Substituent Interactions in Di- and Tri-acyl Derivatives of *cis*- and *trans*-2-Hydrazinocyclopentanol

J. A. CAMPBELL AND DONALD MACKAY

Department of Chemistry, University of Waterloo, Waterloo, Ontario

Received July 17, 1972

The action of thionyl chloride followed by an alkaline work-up quantitatively isomerizes *trans*-1,2-dibenzoyl-1-(2-hydroxylcyclopentyl)hydrazine (**5**) to *cis*-2-benzoyl-1-(2-benzoyloxycyclopentyl)hydrazine (**3**). One equivalent of tosyl chloride in pyridine converts **5** to an intermediate which can be hydrolyzed to a mixture of **3** and **5** or can be transformed to the *N*-tosyl derivative **13** by tosylation and then hydrolysis. Oxazolidine structures are suggested as intermediates for these reactions.

The alcohol **2** can also be isomerized to **3**, using 0.8 *N* aqueous ethanolic hydrochloric acid, to which **5** is inert. The ester **3** is again the major product in the hydrolysis by this acid mixture of the *cis*-tribenzoyl derivative **17**, the *cis*-N_1-*p*-anisoyl derivative **21***a* and the *cis*-N_1-acetyl derivative **21***b*, the amide group being cleaved much more rapidly than the ester, especially in the case of **21***b*. A mechanism involving ester participation by way of an oxazolidinium cation is proposed for these amide hydrolyses, and this is supported by tracer studies.

The *trans*-esters **24***a* and *b* hydrolyze mainly at the ester group with retention of configuration.

Polymorphism is a common phenomenon among the title compounds.

L'action du chlorure de thionyle suivie d'un traitement alcalin isomérise quantitativement le *trans*-dibenzoyl-1,2 (hydroxyl-2 cyclopentyl)-1 hydrazine (**5**) en *cis* benzoyl-2 (benzoyloxy-2 cyclopentyl)-1 hydrazine (**3**). Un équivalent de chlorure de tosyle dans la pyridine transforme **5** en un intermédiaire qui peut être hydrolysé en un mélange de **3** et **5** ou convertit en dérivé *N*-tosyle **13** par tosylation puis hydrolyse. Les structures oxazolidines ont été suggérées comme intermédiaires réactionnels.

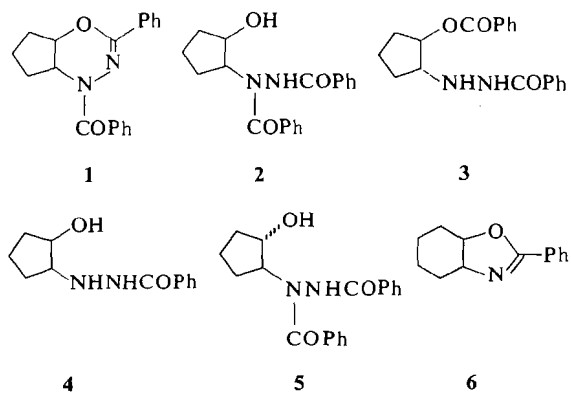
L'isomérisation de l'alcool **2** en **3** est également possible en présence d'une solution aqueuse éthanolique d'acide chlorhydrique 0.8 *N* pour laquelle **5** est inerte. L'ester **3** reste encore le produit majoritaire dans l'hydrolyse par ce mélange acide, du dérivé *cis*-tribenzoyle **17**, du dérivé *cis* N_1-*p*-anisoyle **21***a* et du dérivé cis-N_1-acétyle **21***b*, le groupe amide étant clivé beaucoup plus rapidement que l'ester spécialement dans le cas de **21***b*. Un mécanisme avec participation de l'ester par un cation oxazolidinium a été proposé pour les hydrolyses de ces amides; ce mécanisme a été confirmé par les études par traceur.

Les esters *trans* **24***a* et *b* s'hydrolysent principalement sur le groupe ester avec rétention de configuration. Le polymorphisme est un phénomène commun parmi les composés de cette étude.

[Traduit par le journal]

Can. J. Chem., **51**, 1587 (1973)

In earlier work (1) we used as partial proof of the structure of **1**, the dihydro derivative of the thermal rearrangement product of cyclopentadiene and azodibenzoyl, its ready hydrolysis by acid to *cis*-1,2-dibenzoyl-1-(2-hydroxycyclopentyl)hydrazine (**2**). The alcohol **2** was not itself isolated, but rather its isomer, the ester **3**, and the further hydrolysis product **4**. The intermediacy of **2** was, however, demonstrated by t.l.c., and it was confirmed that under the hydrolysis conditions (0.8 *N* hydrochloric acid in aqueous ethanol) isomerization of **2** to **3** was rapid and efficient. The same ester **3** could also be obtained from the *trans*-isomer **5** of the alcohol **2**, though not under such mild conditions, the use of thionyl chloride or concentrated sulfuric acid being necessary, in which case the yield was quantitative.



1 **2** **3** **4** **5** **6**

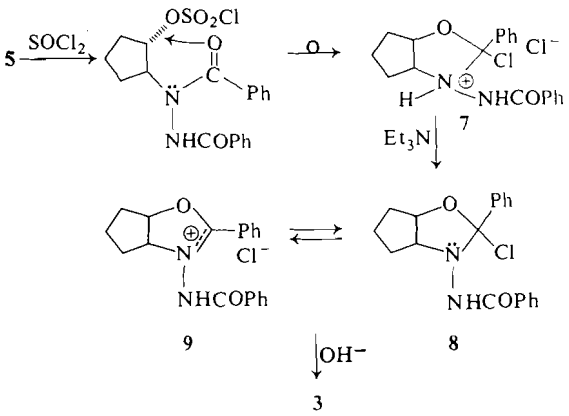
We now wish to discuss in more detail these isomerizations and other acid-catalyzed reactions of related derivatives of *cis*- and *trans*-2-hydrazinocyclopentanol.

