)	83

* mp in sealed capillary.
*[2] Fivefold elution.

TABLE 2. The ^1H NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts (DMSO-d_6), δ, ppm (*J*, Hz)*
2d	[1.64 (3H, s), 1.84 (3H, s)] (5,5-CH_3); [3.90 (1H, d, *J* = 13.3); 4.03 (1H, d, *J* = 13.3)] (4-CH_2Br)
2d	[1.62 (3H, s), 1.78 (3H, s)] (5,5-CH_3); 4.33 (2H, s, 4-CH_2Br)
3d	1.64 (6H, s, 5,5-CH_3); 6.13 (1H, s, 4-CHBr)
7	1.47 (6H, s, 2-$C(CH_3)_2OH$); 4.78 (1H, br. s, 2-$C(CH_3)_2\underline{OH}$); 6.78 (1H, t, H-6); 7.18 (1H, t, H-7); 7.43 (1H, d, *J* = 10.0, H-8); 7.68 (1H, s, H-3); 8.43 (1H, d, *J* = 8.3, H-5)
9	[0.97 (3H, s), 1.76 (3H, s)] (1,1-CH_3); {[2.70 (d, *J* = 4.9), 2.76 (d, *J* = 4.9)] (1H); 2.83-3.00 (1H, m)} (H-6,6); {[3.37 (d, *J* = 4.9), 3.42 (d, *J* = 4.9), 3.47 (d, *J* = 4.9)] (1H); [4.12 (d, *J* = 7.1), 4.17 (d, *J* = 7.1)] (1H)} (H-5,5); 3.80-3.93 (8H, m, 8,9-OCH_3, 10b-CH_2Br); [6.47 (1H, s), 6.67 (1H, s)] (H-7,10)
13	[1.48 (3H, s), 1.52 (3H, s)] (1,1-CH_3); [4.88 (1H, d, *J* = 20.1); 5.19 (1H, d, *J* = 20.1)] (H-11,11); [5.02 (1H, d, *J* = 15.0), 5.11 (1H, d, *J* = 15.0)] (H-5,5); 6.97 (1H, br. s, 11a-OH), 8.11 (1H, t, H-8); 8.25 (1H, d, *J* = 7.8, H-6); 8.64 (1H, t, H-7); 8.97 (1H, d, *J* = 7.8, H-9)

* Compounds **2d** and **9** were recorded in deuterochloroform.

* The opening of the epoxide ring in oxazolidinones of type **11** was described in [9]. The transformation of the oxazolidinones **10** into the oxazolidinones **12** is reversible [5] (see also [2]).

heating of the mother solution is not advised – a highly contaminated salt **13** separates from it. (After 20 h at 50°C the chloroform mother solution also contains a certain amount of unreacted substances, but its further use is inadvisable for the same reason.) The order in which the reagents are mixed is very important in this reaction; the 2-(aminomethyl)pyridine is added to the dioxolanone **3d**, or otherwise the reaction is complicated by side products. It is also recommended to cool the reaction mixture at the beginning of the reaction. The solvents must be dry, or otherwise the salt **13** separates in the form of a noncrystallizing oil.

The mass spectrum of the salt **13** contains [M - 81] (M - HBr), [M - 81 - 18] (M - HBr - H_2O), and [M - 81 - 18 - 44] (M - HBr - H_2O - CO_2) peaks. The signals for the protons of the pyridinium ring in the ^{1}H NMR spectrum of the salt **13** are shifted downfield by ~0.5 ppm compared with the signals of the protons in the unquaternized pyridine rings.

Thus, the dioxolanones **2d** and **3d** are convenient synthons for the synthesis of heterocyclic compounds. Three of the five synthesized compounds **7**, **9**, and **13** contain the pharmacophoric oxazolidinone ring and/or a β-ethanolamine fragment and may therefore be of interest as potential biologically active compounds.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WM-500 instrument (500 MHz; for compound **9** 250 MHz, for **13** 300 MHz) with TMS as internal standard. The IR spectra were obtained on a Perkin-Elmer 577 instrument (potassium bromide). The mass spectra were obtained on a Kratos MS-30 mass spectrometer (direct injection, 70 eV, 250°C). Thin-layer chromatography was carried out on Silufol UV-254 plates with 2:1 benzene–ethyl acetate (A) and 2:1 ethyl acetate–benzene (B) systems. The cooling bath was acetone–dry ice. The extracts were dried by filtration through a layer of cotton wool.

