763. *Synthesis of (±)-Cytisine.*

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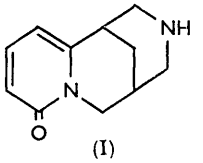
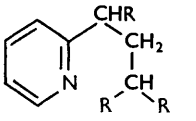
Condensation of ethyl 2-pyridylacetate with diethyl methoxymethylmalonate yielded diethyl α-ethoxycarbonyl-α′-2-pyridylglutarate (II), but attempts to use the derived amide or triol for synthesis of cytisine were unsuccessful. Condensation of diethyl α-cyano-β-ethoxyacrylate with ethyl 2-pyridylacetate did not yield the expected glutaconic acid derivative. Condensation of ethyl 5-cyano-2-methylnicotinate with diethyl ethoxymethylenemalonate yielded 7-cyano-3 : 9-diethoxycarbonylquinolizin-4-one, which on reduction of the cyano-group, decarboxylation, hydrolysis, and re-esterification yielded 7-aminomethyl-9-ethoxycarbonylquinolizin-4-one. Reduction with lithium aluminium hydride followed by selective reduction of one ring and cyclisation afforded (±)-cytisine.

The structure (I) of cytisine [1] has been confirmed by synthesis of tetrahydrodeoxycytisine,[2] (±)-cytisine,[3] and (−)-cytisine.[4] We record here a synthesis of (±)-cytisine by an independent method.

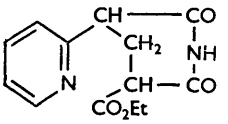
In the first approach, diethyl methoxymethylmalonate was condensed with ethyl 2-pyridylacetate, yielding diethyl α-ethoxycarbonyl-α′-2-pyridylglutarate (II), which was converted by aqueous ammonia at room temperature into the triamide (III), but we



(I)



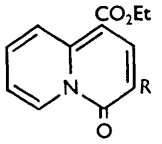
(II) : R = CO_2Et
(III) : R = $CO{\cdot}NH_2$
(IV) : R = $CH_2{\cdot}OH$

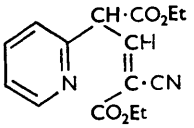


(V)

failed to obtain the imide-ester (V) which might have been converted into cytisine by a simple sequence of reactions. Diethyl methoxymethylmalonate could not be caused to react with 2-pyridylacetamide and condensation with 2-pyridylacetonitrile yielded only resin. The triester (II) was then reduced to the triol (IV) by lithium aluminium hydride. Without isolation of intermediates, the triol was treated successively with hydrogen bromide to convert it into the tribromide, quaternised, treated with ammonia, and oxidised with potassium ferricyanide, but the expected (±)-cytisine was not obtained.

(VI) : R = CO_2Et
(VII) : R = CN



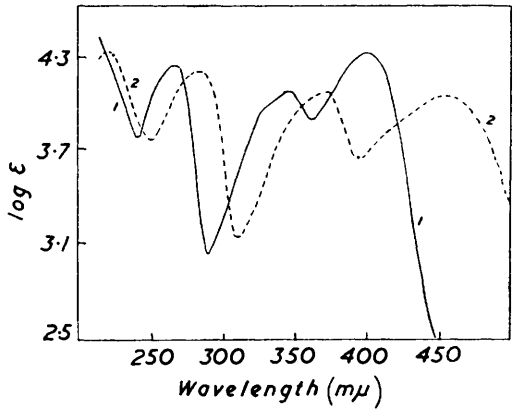


(VIII)

Boekelheide and Lodge [5] obtained 1 : 3-diethoxycarbonylquinolizin-4-one (VI) by treating ethyl 2-pyridylacetate with diethyl ethoxymethylenemalonate at 180°. It was hoped that by treating ethyl 2-pyridylacetate with ethyl α-cyano-β-ethoxyacrylate under mild conditions quinolizinone formation could be avoided and the glutaconic acid derivative

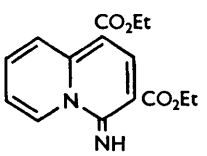
[1] Ing, *J.*, 1931, 2915; 1932, 2778; Späth and Galinovsky, *Ber.*, 1932, **65**, 1526; Partheil, *Arch. Pharm.*, 1892, **230**, 448; Freund, *Ber.*, 1904, **37**, 22; Ewins, *J.*, 1913, **103**, 97.
[2] Galinovsky, Vogl, and Moroz, *Monatsh.*, 1952, **83**, 246.
[3] von Tamelen and Baran, *J. Amer. Chem. Soc.*, 1955, **77**, 4944.
[4] Bohlmann, Englisch, Ottawa, Sander, and Weise, *Chem. Ber.*, 1956, **89**, 792.
[5] Boekelheide and Lodge, *J. Amer. Chem. Soc.*, 1951, **73**, 3681.