The conversion of **5** into **3** is in fact an example of a well established reaction type in which an α-acylamino alcohol is transformed by acidic reagents (most frequently thionyl chloride) into a derivative of the amino alcohol with inversion at the carbinol carbon (2–11). The key step is the formation of an oxazolinium cation by S_N2 attack of the acylamino oxygen.[1] In the 2-acylaminocycloalkanol series the process has been achieved only for the *trans*-isomers which lead to *cis*-fused oxazolines. These have been isolated as the free bases, (*e.g.* **6** from *trans*-2-benzoylaminocyclohexanol) which are usually stable, or as their salts (3–5, 7–10). Hydrolysis of the oxazolines by acids gives the *cis*-2-acyloxycycloalkylamines (C—N cleavage, overall N → O migration) (2, 4, 7, 8, 10), or, if prolonged, the *cis*-alcohols themselves (3, 5–8, 10), while hydrolysis by basic reagents appears to give *cis*-2-acylaminocycloalkanols (C—O cleavage) (8, 9).

The formation of a neutral oxazoline like **6** is of course possible only with an acylaminocycloalkanol containing a free NH, and cannot occur with **5** which has a benzamido group on the nitrogen.

We have tried to obtain some insight into the mechanism of the thionyl chloride isomerization of **5** using n.m.r. studies. Addition of 1 equiv of thionyl chloride to a solution of **5** in chloroform-*d* caused replacement of the broad absorptions for the *tert*-hydrogens at 5.5 τ by two separate multiplets at 3.95 and 4.60 τ. A broad low field absorption for two hydrogens also appeared at −1.0 τ. The same absorptions were observed when this solution (or one obtained by reacting **5** with a large excess of thionyl chloride[2]) was evaporated, pumped briefly[3] over sodium hydroxide, and the residue redissolved in chloroform-*d*.

We attribute this spectrum to the quaternary compound **7** (Scheme 1), the absorption at −1.0 τ being that of the (exchanging) protons



SCHEME 1

on the nitrogens, while that at 3.95 τ is probably due to the C—H adjacent to N^+. Addition of triethylamine (but not of pyridine) caused the two *tert*-hydrogen absorptions to be replaced by a band at 4.7 τ, which must have been due to the *tert*-hydrogens in either the base **8** or the ion **9** (or a mixture of these in equilibrium), since the process was reversed by addition of hydrogen chloride.[4] Neutralization of **7** by alkali gives **3** (1), as expected, and occurs through attack at the electron deficient carbon in **8** or **9**, as in the parallel reaction of the cyclohexane analog (11).

The formulation **7** was also in agreement with the i.r. spectrum, which showed broad absorption for NH^+ between 2900 and 2300 cm^{-1}, but no other absorption in the region down to 1685 cm^{-1}.

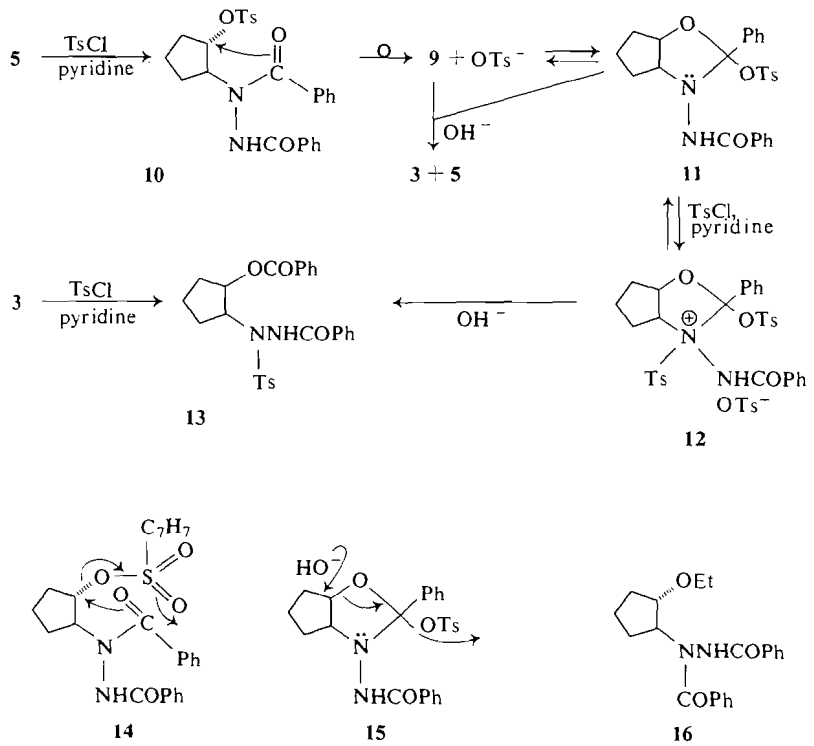
Our original objective in using thionyl chloride was to convert **5** into the chloride of the *cis*-alcohol **2**, a potential precursor to the oxadiazine **1**. As an alternative for the synthesis of **2** we tried to make the tosylate **10** in the expectation that its hydrolysis might occur with inversion. Treatment of **5** with 1 equiv of tosyl chloride in pyridine led to the recovery of 78% of **5** on work-up, and the isolation of 7% of a mono-tosyl derivative. This was not the expected *trans*-*O*-tosyl-*N*-benzoyl compound **10** but rather the *cis*-*O*-benzoyl-*N*-tosyl isomer **13**, its identity being confirmed by its synthesis from **3** with 1 equiv of tosyl chloride in pyridine. With 2

[1]Exceptions have been noted, however, in which stereochemistry is retained (7, 12, 13).

[2]The excess of thionyl chloride may have caused reaction of the *sec*-amide group thus: —NHCOPh → —N=C(Cl)Ph (14). This might cause little change in the appearance of the spectrum and would be of no consequence to the final work-up.

[3]Longer pumping caused the gradual appearance of a broad multiplet at 5.4 τ, which was not discharged by addition of thionyl chloride. It was probably a product of loss of hydrogen chloride, but it was not investigated further.

[4]The ion **9** may be destabilized relative to those derived from acylaminocycloalkanols due to the electron-withdrawing effect of the benzamido group. The neutral form **8** may thus be the dominant species here; it must rank in basicity between pyridine and triethylamine, consistent with the fact that its lone pair is localized.



SCHEME 2

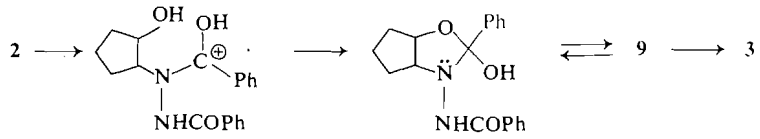
equiv of tosyl chloride, however, **5** gave a 90% yield of **13**. On the basis of these results and a study of the reaction by n.m.r. spectroscopy we propose Scheme 2 to account for these unusual results.