The dioxolanone **1b** was obtained by the procedure described in [10, 11].

4-Bromo-4-(bromomethyl)-5,5-dimethyl-dioxolan-2-one (2d). To a solution of dioxolanone **1a** (6.54 g, 51.13 mmol) in methylene chloride (10 ml) we added a mixture of calcined potassium carbonate ground to a powder (7.07 g) and Trilon B (0.01-0.03 g). To the suspension with cooling at -3 to +3°C and vigorous stirring over 20 min we added dropwise a solution of bromine (8.18 g, 51.13 mmol) in methylene chloride (10 ml). The reaction mixture was allowed to heat up to room temperature. If the pH the mixture was not neutral, the mixture was heated to 30-40°C and stirred to a neutral pH (~20-40 min). The mixture was filtered through cotton wool, the solid residue was washed with methylene chloride (3 × 5 ml), the combined washing liquids and mother solution were evaporated, and the solvent residues were removed under vacuum. The residue was kept at 2-5°C for six days. The crystals were filtered off from the syrupy mother solution, washed with heptane (3 × 5 ml), and dried, 10.33 g (70%) of the technical product was obtained, and benzene (2 ml) was added. The mixture was heated until the crystals had disappeared, and heptane (4 ml) was added to the obtained viscous solution. It was rubbed with a glass spatula on a cooling bath. The crystals were filtered off, washed with heptane (3 × 5 ml), and dried, and 6.60 g of the dioxolanone **2d** was obtained. The combined washing liquids and mother solution were evaporated. The crystals were separated, washed with heptane (3 × 1 ml), and dried, and an additional 1.72 g of the product was obtained. The total yield was 8.32 g. The pure product was fully stable at room temperature for more than two years, but impurities of Fe, Co, Ni, and possibly other heavy metals promote the release of hydrogen bromide. The decomposition is autocatalytic in nature and is appreciably accelerated in a moist atmosphere. A sign that decomposition has begun is the appearance of orange-colored crystals. In this case it is recommended that the substance be recrystallized. The dioxolanone **2d** is best stored at 0-4°C without access to moisture over calcined potassium carbonate in a dark glass vessel.

4-(Bromomethylene)-5,5-dimethyl-1,3-dioxolan-2-one (3d). To a solution of the dioxolanone **2d** (6.59 g, 22.88 mmol) in dry benzene (8 ml) at room temperature we added dry triethylamine (3.1 ml), and after 15 min we heated the mixture at 70-80°C. The mother solution was separated from the NEt_3·HBr, the salt was washed with benzene (3 × 3 ml), and the combined wash liquids and mother solution were evaporated. The

solvent residues were removed under vacuum, the crystals were washed with heptane (4 × 3 ml) and dried, and 4.27 g of the dioxolanone **3d** was obtained. When necessary the substance was purified by vacuum sublimation at 10 mm Hg (bath temperature 140°C). The product must be stored and handled in the same way as the initial dioxolanone **2d**. The dioxolanone **3d** is a weak lacrimator and irritant. Found %: C 34.78; H 3.55; Br 38.47. $C_6H_7BrO_3$. Calculated %: C 34.81; H 3.50; Br 38.50.

