Nitrogen Bridgehead Compounds. Part 41.[1] Ring Transformation of Nitrogen Bridgehead Ring Systems†

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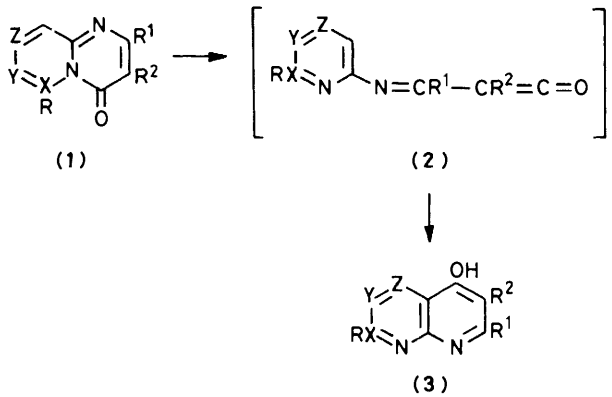
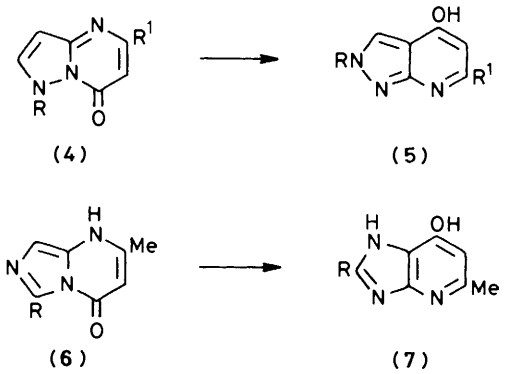
In an investigation of the role of the nitrogen atoms in the ring-transformation reactions of nitrogen bridgehead condensed pyrimidinones (**1**), either the bridgehead or the non-bridgehead nitrogen atom was replaced by a carbon atom. While replacement of the non-bridgehead nitrogen atom did not influence the ring-transformation reaction, replacement of the bridgehead nitrogen atom prevented the rearrangement. Thus, ethyl 1-cyano-6-methyl-4-oxo-4*H*-quinolizine-3-carboxylate (**10**) was transformed into ethyl 8-cyano-5-hydroxy-2-methylquinoline-6-carboxylate (**11**) at 250 °C. *X*-Ray crystallographic analysis confirms the structure of (**11**): monoclinic system with $a = 11.385(1)$, $b = 11.102(1)$, $c = 10.191(2)$ Å, space group $P2_1/n$, $Z = 4$, $D_c = 1.36$ g cm^{-3}, $R = 0.043$. The quinoline (**11**) gave 5-ethoxy-2-methylquinoline-8-nitrile (**12**) at 260 °C.

We recently reported[2,3] that the bicyclic compounds (**1**) or polycyclic nitrogen bridgehead compounds containing the structural unit (**1**) (R ≠ H) can be transformed thermally into the condensed pyridine derivatives (**3**). The intermediate of the rearrangement is presumably[4] the iminoketene (**2**) (Scheme 1). Ring transformation is facilitated by steric interaction between the nearby coplanar C(4)=O and 6–R groups, leading to a lengthening of the C(4)–N(5) bond, which is then ruptured by the input of sufficient energy. {For example, in ethyl 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate the length of the C(4)–N(5) bond is 1.472 Å.[5]} The driving force of the process is the enhanced aromatic character of the thermodynamically more stable condensed pyridine derivative (**3**) as compared with the corresponding nitrogen bridgehead compound (**1**).



Scheme 1.

We have reported the successful application[4,6-8] of this ring transformation to several bi- and poly-cyclic nitrogen bridgehead compounds containing the structural unit of (**1**). A survey of the literature revealed that the reaction is feasible not only with 6/6- but also with 5/6-membered ring systems {*e.g.* the conversion of the pyrazolo[1,5-*a*]pyrimidin-7-one (**4**) into the pyrazolo[3,4-*b*]pyridinol (**5**),[9] and of the imidazo[1,5-*a*]pyrimidin-4-one (**6**) into the imidazo[4,5-*b*]pyridinol (**7**)[10,11] (Scheme 2)}.



Scheme 2.

