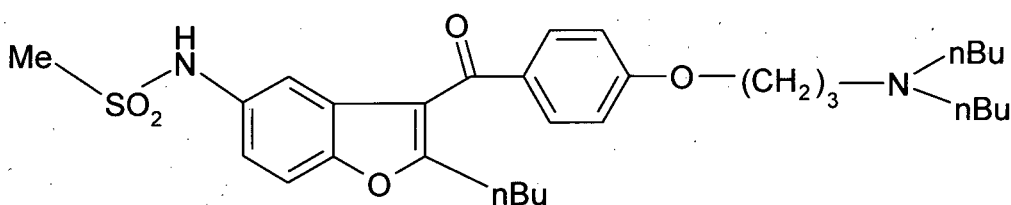


New process for the preparation of dronedarone

The present invention relates to a novel process for the preparation of *N*-[2-butyl-3-{4-[(3-dibutylamino)propoxy]benzoyl}-1-benzofuran-5-yl]methanesulfonamide (dronedarone) of formula I.



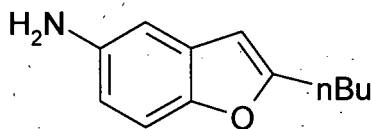
I

and its pharmaceutically acceptable salts, and to the new intermediates of the preparation process.

Dronedarone of formula I is used in the treatment of certain pathological changes of the cardiovascular system, especially in the treatment of angina pectoris, high blood pressure, arrhythmia and insufficient cerebral blood circulation (EP 0471609 B1).

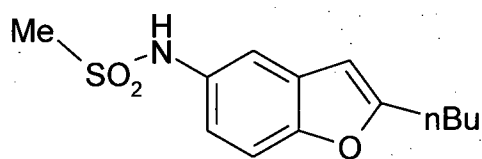
There are several known methods for the preparation of dronedarone of formula I. Patent application of publication number WO 02/48132 discloses the following super-convergent method:

The 5-amino-2-butyl-benzofuran of formula IV

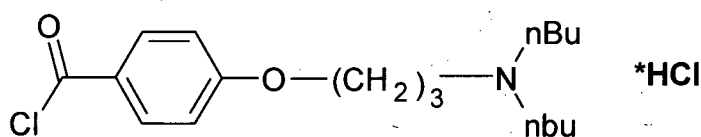


IV

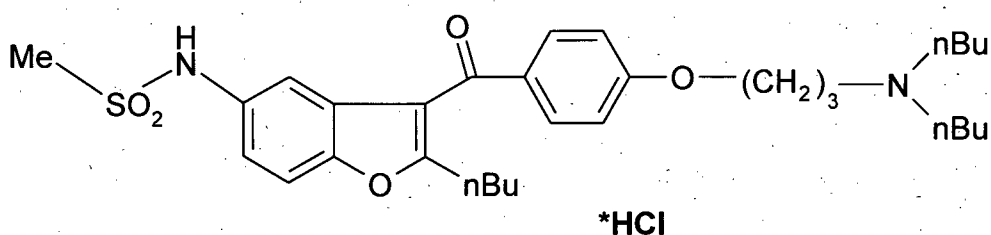
is mesylated and the resulting 2-butyl-5-methanesulfonamido-benzofuran of formula II

**II**

is reacted under Friedel-Crafts conditions with the 4-[3-(dibutylamino)propoxy]-
5 benzoyl chloride hydrochloride salt of formula **III**

**III**

10 to obtain the dronedarone hydrochloride salt of formula **I**.

**I**

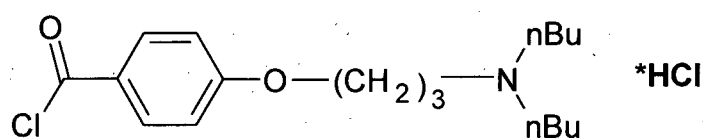
15 This method is very simple and economical as regards the number of the reaction steps. Its drawback is however, that in the last step the hydrochloride salt of dronedarone is obtained in a substantially contaminated form. This can be explained by the presence of the dibutylamino-propyl group in the Friedel-Crafts reaction. In the published examples the yield is 90%, during the purification steps first the raw
20 dronedarone hydrochloride salt, then following treatment with hydrogen chloride solution in isopropanol, the purified dronedarone hydrochloride salt is obtained (90%).