2-Imidazo[1,2-*a*]pyridin-2-yl-2-propanol (7). A mixture of 2-aminopyridine (1.41 g, 15.00 mmol), calcined potassium carbonate ground to a powder (4.14 g, 30.00 mmol), the dioxolanone **3d** (4.54 g, 15.76 mmol), and absolute ethanol (20 ml) was kept at 50°C for 18 h 30 min with periodic stirring. The solvent was evaporated, and the substance was extracted from the solid residue with 20, 15, and 10 ml of chloroform. The extract was filtered through cotton wool and evaporated. The crystals that separated were treated with 3 ml of heptane and dried, and 2.20 g (83%) of the technical product was obtained. It was dissolved in hot benzene (4 ml) and precipitated with heptane (3 ml) with cooling; the crystals were washed with a 5:1 mixture of heptane and benzene (3 × 2 ml) and with heptane (3 ml) and dried under vacuum at 90°C and 3 mm Hg. A small amount of a transparent liquid with unestablished composition distilled into the trap. (According to the mass spectrum, the liquid contained two substances with molecular weights of 187 and 235.) We obtained 1.95 g of light-brown crystals. Found %: C 75.44; H 7.42; N 8.00. $C_{11}H_{13}NO$. Calculated %: C 75.40; H 7.50; N 7.98.

10b-(Bromomethyl)-8,9-dimethoxy-1,1-dimethyl-1,5,6,10b-tetrahydro[1,3-*a*]oxazolo[4,3-*a*]isoquinolin-2-one (9). To a mixture of the dioxolanone **2d** (1.87 g, 6.49 mmol) and calcined potassium carbonate ground to a powder (0.91 g, 6.59 mmol) in methylene chloride (10 ml) at room temperature we added homoveratrylamine (1.06 g, 5.86 mmol) in methylene chloride (5 ml); the mixture was stirred until the release of CO_2 had stopped (~1 h) and left overnight. The inorganic salts were separated and washed with methylene chloride (3 × 2 ml). The combined washing liquids and mother solution were evaporated, the obtained dark oil was dissolved in 99.8% formic acid (20 ml), and the mixture was kept at room temperature for 24 h. The formic acid was distilled, and the residue was treated with 10 ml of water and extracted with 35 ml of methylene chloride. The extract was washed with water (3 × 15 ml) and filtered through cotton wool and evaporated. The substance was precipitated with heptane (30 ml) from a hot solution in methylene chloride (10 ml). The mixture was placed in a cooling bath, and the crystals were separated. They were washed with a 5:1 mixture of heptane and methylene chloride (5 ml) and dried under vacuum, and 1.32 g of light-cream crystals was obtained. Found %: C 51.90; H 5.44; Br 21.58; N 3.79. $C_{16}H_{20}BrNO_4$. Calculated %: C 51.88; H 8.19; Br 21.50; N 4.88.

11a-Hydroxy-1,1-dimethyl-3-oxo-1,5,11,11a-tetrahydro[1,3-*a*]oxazolo[3,4-*a*]pyrido[1,2-*d*]-10-pyrazinium Bromide (13). To a solution of the dioxolanone **2d** (1.44 g, 5.00 mmol) in dry benzene (11 ml) we added dry triethylamine (1.7 ml). After 15 min the mixture was heated to 70-80°C and kept for 30 min. The crystals of NEt_3·HBr were separated and washed with benzene (3 × 3 ml). The combined washing liquids and the mother solution were evaporated, and the dioxolanone **3d** was obtained in the form of a light-brown oil.

A. To a solution of the dioxolanone **3d** in chloroform (5 ml), cooled to -20°C, we added 2-(aminomethyl)pyridine (0.54 g, 5.00 mmol) in dry chloroform (5 ml). The mixture was allowed to heat to room temperature, and the salt **13** separated out. The mixture was heated at 50°C for 20 h. The salt was filtered off, washed with chloroform (3 × 3 ml), and dried, and 0.75 g of light-brown plates was obtained.

B. To a solution of the dioxolanone **3d** in dry benzene (1 ml), cooled to 6-8°C, we added 2-(aminomethyl)pyridine (0.54 g, 5.00 mmol) in benzene (1 ml). The mixture was allowed to heat to room temperature, and the salt **13** separated out. It was filtered off, washed with benzene (3 × 1 ml), and dried, and 1.30 g of dark-brown plates was obtained.

Thin-layer chromatography of the solutions obtained in systems A and B showed the presence of at least two substances, probably the intermediates **11** and **12**, in the form of two spots with R_f 0.60 and 0.85. It was not possible to isolate these compounds.

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