with a solution of sodium naphthalene in THF and then baked under vacuum at 220 °C for 48 h.[12] About 0.2 g of alkyl fluoride was distilled into each tube.

Approximately 0.5-g samples of commercial sublimed naphthalene were vacuum sublimed into breakseal tubes pretreated as above.

Tetrahydrofuran was stored on the vacuum line over benzophenone ketyl and distilled directly into pretreated reaction vessels. Perdeuterated THF (Merck) and the two THF-d_4 compounds[13] were stored on the vacuum line over Na/K alloy before distillation into the reaction vessels. Isotopic purity was found by NMR spectroscopy to be 95% for THF-α-d_4 and at least 99% for all other deuterated compounds.

All-glass reaction vessels, fabricated without stopcocks, were pretreated as above and then filled with solvent and sealed. A breakseal was crushed and naphthalene was introduced by dissolving it in THF. The solution was allowed to react with a sodium metal mirror and then stirred as the alkyl fluoride was allowed to slowly distill through another crushed breakseal. Stirring was continued for about 7 h at room temperature. Approximately half the fluoride reacts in this time. Reaction was quenched by opening the vessel to dry air. The product solutions were analyzed by GC/MS,[14] using 10% Na_2SO_4 on Al_2O_3 as the stationary phase.[15] Mass spectral data were converted to percentage deuterium content by using the computer program HEAVY.[16]

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Registry No. 1, 3481-12-7; 5-hexenyl fluoride, 373-15-9; methylcyclopentane, 96-37-7; 1-hexene, 592-41-6; *trans*-2-hexene, 4050-45-7; *cis*-2-hexene, 7688-213.

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New Synthesis of α-Alkylamino Ketones[1]

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α-Alkylamino ketones are important intermediates for the synthesis of adrenergic compounds (see ref 2 and 3, for example) and, in addition, have considerable potential utility in the Knorr pyrrole synthesis.[4] These substances are commonly prepared by the hydrolysis of α-(*N*-alkyl-*N*-*p*-toluenesulfonylamino) ketones,[5] by the reductive amination of α-diketones,[6] or by the alkylation of primary amines with α-halo ketones.[2,3,4a] The utilization of the last-mentioned synthesis is the most widespread, but other products are often formed[7] as a consequence, at least in part, of the strong basicity of the aliphatic amines. The yields of the desired products can be particularly poor when the halo group being displaced is on a primary carbon atom.[2,3,4a]

Imidates are much less basic[8] than the primary amines from which they are derived, but the nucleophilicity thereof is still appreciable, and N-alkylation with reactive alkyl halides occurs relatively readily.[8a,9] These observations, when considered with the well-known ease of hydrolysis of formamides should, in principle, constitute a synthesis of α-alkylamino ketones. This publication shows that this is indeed the case for methyl *N*-alkylformimidates (**2**, eq 1). Thus, diverse α-bromo ketones

$$\underset{\mathbf{1}}{R^1COCHBrR^2} + \underset{\mathbf{2}}{R^3N{=}CHOCH_3} \rightarrow [R^1COCHR^2NR^3{=}CHOCH_3]^+Br^- \rightarrow \underset{\mathbf{3}}{} \underset{\mathbf{4}}{R^1COCHR^2NR^3CHO} + CH_3Br + HBr \rightarrow \underset{\mathbf{5}}{R^1COCHR^2NHR^3{\cdot}HBr} \quad (1)$$

reacted with excess methyl *N*-methylformimidate[10] (**2**, $R^3 = CH_3$) in dimethoxyethane–toluene solution at 70–80 °C to give fair to good yields (Table I) of the expected *N*-methylformamides (**4**, $R^3 = CH_3$). Methyl *N*-(2-phenylethyl)formimidate (**2**, $R^3 = C_6H_5CH_2CH_2$) reacted, under similar conditions, with a variety of α-bromo ketones to give uniformly excellent yields (Table I) of the anticipated formamides. In the case of 3,4,-bis(benzyloxy)-α-bromopropiophenone (entry 10), however, a large excess of the imidate as well as a protracted reaction period was required to achieve a good yield of the formamide. Both of these parameters could be greatly decreased, without loss in product yield, when acetonitrile was used as the reaction medium (entry 11). The use of this solvent also made it possible to reduce the imidate–bromo ketone ratio by 50% for phenacyl bromide with only a modest reduction in the yield of the formamide (entry 8). This latter result is of particular significance for those instances where the use of a rare or expensive imidate is contemplated. In the above alkylation reactions, it was not determined whether the methyl bromide, formed as a result of the decomposition of the salt **3**, reacted with the excess imidate (to produce the corresponding *N*,*N*-dialkylformamide) or merely escaped from the reaction mixture.