The changes in the n.m.r. spectrum were followed when first one and then a second equivalent of tosyl chloride was added to **5** (0.7 *M*) in chloroform-*d* containing 2.5 equiv of pyridine.[5] The broad peak for the *tert*-hydrogens of **5** at 5.5 τ slowly diminished while absorptions grew at lower field, including ones near 4.0 and 4.6 τ; at the same time the methyl peak of *N*-tosylpyridinium chloride at 7.60 τ[6] was replaced by one at 7.73. The spectrum remained unchanged after about 10 h when the peak at 5.5 τ was about half its original area, and the peak at 7.60 τ had almost disappeared. Addition of D_2O to the sample tube at this point caused most of the methyl peak to disappear into the upper aqueous layer, the spectrum now duplicating that of a mixture of the alcohol **5**, and (on the basis of new peaks formed) smaller amounts of the *N*-tosyl derivative **13** and the ester **3**, the latter being distinguishable by its high field C_1—H absorption at 6.7 τ. As the most soluble of the three products it escaped detection in the original work-up.

Addition of the second equivalent of tosyl chloride resulted in the disappearance over a period of 12 h of the peak at 5.5 τ and all the *tert*-hydrogen absorptions except those at 4.0 and 4.6 τ which continued to grow; the corresponding new methyl peaks formed a broadened line at 7.7 τ. The spectrum remained unchanged over a period of days. Addition of D_2O, however, rapidly produced a quite different spectrum, identical with that of **13** in the same solvent mixture, prepared either from an authentic sample of **13**, or by allowing **3** to react (very rapid reaction) with 1 equiv of tosyl chloride in the presence of the same excess of pyridine. Thus neither **3** nor **13** is at any stage present during the reaction of **5** with 1 or 2 equiv of tosyl chloride.

[5]The reaction was faster with larger amounts of pyridine. The changes in the n.m.r. spectrum were, however, the same as those described here (apart from solvent shifts), even when neat pyridine-d_5 was used.

[6]Control experiment.



SCHEME 3

The multiplets at 4.0 and 4.6 τ had not only the same chemical shift values as the corresponding ones in **7** but *their splitting patterns were identical* (basically a quartet and a triplet respectively, with added fine structure). We take this as powerful evidence that the intermediate with 2 equiv of tosyl chloride is the quaternary structure **12**. The spectrum after reaction with 1 equiv of tosyl chloride can be interpreted as due to a mixture of a small amount of **12** (the second tosylation step is thus competitive with the first), and the major intermediate, one which is capable both of hydrolysis to **5** and to **3** and of tosylation to **12**. We suggest **11** as the most plausible structure for it.

Two paths to the oxazolidine **11** are possible, either by direct displacement of tosylate to the cation **9** (this has analogy elsewhere (3, 9)), which is neutralized by tosylate anion, or directly, in a concerted mechanism as indicated in **14**. The amounts of **3** formed on work-up are small (n.m.r. analysis indicated 10–15% from the reaction in neat pyridine, but slightly more in chloroform-*d*) and must arise from **11**, in competition with hydrolysis to **5**, or from **9**. We can only speculate on why **11** does not give exclusively **3** by direct displacement of tosylate. Concerted loss of tosylate by attack of hydroxide with inversion at cyclopentyl oxygen, as in **15**, may in this case be sterically preferable. Tosylation of **11** occurs on the ring nitrogen which, like that of **8**, is moderately basic. Alkaline work-up involves attack at the very electrophilic benzylic carbon.

Prolonged evaporation under anhydrous conditions of the solution obtained in the reaction with 1 equiv of tosyl chloride gave a glassy residue. Its n.m.r. spectrum was unchanged, and its i.r. spectrum had NH absorption at 3400 cm^{-1} and a carbonyl doublet at 1685 and 1640 cm^{-1}, reconcilable with structure **11**. The residue was unaffected by treatment with methanol for 12 h at room temperature. Evaporation gave material with the same spectra as before, in particular no trace of methoxy absorption being detectable in the n.m.r. spectrum; work-up gave mainly **5**. Similarly addition of sodium ethoxide in ethanol followed by an aqueous work-up led to **5**. The intervention of the ether **16**, expected by analogy to the hydrolysis to **5**, can be discounted, since an authentic sample of it, prepared from **5** and triethyloxonium fluoroborate, was stable to the work-up conditions.

The ready isomerization of the *cis*-alcohol **2** to the ester **3** under conditions (0.8 *N* acid) to which the *trans*-alcohol was inert, indicated the operation of a different mechanism, probably one in which the alcohol oxygen is retained and adds to the protonated amide to give **9** (Scheme 3). For the *trans*-alcohol this reaction would require formation of the rather strained *trans*-fused isomer of **9**; at the same time the acid concentration is probably too low for protonation of the OH group to an extent favorable for the S_N2 displacement to **9**, similar to that shown in Scheme 1.

To test whether the lability of the benzoyl group on N_1 (the inner nitrogen) under such mild conditions was general for the *cis*-series, or depended specifically on the presence of a free OH group, the *cis*-tribenzoyl derivative **17** was examined. Refluxing of **17** for 19 h and work-up led again to the isolation of the ester **3** (as its hydrochloride) as the major product (36%). The reaction was repeated and monitored by n.m.r. analysis utilizing the areas of the absorptions for C_1—H in both the starting material and the product ester. The ratios of **3**:**17** at 3, 7, and 23 h were 0.18:1, 0.56:1, and 2.3:1 respectively. Further hydrolysis was not extensive, though the monobenzoyl derivative **4** could be detected (C_1—H at 6.78 τ) in the n.m.r. spectrum of the hydrolysate after 23 h. The results can only be reconciled with a rate constant of formation of **3** greater than that of any other product. In a control experiment the ester **3** was recovered in a high yield after refluxing in acid for 17 h.

A more intimate analysis of the reaction path was provided using the *cis*-tribenzoyl derivative ^{14}C labelled at the N_1 carbonyl group, obtained

from the ester **3** with ^{14}C-benzoyl chloride in pyridine at 5°. All of the activity was shown to have been incorporated during the benzoylation step,[7] with no further exchange after it, since in a control experiment unlabelled tribenzoyl derivative could not be made active even when refluxed in pyridine with ^{14}C-benzoyl chloride.