Exploring the scope of this ring transformation, we have studied the role of the nitrogen atoms in the amidine moiety. For this purpose either the N(1) atom of the pyrimidinone (quinolizinone) ring or the bridgehead nitrogen was replaced by a carbon atom. In this paper we summarize the results of this work.

Replacement of N(1) *by Carbon; Study of the Ring Transformation of* 1-*Cyano*-3-*ethoxycarbonyl*-6-*methyl*-4H-*quinolizin*-4-*one* (**10**).—Heating of the title compound (**10**) [prepared from 2-cyanomethyl-6-methylpyridine (**8**) and diethyl ethoxymethylenemalonate (**9**) at 190 °C] at 250 °C afforded, in 75% yield, a product with m.p. 162—164 °C, to which structure (**11**) was assigned on the basis of the following arguments. As compared with (**10**), the highest wavelength band in the u.v. spectrum suffers a hypsochromic shift (by 85 nm) and a substantial hypochromic change, indicating the presence of a different chromophore. In alkaline medium the same band of (**11**) undergoes a slight bathochromic and hyperchromic shift, characteristic of phenols. In the i.r. spectrum of the quinolizinone (**10**) the carbonyl band with the highest wavenumber is at 1 730 cm^{-1}, while that in the product (**11**) is at 1 690 cm^{-1}. A comparison of the ^{1}H n.m.r. spectra shows little change as concerns the single proton attached to ring B (δ8.30 and 8.32 respectively) whereas for ring A both proton count and

† This paper is also regarded as Part 9 of the series 'Ring Transformation.' Part 8 is ref. 8.

multiplicity are different [two doublets and a triplet for (**10**) *vs.* two doublets for (**11**)]. The spectrum of compound (**11**) contains a broad signal at δ 12.29 which slowly disappears on deuterium exchange, indicating a hydrogen-bonded proton. All these changes suggest that the quinolizine (**10**) was transformed into a quinolinol (**11**). Structure (**11**) was confirmed by *X*-ray analysis. The *molecular* diagram, bond lengths, and selected bond angles are given in the Figure. The proton of the hydroxy group is involved in intramolecular bonding with the ester oxygen.

Replacement of the Bridgehead Nitrogen by Carbon; Study of the Ring Transformation of the Quinolin-4-one (**14**).—During their work on the cyclization of *meta*-substituted anilinomethylenemalonates, Aqui and his co-workers obtained isomeric 5- and 7-substituted 4-oxoquinoline-3-carboxylates (**14**) and (**15**).[14] For instance, diethyl *m*-toluidinomethylenemalonate (**13**) in a mixture of acetic anhydride and sulphuric acid at 100 °C yielded a 3:2 mixture of 5- and 7-methylquinoline-3-carboxylate (**14**) and (**15**) (Scheme 4), whereas in Dowtherm A at 250 °C the ratio was 1:9. The latter

