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THE SYNTHESIS OF ISOQUINOLINES, INDOLES AND BENZTHIOPHEN BY AN IMPROVED POMERANZ-FRITSCH REACTION, USING BORON TRIFLUORIDE IN TRIFLUOROACETIC ANHYDRIDE

M. J. BEVIS, E. J. FORBES†, N. N. NAIK and B. C. UFF*
Department of Chemistry, University of Birmingham, Birmingham, 15.

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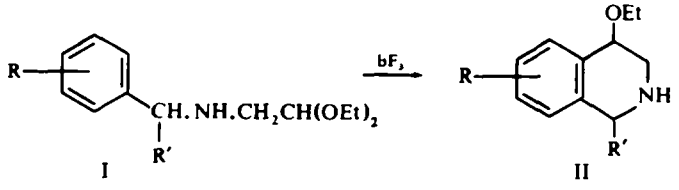
Abstract—Pomeranz-Fritsch cyclisations are reported using a new reagent boron trifluoride-trifluoroacetic anhydride. Isoquinolines carrying 7-OMe groups have been prepared in good yields and the method extended to the formation of N-substituted indoles and of benzthiophen from the corresponding acetals. Benzofuran could not be obtained by this procedure nor could a Bischler-Napieralski type cyclisation be induced. In the latter case the aromatic ring of the starting amide was acetylated when suitably activated.

IN A study of the Pomeranz-Fritsch synthesis of isoquinolines[1] we have investigated the use of reagents alternative to concentrated sulphuric acid for the cyclisation step. We have reported on the use of polyphosphoric acid to obtain, in particular, 8-substituted isoquinolines[2] and here examine the use of the Lewis acid boron trifluoride under various conditions. Vinot and Quelet[3] prepared 4-ethoxy-1,2,3,4-tetrahydroisoquinolines in variable yields (0–70%) by cyclisation of substituted benzylaminoacetals (I → II) in the presence of gaseous boron trifluoride and the method has more recently been applied to the formation of 1-alkoxy-2,3,4,5-1H-benz-3-azepines.[4]



I II

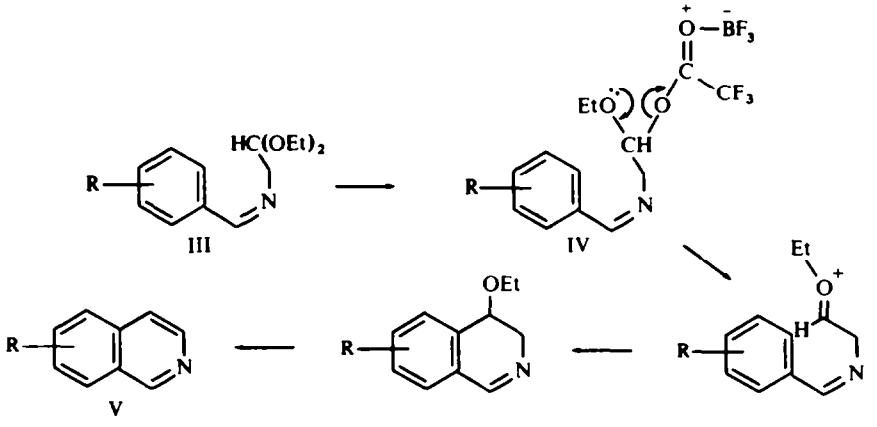
However we found that this method could not be used for the preparation of isoquinolines directly by the cyclisation of benzylideneaminoacetals (III → V). Only resins were obtained. Some success was, however, obtained using a solution of boron trifluoride in the more polar solvent acetic acid which gave moderate yields of 7,8-dioxygenated isoquinolines (Table 1) with the exception of the 7-methoxy-8-benzyloxy analogue. This failed to cyclise, debenzylation being observed. Cleavage of benzyl ethers under similar conditions has been reported.[5]

Cleavage of aliphatic ethers by acid anhydrides takes place rather easily in the presence of Lewis acids to give two moles of an ester.[6] It was considered that this

* Present address: Chemistry Department, Loughborough University of Technology, Loughborough, Leicestershire.