Acid hydrolysis of the active tribenzoyl derivative for 21 h followed by work-up and purification gave, as well as unreacted starting material, the expected products **3**, **4**, and benzoic acid.

The percent molar yields[8] and retention of activity of these are shown in Table 1. The ester **3** was isolated as its hydrochloride which was converted into the free base with pyridine and hydrolyzed to the monobenzoyl derivative **4** with alkali. The initially isolated **4**, which was the most troublesome product to purify,[9] was converted with unlabelled benzoyl chloride into the easily purified tribenzoyl derivative. The per cent molar activities of these derivatives are also shown in Table 1.

The ester **3** had only 20% of the molar activity of the starting material and of this about 90% must have been located at the ester carbonyl since the monobenzoyl derivative **4** had only 1.9% retention of activity.

Had the loss of the N_1-benzoyl group occurred exclusively by the sequence of direct ester hydrolysis to **2** followed by benzoyl migration from N → O (Scheme 3) then **3** would have contained all the label. The actual value of 20% cannot be explained in terms of a dilution effect (100 to 20%) through exchange with benzoic acid since the activity of the latter would then have been ⩽20% and not, as observed, much higher.

It thus appears that the hydrolysis of **17** does not go by way of **2** to an extent greater than 20% and that the ratio of tertiary amide cleavage (other than by way of **2**) to ester hydrolysis is at least 0.59 :1 (isolated yield of **3** is 46%; if the remaining 54% undergoes direct ester hydrolysis the ratio is $0.8 \times 0.46 : 0.54 + 0.2 \times 0.46 =$ 0.59 :1). The true value is probably much higher since losses in the work-up of unreacted **17** and **3** would both contribute to lowering the ratio. In addition the previous hydrolysis experiment indicates that loss of tertiary amide (by all mechanisms) is faster than any other process. We conclude, therefore, that amide hydrolysis is faster than ester hydrolysis and presume that it is assisted by the neighboring ester group.[10]

TABLE 1. Hydrolysis of 18 mmol of **17**-^{14}C after 21 h: yields and activities

Compound	Moles	% Yield	Derivative	% Retention of molar activity*
17 (recovered)	6.1			99.6
3 · HCl	5.5	46		19.7
			3	20.2
			4	1.9
4	0.55	4.6		6.3
			12	8.7
$PhCO_2H$	6.6	55		40.8

*Based on starting material with a value of 3.267×10^8 counts min^{-1} mol^{-1}.

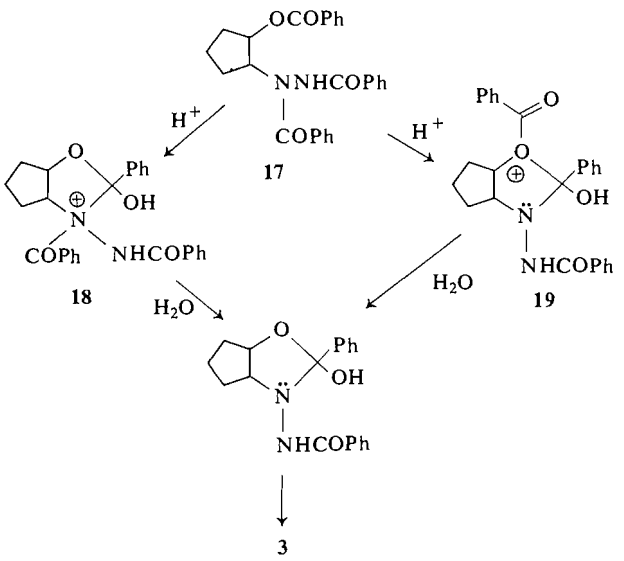
Examples have been described of assisted hydrolysis of amides by carboxyl, amide, amine, hydroxyl (15–19) and, more rarely (20), ester functions; in most of these the assisting group has been in the acyl rather than, as here, the amine moiety. We suggest that the protonated ester group of **17** forms the quaternized cyclol **18** by reaction at N_1 (Scheme 4), thus leading to a faster benzoyl cleavage, and one involving loss of label, than normal hydrolysis. A possible mechanism is also shown in Scheme 4 for ester cleavage, which transfers label directly to the ester position by way of **19**, a less important pathway than through **18** since it puts positive charge on oxygen rather than nitrogen. This is an alternative to the transfer of label by initial hydrolysis to

[7]Scambling during benzoylation, *i.e.* to give label at sites other than at N_1, is considered very unlikely.

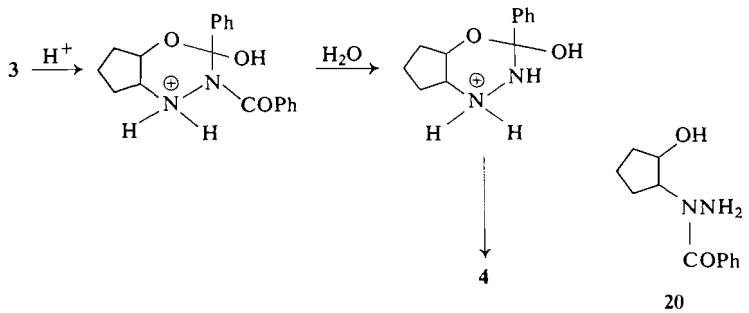
[8]Rigorous purification of the products to constant activity was carried out at the expense of optimization of yields.

[9]The increase in activity after benzoylation shows that it must have been originally contaminated with inactive material.

[10]Some measure of the stability to hydrolysis of the ester and the amide functions in the absence of neighboring group effects can be judged by the hydrolysis of the monosubstituted derivatives cyclopentyl benzoate and 1,2-dibenzoyl-1-cyclopentylhydrazine. After 7 h the ester was 17% hydrolyzed (determined by g.l.c.) and the hydrazide was ⩾20% hydrolyzed (determined gravimetrically). The results from the hydrolysis of **17**, **21***a*, and **21***b* thus show that participation at once assists hydrolysis of the amide and retards that of the ester. The great stability of **3** to these conditions may indeed be due to protection of it as the neutral cyclic structure of Scheme 4 or as its conjugate acid ($3 \cdot H^+$) by protonation on its basic nitrogen.