The above formamides showed the expected physical properties (Table II), including, in several instances, the phenomenon of restricted rotation about the NCO bond. For example, the NMR spectrum of *N*-methyl-*N*-phenacylformamide (**4**; $R^1 = C_6H_5$, $R^2 = H$, $R^3 = CH_3$) showed two sets of absorptions (ca. 1:3 ratio) for the methyl, methylene, and formyl protons, each of which coalesced into a singlet at about 140 °C ($\Delta G^{\ddagger} \approx 23$ kcal/mol). This barrier to rotation is somewhat higher than has been re-

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Table I. Reaction of α-Bromo Ketones with Methyl N-Alkylformimidates

$R^1COCHBrR^2 + R^3N{=}CHOCH_3 \longrightarrow R^1COCHR^2NR^3CHO + CH_3Br$

entry	R^1	R^2	R^3	molar ratio of 2/1	solvent	time, h	purification technique	yield, %
1	CH_3	H	CH_3	2.5	DME–toluene	1.5	TLC [EtOAc–hexane (9:1)]	39
2	CH_3	CH_3	CH_3	2.5	DME–toluene	7	TLC [EtOAc–hexane (3:1)]	36
3	C_6H_5	H	CH_3	2.5	DME–toluene	0.5	TLC [CH_2Cl_2–MeOH (95:5)]	67
4	C_6H_5	CH_3	CH_3	2.5	DME–toluene	7	TLC [EtOAc–hexane (3:1)]	83
5	$C_6H_5CH_2$	H	CH_3	3.5[a]	DME–toluene	1.75	TLC [EtOAc–hexane (4:1)]	44
6	3,4-$(BzO)_2C_6H_3$[b]	CH_3	CH_3	8[c]	DME–toluene	25	TLC [EtOAc–hexane (3:1)]	65
7	C_6H_5	H	$C_6H_5(CH_2)_2$	2.5	toluene	5	TLC [EtOAc–hexane (7:3)]	86
8	C_6H_5	H	$C_6H_5(CH_2)_2$	1.2	acetonitrile	5	TLC [EtOAc–hexane (7:3)]	60
9	C_6H_5	CH_3	$C_6H_5(CH_2)_2$	6[d]	toluene	24	TLC [CH_2Cl_2–acetone–hexane (18:2:1)]	87
10	3,4-$(BzO)_2C_6H_3$[b]	CH_3	$C_6H_5(CH_2)_2$	5[e]	toluene	64	TLC [CH_2Cl_2–acetone–hexane (19:1:0.5)]	75
11	3,4-$(BzO)_2C_6H_3$[b]	CH_3	$C_6H_5(CH_2)_2$	2.5	acetonitrile	19	col chrom [SiO_2; CH_2Cl_2–ether (99:1)]	91

[a] 0.5 molar equiv added initially and the remainder added in six equal portions every 15 min. [b] 3,4-Bis(benzyloxy)phenyl. [c] 2.5 molar equiv added initially and the remainder added in five equal portions every 15 min. [d] 2.5 molar equiv added at 0 and 5 h and the remainder added at 15 h. [e] 2.5 molar equiv added initially and the remainder added in two equal portions at 48 and 56 h.

ported[11] previously for simple formamides. This datum, as well as the observation of two spots on TLC for this compound, indicates that separation of the two isomers should be possible.

As expected, cleavage of the formamides was effected without difficulty. For example, N-methyl-N-phenacylformamide was converted into the known[4a,5] hydrobromide salt of N-methylphenacylamine (5; $R^1 = C_6H_5$, $R^2 = H$, $R^3 = CH_3$; 94% yield) by being heated with hydrogen bromide (10 equiv) in methanol solution (see Experimental Section for other examples).