† To whom enquiries should be addressed.

reaction could be extended to the cleavage of acetals using the highly reactive trifluoroacetic anhydride, in the presence of boron trifluoride as its acetic acid complex. For the Pomeranz-Fritsch synthesis of isoquinolines this would involve the sequence (III → V) through the intermediate ether (IV) with its excellent leaving group. In the manner shown this intermediate (IV) would provide the key intermediate oxonium ion for the cyclisation step. The formal loss of ethanol in the final stage would be expected to be as easy as the replacement of the OEt group by trifluoroacetate in the formation of intermediate IV.



Using this procedure at 5° a number of isoquinolines were obtained in yields as high as 80%, best results being given by those acetals derived from aryl aldehydes carrying an activating group in the *meta* position. *m*-Methoxyacetophenone was less satisfactory (20%) and aryl aldehydes or ketones unsubstituted at the *meta* position failed to cyclise (Table 1).

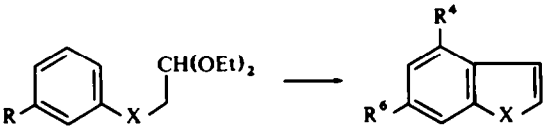
Table 1. Isoquinoline formation using reagents containing BF_3

Reagent	Isoquinoline substituents 1	7	8	Yield
BF_3 gas	H	OMe	OCH_2Ph	0%
BF_3/CH_3COOH	H	OMe	OMe	23%
BF_3/CH_3COOH	H	OMe	OH	32%
BF_3/CH_3COOH	H	OMe	OCH_2Ph	0%
BF_3/CH_3COOH + TFAA*	H	OMe	OMe	60–82%
BF_3/CH_3COOH + TFAA	H	OMe	OH	50–63%
BF_3/CH_3COOH + TFAA	H	OMe	H	73%
BF_3/CH_3COOH + TFAA	Me	OMe	H	20%
BF_3/CH_3COOH + TFAA	Me	H	H	0%
BF_3/CH_3COOH + TFAA	H	H	H	0%
BF_3/CH_3COOH + TFAA	H	H	OMe	0%

* TFAA = $(CF_3CO)_2O$

The success obtained with the 7-methoxyisoquinoline derivatives encouraged us to look at the synthesis of other heterocyclic systems using the boron trifluoride-trifluoroacetic anhydride system. N-Alkylindoles have been prepared by heating the

diethyl acetal of bromoacetaldehyde with secondary amines,[7] but the procedure does not work for indoles unsubstituted at nitrogen. Application of the boron trifluoride-trifluoroacetic anhydride reagent at 5° to the preformed anilinodiethylacetals (VI → VII, X = NH or N-Alkyl) gave the results shown in Table 2. Good yields (60% and above) were obtained for N-substituted indoles but, as with Räth's method,[7] the procedure failed for indoles unsubstituted on nitrogen.



VI VII

The *m*-methoxy-N-methylaniline required was obtained by formylation of *m*-methoxyaniline followed by reduction. Direct N-methylation of acetal (VI, R = OMe, X = NH) was unsuccessful with either dimethyl sulphate in hot alkali or methyl iodide and potassium carbonate. Cyclisation of the acetal (VI, R = OMe, X = NMe) gave a mixture of 4- and 6-methoxy-N-methylindole (75:25) separable by chromatography. It was evident that some demethylation had occurred and so the mixture of indoles was treated directly with dimethyl sulphate and alkali to give the 4- and 6-methoxy-N-methylindoles in almost quantitative yield. For the sake of comparison the acetal from *m*-methoxy-N-methylaniline was also cyclised by Räth's method.[7] Thin layer chromatography revealed that after 2 hrs heating at 180° an appreciable quantity of the indole mixture was formed. Distillation gave a 71% yield of the mixed indoles.