SCHEME 4



SCHEME 5

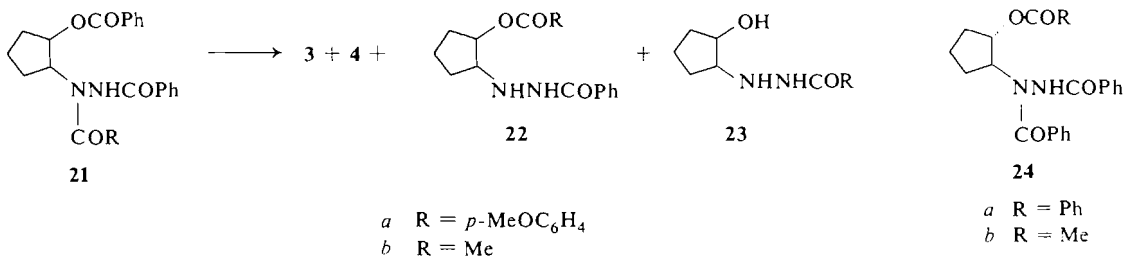
the alcohol **2**, followed by the cyclization of Scheme 3. The labelling experiment does not provide a decision between these.

The surprisingly large (~9%) incorporation of label in the isolated monobenzoyl derivative **4** suggests the possibility of acid-catalyzed transfer of benzoyl in **3** from O to N_2 (Scheme 5). We cannot however exclude the possibility that the monobenzoyl derivative **20** is a transient hydrolysis species which isomerizes to **4** and confers activity on it. The isomerization analogous to **20** → **4** in the cyclohexane series has been shown to be efficient in acid, a diaziridine intermediate being proposed to account for it (11).

The hydrolysis of the N_1-*p*-anisoyl derivative **21***a* (Scheme 6) under the same conditions was examined briefly, being followed by n.m.r. analysis, both in the non-acidic hydrolysate by the disappearance of the methoxy singlet relative to the methylene envelope, and in the carboxylic acid fraction by changes in the aromatic region.

After 8 h the products on removal of acid showed a 31% loss of methoxy-containing material (as *p*-anisic acid), the n.m.r. spectrum being readily interpreted through its tertiary proton absorptions as due to starting material, the ester **3**, and probably some **22***a*, with only very little of **23***a*. Work-up of this fraction with cold aqueous methanol gave a 40% recovery of starting material, and by addition of hydrochloric acid to the mother liquor a 33% yield (based on unreacted **21***a*) of the hydrochloride of **3** was isolated. The carboxylic acid fraction had a *p*-anisic – benzoic acid ratio of 2.5 :1. The extent of hydrolysis is thus comparable with that of **17** with cleavage of *tert*-amide again being faster than that of ester.

Hydrolysis of **21***b* was very rapid and occurred



SCHEME 6

almost exclusively at the acetyl group, with 50% hydrolysis after 1 h and 90% after 3.5 h. Work-up at this point led to recovery of 85% of the starting weight after removal of acids. The i.r. and n.m.r. spectra were substantially those of **3** which was isolated pure as its hydrochloride in 50% overall yield. The lability of the acetyl group can be explained if the rate-determining step in amide hydrolysis is typified by the formation of **18** in Scheme 4. The counterpart from **21***b* would be less subject to steric constraints at the quaternized nitrogen than either **18** or the corresponding ion from **21***a*.

The behavior of the *trans*-esters **24***a* and *b* on hydrolysis was examined briefly and found to be more straightforward. The benzoate **24***a* was 40% hydrolyzed in 7 h and 70% in 24 h, the main product being the *trans*-alcohol **5**, identified by t.l.c. At least one minor product was present which was neither the ester **3** nor the alcohol **4** (from the n.m.r. spectrum), the products of inverted stereochemistry. The acetate **24***b* was hydrolyzed much more rapidly, (the differences may be simply steric), again at the ester group, which was completely removed in 7 h. The product was slightly impure **5** (80%). It thus appears that assistance of amide hydrolysis is confined to the *cis*-series.

A number of the di- and tri-substituted *cis*- and *trans*-hydrazinocyclopentanols discussed above showed polymorphism. The *trans*-benzoate **24***a* was typical. From benzene – petroleum ether (b.p. 60–80°) it gave rosettes which melted at 139–139.5°, without prior change in the appearance of the crystals. From aqueous ethanol it gave prisms, the metastable form, which on heating slowly changed appearance; the final m.p. was again 139–139.5°. The i.r. spectra were of course identical in solution but showed differences in the crystalline state, especially so in the NH and CO regions. The stable form had in Nujol NH absorption at 3230 cm^{-1} and CO absorptions at 1715, 1670, and 1652 cm^{-1}. The metastable form had corresponding absorptions at 3320, 1685, and 1664 cm^{-1}. If a sample of the latter was kept at 100° for 10 h, its spectrum changed completely to that of the stable form.

The compounds showing polymorphism are listed in Table 2, polymorph I in each case being the stable form. Included are the solvent from which each polymorph was obtained, and the i.r. absorptions in the OH/NH and CO regions.

The i.r. differences are strongly indicative of differences in hydrogen-bonding types. Models of any of these compounds readily show that free rotation round the sigma bonds of the ester and hydrazine substituents leads to a large number of conformational possibilities with five- or six-membered rings containing hydrogen bonds. The polymorphic pairs presumably correspond to two of these.

Experimental

I.r. spectra were obtained on a Beckman IR 10 spectrophotometer. For the n.m.r. analyses a JEOL C60 or a Varian T60, were used, the τ values quoted being against tetramethylsilane as internal standard.

Thionyl chloride was purified as described by Rigby (21).

The synthesis of compounds **2–5**, **24***a*, and **17** has been described previously (1).

*cis-1-Acetyl-2-benzoyl-1-(2-benzoyloxycyclopentyl)-hydrazine (**21***b*)

A solution of acetyl chloride (1.0 g) and the hydrochloride of **3** (2.0 g, 5.5 mmol) in pyridine (7 ml) was set aside at room temperature for ½ h. Addition of water (100 ml) caused an oil to separate which crystallized overnight (54%). Recrystallization from benzene – petroleum ether (b.p. 60–80°) gave the *N*-acetyl derivative of m.p. 117–118°; ν(CCl_4) 3450, 3380 (NH), 1730, 1707 and 1685 cm^{-1} (ester, *sec*-amide and *tert*-amide C=O); τ($CDCl_3$) 1.5 (NH), 1.9–2.8 (10 phenyl H), 4.50 (C_2—H), 4.90 (C_1—H), 8.00 (Me), 7.3–8.5 p.p.m. (6 methylene H).