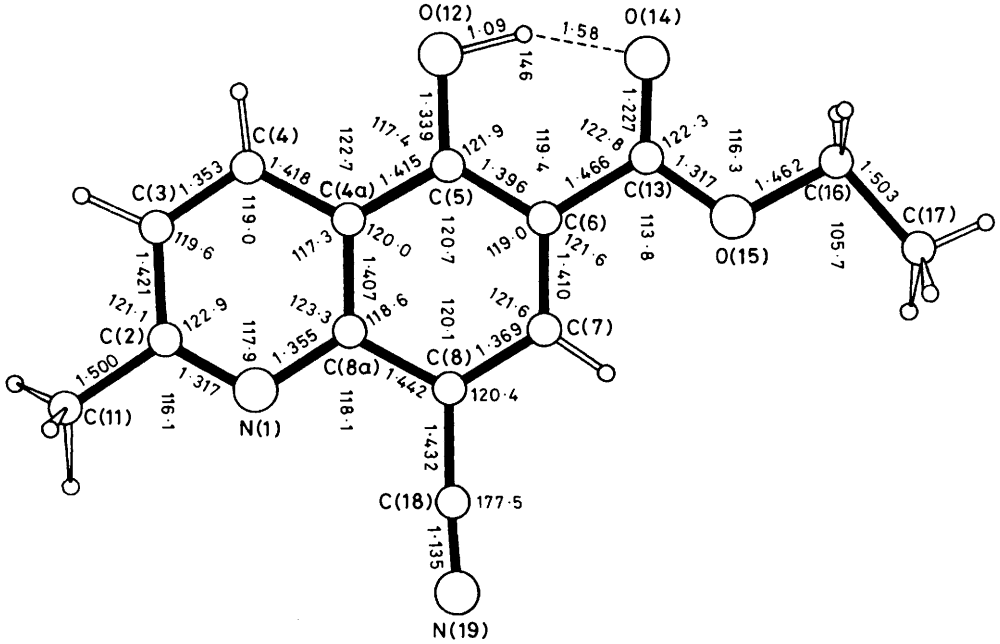
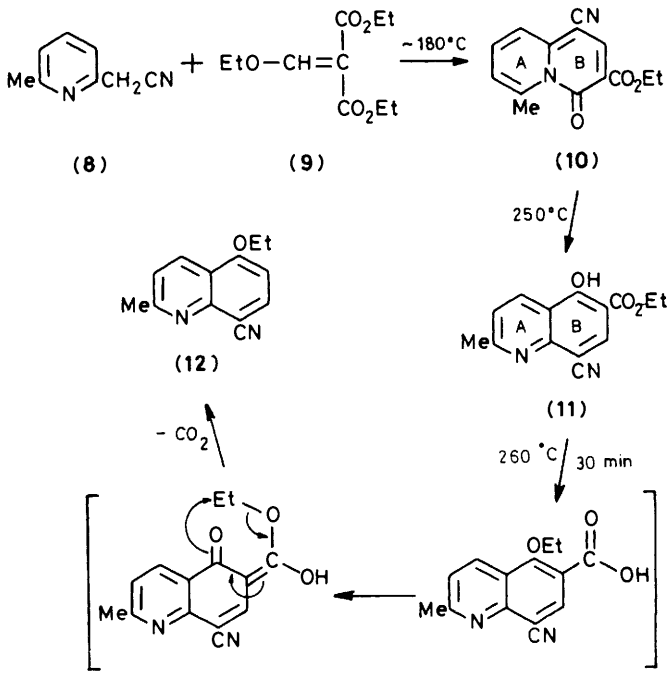


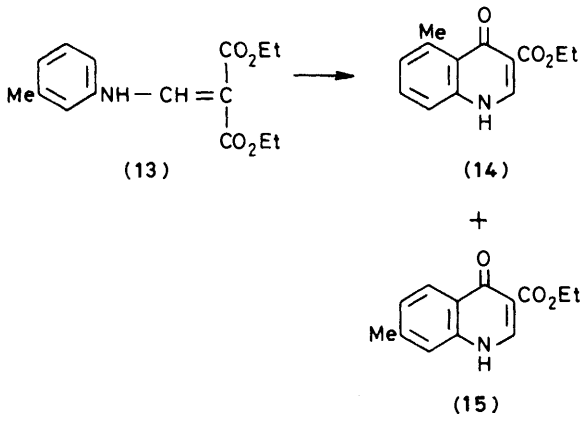
Figure. Molecular diagram for compound (**11**) with crystallographic atomic numbering, bond lengths (Å), and selected angles (°) for the non-hydrogen atoms. The all non-hydrogen atoms are approximately in the plane of the drawing. E.s.d.s are in the range ≤ 0.003 Å and ≤ 0.5° for bond lengths and bond angles, respectively

T.l.c. of the reaction mixture revealed a by-product, which could be isolated in 85% yield when the primary product (**11**) was further heated at somewhat higher temperature (260 °C). As compared with the quinolinol (**11**), a slight additional hypsochromic shift can be observed in the u.v. spectrum of the new product (**12**), which remains unchanged on the addition of alkali. The i.r. spectrum lacks a carbonyl stretching band. In the n.m.r. spectrum the signal at δ 7.88 for the solitary B-ring proton was split into a doublet and a new doublet appeared at δ 6.80. The high-field signal characteristic of an exchangeable proton was absent from the spectrum of (**12**). The molecular formula for the new product (**12**), as determined by m.s., was $C_{13}H_{12}N_2O$, *i.e.* one CO_2 group less than that of the parent compound (**11**). Compound (**12**) is thus derivable from (**11**) by ethyl migration and decarboxylation. This process seems to be unique because salicylic-type esters are generally not inclined to undergo decarboxylation with transalkylation on being heated. The rearrangement of (**11**) into (**12**) probably proceeds through an ethyl migration by a symmetry-allowed [1,5]sigmatropic shift[12] followed by decarboxylation (see Scheme 3). The ether (**12**) can also be prepared directly from compound (**10**) in 70% yield.