The boron trifluoride-trifluoroacetic anhydride reagent was next applied to the formation of the benzthiophen ring. Tilak[8] had previously cyclised the acetal (VI, X = S, R = H) in 32% yield using polyphosphoric acid at 120°. Under our conditions the reaction gave a comparable yield (36%). thus providing an alternative mode of synthesis utilising milder conditions (5°). When applied to the formation of benzofuran (VI → VII, X = O, R = H) the procedure gave only a polymer. Pomeranz[9] attempted to cyclise the phenoxyacetal to benzofuran with mineral acids but obtained

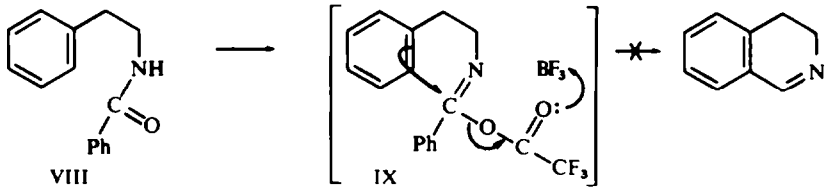
TABLE 2. PREPARATION OF INDOLES, BENZTHIOPHEN AND BENZOFURAN (VI → VII) USING BF_3/CH_3COOH + TFAA

Heterocycle (VII)			
X	R^4	R^6	Yield
NH	H	H	0%
NMe	H	H	60%
NEt	H	H	60%
NH	H	OMe	0%
NMe	OMe	H	100%*
NMe	H	OMe	
S	H	H	36%
O	H	H	0%

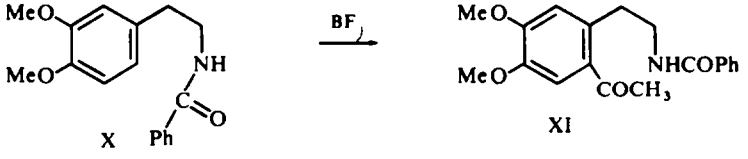
* Obtained as a mixture after methylation of crude product mixture.

only polymers. However, phenoxyacetals have been cyclised using zinc chloride in acetic acid.[10]

Finally, it seemed possible that the new reagent might be used for obtaining isoquinoline by the Bischer-Napieralski reaction by effecting O-acylation of the amide function,[11] thus producing an intermediate of the type (IX).



The reaction, however, was not successful with N-benzoylphenylethylamine (VIII), only starting material being obtained. In the case of an activated ring, using the dimethyl analogue (X), acetylation was observed, giving the ketone (XI) in 80% yield. Analogously veratrole gave 3,4-dimethoxyacetophenone in quantitative yield under the same conditions. Trifluoroacetic anhydride and organic acids have been reported previously as effecting acylations of activated aromatic rings.[12] It is therefore notable that this acylation did not proceed to any observable extent in the Pomeranz–Fritsch isoquinoline reaction or in the formation of indoles and benzthiophen described above.



EXPERIMENTAL

2-Benzyloxy-3-methoxybenzaldehyde. *o*-Vanillin was benzylated by the method used by Späth *et al.*[13] for the preparation of 3-benzyloxy-4-methoxybenzaldehyde. The product (83%) crystallised from ether as colourless needles m.p. 44·0–44·5° (Found: C, 74·3; H, 5·7: $C_{15}H_{14}O_3$ requires: C, 74·4; H, 5·8%). *m-Methoxyacetophenone* was prepared by addition of lithium methyl to the lithium salt of *m*-methoxybenzoic acid, b.p. 123–124/9·3 mm, yield 54%.[2]

Isoquinoline preparation using BF_3/CH_3COOH *with* $(CF_3CO)_2O$

7,8-Dimethoxyisoquinoline. Trifluoroacetic acid (100g) was allowed to stand with P_2O_5 (*ca* equal weight-volume) for 24 hrs. The mixture was distilled and the distillate redistilled form a second quantity of P_2O_5 (*ca* half of previous weight) through a Vigreux column (12") to give trifluoroacetic anhydride (*ca* 80 g) b.p. 38–40°, as a colourless liquid.

When 2,3-dimethoxybenzaldehyde (4·0 g) and aminoacetal (3·85 ml) were warmed together an immediate cloudiness was produced. The mixture was boiled under reflux with benzene for 45 mins and a further 2 hrs with addition of a Dean–Stark trap. Removal of the solvent and excess aminoacetal left the Schiff's base (6·77 g, 1 mole).