Anal. Calcd. for $C_{21}H_{22}N_2O_4$: N, 7.65. Found: N, 7.58.

TABLE 2. Polymorphic derivatives of *cis*- and *trans*-2-hydrazinocyclopentanol

Compound		M.p. (°C)	Solvent of crystallization	ν(Nujol) NH/OH	ν(Nujol) C=O		
5	I	177.5–178	aqueous MeOH	3325	1672	1656	
	II		C_6H_6	3230	1682	1628	
17	I	177.5–178.5	aqueous MeOH	3310	1702	1678	1666
	II		C_6H_6	3240	1722	1672	1628
24*a*	I	139 –139.5	C_6H_6–P.E.*	3330	1688	1667	
	II		aqueous EtOH	3240	1715	1670	1652
21*a*	I	183 –184	aqueous MeOH	3325	1690	1678	1655
	II		C_6H_6	3220	1715	1670	1621
21*b*	I	117 –118	C_6H_6–P.E.*	3350	1720	1685	1660
	II		aqueous EtOH	3380,3280	1710	1665	1655

*Petroleum ether (b.p. 60–80°).

*trans-1,2-Dibenzoyl-1-(2-acetoxycyclopentyl)hydrazine (**24b**)*

A solution of the *trans*-alcohol **5** (100 mg, 0.30 mmol) and acetic anhydride (0.3 ml) in pyridine (3 ml) was refluxed for ½ h and evaporated to a small volume. Crystallization occurred on addition of water (5 ml), and the acetate (95%) was recrystallized from aqueous ethanol as prisms, m.p. 168.5–169°; ν(CCl_4) 3370 (NH), 1721, 1698 and 1673 cm^{-1} (ester, *sec*-amide and *tert*-amide C=O); τ($CDCl_3$) 1.93 (NH), 2.3–3.1 (10 phenyl H), 4.5–5.7 (2 *tert*-H, overlapping), 7.88 (Me), 7.5–8.7 p.p.m. (6 methylene H).

Anal. Calcd. for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.59; H, 5.90; N, 7.42.

*cis-1-p-Anisoyl-2-benzoyl-1-(2-benzoyloxycyclopentyl)-hydrazine (**21a**)*

A solution of the hydrochloride of **3** (2.6 g, 7.2 mmol) and *p*-anisoyl chloride (1.0 ml, 7.2 mmol) in pyridine (20 ml) was refluxed for 15 min and then kept at room temperature for 10 h. Addition of water (100 ml) caused precipitation of **21***a* (94%) which after two crystallizations from aqueous methanol had m.p. 182–184°; ν(CCl_4) 3320 (NH), 1728, 1700 and 1670 cm^{-1} (ester, *sec*-amide and *tert*-amide C=O; τ($CDCl_3$) 1.85 (NH), 2.10 (2 methoxyphenyl H, d), 2.3–3.0 (10 phenyl H), 3.30 (2 methoxyphenyl H, d), 4.40 (C_2—H), 5.10 (C_1—H), 6.27 (Me), 7.5–8.9. p.p.m. (6 methylene H).

Anal. Calcd. for $C_{27}H_{26}O_5N_2$: C, 70.73; H, 5.72; N, 6.11. Found: C, 70.43; H, 5.73; N, 6.10.

*trans-1,2-Dibenzoyl-1-(2-ethoxycyclopentyl)hydrazine (**16**)*

The alcohol **5** (0.50 g, 1.6 mmol) was refluxed for 6 h in methylene chloride (10 ml) containing a slight excess of triethyloxonium fluoroborate. The solution was shaken out with aqueous sodium hydrogen carbonate and the organic layer was dried and evaporated, leaving a crystalline residue of high purity (i.r.). Two crystallizations from aqueous methanol gave prisms, m.p. 182–183°; ν(Nujol) 3285 (NH), 1685, 1615 cm^{-1} (*sec*-amide and *tert*-amide C=O); τ($CDCl_3$) 1.3 (NH), 2.2–2.9 (10 phenyl H), 5.60 (C_1—H), 6.00 (C_2—H), 6.53 (OCH_2, J = 8 Hz), 7.8–8.7 (6 methylene H), 8.83 p.p.m. (CH_3).

Anal. Calcd. for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.91; H, 6.88; N, 8.21.

In a control experiment the ether (20 mg) was kept in a 1 *N*-sodium hydroxide solution of water–ethanol (3:1, 5 ml) for 5 min. The solution was neutralized with acetic acid, the volume reduced, and water added to induce crystallization. The product was analytically pure starting material.

Thionyl Chloride Reactions

*(a) Formation of cis-Ester **3***

Thionyl chloride (50 μl, 0.70 mmol) was added to a suspension of the alcohol (3 ml) at room temperature. The alcohol rapidly dissolved, sulfur dioxide being evolved. After 5 min a solution of sodium hydrogen carbonate (250 mg, 3.0 mmol) in water (10 ml) was added, and the whole was shaken and warmed in a stream of nitrogen to remove the solvent. The gummy residue rapidly crystallized on cooling and scratching (190 mg, 95%), and had the i.r. spectrum and m.p., 86–87.5°, of analytically pure ester without further crystallization.

(b) Nuclear Magnetic Resonance Reactions

Thionyl chloride was added dropwise to a suspension of **5** (100 mg) in chloroform-*d* (0.3 ml) in the sample tube till a clear solution was obtained. The spectrum showed a trace of a broad band at 5.5 τ due to unreacted **5** (C_1— and C_2—H), since it could be intensified by addition of more **5** or removed by addition of more thionyl chloride. The product had τ −1.1 (2H, broad, NH and NH^+), 1.4–2.9 (10 phenyl H), 3.95 (C_1—H, quartet), 4.60 (C_2—H, triplet, the intensities suggesting its origin from two superimposed doublets), 7.0–8.8 p.p.m. (6 methylene H).

Identical spectral patterns were observed for the product with an excess of thionyl chloride, or if thionyl chloride was used as the solvent. In the latter case there were considerable downfield shifts of all absorptions, but the splittings of and the shift between the *tert*-hydrogens were the same.