Another drawback of the method is that the reactants used in the Friedel-Crafts reaction and the obtained by-products are insoluble in water, thus they cannot be removed from the system by aqueous washing.

A further drawback of the method is that during the mesylation of the 5-amino-2-butyl-benzofuran **IV** a double mesylated derivative always appears as a by-product of the reaction. Purification is solved by recrystallisation, its yield is 78.5%.

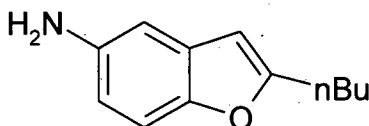
Our aim was to work out a novel method for the preparation of dronedarone and its pharmaceutically acceptable salts, which method avoids the above mentioned disadvantages, and is economical and industrially applicable.

We have found that if in the course of the process, instead of the 2-butyl-5-methanesulfonamido-benzofuran **II**, its alkali- or alkali earth metal salt is reacted with the 4-[3-(dibutylamino)propoxy]benzoyl chloride hydrochloride salt of formula **III**



under Friedel-Crafts conditions, then the above mentioned disadvantages can be avoided.

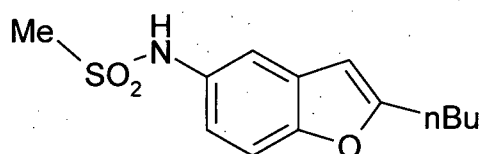
According to our invention the 5-amino-2-butyl-benzofuran of formula **IV**



IV

is mesylated by a method known from the literature (WO 02/48132) and

5 the resulting 2-butyl-5-methanesulfonamido-benzofuran of formula II



II

10

is reacted with an appropriate alkali- or alkali earth metal salt to give the respective alkali- or alkali earth metal salt of the compound of formula II,

which is then reacted as described above, with the 4-[3-(dibutylamino)propoxy]-benzoyl chloride hydrochloride salt of formula III under
15 Friedel-Crafts conditions, to obtain the *N*-[2-butyl-3-{4-[(3-dibutylamino)propoxy]benzoyl}-1-benzofuran-5-yl]-methanesulfonamide of formula I, which is optionally transformed into its salt, or liberated from its salt.

The advantage of the process according to the invention is that the by-
20 product which is formed during the mesylation of the compound of formula IV will not disturb the further reaction steps, because to the obtained reaction mixture the alkali- or alkali earth metal salt solution is added, and the alkali- or alkali earth metal salt of the desired compound of formula II will dissolve and remain in the aqueous phase.

25

By choosing suitable reaction conditions the compound of formula I is obtained in the required purity and yield, the by-product is not formed, only a few percent of unreacted starting material may remain in the reaction mixture, which can easily be removed by aqueous washing and may be re-used.

According to one embodiment of the invention an alkali metal salt of the compound of formula **II** is reacted with the compound of formula **III**. The term alkali metal includes lithium, sodium or potassium.

5 The lithium, sodium or potassium salt of the compound of formula **II** is prepared by reacting the 2-butyl-5-methanesulfonylamido-benzofuran of formula **II** with the appropriate alkali metal hydroxide (lithium hydroxide, sodium hydroxide, potassium hydroxide).

10 According to another embodiment of the invention an alkali earth metal salt of the compound of formula **II** is reacted with the compound of formula **III**. The term alkali earth metal includes magnesium or calcium. The magnesium or calcium salt of the 2-butyl-5-methanesulfonylamido-benzofuran of formula **II** is prepared by reacting the 2-butyl-5-methanesulfonylamido-benzofuran of formula **II** first with an
15 alkali metal hydroxide (lithium hydroxide or potassium hydroxide) and then with the appropriate alkali earth metal halogenide (calcium chloride, calcium bromide, magnesium chloride, magnesium bromide).

According to a preferred version of our invention the reaction of the alkali
20 metal or alkali earth metal salt of the compound of formula **II** and the compound of formula **III** is performed in an inert organic solvent, or in the mixture of inert organic solvents. As inert organic solvent, halogenated hydrocarbons (dichloromethane, dichloroethane, chlorobenzene) or the mixture of them can be used.

