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SCHIFF BASE–CYCLIC ANHYDRIDE REACTIONS: A REVIEW OF OXAZEPINE-DIONE FORMATION, COMPETING LACTAM PATHWAYS AND SPECTROSCOPIC PROOF

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ABSTRACT
Heating a Schiff base with a cyclic anhydride is a popular way to make seven-membered 1,3-oxazepine-diones, and the products are usually described as the result of a "[2+5] cycloaddition". The same two partners are also the classical substrates of the Castagnoli–Cushman reaction, which forms γ-lactam, δ-lactam and tetrahydroisoquinolone acids through a new carbon–carbon bond. A third outcome, hydrolysis of the imine followed by amic acid or imide formation, is easily overlooked. This review brings the three together. We first describe the partners and stress one structural question: does the anhydride carry an enolisable α-carbon? Forty oxazepine-dione reports are then examined for their conditions and for the evidence offered for each structure. We argue that the step drawn as a cycloaddition is better seen as N-acylation followed by closure of an N-acyliminium carboxylate, so that the product is a cyclic N-acyl-N,O-acetal. The lactam literature is summarised with attention to mechanism, stereochemistry and the conditions under which it overlaps with oxazepine protocols. Because the oxygen-closed and carbon-closed products of enolisable anhydrides are isomers, mass spectra and elemental analysis cannot separate them. We therefore compile the infrared, ^{1}H and ^{13}C NMR data that can, show how DEPT, COSY and HMBC settle the connectivity, and propose a minimum evidence set for future work, with single-crystal diffraction and computed shifts for the cases that remain open.

Keywords: *Schiff base; cyclic anhydride; 1,3-oxazepine-4,7-dione; Castagnoli–Cushman reaction; N-acyliminium ion; γ-lactam; NMR structure elucidation.*

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1. INTRODUCTION

Imines were first described by Hugo Schiff in 1864 [1], and the C=N group has kept a central place in organic and coordination chemistry ever since [2,3]. Part of its appeal is the ease with which both ends of the C=N bond can be drawn into a new ring. A cheap and widely used example is the reaction of a Schiff base with a cyclic carboxylic anhydride. The imine is heated with maleic, succinic or phthalic anhydride in a dry solvent, and the product is reported as a 1,3-oxazepine-4,7-dione or a benzo-fused oxazepine-dione [4–6]. Seven-membered N,O-heterocycles are attractive targets, and benzoxazepines in particular have a solid record in medicinal chemistry [7,8]. The step is usually called a [2+5] cycloaddition, because two atoms of the C=N bond and five atoms of the anhydride make up the new ring. A second body of work uses exactly the same partners for a different purpose. Since the reports of Castagnoli and Cushman, imines and enolisable cyclic anhydrides have been known to give γ- and δ-lactams that carry a carboxylic acid [9,10], and the Castagnoli–Cushman reaction (CCR) is now a standard tool for nitrogen heterocycles [11,12]. Its products are joined through a carbon–carbon bond, not an oxygen–carbon bond, and they are often isomers of the oxazepine-diones. The two literatures rarely meet. Oxazepine papers almost never mention lactams, and the lactam papers mention a seven-membered N,O-acetal only as

a passing side intermediate [13]. This matters because the evidence usually offered for the seven-membered ring, namely the loss of the C=N band, new carbonyl bands and a singlet for the ring CH, does not exclude the alternatives. Structure revision is a familiar story in organic chemistry [14], and isomer pairs like these invite it. The aim of this review is practical. We describe the partners and the conditions used, examine previous studies on oxazepine-dione formation, set out the competing lactam and hydrolytic pathways, and define the spectroscopic data that can prove, or disprove, a seven-membered N,O-acetal.

2. THE TWO PARTNERS

2.1. Schiff bases: a reversible, ambident partner

A Schiff base is a polarised C=N bond. The nitrogen carries a lone pair and is the nucleophilic end, while the carbon is electrophilic, more so once the nitrogen has been protonated or acylated [2]. The aromatic aldimines used in most of the work discussed here are crystalline E isomers, easy to make and easy to purify.

Their second property matters just as much. Imine formation runs through a carbinolamine, and each step can go backwards; Cordes and Jencks dissected the hydrolysis of Schiff bases kinetically more than sixty years ago [15]. In water the position of the equilibrium depends strongly on structure and pH [16], and this reversibility is exactly what dynamic covalent chemistry exploits [17]. For the present topic the lesson is simple. A trace of water in the solvent, in an anhydride that has partly gone back to its diacid, or in the work-up can return the aldehyde and the amine. The free amine opens the anhydride quickly, even at room temperature [18,19], and the product mixture is then no longer the one drawn in the scheme.

2.2. Cyclic anhydrides: with or without an enolisable carbon

A cyclic anhydride offers two activated carbonyl groups held in one ring. Its best known reaction is ring opening by an amine to an amic acid, a molecule carrying an amide and a free carboxylic acid. Heat or a dehydrating agent then closes the amic acid to a five-membered imide, as in the classical preparation of N-phenylmaleimide [18]. With some dehydrating agents the closure goes through oxygen instead, and an isoimide forms in place of, or alongside, the imide [20,21]. We will meet this choice between N- and O-closure again.