When the sample from addition of 1 equiv of thionyl chloride was treated with an excess of pyridine there was no effect on the non-aromatic region of the spectrum. Dropwise addition of triethylamine, however, caused

disappearance of the *tert*-hydrogen absorptions and formation of a broad band at 4.7 τ. Passage of dry hydrogen chloride regenerated the original spectrum.

(c) Examination of Product

A sample of the product prepared as above from 1 equiv of thionyl chloride had ν($CDCl_3$) 2900–2300 (NH and $NH^{\oplus}$), 1685 cm^{-1} (*sec*-amide C=O).

When a solution prepared from an excess of thionyl chloride in dry methylene chloride (as in section *a*), or in neat thionyl chloride, was evaporated in a stream of dry nitrogen and then pumped over sodium hydroxide (liquid nitrogen trap) the residue frothed but did not crystallize. Redissolved in chloroform-*d* it had the spectrum described above. On prolonged pumping there was a gradual loss of weight from about 1.2 to 1.1 times that of the original alcohol over a period of 3 days. The n.m.r. spectrum of the residue showed a new broad multiplet at 5.4 τ, formed at the expense of the original *tert*-hydrogens. This product was not examined further.

Reactions with p-Toluenesulfonyl Chloride

(a) On cis-Ester 3

The ester (0.20 g, 0.62 mmol) was allowed to react with tosyl chloride (0.12 g, 0.62 mmol) at 5° for 1 day in pyridine (5 ml). Addition of water gave crystalline *cis-1-p-toluenesulfonyl-2-benzoyl-1-(2-benzoyloxycyclopentyl)hydrazine* (**13**) which formed dense prisms (86%), m.p. 153.5–154°, from aqueous methanol; ν(CCl_4) 3410 (NH), 1730, 1708 cm^{-1} (ester, *sec*-amide C=O); τ($CDCl_3$) 1.9–3.0 (14 aromatic H and one H exchangeable with D_2O), 4.45 (C_2—H), 5.45 (C_1—H), 7.68 (Me), 7.4–8.5 p.p.m. (6-methylene H).

Anal. Calcd. for $C_{26}H_{26}N_2O_5S$: N, 5.85. Found: N, 5.93.

(b) On trans-Alcohol 5

The alcohol (0.32 g, 1 mmol) was treated with tosyl chloride (0.19 g, 1 mmol) in pyridine (15 ml) for 17 h at room temperature. Addition of water caused precipitation of a small amount (7%) of the *N*-tosyl derivative **13**. Evaporation of the filtrate and crystallization from aqueous methanol gave the starting alcohol (78%).

Repetition of this reaction on the same scale, but with *2* equiv of tosyl chloride, followed by addition of water gave the *N*-tosyl derivative **13** in 90% yield. Its identity was confirmed by mixed m.p. with the product in section *a*.

(c) Nuclear Magnetic Resonance Reactions

The alcohol **5** (115 mg, 0.35 mmol) was dissolved in chloroform-*d* (5 ml) containing pyridine (0.10 ml, *ca.* 2.5 equiv), and tosyl chloride (67 mg, 0.35 mmol) was added. The volume was reduced to about 0.5 ml by evaporation under dry nitrogen and the solution (0.7 *M*) transferred to a sample tube. The changes in the spectrum till reaction was complete, and thereafter when a second equiv of tosyl chloride was added, are described in the discussion.

The reactions with 1 and 2 equiv of tosyl chloride were also monitored in pyridine-d_5. No significant differences were observed other than solvent shifts.

Addition of D_2O at either stage in the above reactions led to rapid changes in the spectra. The major product from the first stage was the starting alcohol **5** with smaller amounts of the *N*-tosyl derivative **13** and the ester **3**. The yield of the latter from the reaction in pyridine was estimated as 12% by comparison of the area of its C_1—H with that of the total methylene envelope. In the chloroform-*d* reaction the yield appeared to be slightly greater. From the second stage of the reaction the addition of D_2O indicated that **13** was the exclusive product.

Control experiments. To interpret the assignments in the tosylation reactions the spectra of the following compounds or mixtures of reagents were required in chloroform-*d* containing appropriate amounts of pyridine or in pyridine itself: (*i*) tosyl chloride; (*ii*) the ester **3**, alone and with 1 equiv of tosyl chloride; (*iii*) the *N*-tosyl derivative **13**; (*iv*) the alcohol **5**.

(d) Reaction with Methanol and with Sodium Ethoxide

The solution prepared from the alcohol and tosyl chloride (0.50 mmol each) in pyridine (2 ml) was kept for 36 h and then evaporated under reduced pressure (liquid nitrogen trap). The glassy residue was found to have an n.m.r. spectrum the same as that described before; its i.r. spectrum had ν($CDCl_3$) 3400 (NH), 1685 and 1640 cm^{-1} (C=O). The main portion was dissolved in methanol (0.5 ml), kept for 12 h, and pumped down as before. The n.m.r. and i.r. spectra were unchanged. Treatment with aqueous methanol gave a crystalline solid whose i.r. spectrum showed it to be mainly **5**.

To a solution of the complex from 0.30 mmol each of alcohol and tosyl chloride, prepared in pyridine (1.5 ml) and kept 11 h at room temperature, was added a solution of sodium ethoxide (1.0 mmol) in ethanol (1 ml). A flocculent precipitate formed and the whole was briefly warmed to 80° which made it yellow. It was quenched with ice and neutralized with acetic acid. Extraction with methylene chloride gave a residue which crystallized on trituration with a few drops of methanol. The product (80%) was washed with much water and identified as almost pure **5**.

Hydrolysis Reactions

General

The acid solution was prepared by mixing 2 l ethanol, 1 l water, and 200 ml 12 *N* hydrochloric acid. There was a 2.5% shrinkage making the final solution 0.770 *N* in acid. All hydrolyses were done on a scale of 1 mmol in 19.5 ml acid at reflux temperature.

Aliquots were withdrawn at intervals, basified with sodium hydrogen carbonate, evaporated, and shaken with water and methylene chloride. The methylene chloride extraction was repeated four times. The dried extracts were evaporated and the residue analyzed as necessary by i.r. or n.m.r. spectrometry.