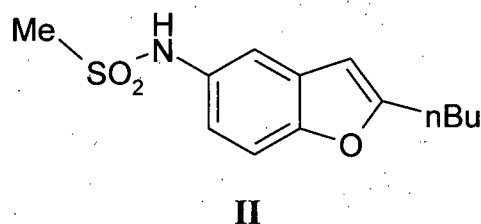
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According to a preferred version of our invention the reaction of the alkali metal or alkali earth metal salt of the compound of formula **II** with the compound of formula **III** is carried out in the presence of a Friedel-Crafts catalyst (iron(III) chloride, aluminum chloride).

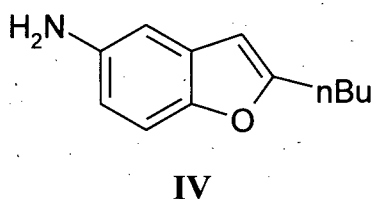
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According to a preferred version of our invention the reaction of the alkali metal or alkali earth metal salt of the compound of formula **II** with the compound of formula **III** is carried out at a temperature between 10-100 °C.

5 The 2-butyl-5-methanesulfonylamido-benzofuran of formula **II**

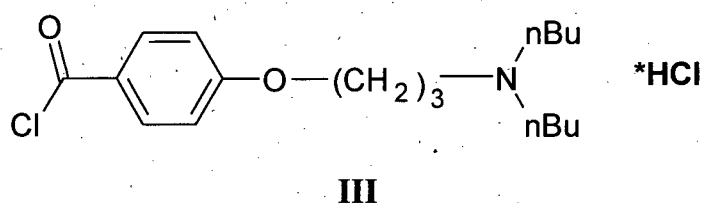


10 and its preparation by mesylation of the 5-amino-2-butyl-benzofuran of formula **IV**



15 is known from the literature (WO 02/48132).

The 4-[3-(dibutylamino)propoxy]benzoyl chloride hydrochloride of formula **III**



20 which is used in the process, and its preparation is known from the literature (WO 02/48078).

The lithium salt **IIa**, sodium salt **IIb**, potassium salt **IIc**, magnesium salt **IIId** and calcium salt **IIe** of the compound of formula **II** are new compounds, not known from the literature.

Further details of the invention are demonstrated by the following examples
- without limiting the claims to the examples.

5 EXAMPLES

Example 1.

10 *N*-[2-butyl-3-{4-[(3-dibutylamino)propoxy]benzoyl}-1-benzofuran-5-yl]-methanesulfonamide I

To the suspension made of 5.2 g 2-butyl-5-methanesulfonamido-benzofuran sodium salt **IIb** and 20 ml dichloromethane, the solution of 6.29 g 4-{3-(dibutylamino)-propoxy}benzoyl chloride hydrochloride salt **III** in 25 ml dichloromethane is added.
15 The reaction mixture is stirred for 30 minutes. In 15 minutes at 5-10°C 3.57 g iron(III) chloride is added and the reaction mixture is stirred at 20-25°C for 2 hours. At 40°C in 10 minutes 20 ml water is added to the mixture and the phases are separated. The dichloromethane phase is washed by stirring with 15 ml water, then with 15 ml 5% sodium hydrogen carbonate solution. The dichloromethane phase is
20 evaporated.

9.8 g (98.0%) yellow oil is obtained.

Purity by HPLC: 98.6%

¹H NMR (DMSO): 0.8-0.9ppm (m, 9H); 1.2-1.5ppm (m, 10H); 1.67ppm (5', 2H); 1.87ppm (5', 2H); 2.38ppm (t, J= 7.2Hz, 4H); 2.57ppm (m, 2H); 2.81ppm (t, J= 7.5Hz, 2H); 2.91ppm (s, 3H); 9.51ppm (t, J= 6.2Hz, 2H); 7.09ppm (d, J= 8.8Hz, 2H); 7.24ppm (dd, J= 8.9, 2.2Hz, 1H); 7.38ppm (d, J= 2.1Hz, 1H); 7.65ppm (d, J=8.8Hz, 1H); 7.81ppm (d, J= 8.8Hz, 2H)

Example 2.

N-[2-butyl-3-{4-[(3-dibutylamino)propoxy]benzoyl}-1-benzofuran-5-yl]-methanesulfonamide **I**

5

The procedure as described in Example 1. was followed, but chlorobenzene was used, instead of dichloromethane.