For this review the anhydrides fall into two broad groups (Figure 1). Maleic, phthalic, substituted phthalic and pyromellitic anhydrides have no sp^3 carbon next to a carbonyl group. They cannot enolise, so they can only act as acylating agents. Succinic, glutaric and homophthalic anhydrides do have such CH_2 groups. Their enols, or enolates, are carbon nucleophiles that can add to an imine [11,22]. Alkyl-substituted maleic anhydrides such as citraconic anhydride sit in between: they have been turned into unsaturated lactams with imines [23]. In practice, asking whether the anhydride can enolise is the quickest way to know which products are even possible.

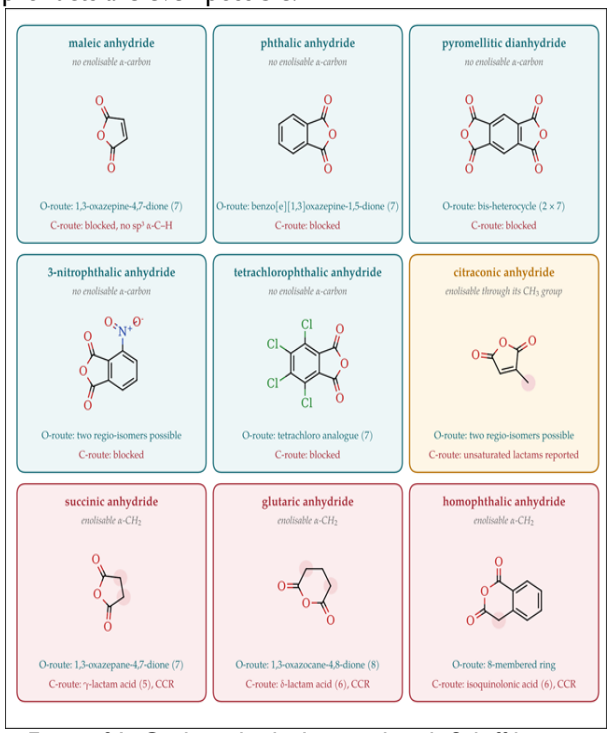


Figure 01: Cyclic anhydrides used with Schiff bases, grouped by whether they carry an enolisable α-carbon (red halo). The two lines in each tile give the ring that O-closure would form and whether the Castagnoli–Cushman (carbon) route is open.

3. OXAZEPINE-DIONE FORMATION

3.1. The reaction as reported

Most procedures follow one pattern (Figure 2; Table 1). The imine and the anhydride are mixed 1:1, or 1:2 for bis-imines, and heated in dry benzene, less often in ethanol, THF, dichloromethane, dioxane or toluene, for two hours to a day; a few groups grind the solids together and use microwave heating instead [24,25]. The solid that separates on cooling is recrystallised and described as the seven-membered dione. Maleic anhydride gives 2,3-dihydro-1,3-oxazepine-4,7-diones, succinic anhydride the saturated 1,3-oxazepane-4,7-diones, and phthalic anhydride and its tetrahalo or nitro derivatives the benzo-fused diones [5,26]. Bis-imines from benzidine, o-tolidine and other diamines are converted into bis-heterocycles in the same way [4,27]. The one report that used glutaric anhydride still named its product a 1,3-oxazepine-4,7-dione, although insertion into a six-membered anhydride must give an eight-membered ring [28]. Naming is loose in general. The benzo-fused skeleton appears under several names; with fused-ring numbering it is a 3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione, and its acetal carbon is C-3, not C-2.

Unsymmetrical anhydrides raise a question that these reports leave open. With 3-nitrophthalic or citraconic

anhydride the imine nitrogen can attack either carbonyl group, and the two choices lead to different regioisomers of the dione. Steric hindrance next to one carbonyl and the electronic pull of the nitro or methyl group should favour one site, yet the regiochemistry is not discussed, for example, in the report on citraconic anhydride [29]. HMBC correlations from the ring CH and from the remaining ring protons to the two carbonyl carbons would settle the point.

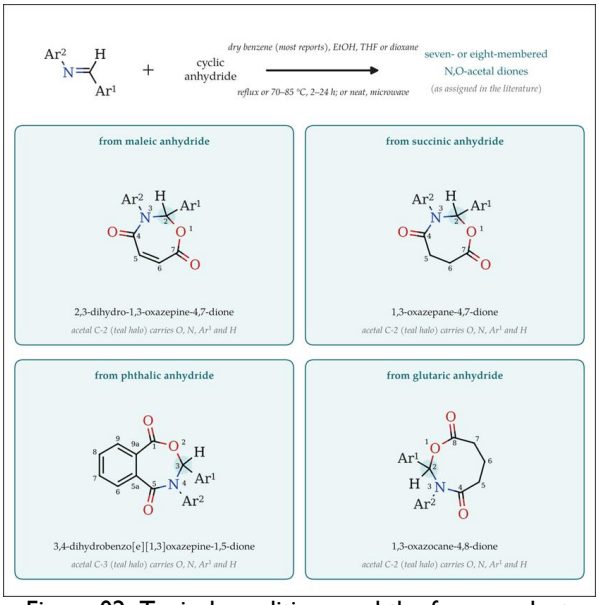


Figure 02: Typical conditions and the four product skeletons assigned in the literature, with ring numbering. The acetal carbon (teal halo) is C-2 in the monocyclic series and C-3 in the benzo-fused series.