Finally, we have recently[12] utilized the methodology described herein to prepare 1-(methylamino-4-phenylbutan-2-one hydrochloride (5; $R^1 = C_6H_5CH_2CH_2$, $R^2 = H$, $R^3 = CH_3$; HCl instead of HBr) which was required for the synthesis of a tricyclic N-methylpyrroleacetic acid derivative.

Experimental Section

The NMR spectra were recorded with a Varian T-60 spectrometer. The variable-temperature NMR experiment was carried out by using a Varian XL-200 spectrometer. All chemical shifts are expressed as parts per million (δ) from internal tetramethylsilane. The mass spectrum of methyl N-(phenylethyl)formimidate was measured with a Varian MAT 311A spectrometer at 70 eV and an ion-source temperature of 140 °C. A meaningful spectrum could only be obtained if the sample was first absorbed on charcoal and then introduced via a direct-insertion probe in a gold crucible.

Methyl N-Methylformimidate (2, $R^3 = CH_3$). This compound was prepared in ca. 20% yield by the method of Bredereck et al.[10] except that dimethoxyethane was used as the solvent (instead of benzene). The dimethoxyethane solution of the imidate was redistilled to give a solution which contained 20–40 g of the desired material in 100 mL of the solvent as determined by gas–liquid chromatography [10% OV-17, 80 °C, N_2 (1 mL/min), thermal conductivity]. This solution was used as such in the alkylation experiments.

Methyl N-(2-Phenylethyl)formimidate (2, $R^3 = C_6H_5CH_2CH_2$). Dimethyl sulfate (50.4 g, 0.4 mol) was added, at room temperature with stirring, to N-phenylethylformamide (29.8 g, 0.2 mol). The mixture was stirred for 9 h and then left to stand for 48 h. The resultant was stirred vigorously with anhydrous ether (3 × 50 mL), the ether layer being separated by decantation. The remaining ether was then removed in vacuo to give an oil (52.3 g) which slowly crystallized on being allowed to stand. This material was used without purification for the synthesis of the imidate. Thus, triethylamine (38 g, 0.37 mol) was added, during a 15-min period, to a stirred suspension of the above methosulfate (77 g, 0.28 mol) in dry dimethoxyethane (150 mL) maintained at 0 °C in an inert atmosphere. The cooling bath was removed, and after 10 min the mixture was poured into cold water (300 mL) and saturated sodium bicarbonate solution (50 mL). The product was extracted into dichloromethane, and the extract was dried over sodium sulfate and then evaporated in vacuo ($T < 30$ °C). The residue was distilled in vacuo, the fraction with a boiling point of 60–62 °C (4 mm) being collected: 28 g, (61%); IR ($CHCl_3$) 1668 cm^{-1}; NMR ($CDCl_3$)δ 2.82 (t, 2 H, $J = 7.1$ Hz), 3.50 (t, 2 H, $J = 7.1$ Hz), 3.68 (s, 3 H), 7.20 (s, 5 H), 7.38 (s, 1 H); mass spectrum, m/e (relative intensity) 163 (10), 132 (20), 104 (12), 91 (12), 72 (100), 42 (22); calcd for $C_{10}H_{13}NO$ (molecular ion) m/e 163.0997, found m/e 163.0978.

The compound was further characterized by conversion into the picrate in benzene. After crystallization from benzene this material had a melting point of 108–109 °C.

Anal. Calcd for $C_{16}H_{16}N_4O_8$: N, 14.28. Found: N, 14.34.

Reaction of α-Bromo Ketones with Methyl N-Methylformimidate. A round-bottomed flask, containing a magnetic stirring bar and fitted with a dry ice condensor, was charged with the α-bromo ketone (10 mmol) and anhydrous toluene (3–10 mL) and then placed in an oil bath maintained at 70–80 °C. After a few minutes, the requisite amount of the dimethoxyethane solution of the imidate was added, either all at once or in portions, as described in Table I. After being stirred for the prescribed time (Table I), the reaction was poured into ice–water and extracted with dichloromethane. The extract was washed with water, dried over over sodium sulfate, and evaporated in vacuo. The residue was then subjected to purification by TLC on silica gel with the solvent system shown in Table I. The physical constants of the formamides obtained in this way are given in Table II.