BF_3–AcOH complex (40% BF_3, 12·3 g, 3 moles) was diluted at 5° with trifluoroacetic anhydride (20 ml). The Schiff's base was diluted at 5° with trifluoroacetic anhydride (17 ml). This soln was added dropwise at 5° to the BF_3–trifluoroacetic anhydride mixture. The deep cherry-red mixture was allowed to stand at room temp for 2 days. It was poured into ice-water and basified with *ca* 20% ammonia soln, and the product extracted 4 times with chloroform. The combined chloroform layers were extracted with 4N HCl. Basification of the acid extracts and subsequent work up in the usual manner afforded *7,8-dimethoxyisoquinoline* (3·75 g, 82%) as an oil, b.p. 107–109°(0·15 mm, n_D^{21} 1·6039. (Found: C, 69·9; H, 7·5; CH_3O—,

32·2. $C_{11}H_{11}O_2N$ requires: C, 69·8; H, 5·9; N, 7·4; CH_3O—, 32·8%). Its methiodide melted at 178° (lit.[2] 178°), and its *picrate* crystallised with one mole of solvent as whispy needles from EtOH, m.p. 204°. (Found: C, 49·3; H, 4·2; N, 12·1. $C_{17}H_{14}N_4O_9 . C_2H_6O$ requires: C, 49·1; H, 4·3; N, 12·1%). The methobromide was also prepared m.p. 175–178°. Djerassi *et al.*[14] cite m.p. 166–170° when heated slowly but 193° when placed in a preheated bath at 170°.

8-*Hydroxy*-7-*methoxyisoquinoline* was prepared similarly from *o*-vanillin. It crystallised from benzene–chloroform as pale yellow prisms m.p. 183–184°. (Found: N, 8·2. $C_{10}H_9O_2N$ requires: N, 8·0%). Its methiodide had m.p. 196–197° undepressed on admixture with an authentic specimen.[2]

7-*Methoxyisoquinoline* was prepared similarly from 3-methoxybenzaldehyde and distilled with b.p. 118–120°/7 mm to give a straw coloured oil which solidified, m.p. 49–50° (lit.[15] 49°). A picrate was prepared and crystallised from hot water, m.p. 202–204° (lit.[15] 194–195°).

7-*Methoxy*-1-*methylisoquinoline* was prepared similarly from *m*-methoxyacetophenone. The product formed a methiodide, m.p. 277–278° undepressed on admixture with an authentic sample.[2]

Cyclisations using BF_3/CH_3COOH *alone*

General procedure. The Schiff base (1 mole) was added dropwise to BF_3–AcOH complex. (40% BF_3, 4 moles), when an exothermic reaction ensued, the temp being maintained at 5°. The mixture was allowed to stand for 24 hrs at room temp, added to ice-water and basified with ammonia to pH 8. A portion of the product precipitated and more was obtained by benzene extraction of the filtrate. Washing with 4N HCl followed by work-up in the usual manner gave the isoquinolines as shown in Table 1.

N-*Phenylaminoacetal* was prepared in 54% yield from bromoacetal and aniline by the method of Janetsky *et al.*[7d] but using a 62 hr reflux time and maintaining the reaction under N_2 and in the dark, b.p. 116–119°/0·8 mm (lit.[16] 108–110/0·4 mm).

N-*Ethyl*-N-*phenylaminoacetal* was prepared in 63% yield from bromoacetal and N-ethylaniline. The product was a colourless liquid b.p. 122–125°/3 mm (lit.[7d] 160–161°/17 mm). N-*Methyl*-N-*phenylaminoacetal* was prepared in 50% yield from bromoacetal and N-methylaniline. The product was a pale yellow liquid b.p. 119–120°/2 mm (Found: C, 69·9; H, 10·0; N, 6·5. $C_{13}H_{21}O_2N$ requires: C, 69·9; H, 9·5; N, 6·3%).

N-(*m-Methoxyphenyl*)*aminoacetal* was prepared similarly in 82% yield from bromoacetal and *m*-anisidine. The product was a colourless liquid b.p. 134–135°/0·7 mm. (Found: N, 5·85. $C_{13}H_{21}NO_3$ requires: N, 5·85%).