3.2. What the "[2+5] cycloaddition" label does and does not say

IUPAC defines a cycloaddition as a reaction in which two or more unsaturated molecules, or parts of one molecule, combine to form a cyclic adduct with a net reduction of bond multiplicity [30]. The imine–anhydride reaction fits that wording, since the C=N π bond is consumed and a ring appears. The bracket, however, counts ring atoms, not electrons, and the same IUPAC entry notes that a cycloaddition may be pericyclic or may run stepwise. The five-atom component (C(=O)–C=C–C(=O)–O in maleic anhydride) is not a conjugated π system that could take part in a concerted, orbital-symmetry-controlled addition of the type analysed by Woodward and Hoffmann [31]. A C–O bond of the anhydride must also break, and a single concerted transition state that breaks this bond and makes two new ones is hard to defend.

A stepwise polar path fits the known chemistry better (Figure 3). The imine nitrogen attacks one carbonyl carbon, the tetrahedral intermediate collapses and the anhydride ring opens. The nitrogen is now part of an N-acyliminium ion, and the other end of the chain is a carboxylate. N-Acyliminium ions are powerful electrophiles with a large literature of their own [32,33]. Here the nearest nucleophile is the carboxylate on the same chain. Its oxygen adds to the iminium carbon and closes the seven-membered ring, a 7-endo-trig closure that Baldwin's rules allow [34].

The product deserves a more exact name than "oxazepine". Its C-2 carbon carries an oxygen, a nitrogen, an aryl group and a hydrogen, so the ring is a cyclic N-acyl-N,O-acetal. Its open-chain relatives, N-(1-acyloxyalkyl)amides, form when imines meet acyclic anhydrides in the presence of a base [35], and amides of this kind are classical sources of N-acyliminium ions [32,36]. Two consequences follow. The ring can open again to the same ion pair, above all in polar or acidic media, and the ion pair can then be captured by water. Also, closing a seven-membered ring is entropically harder than closing a five- or six-membered one [37], so any faster competing step will win. The oxazepine-dione is better viewed as one resting state of a reactive intermediate than as the fixed result of a concerted event.

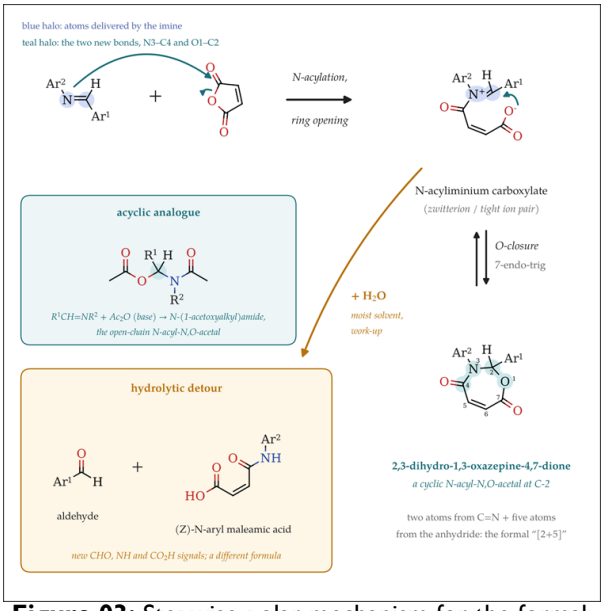


Figure 03: Stepwise polar mechanism for the formal "[2+5]" reaction. N-Acylation and ring opening give an N-acyliminium carboxylate, which closes through oxygen (7-endo-trig) to the cyclic N-acyl-N,O-acetal or is captured by water. The open-chain analogue formed from imines and acetic anhydride is shown for comparison [35].

4. PREVIOUS STUDIES ON OXAZEPINE-DIONES

To see what the oxazepine-dione literature actually rests on, we read forty reports in full, published between 2006 and 2026; Table 1 lists twenty representative ones. The procedures are remarkably uniform. Dry benzene was the solvent in 22 of the 40, ethanol in 10, THF, dichloromethane or dioxane in 4 and toluene in 1, while two used solvent-free

microwave heating. Ethanol deserves a remark, since it can itself open a cyclic anhydride to a half-ester. Infrared spectra appear in 38 papers, usually with melting points, and loss of the C=N band is stated in 20. Some ^{1}H NMR data appear in 31, often for one compound only. ^{13}C NMR was reported in 8 papers, CHN analysis in 19 and mass spectra in only 3. One study used DEPT, COSY, HMQC and HMBC [38], and one used DFT, on the imines only [5]. None reports a single-crystal structure, and our searches found no X-ray-confirmed oxazepine-dione made by this route. Alternatives were considered in just one paper, which rejected a fused β-lactone/γ-lactam and a [2+2] adduct [39]. One other warned that IR cannot tell the possible products apart and that more work was needed [40].

Table 01: Representative reports of Schiff base–cyclic anhydride reactions assigned as oxazepine-dione (or oxazepane-dione) formation. Data are given as printed in each paper (DMSO-d_6 unless stated); n.r., not reported.