Yield: 97.8%.

Purity by HPLC: 98.4%

10

Example 3.

N-[2-butyl-3-{4-[(3-dibutylamino)propoxy]benzoyl}-1-benzofuran-5-yl]-methanesulfonamide **I**

15

The procedure as described in Example 1. was followed, with the difference that instead of 2-butyl-5-methanesulfonamido-benzofuran sodium salt **IIb**, equivalent amount of 2-butyl-5-methanesulfonamido-benzofuran potassium salt **IIc** was used. The resulting material is identical with the product of Example 1.

20

Yield: 99.1%.

Purity by HPLC: 98.4%

Example 4.

N-[2-butyl-3-{4-[(3-dibutylamino)propoxy]benzoyl}-1-benzofuran-5-yl]-methanesulfonamide **I**

25

The procedure as described in Example 1. was followed, with the difference that instead of 2-butyl-5-methanesulfonamido-benzofuran sodium salt **IIb**, equivalent amount of 2-butyl-5-methanesulfonamido-benzofuran lithium salt **IIa** was used. The resulting material is identical with the product of Example 1.

30

Yield: 98.1%.

Purity by HPLC: 98.7%

Example 5.

N-[2-butyl-3-{4-[(3-dibutylamino)propoxy]benzoyl}-1-benzofuran-5-yl]-methanesulfonamide I

The procedure as described in Example 1. was followed, with the difference that instead of 2-butyl-5-methanesulfonamido-benzofuran sodium salt **IIb**, equivalent amount of 2-butyl-5-methanesulfonamido-benzofuran magnesium salt **IIe** was used. The resulting material is identical with the product of Example 1.

Yield: 97.8%.

Purity by HPLC: 99.0%

Example 6.

N-[2-butyl-3-{4-[(3-dibutylamino)propoxy]benzoyl}-1-benzofuran-5-yl]-methanesulfonamide I

The procedure as described in Example 1. was followed, with the difference that instead of 2-butyl-5-methanesulfonamido-benzofuran sodium salt **IIb**, equivalent amount of 2-butyl-5-methanesulfonamido-benzofuran calcium salt **IId** was used. The resulting material is identical with the product of Example 1.

Yield: 97.7%.

purity by HPLC: 97.6%

Example 7.

N-[2-butyl-3-{4-[(3-dibutylamino)propoxy]benzoyl}-1-benzofuran-5-yl]-methanesulfonamide I

The procedure as described in Example 1. was followed, but 2.93 g aluminum chloride was used, instead of iron(III) chloride.

The resulting material is identical with the product of Example 1.

5 Yield: 89.9%.

Purity by HPLC: 96.1%

Example 8.

10 2-butyl-5-methanesulfonamido-benzofuran lithium salt IIa

2.23 g 2-butyl-5-methanesulfonamido-benzofuran **II** is added under stirring to the solution of 0.20 g lithium hydroxide in 5 ml water. The reaction mixture is stirred at room temperature for 1 hour and then kept at 0-5°C for 8 hours. The precipitated
15 white material was collected, washed with 1 ml 5°C water and dried at 70°C.

Mass of the product: 1.7 g (74.5%)

Melting point: 252.1-253.7°C

Elemental analysis: C:51.98%, H:5.79%, N:4.61%, S:10.44%, Li:2.41%

(Calculated values: C:57.1%, H:5.86%, N:5.13%, S:11.7%, Li:2.56%)

20

Example 9.

2-butyl-5-methanesulfonamido-benzofuran sodium salt IIb

25 2.12 g 2-butyl-5-methanesulfonamido-benzofuran **II** was added to the solution of 1g sodium hydroxide in 75 ml water. The resulting suspension was warmed to 70°C, then allowed to cool to 20°C and stirred at 5-10°C for 1 hour. The product was filtered off, dried in vacuum.

Mass of the product: 2.04 g (89.0%)

30 Melting point: 226.3-228.9°C

Elemental analysis: C: 59.9%; H: 5.63%; N: 5.16%; S: 11.14%; Na: 7.2%;

(Calculated values: C: 59.98%; H: 5.54%; N: 4.84%; S: 11.07%; Na: 7.94%)

Example 10.