Reaction of α-Bromo Ketones with Methyl N-(2-Phenylethyl)formimidate. A. In Toluene. A solution of the bromo ketone (10 mmol) in anhydrous toluene (20–40 mL) was placed in an oil bath at 90–100 °C. After a few minutes, the imidate was added neat, all at once or in portions, as described in Table I. The reaction was then worked up in the manner described above. The physical constants of these formamides are found in Table II.

B. In Acetronitrile. A solution of the bromo ketone (10 mmol) in dry acetonitrile (20–40 mL) containing the specified quantity of the imidate was heated at reflux temperature for the

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Table II. Physical Constants of Formamido Ketones and Alkylamino Ketone Hydrobromides

compd	R^1	R^2	R^3	mp, °C (solvent)	anal. found (calcd), %	IR,[a] cm^{-1}	NMR,[b] δ
4	CH_3	H	CH_3	oil	C, 52.12 (52.15); H, 8.15 (7.89); N, 11.85 (12.17)	1740, 1678	2.17 (s, 3 H), 2.86, 2.99 (2 s, total 3 H), 4.03, 4.12 (2 s, total 2 H), 7.90, 8.07 (2 s, total 1 H)
4	CH_3	CH_3	CH_3	oil	C, 55.77 (55.78); H, 8.76 (8.60); N, 10.52 (10.85)	1733, 1675	1.35, 1.41 (2 d, total 3 H, J = 7.3, 7.1 Hz), 2.17 (s, 3 H), 2.77, 2.95 (2 s, total 3 H), 4.24, 4.92 (2 q, total 1 H, J = 7.1, 7.3 Hz)
4	C_6H_5	H	CH_3	73–75 (EtOAc–hexane)	C, 67.47 (67.77); H, 6.30 (6.27); N, 7.82 (7.91)	1710, 1680	2.92, 3.03 (2 s, total 3 H), 4.65, 4.75 (2 s, total 2 H), 7.39–8.00 (m, 5 H), 7.99, 8.17 (2 s, total 1 H)
4	C_6H_5	CH_3	CH_3	oil	C, 67.12 (66.98);[c] H, 7.11 (6.98); N, 6.92 (7.10)	1693, 1670	1.41, 1.53 (2 d, total 3 H, J = 6.8, 7.1 Hz), 2.81 (s, 3 H), 5.15, 5.82 (2 q, total 1 H, J = 7.1, 6.8 Hz), 7.33–8.01 (m, 5 H), 8.29 (s, 1 H)
4	$C_6H_5CH_2$	H	CH_3	60–62 (EtOAc–hexane)	C, 69.20 (69.08); H, 6.79 (6.87); N, 7.19 (7.33)	1738, 1678	2.72, 2.84 (2 s, total 3 H), 3.71 (s, 2 H), 4.02, 4.12 (2 s, total 2 H), 7.28 (s, 5 H), 7.84, 8.02 (2 s, total 3 H)
4	3,4-$(BzO)_2C_6H_3$	CH_3	CH_3	90–92 (CH_2Cl_2–MeOH)	C, 74.19 (74.41); H, 6.03 (6.26); N, 3.40 (3.47)	1670	1.35 (d, 3 H, J = 6.6 Hz), 2.76 (s, 3 H), 5.22 (s, 4 H), 5.93 (q, 1 H, J = 6.6), 6.94 (d, 1 H, J = 8.6), 7.27–7.75 (m, 12 H), 8.01 (s, 1 H)
4	C_6H_5	H	$C_6H_5(CH_2)_2$	77–79 (EtOAc–hexane)	C, 76.22 (76.37); H, 6.34 (6.42); N, 5.08 (5.24)	1710, 1674	2.86 (t, 2 H, J = 7.1 Hz), 3.61 (t, 2 H, J = 7.1 Hz), 4.72 (s, 2 H), 7.25–7.92 (m, 10 H), 8.04 (s, 1 H)
4	C_6H_5	CH_3	$C_6H_5(CH_2)_2$	oil	C, 74.71 (74.44);[d] H, 6.69 (6.95); N, 4.76 (4.82)	1669	1.43 (d, 3 H, J = 7.2 Hz), 2.51–2.88 (m, 2 H), 3.27–3.62 (m, 2 H), 5.98 (q, 1 H, J = 7.2), 6.87–8.08 (m, 10 H), 8.34 (s, 1 H)
4	3,4-$(BzO)_2C_6H_3$	CH_3	$C_6H_5(CH_2)_2$	oil	C, 75.23 (75.11);[e] H, 6.76 (6.51); N, 2.51 (2.74)	1665	1.34 (d, 3 H, J = 6.9 Hz), 2.41–2.83 (m, 2 H), 3.21–3.47 (m, 2 H), 5.17 (s, 2 H), 5.21 (s, 2 H), 5.90 (q, 1 H, J = 6.9 Hz), 6.82–7.67 (m, 15 H), 7.79 (s, 1 H)
5	C_6H_5	H	CH_3	204–206 (CH_2Cl_2–MeOH; lit.[5] 203)	C, 47.09 (47.18); H, 5.02 (4.85); Br, 34.67 (34.87); N, 6.05 (6.11)	2787,[f] 2762, 2660, 2355, 2327, 1688	2.83 (s, 3 H),[g] 3.04 (s, 2 H), 7.50–8.07 (m, 5 H)
5	$C_6H_5CH_2$	H	CH_3	161–163 (MeOH–CH_2Cl_2–hexane)	C, 49.09 (49.39); H, 5.55 (5.40); Br, 32.57 (32.86); N, 5.66 (5.76)	2788,[f] 2700, 1738	2.67 (s, 3 H),[h] 3.86 (s, 2 H), 4.09 (s, 2 H), 7.28 (s, 5 H)
5	C_6H_5	H	$C_6H_5(CH_2)_2$	235–237 °C (MeOH–CH_2Cl_2–hexane)	C, 59.91 (60.19); H, 5.57 (5.38); Br, 24.76 (25.03); N, 4.38 (4.39)	2778,[f] 2588, 2516, 2388, 1692	3.07–3.54 (m, 4 H), 3.65 (s, 2 H), 4.74 (s, 2 H), 7.32–8.02 (m, 10 H)