Quantitative determinations on the n.m.r. absorptions of protons were carried out at 1 Hz s^{-1} sweep rates in both directions at r.f. power levels low enough to prevent saturation. The traces were photocopied, cut out, and weighed. The absorptions used in individual experiments, the scale and other details follow.

(a) cis-Tribenzoyl Derivative 17 (4 mmol)

C_2—H at 4.3 τ in **17** and C_2—H at 4.7 τ in the product ester **3** were used; they overlapped slightly. In the late stages of the reaction the peak for C_1—H at 6.8 τ in the alcohol **4** was detectable. Ratios of **3**:**17** were, at 3, 7, and 23 h, 0.18:1, 0.56:1, and 2.3:1 respectively.

In a separate experiment **17** (2.3 mmol) was hydrolyzed for 19 h. The residue from the reaction was treated with

ethanol containing a little hydrochloric acid which precipitated the pure hydrochloride of **3** (36%).

In a control experiment **3** (0.12 mmol) was refluxed for 17 h. On work-up **3** was recovered, contaminated only with a small amount of **4**; it was isolated and identified as its hydrochloride.

*(b) p-Anisoyl Derivative **21a** (4 mmol)*

The area ratio of the methylene envelope to the methoxy singlet was measured in pure **21***a* and its value of 2.35 used in determining the loss of the *p*-anisoyl group during hydrolysis. The sodium hydrogen carbonate solution was acidified and the mixed carboxylic acids extracted with methylene chloride (5 times). Their ratios were determined by n.m.r. analysis by comparing the two high field *p*-anisoyl protons (H_3 and H_5) with the three high field benzoic acid ones (meta and para). At 3, 8, and 19 h the loss of methoxy signal in the non-acidic fraction was 7, 31, and 71% and the ratios of *p*-anisic to benzoic acid at the same times were 2.5:1, 2.5:1, and 0.5:1.

In a separate experiment (1.02 mmol) the hydrolysate was freed from carboxylic acids after 8 h and the non-acidic fraction was crystallized from aqueous methanol. The crystalline product (186 mg, 40%) was identified as starting material. The mother liquor was evaporated and methanolic hydrochloric acid added. An initial crop of crystals was removed, and the soluble fraction worked-up similarly to give a second crop (68 mg in all, 33% based on unrecovered **21***a*); these were combined and identified as the hydrochloride of **3** (superimposable i.r. spectrum). Recrystallization from methanolic hydrochloric acid gave prisms, m.p. 162–164°.

*(c) Acetyl Derivative **21b** (8 mmol)*

The overlapping C_2—H in **21***b* and C_2—H in the product **3** at 4.5 τ were compared with C_1—H in **3** at 6.5 τ. After 1 and 3.5 h the ratios of **3**:**21***b* were 1:1 and 9:1.

After removal of acid, the residue from the reaction (85% by weight of starting material, equivalent to 95% of **3**) had an i.r. spectrum almost identical with that of **3**. Addition of methanol containing 3 *N* hydrochloric acid gave the hydrochloride (50%), m.p. 163–166°, alone or in admixture with an authentic sample.

*(d) trans-Tribenzoyl Derivative **24a** (2 mmol)*

The overlapping C_1—H and C_2—H of **7***d*, between 4.3–5.3 τ, were compared with the sum of the overlapping C_1—H and C_2—H of the product alcohol **5**, between 5.4—6.2τ, and a smaller peak from another product at 6.4 τ. These gave ratios of products: **24***a* of 0.4:1 at 7 h and 1.5:1 at 24 h. T.l.c. on silica gel plates from benzene–ether showed two main spots only, for **24***a* and **5**.

*(e) trans-Acetate **24b** (2 mmol)*

After hydrolysis for 7 h the residue, on removal of acid, was free of an acetyl peak in its n.m.r. spectrum and corresponded to 71% by weight of the starting weight, or a maximum yield of 80% of the *trans*-alcohol **5**. The i.r. spectrum was that of slightly impure alcohol. One crystallization from aqueous methanol gave material of m.p., and mixed m.p. 174–176°.

^{14}C Labeling Experiment

The activity of all compounds was obtained by dissolving a known weight (*ca.* 150 mg) in 20 ml of scintillation fluid and measuring the counts min^{-1} in a Tri-Carb Liquid Scintillation Spectrometer, background count being subtracted. Four determinations were made for each sample. The scintillation fluid consisted of 2,3-diphenyloxazole (PPO, 2.8 g), *p*-bis-[2-(4-methyl-5-phenyloxazolyl)] benzene (dimethyl POPOP, 0.7 g) and Cab-O-Sil (30 g) dissolved in toluene (700 ml) and absolute ethanol (300 ml).

Benzoyl chloride (35 g, 0.25 mol) was made ^{14}C active by heating it at 100° for 2 h with a sample of benzoic acid containing 100 μCi of ^{14}C in the carbonyl group.

The ester **3** as its hydrochloride was converted into the N_1-benzoyl-^{14}C derivative (**17**-^{14}C) with benzoyl chloride-^{14}C in pyridine as described for the synthesis of the unlabelled compound (1). It was crystallized to a constant activity of 3.267×10^8 counts min^{-1} mol^{-1}.

In a control experiment inactive **17** could not be made ^{14}C-active by treatment with benzoyl chloride-^{14}C in refluxing pyridine.

The active ester (18.0 mmol) was hydrolyzed for 21 h. On cooling unreacted ester (6.1 mmol) crystallized out. Concentration of the mother liquor and addition of 3 *N* hydrochloric acid gave the hydrochloride of **3** (5.5 mmol). The remainder of the work-up, as described for the hydrolysis of **1** (1), gave the alcohol **4** (0.37 mmol) and benzoic acid (6.6 mmol).

A portion of the hydochloride of **3** was converted into the free base with pyridine and the remainder was hydrolyzed by heating it at reflux for 3 min in 0.8 *N* sodium hydroxide in aqueous ethanol (1:1). The chilled solution was then extracted thoroughly with ether to give the alcohol **4**.

A portion of the alcohol **4** from the original work-up was converted into the tribenzoyl derivative by treatment with 2 equiv of benzoyl chloride in pyridine at 5° (1).

The percent molar activities of all compounds, based on that of the starting material, are given in Table 1.

We thank the Province of Ontario for a Graduate Fellowship (to J.A.C.) and the National Research Council of Canada for support of this work and for a Scholarship (to J.A.C.).

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