(VIII) prepared. However, condensation in alcoholic sodium ethoxide at room temperature yielded a neutral compound, $C_{13}H_{10}O_3N_2$, which was evidently 3-cyano-1-ethoxycarbonylquinolizin-4-one (VII) from the similarity of its ultraviolet spectrum (see Figure) to that of 1 : 3-diethoxycarbonylquinolizin-4-one [5] and the presence of an infrared absorption band at 4·50 μ (cyano-group). Condensation in absolute ether in the presence of sodium ethoxide yielded as the main product a basic compound, $C_{15}H_{16}O_4N_2$, whose infrared spectrum showed no absorption in the 4·5 μ region, but absorption at 3·05 μ (NH group). Its formulation as 1 : 3-diethoxycarbonyl-4-iminoquinolizine (IX) was confirmed by conversion into 1 : 3-diethoxycarbonylquinolizin-4-one by nitrous acid. The compound was converted at its melting point into 3-cyano-1-ethoxycarbonylquinolizin-4-one (VII), presumably by ring opening and recyclisation with elimination of ethanol. Since reduction may cleave amidines in two ways,[6] it was hoped that the iminoquinolizine (IX) could be

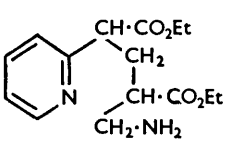


Absorption spectra of (1) *3-cyano-1-ethoxycarbonylquinolizin-4-one and* (2) *1 : 3-diethoxycarbonyl-4-iminoquinolizine in ethanol.*

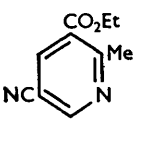
made to yield diethyl α-aminomethyl-α′-2-pyridylglutarate (X). Reduction of compound (IX) in presence of Adams catalyst yielded two compounds having the expected formula $C_{15}H_{22}O_4N_2$: one compound had ultraviolet absorption maxima at 276 and 327 mμ, and



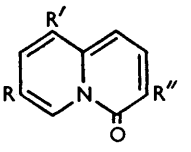
(IX)



(X)



(XI)



(XII): R = CN, R′ = R″ = CO_2Et

(XIII): R = $CH_2·NH_2$, R′ = R″ = CO_2Et

(XIV): R = $CH_2·NH_2$, R′ = CO_2Et, R″ = H

(XV): R = $CH_2·NH_2$, R′ = $CH_2·OH$, R″ = H

infrared bands at 5·79 (unconjugated ester), 5·90 (conjugated ester), and 2·94, 3·05, and 3·19 μ (NH_2 and NH groups); the second had maxima at 232, 289, and 380 mμ; neither could be the desired pyridine derivative (X), as judged by the ultraviolet absorption spectra.

A different approach, starting with the middle ring of cytisine, was then made. Ethyl 5-cyano-6-hydroxy-2-methylnicotinate [7] was converted into the 6-chloro-ester by phosphorus pentachloride and reduced to ethyl 5-cyano-2-methylnicotinate (XI), the yield

[6] Shriner and Newmann, *Chem. Rev.*, 1944, **35**, 351.
[7] Errera, *Ber.*, 1900, **33**, 2969.