[a] Measured in chloroform solution unless specified otherwise. [b] Measured in $CDCl_3$ with internal Me_4Si unless specified otherwise. [c] Calcd for $C_{11}H_{13}NO_2 \cdot 0.33H_2O$. [d] Calcd for $C_{18}H_{19}NO_2 \cdot 0.5H_2O$. [e] Calcd for $C_{32}H_{31}NO_4 \cdot H_2O$. [f] Measured as a dispersion in KBr. [g] Measured in $CDCl_3$ plus Me_2SO-d_6 solution. [h] Measured in $CDCl_3$ plus CD_3OD solution.

time period indicated in Table I. The products were isolated as described above.

Hydrolysis of the Formamides. A solution of the formamide (2.5 mmol) in methanol which was 1.045 N in hydrogen bromide (23.9 mL, 25 mmol) was heated at reflux temperature for 12-48 h. The solvent was removed in vacuo, and the residue was crystallized from a suitable solvent system (see Table II). In this way the hydrobromide salts of *N*-methylphenacylamine, *N*-(2-phenylethyl)phenacylamine, and 1-(methylamino)-3-phenylacetone were obtained in 94%, 98%, and 85% yields, respectively. The physical constants of these compounds are given in Table II.

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Communications

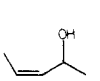
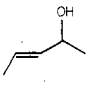
Stereoselective Bromination of Allylic Alcohols. A Facile Synthesis of (*E*)- or (*Z*)-Bromo Epoxides from a Common Starting Material

Summary: The addition of bromine to (*E*)- or (*Z*)-3-penten-2-ol may be directed to either face of the double bond. Depending upon the conditions subsequent reaction with base produces either an (*E*)- or (*Z*)-bromo epoxide.