Ref.	Imine (amine + aldehyde)	Anhydride(s)	Conditions; yield (%)	Evidence reported	Ring CH as reported, δ_H; δ_C
[39]	melamine-derived mono-, bis- and tris-imines of 4-Me_2N-benzaldehyde	maleic, succinic	EtOH, reflux, 2 h; ≈59–85	IR, ^{1}H, CHN, UV	not assigned; a fused β-lactone/γ-lactam and a [2+2] adduct were considered and rejected
[41]	thiourea + 2-HO- or 4-Me_2N-benzaldehyde (mono and bis)	maleic, phthalic, succinic	EtOH, 78 °C, 2–3 h; 55–77	IR, ^{1}H, CHN, UV	not assigned
[38]	N-alkyl imines of 3-hydroxybenzaldehyde	succinic	n.r. (synthesis cited as reported elsewhere)	^{1}H, ^{13}C, DEPT-135, COSY, HMQC, HMBC	7.56–7.93 (s); 67.6–70.6
[26]	4-aminoantipyrine + vanillin or o-vanillin	maleic, phthalic, 3-nitrophthalic	benzene, 75 °C, 5 h; 60–72	IR, ^{1}H (one compound), CHN	within 7.35–7.42 (m)
[4]	o-tolidine bis-imines of substituted benzaldehydes	maleic, phthalic	CH_2Cl_2, THF or dioxane, N_2, reflux 2.5–6 h; 41–89	IR, ^{1}H, CHN	7.97–9.78 (s)
[42]	heteroaryl aldimines	phenylsuccinic	benzene, reflux 5 h; 45–80	IR, ^{1}H, UV	3.58 (“ring CH”)
[5]	4,4′-oxydianiline bis-imines of 4-X-benzaldehydes	tetrachloro- and tetrabromophthalic	benzene, reflux 4 h; 56–71	IR, ^{1}H, ^{13}C, CHN; DFT on the imines	10.62–10.85 (s); 115.6–116.9
[43]	4-aminodiphenylamine + ten benzaldehydes	phthalic	benzene, 85 °C, 5–6 h; 53–96	IR, ^{1}H, ^{13}C (DEPT), UV	9.67–10.18 (s); n.r.
[24]	hydrazones of a benzotriazolyl acetohydrazide	maleic	solvent-free, microwave 700 W; 60–90	IR, ^{1}H, UV	8.1
[40]	hydrazones of a pyrimidinone hydrazine	maleic, phthalic	EtOH, reflux 4 h; 72–86	IR, ^{1}H, ^{13}C	n.r.; the authors note that IR cannot distinguish the products
[29]	4-methylaniline aldimines	citraconic, tetrachloro-phthalic, epoxy-tetrahydro-phthalic	benzene, reflux 4 h; 67–78	IR, ^{1}H	10.08–10.70 (s)
[27]	bis-imines of an aromatic diamine	maleic	benzene, reflux 7 h; 59–75	IR, ^{1}H (selected), CHN, UV	8.62 (br s)

[44]	1,7-diaminoheptane and 1,8-diaminooctane bis-imines	phthalic	benzene, 70 °C, 5 h; 70–85	IR, ^{1}H, ^{13}C, HRMS ($CDCl_3$)	within 6.90–8.23 (m)
[45]	methyldopa + vanillin or 4-Cl-, 2,4-Cl_2-, 4-O_2N-benzaldehyde	phthalic, tetrachlorophthalic	reflux 6–8 h; 65–90	IR, ^{1}H, ^{13}C	7.53–7.89 (s); 84.0–86.8
[6]	4-(6-methylbenzothiazol-2-yl)aniline + benzaldehydes	phthalic	benzene, 85 °C, 7–9 h; 63–75	IR, ^{1}H, ^{13}C	9.44–9.95 (s); 113.96–114.28
[46]	benzidine bis-imines of 4-substituted cinnamaldehydes	succinic	benzene, reflux overnight; 76–78	IR, ^{1}H	n.r.
[25]	benzidine and aminoanthraquinone imines	maleic, phthalic, succinic	solvent-free, microwave 280 W, 20–25 min; 69–89	IR, ^{1}H, ^{13}C	9.6
[47]	sulfamethoxazole + substituted benzaldehydes	maleic	benzene, 75–80 °C, 6 h; 72–80	IR, ^{1}H, MS (M+H), CHN	assigned inconsistently (6.33, or 10.03–11.89)
[48]	bis-imines of 1,2-bis(4-aminophenoxy)ethane	maleic, phthalic	benzene, reflux 5 h; n.r.	IR, ^{1}H (one compound)	n.r.; a CH=N singlet (8.9) is still listed for the product
[28]	an imidazolyl aldimine	maleic, phthalic, succinic, glutaric	benzene, reflux 14–15 h; 67–74	IR, ^{1}H, ^{13}C	n.r.; 88–90 (assigned to an "oxazepine methylene")

The reported spectra are also hard to reconcile with a single structure (Figure 4). The singlet assigned to the ring CH runs from δ 7.53 to 10.85 in most papers [5,45], with one value as low as δ 3.58 [42]. Its carbon has been placed at δ 67.6–70.6 [38], 84.0–86.8 [45], 88–90 [28] and 113.96–116.94 [5,6]. The highest values lie in the aromatic window, far from the δ 79.5 found for the O–CH_2–N carbon of a related N-acyl N,O-acetal [49]. Many of the proton values overlap the CH=N singlet of the starting imines, δ 8.45–8.55 [6,50]. In one recent report the azomethine singlet is still listed for the product [48], and in another the ring protons are assigned in two contradictory ways [47]. None of the maleic-anhydride papers gives the coupling constant of the ring CH=CH protons.