being less than 50% under the best conditions (palladised charcoal in benzene) (reduction of 2-halogenopyridines carrying negative substituents at the 3 : 5-positions has been reported to proceed in poor yields [8]). An attempt to synthesise the cyano-ester (XI) directly by condensation of cyanomalonaldehyde with ethyl β-aminocrotonate led to a poor yield of a compound, $C_{10}H_{12}O_3N_2$, which may be 5-ethoxycarbonyl-6-methylnicotinamide. Condensation of ethyl 5-cyano-2-methylnicotinate (XI) with diethyl ethoxymethylenemalonate in alcoholic potassium ethoxide yielded 7-cyano-3 : 9-diethoxycarbonylquinolizin-4-one (XII). Attempts to remove the 3-ethoxycarbonyl group by selective hydrolysis and decarboxylation did not proceed in satisfactory yield. In alcohol in presence of Adams catalyst the quinolizinone (XII) absorbed two mols. of hydrogen, yielding a base which is presumably (XIII). Decarboxylative hydrolysis of this product followed by esterification yielded the ester (XIV) which was then reduced to the amino-alcohol (XV) by lithium aluminium hydride. Boekelheide and Lodge [5] found that reduction of 1-methoxycarbonylquinolizin-4-one in acid solution afforded only 6 : 7 : 8 : 9-tetrahydro-1-methoxycarbonylquinolizin-4-one. In acid solution at atmospheric pressure the amino-alcohol (XV) absorbed two mols. of hydrogen: the product, on successive treatment with phosphorus pentabromide and potassium carbonate, gave a gum which on sublimation and crystallisation yielded (±)-cytisine, m. p. 147°, whose infrared (in $CHCl_3$) and ultraviolet absorption spectra were identical with those of (−)-cytisine.

Experimental

Diethyl α-Ethoxycarbonyl-α'-2-pyridylglutarate (II).—To powdered potassium (1·2 g.) in dry ether (50 ml.) was added, with ice-cooling and stirring, ethyl 2-pyridylacetate [9] (5 g.). Next day ethyl methoxymethylmalonate (6·2 g.) in dry ether (20 ml.) was added with ice-cooling during 2 hr. and next morning the mixture was poured on crushed ice, and the ether layer was separated. The aqueous solution was extracted with more ether, and the combined extracts were shaken with N-hydrochloric acid until the acid remained colourless. The acid extracts were neutralised with solid sodium hydrogen carbonate, and the oil which separated was taken up in ether and dried (Na_2SO_4). Removal of solvent and fractionation gave ethyl 2-pyridylacetate (0·5 g.), b. p. 70°/0·01 mm., and the *diethyl glutarate* (2 g.), b. p. 152°/0·01 mm. (slight decomp.) (Found: C, 61·1; H, 6·4. $C_{17}H_{23}O_6N$ requires C, 60·6; H, 6·8%).

The crude triester (1·8 g.), left with 30% aqueous ammonia (10 ml.) for 2 days, slowly dissolved with separation of a white powder. This crystallised from hot water, yielding the *triamide* (0·7 g.), m. p. 242° (decomp.) (Found: C, 53·0; H, 5·2; N, 22·4. $C_{11}H_{14}O_3N_4$ requires C, 52·8; H, 5·6; N, 22·4%).

2-Hydroxymethyl-4-2'-pyridylpentane-1 : 5-diol (IV).—To a solution of lithium aluminium hydride (2 g.) in ether (100 ml.) was added the glutarate (II) (6 g.) in ether (20 ml.) with stirring. The mixture was stirred for 1 hr. and left overnight. After decomposition in the usual way, the ether layer was decanted, dried (Na_2SO_4), and evaporated to an oil (0·2 g.). The inorganic hydroxides were dried *in vacuo* and extracted with hot methanol. The extracts were then saturated with carbon dioxide, filtered, and evaporated. The residue was extracted with ethanol–ether (2 : 1), and the extracts were evaporated, finally *in vacuo*. The residual triol (2 g.) could not be purified, but gave a crystalline *tribenzoate*, m. p. 93° (from methanol containing a few drops of water) (Found: C, 70·8; H, 5·4. $C_{32}H_{29}O_6N,H_2O$ requires C, 71·0; H, 5·7%). The substance on prolonged drying at 85° became gummy. It was analysed after drying to constant weight (Found: C, 72·9; H, 5·7. $C_{32}H_{29}O_6N$ requires C, 73·4; H, 5·5%).