Ring transformation of 6-amino-4-quinolizone has been reported by Van Allen and Reynolds,[13] but in their case instead of the C(4)–N(5) bond the N(5)–C(6) bond was cleaved, giving rise to a quinolin-2-one.



Scheme 3.



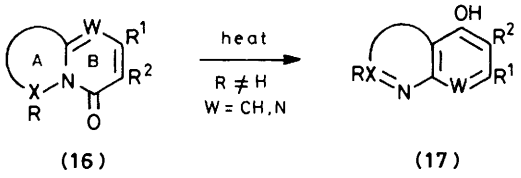
Scheme 4.

result might be explained by isomerization of the 5-methyl derivative (**14**) to the 7-methyl isomer (**15**) in Dowtherm. If this assumption were true, then at higher temperature or after prolonged treatment the 7-methyl derivative (**15**) should finally be obtained exclusively, regardless of whether one starts from the malonate (**13**) or from the 3:2 mixture of isomers obtained by the acetic anhydride–sulphuric acid method. However, when the latter mixture was heated for 5 h at 250 °C in Dowtherm A, the ratio of the isomers (**14**) and (**15**), as determined by the intensity ratio of the ^{1}H n.m.r. methyl signals, remained practically unchanged.

Discussion

A study of the scope of the ring-transformation reactions of bi- and poly-cyclic nitrogen bridgehead compounds of type (**1**) has revealed that, besides substitution of the carbon atom in the *peri* position to the carbonyl group, an essential condition is that there should be a nitrogen atom at the bridgehead; the homonuclear C–C(4)O bond, being at least 10 kcal mol^{-1} stronger,[15] cannot be cleaved thermally and thus ring transformation cannot take place. Replacement of the other nitrogen, *i.e.* N(1), by carbon has no essential influence upon the ring transformation.

Our findings show that ring transformation (Scheme 5) is characteristic for nitrogen bridgehead compounds containing the structural unit (**16**), in which R ≠ H; W is a nitrogen or =CH– group, and ring A can be 5- or 6-membered.



Scheme 5.

Experimental

M.p.s are uncorrected. Yields were not optimized. I.r. spectra were recorded in KBr pellets with a Pye Unicam SP 1200 spectrophotometer; u.v. spectra in ethanolic solutions with a Pye Unicam SP 8200 spectrophotometer; and ^{1}H and ^{13}C n.m.r. spectra in $CDCl_3$ solutions ($SiMe_4$ as internal standard) with a JEOL JNM-PS-100 or a Bruker WP-80 DS spectrometer.

Ethyl 1-*Cyano*-6-*methyl*-4-*oxo*-4H-*quinolizine*-3-*carboxylate* (**10**).—2-Cyanomethyl-6-methylpyridine (**8**)[16] (3.3 g, 25 mmol) and diethyl ethoxymethylenemalonate (**9**) (5.4 g, 25 mmol) were heated at 190 °C for 2 h. The reaction mixture was cooled to 80 °C and diluted with acetone (10 ml). The solution was cooled to 0 °C, and the crystals were filtered off and recrystallized from acetone to give the *quinolizine* (**10**) (4.5 g, 70.3%), m.p. 170—172 °C; $\nu_{max.}$ 2 220, 1 680, 1 630, 1 590, and 1 500 cm^{-1}; $\lambda_{max.}$ (log ε) 430 (4.19), 350 (3.90), and 270 nm (4.14); δ 1.45 (3 H, t, CH_2*Me*), 3.16 (3 H, s, 6-Me), 4.43 (2 H, q, OCH_2), 6.93 (1 H, dd, $J_{7,8}$ 6.5, $J_{7,9}$ 1.5 Hz, 7-H), 7.56 (1 H, dd, $J_{7,8}$ 6.5, $J_{8,9}$ 8 Hz, 8-H), 7.73 (1 H, dd, $J_{8,9}$ 8, $J_{7,9}$ 1.5 Hz, 9-H), and 8.30 (1 H, s, 2-H) (Found: C, 65.6; H, 5.05; N, 10.95. $C_{14}H_{12}N_2O_3$ requires C, 65.62; H, 4.86; N, 10.93%).