Sir: The control of stereochemistry in an acyclic system is an important consideration in the synthesis of many complex molecules. However, despite the great advances which have been made in stereochemical control in cyclic systems, the control of stereochemistry in acyclic systems remains a challenge.[1] We report herein methods for controlling the addition of bromine to either diastereotopic face of the double bond of an allylic alcohol. Depending upon the procedure, further reaction produces either an (*E*)- or a (*Z*)-bromo epoxide of exceptionally high isomeric purity.

The hydroxyl group of allylic alcohols often provides a moderate to strong stereodirecting effect during additions to double bonds.[2] However, very little information is available on the stereodirecting effect of an alcohol group during the halogenation of acyclic allylic alcohols. It has been shown that allylic alcohols do not exhibit a neighboring-group effect.[3] On the other hand, Viala has shown that in certain instances bromination in sodium hydroxide solution can be highly selective while in most cases complex mixtures are formed.[4] According to Viala the stereochemistry was a consequence of product forming via direct closure of a bromonium ion or via formation of a dibromide. In cases where a directive effect of the hydroxyl group could be observed, the question of which diastereotopic face of the olefin reacts with bromine was not addressed. We have recently developed procedures to prepare simple straight-chain allylic alcohols (RCH=CHCHOHR) in high optical purity.[5] Development of effective stereoselective bromination procedures for these compounds could lead to the preparation of optically active epoxides. Hence we have investigated the stereochemistry of the bromination of such compounds.

Table I. Stereoselectivity of Bromination in Various Solvents

solvent	ratio of diastereomers 	
CH_2Cl_2[a]	3:1	2:1
n-C_5H_{12}[a]	4:1	2.5:1
$(C_2H_5)_2O$[a]	3.5:1	2.5:1
CH_3SOCH_3[b]		5:4
CH_3CO_2H[b]	2:1	1:1
CH_3OH[a]	10:1	4:1
C_2H_5OH[a]	10:1	3:1
H_2O[b]	5:1	2:1

[a] -78 °C. [b] 0 °C.

For our model study the bromination of (*E*)- and (*Z*)-3-penten-2-ols was investigated. The olefin was placed in a solvent and titrated with bromine at -78 or 0 °C. The products were then analyzed by VPC (Table I). In each case the *Z* isomer exhibited a greater stereoselectivity than the *E* isomer. The ratio of dibromo products was relatively insensitive to the solvent except in the case of the polar-protic solvents ethanol and methanol. In these cases the *Z* isomer gave a 10:1 ratio of products. The ratio could be increased to 12:1 by running the reaction at -120 °C. However, in the alcohol solvents, participation by the solvent to give ether products became a serious side reaction. The undesired ether product could be suppressed by saturating the alcohol with lithium bromide. The dibromo alcohol was then greater than 95% of the product. Simple extraction of the product into hexane, washing with water, drying ($MgSO_4$), and solvent removal give the dibromide in 88% yield.

The structure of the products was determined by conversion of the dibromide into the bromo epoxide (3 N NaOH, 60 °C, 1 h, 80% yield). The major isomer from either the *E* or *Z* allylic alcohol was identified as the *Z* epoxide by NMR analysis of the coupling constant across the epoxide (major product J = 3.2 Hz, minor product J = 1.8 Hz).[6]

The steric course of the reaction is outlined in Scheme I. For simplicity only one enantiomer of the alcohol is shown. The reaction was run on the racemic mixture. It

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(2) For example, epoxidation: (a) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733; (b) Chautemps, P.; Pierre, J.-L. *Tetrahedron* **1976**, *32*, 549. Cyclopropanation: (c) Ratier, M.; Castaing, M.; Godet, J.-Y.; Pereyre, M. *J. Chem. Res. (S)* **1978**, 179, 2309.
(3) Winstein, S.; Goodman, L. *J. Am. Chem. Soc.* **1954**, *76*, 4368. However, under alkaline conditions 2-methyl-3-buten-2-ol does show neighboring group participation: Winstein, S.; Goodman, L. *Ibid.* **1954**, *76*, 4373.
(4) Santelli, M.; Viala, J. *Tetrahedron Lett.* **1977**, 4397. However, allylic alcohols of the RCH=CHCHOHR type were not studied.
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