3-Cyano-1-ethoxycarbonylquinolizin-4-one (VII).—Ethyl 2-pyridylacetate (10 g.) was added to a well-cooled solution of sodium (1·4 g.) in dry ethanol (40 ml.) with stirring. After ½ hr. diethyl α-cyano-β-ethoxyacrylate [10] (10·5 g.) was added, stirring continued for ½ hr., and the mixture left overnight at 30°. The alcohol was then removed in vacuum below 40° and crushed ice was added. Pale yellow *3-cyano-1-ethoxycarbonylquinolizin-4-one* which separated

[8] Bohlmann and Bohlmann, *Chem. Ber.*, 1953, **86**, 1417.
[9] Woodward and Kornfeld, *Org. Synth.*, 1949, **29**, 44.
[10] Bollement, *Bull. Soc. chim. France*, 1901, **25**, 20.

was washed with dilute hydrochloric acid and then with water, and crystallised from ethanol (yield, 6 g.; m. p. 197°) (Found: C, 64·5; H, 3·8; N, 11·3. $C_{13}H_{10}O_3N_2$ requires C, 64·5; H, 4·1; N, 11·6%).

1 : 3-*Diethoxycarbonyl-4-iminoquinolizine* (IX).—To a stirred suspension of powdered sodium (0·7 g.) in dry ether (80 ml.) was added ethyl 2-pyridylacetate (10 g.), and the mixture stirred for 5 hr. Next day diethyl α-cyano-β-ethoxyacrylate (10·2 g.) in dry ether (60 ml.) was added during 20 min. to the sodium salt with stirring and ice-cooling. After a total of 7 hours' stirring, the solution was poured on crushed ice (200 g.), and the ether layer separated. The aqueous solution was filtered from the yellow solid and extracted with ether, and the solid was also washed with ether and crystallised from ethanol, giving 3-cyano-1-ethoxycarbonylquinolizin-4-one (1·5 g.), m. p. and mixed m. p. 197°. The combined ether extracts were shaken four times with 0·5N-hydrochloric acid, and the acid extracts were filtered and neutralised with a saturated solution of sodium hydrogen carbonate. The precipitate was filtered, repeatedly washed with water, and crystallised from methanol, yielding orange needles of 1 : 3-*diethoxycarbonyl-4-iminoquinolizine* (3·5 g.), m. p. 128° (Found: C, 62·8; 62·7; H, 5·9, 5·8; N, 9·5. $C_{15}H_{16}O_4N_2$ requires C, 62·5; H, 5·6; N, 9·7%), yielding a *hydrochloride* (from ethanol–ether), m. p. 178—179° (decomp.) (Found: C, 55·2; H, 4·9. $C_{15}H_{16}O_4N_2$,HCl requires C, 55·5; H, 5·2%). The iminoquinolizine (0·5 g.) was heated at 180—190° (2 hr.); the residue after successive washings with dilute acid and water and crystallisation from ethanol (Norite) yielded yellow needles (0·2 g.), m. p. 197°, identical with the quinolizone (VII) (Found: C, 64·3; H, 4·3%).

Reduction of the Iminoquinolizine (IX).—The iminoquinolizine (1·8 g.) in ethanol (100 ml.) containing platinum oxide (0·15 g.), shaken with hydrogen at 45 lb./sq. in., absorbed 3 mols. of hydrogen in ½ hr., and no more during another 2 hr. The solution was filtered, concentrated to about 15 ml., and cooled. A light brown *substance* A (0·3 g.) separated and on crystallisation from methanol or benzene had m. p. 143° (Found: C, 61·4, 61·0; H, 7·5, 7·4; N, 9·8, 9·3. $C_{15}H_{22}O_4N_2$ requires C, 61·2; H, 7·5; N, 9·5%). The mother-liquor was evaporated, finally *in vacuo*. The residue was passed in benzene through alumina. The benzene washings were concentrated and light petroleum (b. p. 40—60°) was added, giving almost colourless crystals of *substance* B (0·65 g.), m. p. 153°, mixed m. p. with substance A, 110—130° (Found: C, 61·4, 61·8; H, 7·3, 7·5; N, 9·1, 9·8%). Substances A and B dissolved in 4N-hydrochloric acid and were reprecipitated by sodium hydrogen carbonate.