N-*Formyl*-m-*methoxyaniline*. A mixture of *m*-methoxyaniline (18·5 g) and formic acid (98%, 50 ml) was refluxed for 1 hr. The excess of formic acid was removed under reduced pressure to leave a faint yellow thick pasty mass. It was triturated with 10% ice-cold dil HCl (20 ml), and then washed with water. The solid residue was taken up in ether, the soln dried ($MgSO_4$) and the solvent removed under reduced pressure to give an almost colourless paste which solidified on standing to give N-*formyl*-m-*methoxy aniline* in quantitative yield. A portion of it was recrystallised from CCl_4 to give colourless thin plates, m.p. 51–52°, (Found: C, 74·4; H, 6·4; N, 6·3. $C_8H_9O_2N$ requires: C, 74·7; H, 6·3; N, 5·8%).

N-*Methyl*-m-*methoxyaniline*. N-Formyl-*m*-methoxyaniline (10 g) was taken up in dry ether (500 ml). LAH (2·5 g, 1 mole) in excess was quickly added and the whole was heated under reflux on a water-bath with the exclusion of moisture for 8 hr. The excess of LAH was decomposed with wet-ether (250 ml), and the mixture was treated with ice-cold 10% H_2SO_4 (200 ml). The aqueous layer was basified and extracted with ether. The ether extract was separated, washed with water, dried ($MgSO_4$) and the ether removed under reduced pressure to leave almost colourless liquid (8·86 g, 98%). It was pure enough for further work. On distillation it was collected as a colourless oil b.p. 84–85°/0·5 mm (lit.[17] 118–119·5°/8 mm). Its picrate crystallised from water as golden yellow leaflets m.p. 140° (lit.[17] 147°). (Found: C, 45·8; H, 3·9; N, 15·5; Calc. for $C_{14}H_{14}N_4O_8$: C, 45·9; H, 3·9; N, 15·3%). On heating N-methyl-*m*-methoxyaniline under reflux for 2 hrs with benzoyl chloride and anhyd K_2CO_3 in benzene followed by the usual work up the N-*benzoyl derivative* was isolated as a pale yellow liquid which solidified on standing. Recrystallisation from light petroleum (b.p. 60–80°) gave colourless plates m.p. 55·56°, yield 96%. (Found: C, 74·4; H, 6·4; N, 6·2. $C_{15}H_{15}O_2N$ requires: C, 74·7; H, 6·3; N, 5·8%).

N-(*m-Methoxyphenyl*)-N-*methylaminoacetal*. A mixture of N-methyl-*m*-methoxyaniline (6 g), bromoacetal (11·6 g, 1·5 moles), anhyd Na_2CO_3 (4·4 g, 1·25 moles), and n-BuOH (25 ml), was heated to reflux under N_2 with the exclusion of moisture with stirring for 85 hr. The mixture was worked-up in the usual way but not distilled (to avoid thermal cyclisation).

Phenyl 2,2-diethoxyethyl sulphide. A mixture of thiophenol (11·1 g) NaOEt (2·3 g Na in 50 ml EtOH), and 2-bromo-1,1-diethyl acetal (19·7 g, 1 mole), and NaI (1·5 g, 0·1 mole) was boiled under reflux for 3 hr, with the exclusion of moisture. The mixture was allowed to cool and the solid filtered off. The solvent was removed under reduced pressure to leave an almost colourless liquid, which was taken up in ether (150 ml) and washed with water (2 × 30 ml). The organic layer was dried ($MgSO_4$) and the ether removed under pressure. The residue was fractionally distilled to give phenyl 2,2-diethoxyethyl sulphide as a colourless liquid b.p. 98–100°/0·6 mm (20 g, 88·9%). (Lit.[8] b.p. 120–130°/2 mm.) (Found: C, 63·8; H, 8·0. Calc for $C_{12}H_{18}O_2S$: C, 63·7; H, 8·0%).

Phenyl 2,2-diethoxyethyl ether. To a stirred and heated mixture of phenol (9·4 g), sodium n-butoxide [from Na (2·3 g, 1 mole) in BuOH (50 ml)] and NaI (1·5 g, 0·1 mole) was added 2-bromo-1,1-diethoxy-acetaldehyde (19·7 g, 1 mole), dropwise over a period of 1 hr. The mixture was heated under reflux with exclusion of moisture for 8 hr. After cooling the soln it was filtered and the residue washed with ether (25 ml). The solvents were removed under reduced pressure leaving a brown liquid. It was taken up in ether (200 ml), and washed with 2N NaOH (50 ml), followed by water washing (2 × 40 ml). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was fractionally distilled to give the product as a colourless liquid, b.p. 85°/0·6 mm (9 g, 43%). (Found: C, 68·5; H, 8·8. Calc for $C_{12}H_{18}O_3$: C, 68·5; H, 8·6%).