Ethyl 8-*Cyano*-5-*hydroxy*-2-*methylquinoline*-6-*carboxylate* (**11**).—Ethyl 1-cyano-6-methyl-4-oxo-4*H*-quinolizine-3-carboxylate (**10**) (1.28 g, 5 mmol) was heated at 250 °C for 0.5 h on a metal bath. The reaction mixture was cooled to 50 °C and dissolved in ethanol (100 ml), and the solution was decolourized with charcoal and evaporated under reduced pressure. The residue was crystallized from acetone to give the *quinolinecarboxylate* (**11**) (0.95 g, 74.2%), m.p. 162—164 °C; $\nu_{max.}$ 3 300—2 700, 2 230, 1 700, 1 640, and 1 600 cm^{-1}; $\lambda_{max.}$ (log ε) 345 (3.65), 310 (3.78), 265 (4.57), and 230 nm (4.36); δ 1.53 (3 H, t, CH_2*Me*), 2.90 (3 H, s, 2-Me), 4.53 (2 H, q, OCH_2), 7.36 (1 H, d, $J_{3,4}$ 8 Hz, 3-H), 8.32 (1 H, s, 7-H), 8.46 (1 H, d, $J_{3,4}$ 8 Hz, 4-H), and 12.29 (1 H, s, OH) (Found: C, 65.7; H, 4.8; N, 11.0. $C_{14}H_{12}N_2O_3$ requires C, 65.62; H, 4.86; N, 10.93%).

8-*Cyano*-5-*ethoxy*-2-*methylquinoline* (**12**).—(a) *From quinolizinecarboxylate* (**10**). Ethyl 1-cyano-6-methyl-4-oxo-4*H*-quinolizine-3-carboxylate (**10**) (1.28 g, 5 mmol) was heated at 260 °C for 0.5 h on a metal bath. The reaction mixture was treated as described above for compound (**11**). The residue was crystallized from acetone to give the *quinoline* (**12**) (0.75 g, 70.7%), m.p. 154—155 °C; $\nu_{max.}$ 2 220, 1 620, 1 600, and 1 580 cm^{-1}; $\lambda_{max.}$ (log ε) 320 (3.94), 250 (4.59), and 220 nm (4.38); δ_H 1.65 (3 H, t, CH_2*Me*), 2.90 (3 H, s, 2-Me), 4.34 (2 H, q, OCH_2), 6.80 (1 H, d, $J_{6,7}$ 8 Hz, 6-H), 7.31 (1 H, d, $J_{3,4}$ 8 Hz, 3-H), 7.88 (1 H, d, $J_{6,7}$ 8 Hz, 7-H), and 8.36 (1 H, d, $J_{3,4}$ 8 Hz, 4-H); δ_C 14.5 (q, CH_2*Me*), 25.5 (q, 2-Me), 65.0 (t, OCH_2), 104.0 (s, C-8), 104.3 (d, C-6), 118.4 (s, CN), 119.0 (s, C-4a), 122.6 (d, C-3), 131.4 (d, C-7), 136.7 (d, C-4), 148.7 (s, C-8a), 158.8 (s, C-2), and 162.1 p.p.m. (s, C-5) (Found: C, 73.95; H, 5.3; N, 13.3. $C_{13}H_{11}N_2O$ requires C, 73.92; H, 5.25; N, 13.26%).

(b) *From quinolinecarboxylate* (**11**). Ethyl 8-cyano-5-hydroxy-2-methylquinoline-6-carboxylate (**11**) (1.28 g, 5 mmol) was heated at 260 °C for 20 min on a metal bath. The reaction mixture was treated as described for the preparation of compound (**11**). The residue was crystallized from acetone to give the quinoline (**12**) (0.85 g, 80%), m.p. 153—155 °C.