Ethyl 6-Chloro-5-cyano-2-methylnicotinate.—Ethyl 5-cyano-6-hydroxy-2-methylnicotinate [7] (40 g.), phosphorus pentachloride (50 g.), and chlorobenzene (100 ml.) were refluxed at 135—145° until the evolution of hydrogen chloride ceased (2—3 hr.). The chlorobenzene and phosphorus oxychloride were removed *in vacuo* and the residual oil was poured on crushed ice. The precipitated *chloro-ester* was filtered off, washed with water, dried, filtered in benzene through Norite, and recovered. Crystallisation from light petroleum (b. p. 40—60°) gave pale yellow crystals (32 g.), m. p. 65—66° (Found: C, 53·3; H, 3·9; N, 12·6. $C_{10}H_9O_2N_2Cl$ requires C, 53·5; H, 4·0; N, 12·5%).

Ethyl 5-Cyano-2-methylnicotinate (XI).—The chloro-compound (4 g.) in dry benzene (80 ml.) containing freshly prepared 5% palladium–charcoal (8 g.) was shaken with hydrogen at a pressure of 20 lb./sq. in. The reduction was stopped when 1 mol. of hydrogen had been absorbed and the solution was filtered from the catalyst, which was washed with boiling benzene. The combined benzene solutions were evaporated, leaving a viscous oil (3 g.) which was treated in ether (40 ml.) with dry hydrogen chloride until precipitation was complete. The precipitate was filtered off, washed with ether saturated with hydrogen chloride and once with dry ether, and then ground with a saturated solution of sodium hydrogen carbonate, to give *ethyl 5-cyano-2-methylnicotinate* (0·9—1·0 g.), m. p. 59° (Found: C, 63·1; H, 5·1; N, 14·4. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3; N, 14·7%). The ethereal filtrates were washed with water, dried (Na_2SO_4), and evaporated, to give unchanged ethyl 6-chloro-5-cyano-2-methylnicotinate (2 g.), m. p. 64—65°. Reduction of quantities greater than 4 g. gave lower yields.

Condensation of Cyanomalonaldehyde with Ethyl β-Aminocrotonate.—To a stirred suspension of powdered sodium (0·5 g.) in dry ether (20 ml.) was added a mixture of cyanoacetaldehyde diethyl acetal (3 g.) and ethyl formate (1·8 g.) in ether (10 ml.), and the mixture left overnight. Ice-water was then added, the ether layer separated, and the aqueous solution washed with ether. The solution of the sodium salt of cyanomalonaldehyde [11] thus obtained was added

[11] Uhle and Jacobs, *J. Org. Chem.*, 1945, **10**, 80.

dropwise with stirring to a mixture of ethyl β-aminocrotonate (2·8 g.) and water (30 ml.). The mixture was cooled in ice and acidified with 0·5N-hydrochloric acid until acid to litmus. A precipitate was formed within 10 min. and was filtered off and recrystallised from ethanol, giving a colourless *substance* (0·3 g.), m. p. 161° (Found: C, 57·2; H, 5·7; N, 13·8. $C_{10}H_{12}O_3N_2$ requires C, 57·7; H, 5·8; N, 13·5%).

7-Cyano-3 : 9-diethoxycarbonylquinolizin-4-one (XII).—To a solution from potassium (0·6 g.) in absolute ethanol (80 ml.; >99·5%, distilled over sodium and diethyl succinate) was added with stirring ethyl 5-cyano-2-methylnicotinate (3 g.) in ethanol (20 ml.). After ½ hour's stirring, ethyl ethoxymethylenemalonate (3·5 g.) was added and the solution was refluxed with stirring for 4 hr. and left overnight. The alcohol was then removed *in vacuo* and the residue decomposed with ice-water. The mixture was extracted with ether until the aqueous layer was clear. The aqueous solution was then cooled in ice and treated with 4N-hydrochloric acid till acidic to Congo-red. The reddish-brown precipitate was filtered off, washed with saturated sodium hydrogen carbonate solution and then with water, and dried. Recrystallisation from ethanol gave red needles of *quinolizinone* (1·8 g.), m. p. 130—132° (Found: C, 60·8; H, 4·9; N, 8·7. $C_{16}H_{14}O_5N_2$ requires C, 61·1; H, 4·5; N, 8·9%). This dissolved in 10N-hydrochloric acid and was reprecipitated on dilution. It also dissolved slowly in 8% sodium hydroxide solution from which it could be recovered by acidification but not by means of carbon dioxide.