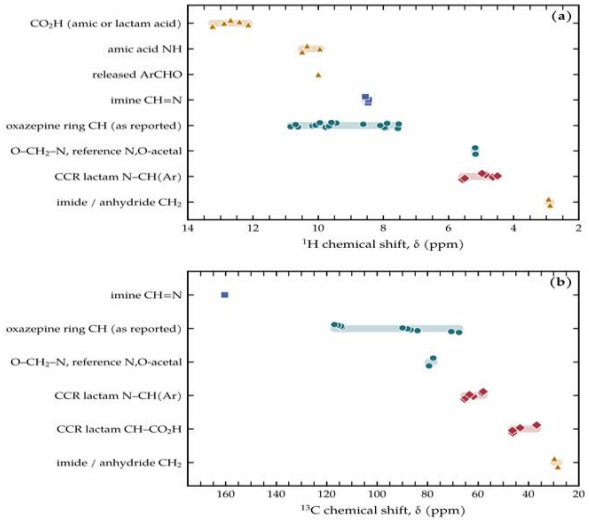


Figure 04: Literature chemical shifts of the diagnostic CH groups: (a) ^{1}H, (b) ^{13}C. Teal circles, ring CH as assigned in oxazepine-dione reports [4–6,24,25,27–29,38,43,45] and the O–CH_2–N group of a reference N-acyl N,O-acetal [49]; blue squares, imine CH=N [6,50]; crimson diamonds, Castagnoli–Cushman lactam acids [13,51,52]; amber triangles, groups from hydrolysis or fragmentation [13,51,53–55]. Bars join the extreme values in each row.

Independent work points the same way. Kumar et al. heated benzylideneanilines with phthalic, succinic or maleic anhydride in acetic acid and isolated N-arylimides together with the free aldehyde [56]. In a solvent-free CCR study, discussed below, the seven-membered N,O-acetal appears only as a short-lived intermediate on the way to the imide [13]. None of this proves that a given oxazepine-dione is misassigned. It does show that the usual evidence cannot exclude the alternatives.

5. COMPETING LACTAM PATHWAYS

5.1. The Castagnoli–Cushman reaction

In 1969 Castagnoli heated succinic anhydride with N-benzylidenemethylamine and isolated a γ-lactam acid, 1-methyl-5-oxo-2-phenylpyrrolidine-3-carboxylic acid, in both trans and cis forms [9]. The scope was soon widened to substituted succinic anhydrides and to glutaric anhydride, which gives δ-lactam acids [10,57]. Homophthalic anhydride, whose benzylic CH_2 is activated by the ring, gives 1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids [58,59]. Fifty years on, the CCR covers heteroatom-substituted and ring-expanded anhydrides, three- and four-component formats and catalytic asymmetric versions [11,12,22,60–62]. Representative examples are collected in Table 2.

Table 02: Representative Castagnoli–Cushman (carbon–carbon) reactions of imines with enolisable or latently enolisable anhydrides.

Ref.	Anhydride	Imine partner / format	Product (ring size)	Conditions and outcome
[9]	succinic	N-benzylidene-methylamine	1-methyl-5-oxo-2-phenyl-pyrrolidine-3-carboxylic acid (5)	first report; trans and cis acids
[10]	substituted succinic	Schiff bases	γ-lactam acids (5)	scope and first mechanistic proposal
[57]	glutaric	imines	δ-lactam acids (6)	route to nitrogen analogues of the tetrahydrocannabinols
[58]	homophthalic	azomethines	3,4-dihydroisoquinolin-1(2H)-ones (6)	highly stereoselective
[59]	homophthalic	imines	tetrahydroisoquinolonic acids (6)	cis- and trans-13-methyltetrahydroprotoberberines
[63]	homophthalic; 3-phenylsuccinic	Schiff bases	(6); (5)	electronic and steric control of cis/trans ratios
[64]	3-thiosuccinic	imines	γ-lactams (5)	tricyclic core of martinellic acid
[65]	maleic + thiol (thiosuccinic in situ)	amine + aldehyde, four-component	γ-lactams (5)	one pot, diastereoselective
[23]	alkyl-substituted maleic	imines	unsaturated lactams	complex N-heterocycles in one step
[66]	cyanosuccinic	imines	γ-lactams (5)	room temperature; high yields and dr
[13]	succinic, glutaric	aryl aldimines incl. N-benzylideneaniline	γ- and δ-lactam acids (5, 6)	neat, 150–170 °C; trans major; imide and amic acid by-products
[51]	succinic, glutaric	imines	γ- and δ-lactam acids (5, 6)	DMF gives the rare cis isomers; ^3J criteria
[61]	an enolisable anhydride	imines	lactam acids	first catalytic asymmetric version
[62]	seven-membered anhydrides formed in situ from diacids	imines	arene-fused seven-membered lactams (7)	extends the reaction beyond five- and six-membered rings
[60]	homophthalic acid	amine + aldehyde, three-component	trans-tetrahydroisoquinolonic acids (6)	no dehydrating agent needed
[52]	succinic, glutaric, diglycolic, thiodiacetic	cyclic imines	fused lactam acids (5, 6)	xylene, 120 °C, 6 h; cis:trans ≈ 1:1
[67]	homophthalic	amine + aldehyde, three-component	dihydroisoquinolones (6)	cis forms first and epimerises to trans at ≥110 °C

5.2. Mechanism and stereochemistry

Two pictures of the CCR have been argued over. In the older one the imine nitrogen is acylated first, much as in Figure 3, and the enolised arm of the resulting iminium carboxylate then closes onto the iminium carbon. In the other, the enol or enolate of the intact anhydride adds to the imine carbon in a Mannich-type step, and the new amine nitrogen then attacks the remaining anhydride carbonyl to close the lactam. Kaneti and co-workers once proposed a concerted path through the anhydride enol [68], but later work favours the stepwise Mannich sequence. Calculations on cyanosuccinic anhydrides place a Mannich addition of the anhydride enol to the E-imine before a transannular acylation [69]. For homophthalic anhydride, DFT supports a Perkin–Mannich path under $TiCl_4$ catalysis [70], and an amino-anhydride Mannich intermediate has been intercepted [71]. Mechanistic and crossover experiments on three-component versions show that the amide-acid formed from amine and anhydride is only a reversible reservoir; the productive steps are imine formation, Mannich addition and acylation [67]. Anionic versions of the anhydride Mannich step have even been used in total synthesis [72]. The recent review by Ramiro et al. summarises the current consensus [12].