5 2-butyl-5-methanesulfonamido-benzofuran sodium salt IIb

The procedure as described in Example 9. was followed, but 40 ml water was used in the reaction. The resulting material is identical with the product of Example 9.

Yield: 95.0%.

Example 11.

2-butyl-5-methanesulfonamido-benzofuran potassium salt IIc

15 2.12 g 2-butyl-5-methanesulfonamido-benzofuran II was added to the solution of 1g of 85% potassium hydroxide in 25 ml water. The reaction mixture was stirred at room temperature for 1 hour, and then at 5°C for 2 hours. The product was filtered off, dried in vacuum.

Mass of the product: 2.0 g (82.0%)

20 Melting point: 103.2-105.7°C

Elemental analysis: C: 50.37%; H: 5.16%; N: 4.54%; S: 9.53%; K: 12.0%

(Calculated values: C: 51.07%; H: 5.24%; N: 4.58%; S: 10.47%; K: 12.8%)

Example 12.

25

2-butyl-5-methanesulfonamido-benzofuran potassium salt IIc

The procedure as described in Example 11. was followed, but 10 ml water was used in the reaction. The resulting material is identical with the product of Example 11.

30 Yield: 94.0%.

Example 13.**2-butyl-5-methanesulfonamido-benzofuran calcium salt IIe**

- 5 2.0 g 2-butyl-5-methanesulfonamido-benzofuran **II** was added to the solution of 0.5 g 85% potassium hydroxide in 20 ml water. The reaction mixture was stirred for 30 minutes. To the obtained solution 0.89 g calcium chloride dissolved in 5 ml water was added in 10 minutes, the resulting suspension was stirred at 20-25°C for 1 hour and then at 5°C for 2 hours. The product was filtered off and dried.

10 Mass of the product: 1.8 g (86.1%)

Melting point: 103.4-105.7°C

Elemental analysis: C: 51.74%; H: 5.50%; N: 4.55%; S: 10.29%; Ca: 5.8%

(Calculated values: C: 54.47%; H: 5.58%; N: 4.89%; S: 11.17%; Ca: 6.99%)

15 **Example 14.**

2-butyl-5-methanesulfonamido-benzofuran calcium salt IIe

- The procedure as described in Example 13. was followed, but 15 ml water was used
20 in the reaction, instead of 20 ml. The resulting material is identical with the product of Example 13.

Yield: 92.0%.

Example 15.

25

2-butyl-5-methanesulfonamido-benzofuran magnesium salt IIId

- 1.6 g 2-butyl-5-methanesulfonamido-benzofuran **II** was added to the solution of 0.28 g 85% potassium hydroxide in 16 ml water. The reaction mixture was stirred
30 for 30 minutes. To the obtained solution 0.76 g magnesium chloride dissolved in

5 ml water was added in 10 minutes, the resulting suspension was stirred at 20-25°C for 1 hour and then at 5°C for 2 hours. The product was filtered off and dried.

Yield: 1.4 g (83.8%)

Melting point: above 270°C

5 Elemental analysis: C: 51.74%; H: 5.50%; N: 4.55%; S: 10.29%; Mg: 4.8%;
(Calculated values: C: 56.0%; H: 5.74%; N: 5.03%; S: 11.49; Mg: 4.36%)

Example 16.

10 2-butyl-5-methanesulfonamido-benzofuran magnesium salt IIId

The procedure as described in Example 15. was followed, but 10 ml water was used in the reaction, instead of 16 ml. The resulting material is identical with the product of Example 15.

15 Yield: 93.7%

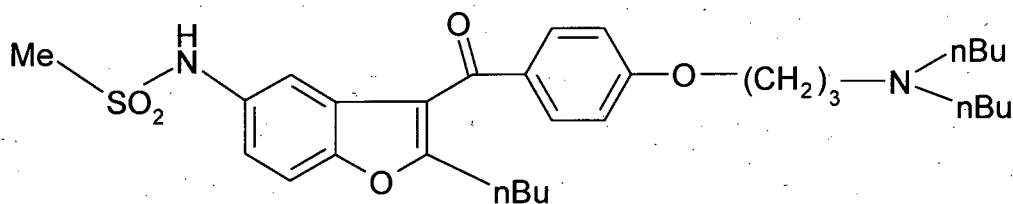
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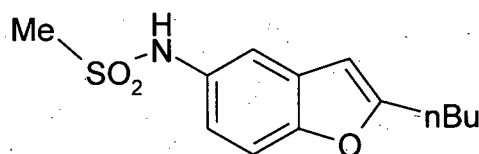
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Claims