Hydrolysis of the Quinolizinone (XII).—(*a*) The quinolizinone (0·3 g.) was boiled with 10N-hydrochloric acid for 3 min. and then cooled. A yellow solid separated and was washed with concentrated hydrochloric acid and then with ice-water. It was dried and crystallised from acetone, yielding feathery crystals (0·15 g.), m. p. 276° (decomp.) (Found: C, 55·2; H, 3·6; $C_{14}H_{12}O_6N_2$ requires C, 55·3; H, 4·0%) of, probably, 3-carboxy-9-ethoxycarbonyl-4-oxo-quinolizine-7-carboxyamide.

(*b*) The quinolizinone (0·3 g.) was boiled with 6N-hydrochloric acid (10 ml.) for 1 hr., the solution was decanted from the small amount of gum, water (8 ml.) was added, and the whole left overnight. The reddish-brown precipitate was filtered, dried in vacuum and crystallised from acetone, yielding reddish-yellow crystals (0·15 g.), m. p. 325° (decomp.) (Found: C, 56·9; H, 2·8. $C_{11}H_7O_5N$ requires C, 56·7; H, 3·0%), regarded as *4-oxoquinolizine-7 : 9-dicarboxylic acid.*

7-Aminomethyl-9-ethoxycarbonylquinolizin-4-one (XIV).—The quinolizinone (XII) (3 g.) in ethanol (100 ml.) containing platinum oxide (0·5 g.), shaken with hydrogen at 20 lb./sq in., absorbed 2 mols. of hydrogen in 15 min. The catalyst alcoholic solution was filtered and concentrated *in vacuo*. The residual red gum was boiled with 6N-hydrochloric acid (40 ml.) for 1 hr. The solution was decanted from a small amount of gum and evaporated to dryness *in vacuo*. The residue was taken up in absolute alcohol (75 ml.) and esterified by the Fischer–Speier method. After the removal of alcohol *in vacuo*, the residue was basified with saturated sodium hydrogen carbonate solution and extracted with chloroform. The ester (1 g.) was obtained as a red gum but gave a crystalline *benzoate*, m. p. 100—102° (from light petroleum, b. p. 40—60°) (Found: C, 69·1; H, 5·4. $C_{20}H_{18}O_4N_2$ requires C, 68·9; H, 5·1%).

7-Aminomethyl-9-hydroxymethylquinolizin-4-one (XV).—To a solution of lithium aluminium hydride (1·5 g.) in ether (50 ml.) was added the ester (XIV) (1 g.) in ether (250 ml.) with stirring. The mixture was stirred for 1 more hr. and left overnight. After decomposition in the usual way, the ether layer was decanted, dried (Na_2SO_4), and evaporated to an oil (0·2 g.). This *base* was analysed after 2 sublimations at $5·8 \times 10^{-4}$ mm. (bath-temp. 120—130°) (Found: C, 64·3; H, 6·0. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9%).

(±)-Cytisine.—The above amino-alcohol (XV) (0·15 g.) in alcohol (25 ml.) containing concentrated hydrochloric acid (1·5 ml.) and platinum oxide (100 mg.) was shaken with hydrogen at atmospheric pressure. After 2 mols. of hydrogen had been absorbed, hydrogen uptake slackened considerably. The solution was filtered from the catalyst and the alcohol was removed *in vacuo*. The residue was taken up in benzene (20 ml.), phosphorus pentabromide (0·15 g.) added in 3 portions during 20 min., and the mixture heated for 4 hr. at 100°. The solvent was then distilled off *in vacuo*, and the residue ground with saturated sodium hydrogen carbonate solution and extracted with chloroform; the extract was dried (Na_2SO_4) and evaporated in a Carius tube, leaving a brown gum. Anhydrous potassium carbonate (0·2 g.) was added to it and mixed intimately. The tube was sealed and heated for 18 hr. at 100°. The contents were treated with water (10 ml.) and extracted with chloroform. After removal of the solvent, the residual gum was sublimed *in vacuo*, and the sublimate crystallised from

acetone–ether, to give (±)-cytisine (6 mg.), m. p. 147° (Found: C, 69·1; H, 7·4. Calc. for $C_{11}H_{14}ON_2$: C, 69·4; H, 7·4%) (Bohlmann *et al.*[4] reported m. p. 147—147·5°).

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