A simple geometric point supports this choice and links the two literatures. If the imine is acylated first, the carbon nucleophile must attack an iminium carbon that lies inside the ring being formed, a 5-endo-trig closure that Baldwin's rules disfavour [34]. If the Mannich step comes first, the lactam closes by attack of nitrogen on an exocyclic carbonyl, a favoured 5-exo-trig process. The N-acyliminium carboxylate of Figure 3 therefore has an easy exit through oxygen (7-endo-trig) and a poor one through carbon. Acylation first leads towards the oxazepine-dione; enolisation first leads towards the lactam.

Stereochemistry follows the conditions. Under classical conditions, benzene, toluene or xylene at high temperature, the trans lactam acid predominates [12]. Reactions in DMF give the rarer cis isomers [51], and in homophthalic three-component reactions the cis product forms first and epimerises to trans above about 110 °C [67]. Electronic and steric effects on the cis/trans ratio were analysed early by Cushman and Madaj [63].

5.3. Where the two manifolds meet

Maleic and phthalic anhydrides cannot enolise, so with them the carbon route is closed and only acylation, O-closure or hydrolysis remain. Even so, maleic anhydride can be diverted: thiols add to it to give enolisable 3-thiosuccinic anhydrides, which take part in the CCR [64,65]. Succinic and glutaric anhydrides are a different matter. The conditions used in most oxazepine-dione papers, dry benzene under reflux for hours (Table 1), are close to classical CCR conditions, and the products the CCR predicts are isomers of the claimed seven-membered rings. For the parent pair, benzylideneaniline and succinic anhydride, the CCR product is trans-5-oxo-1,2-diphenylpyrrolidine-3-carboxylic acid, fully characterised by Krasavin and co-workers [13], while the O-route product would be 2,3-diphenyl-1,3-oxazepane-4,7-dione. Both are $C_{17}H_{15}NO_3$ (Figure 05).

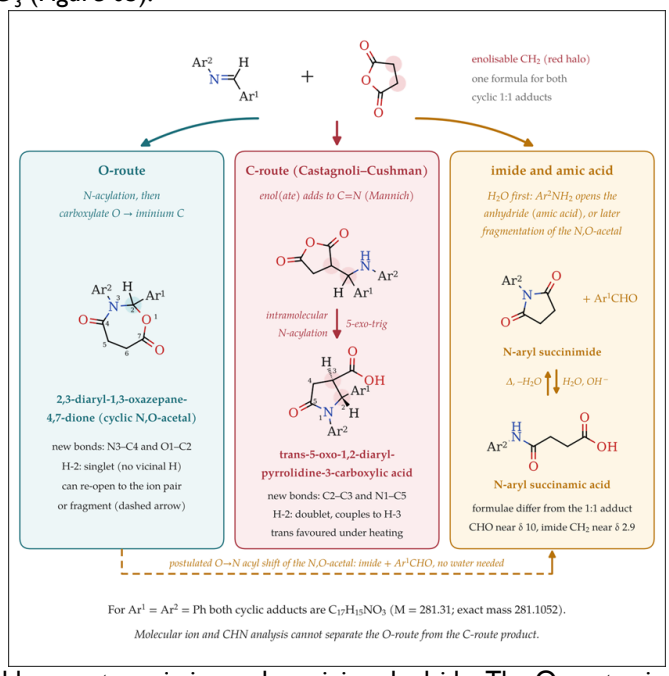


Figure 05: The three manifolds open to an imine and succinic anhydride. The O-route gives the cyclic N,O-acetal, the C-route gives the isomeric trans-γ-lactam acid, and water or fragmentation of the N,O-acetal gives the imide, the aldehyde and the amic acid. The dashed arrow follows the pathway postulated by Lepikhina et al. [13].

The most telling observation comes from that same CCR study. Products made from succinic anhydride were often contaminated with succinic acid monoanilide, and the crude spectra showed an aldehyde proton near δ 10.0 and the

succinimide CH_2 near δ 2.9. To explain this the authors proposed that the acylated imine is trapped by its own carboxylate to give a cyclic aminal, which either returns to the zwitterion or loses the aldehyde to give N-phenylsuccinimide; the imide is then opened to the monoanilide during the basic work-up [13]. That cyclic aminal is, ring for ring, the 1,3-oxazepane-4,7-dione of the oxazepine literature. Glutaric anhydride gave fewer by-products, which the authors linked to the less favourable eight-membered analogue. So the CCR literature treats the seven-membered N,O-acetal as a short-lived side intermediate, whereas the oxazepine literature treats it as an isolable product.