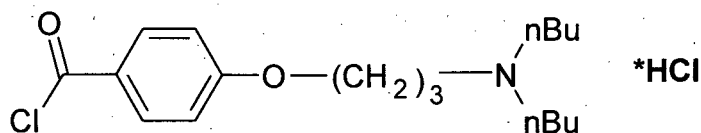
1. Process for the preparation of *N*-[2-butyl-3-{4-[(3-dibutylamino)propoxy]-benzoyl}-1-benzofuran-5-yl]methanesulfonamide of formula I

**I**

and its pharmaceutically acceptable salts, characterized in that an alkali- or alkali earth metal salt of the compound of formula II

**II**

is reacted with the 4-[3-(dibutylamino)propoxy]benzoyl chloride hydrochloride of formula III

**III**

in the presence of a catalyst, and optionally, the compound of formula I is transformed into its salt, or liberated from its salt.

2. The process as defined in claim 1., **characterized in that** the term alkali metal includes lithium, sodium or potassium, and the term alkali earth metal includes magnesium or calcium.

3. The process as defined in any of claims 1-2., **characterized in that** the reaction of the compound of formula **II** and the compound of formula **III** is carried out in an inert solvent or in the mixture of them.

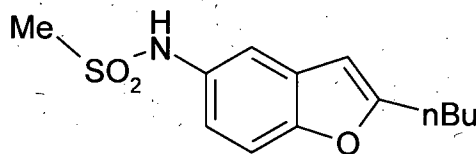
4. The process as defined in claim 3., **characterized in that**, as for inert solvent, halogenated hydrocarbons are applied.

5. The process as defined in claim 4., **characterized in that**, as for halogenated hydrocarbons, dichloromethane, dichloroethane, chlorobenzene or the mixtures of them are used.

6. The process as defined in any of claims 1-5., **characterized in that**, as for catalyst, iron(III) chloride or aluminum chloride is used.

7. The process as defined in any of claims 1-6., **characterized in that** the reaction is carried out at a temperature between 10-100 °C.

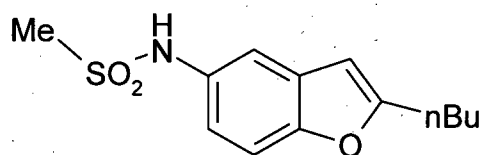
8. The alkali metal- and alkali earth metal salts of the 2-butyl-5-methanesulfonamido-benzofuran of formula **II**.



II

9. Of the compounds according to claim 8., the lithium salt **IIa**, sodium salt **IIb**, potassium salt **IIc**, magnesium salt **IId** and calcium salt **IIf** of the compound of formula **II**.

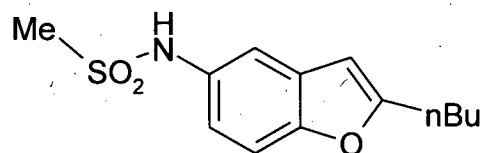
10. Process for the preparation of the alkali metal salts of compound **II** according to any of claims 8-9., **c h a r a c t e r i z e d i n t h a t** the compound of formula **II**

**II**

is reacted with the appropriate alkali metal hydroxide.

11. The process according to claim 10. **c h a r a c t e r i z e d i n t h a t** the term alkali metal hydroxide comprises lithium hydroxide, sodium hydroxide or potassium hydroxide.

12. Process for the preparation of the alkali earth metal salts of compound **II** according to any of claims 8-9., **c h a r a c t e r i z e d i n t h a t** the compound of formula **II**

**II**

is first reacted with lithium hydroxide or potassium hydroxide, and then with the appropriate alkali earth metal halogenide.

13. The process according to claim 12. **c h a r a c t e r i z e d i n**
t h a t the term alkali earth metal halogenide comprises magnesium chloride,
magnesium bromide, calcium chloride or calcium bromide.

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