X-*Ray Crystal Structure of Compound* (**11**).—Crystal data for (**11**): $C_{14}H_{12}N_2O_3$, M = 256.3. Monoclinic, a = 11.385(1), b = 11.102(1), c = 10.191(2) Å, β = 103.63(2)°, V = 1 252 Å^3, D_c = 1.36 g cm^{-3}, F(000) = 536, Mo-K_α radiation, λ = 0.7107 Å, μ(Mo-K_α) = 0.91, space group $P2_1/n$, Z = 4. Data were collected on an Enraf-Nonius CAD-4 diffractometer with monochromated Mo-K_α radiation up to θ = 30°. 1 907 Out of 4 165 reflections were considered observed [$I > 3\sigma(I)$]. All calculations were carried out on a PDP 11/34 minicomputer by the use of the Enraf-Nonius SDP program package (Version 18) with local modifications. The structure was solved by direct methods applying 203 E values, 1 811 phase relationships, and 5 starting reflections. The set with the best combined figure of merit revealed 16 atoms (R = 0.38). Full matrix refinement for the non-hydrogen atoms resulted in R = 0.08. The difference

Table 1. Final fractional co-ordinates (× 10^4) and B_{eq} values[a] for atoms of compound (**11**) (e.s.d.s in parentheses)

	x	*y*	*z*	B_{eq}/B
N(1)	3 650(1)	1 962(1)	985(1)	3.58(4)
C(2)	4 296(1)	2 482(1)	230(1)	4.01(6)
C(3)	5 479(1)	2 095(1)	201(1)	4.11(6)
C(4)	5 990(1)	1 166(1)	994(1)	3.77(5)
C(4a)	5 319(1)	585(1)	1 821(1)	3.14(5)
C(5)	5 777(1)	−404(1)	2 664(1)	3.20(5)
C(6)	5 077(1)	−957(1)	3 447(1)	3.13(4)
C(7)	3 897(1)	−530(1)	3 371(1)	3.09(5)
C(8)	3 433(1)	429(1)	2 571(1)	3.07(5)
C(8a)	4 147(1)	1 018(1)	1 764(1)	3.10(5)
C(11)	3 715(2)	3 529(2)	−607(2)	5.61(8)
O(12)	6 894(1)	−784(1)	2 670(1)	4.51(4)
C(13)	5 577(1)	−1 980(1)	4 309(1)	3.39(5)
O(14)	6 564(1)	−2 428(1)	4 315(1)	4.69(4)
O(15)	4 878(1)	−2 361(1)	5 084(1)	3.42(3)
C(16)	5 278(1)	−3 444(1)	5 879(1)	3.75(5)
C(17)	4 232(1)	−3 815(1)	6 455(2)	4.44(6)
C(18)	2 246(1)	869(1)	2 547(1)	3.27(5)
N(19)	1 301(1)	1 186(1)	2 561(1)	4.59(5)
H(3)	589(1)	251(1)	−44(1)	4.9(4)
H(4)	675(1)	85(1)	89(1)	4.5(4)
H(7)	341(1)	−88(1)	385(1)	3.7(4)
H(111)	275(1)	355(1)	−96(2)	6.5(5)
H(112)	384(1)	420(2)	−3(2)	6.7(5)
H(113)	394(1)	359(1)	−129(2)	6.5(5)
H(12)	709(2)	−142(2)	351(2)	8.1(6)
H(161)	608(1)	−328(1)	654(1)	4.5(4)
H(162)	550(1)	−409(1)	527(1)	4.5(4)
H(171)	338(1)	−390(1)	577(2)	5.3(4)
H(172)	443(1)	−446(1)	697(1)	4.9(4)
H(173)	408(1)	−323(2)	713(2)	5.8(4)

[a] B_{eq} Values are defined as: $B_{eq} = 4\,[b_1/a^{*2} + b_{22}/b^{*2} + b_{33}/c^{*2}]^{1/3}$

map gave the positions of all hydrogen atoms and they were refined isotropically after that. The refinement concluded with $R = 0.043$, $R_w = 0.061$ for 1 907 reflections. The weighting scheme was $w = 1/[\sigma^2(F_o) + 0.01F_o^2]$. Atomic co-ordinates are given in the Table, the anisotropic thermal parameters and the structure factors are listed in Supplementary Publication [No. SUP 23935 (13 pp.)].*

* For details of the Supplementary Publications Scheme see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1984, Issue 1.

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