5.4. Hydrolysis, amic acids and imides

Water opens a third door. Hydrolysis of the imine releases the amine, which opens the anhydride to an amic acid [15,18]. On heating, or with acetic anhydride, the amic acid closes to the imide, and with some reagents to the isoimide first [18,20,21]. The imide can also be reached without water, through the O→N acyl shift just described [13], and in hot acetic acid it is the main product [56]. These products have formulae different from the 1:1 adduct, so careful CHN analysis or HRMS should expose them. Infrared spectra alone will not: an amic acid also lacks the C=N band and shows two carbonyl absorptions, and an imide has a carbonyl pair of its own. Imines that carry an α-hydrogen, for example those from aliphatic aldehydes or methyl ketones, can avoid both rings altogether: with enolisable anhydrides they usually give N-acyl enamines instead of lactams [12].

6. SPECTROSCOPIC PROOF

6.1. Infrared spectra

IR is the cheapest test and the one most often quoted, but it is the weakest. Cyclic anhydrides absorb at two high frequencies, 1853 and 1780 cm^{-1} for maleic anhydride [73], so a band in that region signals unreacted anhydride. Beyond that, the windows overlap (Table 3). Bands assigned to the "lactone" and "lactam" carbonyls of oxazepine-diones are reported at about 1680–1760 and 1530–1670 cm^{-1} [4,5,24,25,45], whereas a fused γ-lactam acid absorbs at 1709–1710 and 1674–1675 cm^{-1} [52] and tetrahydroisoquinolonic acids at 1720–1730 and 1630 cm^{-1} [74]. Loss of the C=N band is shared by every product. IR is best used to show that the starting materials are consumed and to look for the broad O–H absorption of a carboxylic acid, not to prove a ring [75,76].

Table 03: Literature spectroscopic data for the parent imine and for the possible products of imine–anhydride reactions. Values as printed in the cited sources.

Species (solvent)	Diagnostic δ_H (ppm)	Diagnostic δ_C (ppm)	IR ν(C=O), cm^{-1}	Ref.
N-benzylideneaniline ($CDCl_3$)	CH=N 8.47 (s)	CH=N 160.4	–	[50]
maleic / succinic / phthalic anhydride (DMSO-d_6)	CH= 6.67 (s) / CH_2 2.93 (s) / –	C=O 166.9 / 174.0 / 164.1	1853, 1780 (maleic)	[55,73]
1,3-oxazepane-4,7-diones, as reported (DMSO-d_6)	ring CH 7.56–7.93 (s); CH_2 2.21–2.48 (two t)	ring CH 67.6–70.6; C=O 171.5–176.7	n.r.	[38]
benzo-fused oxazepine-diones, as reported (DMSO-d_6)	ring CH 7.53–7.89, 9.44–9.95 or 10.62–10.85 (s)	ring CH 84.0–86.8, 113.96–114.28 or 115.6–116.9	1678–1725 and 1643–1672	[5,6,45]
trans-5-oxo-1,2-diphenylpyrrolidine-3-carboxylic acid, CCR (DMSO-d_6)	H-2 5.58 (d, J 5.3); H-3 3.10 (ddd); H-4 2.97, 2.76 (dd); CO_2H 12.89	C-2 65.2; C-3 46.2; C-4 34.6; C=O 174.0, 172.3	n.r.	[13]
cis/trans γ-lactam acids, CCR (DMSO-d_6)	$^3J_{2,3}$ 8.6–9.3 Hz (cis), 1.0–6.2 Hz (trans)	C-2 61.9 (cis), 63.5 (trans)[a]	–	[51]
fused γ-lactam acids, CCR (DMSO-d_6)	N–CH(Ar) 4.87–4.97 (d)	N–CH(Ar) 58.0–58.2	1709–1710, 1674–1675	[52]
tetrahydroisoquinolonic acids, CCR	$^3J_{3,4}$ <1 Hz (trans), ≈6 Hz (cis)	–	1720–1730, 1630	[74,77]
N-phenylmaleamic acid (DMSO-d_6)	CH=CH 6.34, 6.51; NH 10.50; CO_2H 13.25; vinyl ^3J ≈ 12.5 Hz in an N-alkyl analogue	C=O 163.3, 166.8	–	[53,78]
N-phenylmaleimide ($CDCl_3$)	CH=CH 6.84 (s, 2H)	C=O 169.3; CH= 133.9	–	[79,80]
N-phenylsuccinamic acid (DMSO-d_6)	CH_2 2.56 (4H); NH 9.95; CO_2H 12.15	C=O 170.2, 173.9	–	[53]
N-phenylsuccinimide ($CDCl_3$)	CH_2 2.89 (s, 4H)	C=O 176.1; CH_2 28.4	–	[54]

N-phenylphthalimide ($CDCl_3$)	7.94–7.96 and 7.75–7.82 (m)	C=O 167.4	–	[81]
3-methyl-2,3-dihydro-1,3-benzoxazin-4-one, a reference N-acyl N,O-acetal ($CDCl_3$)	O–CH_2–N 5.17 (s)	O–CH_2–N 79.5	–	[49]
crude CCR mixtures	ArCHO ≈10.0; succinimide CH_2 ≈2.9	–	–	[13]

[a] 1-benzyl-2-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid. n.r., not reported; –, not applicable or not given in the cited source.