Cyclisation of acetals to give indoles, benzthiophen and benzofuran. The procedure followed that for 7,8-dimethoxyisoquinoline (above) using BF_3-AcOH (3 moles) with $(CF_3CO)_2O$ (2 moles) per mole of acetal at 5°. In the cases of the methoxyindoles, benzthiophen and benzofuran the reagents were reduced in quantity to one mole of each per mole of acetal as this lessened resinification. The yields obtained are given in Table 2. *N-Methylindole* was characterised as its picrate m.p. 150° (lit.[18] 150°), as also was *N-ethylindole*, picrate m.p. 104–105° (lit.[19] 105°).

4-Methoxy-N-methylindole crystallised from light petroleum (b.p. 60–80°) as colourless plates m.p. 90° undepressed on admixture with an authentic sample.* Its picrate crystallised from benzene as dark-red flat needles m.p. 152-153°, undepressed on admixture with an authentic specimen.*

6-Methoxy-N-methylindole was obtained as a colourless oil and characterised as its picrate, crystallising from benzene–light petroleum (b.p. 60–80°) as dark-red needles m.p. 123 (lit.[20] 123°).

Benzthiophen crystallised as pale yellow flat needles from light petroleum (60–80°) with m.p. 31° (lit.[21] 32°).

Attempted preparation of 1-phenyl-3,4-dihydro-6,7-dimethoxyisoquinoline. Benzoyl chloride (4·78 g) was added to a suspension of 2-(3,4-dimethoxyphenyl)-ethylamine (5 g) in 10% NaOH aq (50 ml), and the mixture was shaken vigorously during 10–15 min. The mixture was warmed on a water-bath for 5–7 min. The compound which solidified on cooling the mixture was separated, washed with water and dried. One crystallisation from aqueous EtOH gave colourless plates of pure N-benzoyl-2-(3,4-dimethoxyphenyl)-ethylamine (7·55 g, 96%) m.p. 89–90° (lit.[22] 90°). (Found: C, 71·5; H, 6·5; N, 5·1. Calc for $C_{17}H_{19}O_3N$: C, 71·6; H, 6·7; N, 5·1%).

To a cooled mixture of N-benzoyl-2-(3,4-dimethoxyphenyl)-ethylamine (1 g), and CCl_4 (2 ml), was added a mixture of trifluoroacetic anhydride (1 ml; 2 mole), and BF_3-AcOH complex (1·8 g, 3 mole), with stirring and exclusion of moisture. The mixture was decomposed with ice-water after 1 hr. at room temp and then basified with NaOH aq to pH 9–10. The solid was filtered off, washed thoroughly with water (2 × 20 ml), and dried to give slightly grey solid (1·1 g, m.p. 137°). The solid was chromatographed on a silica-gel column (30 g) and eluted with a mixture of benzene-chloroform (17:3). Later fractions gave almost pure *N-benzoyl-2(6-acetyl-3,4-dimethoxyphenyl)-ethylamine* which crystallised from benzene in shining colourless soft needles, m.p. 153–154° (0·77 g, 77%). (Found: C, 69·7; H, 6·2; N, 3·6. $C_{19}H_{21}NO_4$ requires: C, 69·7; H, 6·4; N, 4·3%).

Attempted preparation of 1-phenyl-3,4-dihydroisoquinoline. 2-Phenylethylamine was treated with benzoyl chloride in the presence of NaOH aq to give N-benzoyl-2-phenylethylamine (98%) m.p. 117° (lit.[23] 113–114°). When this amide (1 mole) was treated with BF_3-AcOH (3 moles) and $(CF_3CO)_2O$ (2 moles) as described above only starting material was recovered. *3,4-Dimethoxyacetophenone* b.p. 120–121°/0·8 mm, m.p. 53° (lit.[24] b.p. 207°/15 mm, m.p. 48–49°) resulted from similar treatment of *o*-dimethoxybenzene with BF_3-AcOH and $(CF_3CO)_2O$. (Found: C, 66·6; H, 6·7. Calc for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%).

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