6.2. ^{1}H NMR

Four features carry most of the weight. The first is multiplicity. The acetal H-2 of a seven-membered N,O-acetal has no vicinal partner and must be a singlet, whereas H-2 of a CCR γ-lactam acid is a doublet coupled to H-3, at δ 5.58 (J = 5.3 Hz) for the parent trans-diphenyl acid [13]. The size of that coupling also fixes the configuration: 8.6–9.3 Hz for cis and 1.0–6.2 Hz for trans γ-lactam acids [51], and below 1 Hz for trans tetrahydroisoquinolonic acids against about 6 Hz for cis [77]. The second is position. A singlet near δ 8.4–8.6 must be checked against the CH=N signal of the starting imine, δ 8.47 for N-benzylideneaniline in $CDCl_3$ [50]. The third is the exchangeable protons. Amic acids show NH at δ 9.9–10.5 and CO_2H at δ 12.2–13.3 in DMSO-d_6 [53], lactam acids a CO_2H near δ 12.9 [13], and D_2O exchange identifies both. The fourth is the "spectator" signals. A released aldehyde gives a CHO singlet near δ 10.0 and N-aryl succinimide a four-proton singlet near δ 2.9 [13,54]. N-Phenylmaleimide gives a two-proton singlet at δ 6.84 in $CDCl_3$ [79], whereas maleamic acids show two vinyl doublets with J ≈ 12.5 Hz [78]. Unreacted succinic anhydride (δ 2.93) [55] and the residual DMSO signal sit in the same region as the ring CH_2 of an oxazepane-dione, so that region needs care.

6.3. ^{13}C NMR, DEPT and two-dimensional spectra

The ring carbon is the single most informative atom (Figure 6). In a genuine N-acyl-N,O-acetal it is an sp^3 CH bonded to oxygen and nitrogen. A six-membered analogue, 3-methyl-2,3-dihydro-1,3-benzoxazin-4-one, shows its O–CH_2–N carbon at δ 79.5 [49], and an aryl substituent should move a CH further downfield [82]. The CCR alternative places C-2 at δ 61.9–65.2 and C-3 at δ 46.2 [13,51], and the imine carbon resonates at δ 160.4 [50]. A DEPT-135 spectrum then counts the sp^3 ring carbons: one CH and two CH_2 for the oxazepane-dione, two CH and one CH_2 for the lactam acid. HSQC ties the singlet to its carbon, and HMBC should show the acetal proton correlating with both ring carbonyls, the amide through nitrogen and the ester through oxygen [83,84]. The second correlation is the one that proves closure through oxygen. In the only 2D study so far, the two CH_2 groups appeared as mutually coupled triplets linked by HMBC to both carbonyls, which fits an isolated –CH_2CH_2– bridge and argues against the CCR lactam. The correlation from the ring CH to the ester carbonyl was not listed, however, and the ring carbon was found at δ 67.6–70.6 [38].

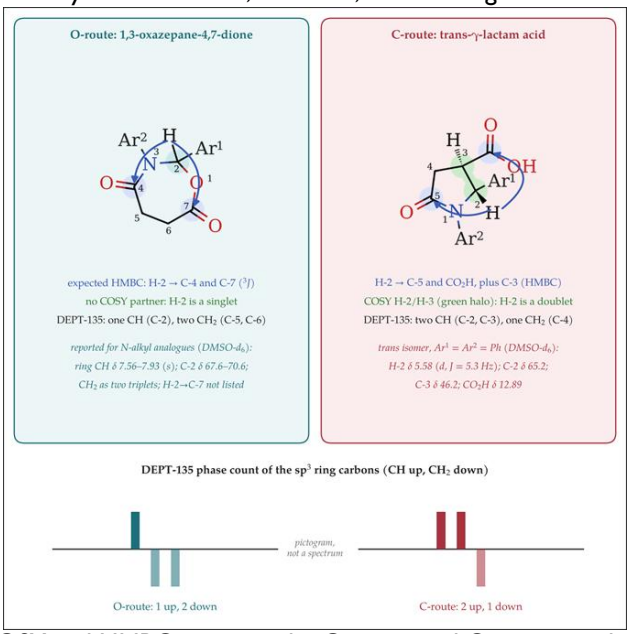


Figure 06: How DEPT-135, COSY and HMBC separate the O-route and C-route products of the succinic series. Blue arrows, key HMBC correlations; green halo, the H-2/H-3 COSY pair of the lactam. Values are from Mohammad et al. [38] and Lepikhina et al. [13]. The bottom panel is a pictogram of the expected DEPT-135 phase pattern, not a recorded spectrum.

6.4. Mass spectrometry and elemental analysis

Both techniques are good at excluding hydrolysis and fragmentation products, whose formulae differ from the 1:1 adduct. Neither can distinguish an oxazepine-dione from a lactam acid of the same formula (Figure 5). HRMS should therefore be reported as a formula check, not as proof of ring size. That only three of the forty papers we read reported a mass spectrum at all is a gap in itself.

6.5. X-ray diffraction and computed shifts

A single-crystal structure would end most debates, and we found no report of one for an oxazepine-dione made from an imine and an anhydride. Deposition with the Cambridge Structural Database would also give later workers a reference point [85]. Where crystals cannot be grown, computed NMR shifts are the next best check. GIAO-DFT shifts calculated for each candidate isomer can be compared with experiment, and DP4-type statistics then rank the candidates [86,87]. Such calculations are cheap compared with the cost of a wrong structure in the literature.

6.6. Authentic samples and sample handling

Two simple habits would remove much of the doubt. The first is comparison with authentic samples. The amic acid and the imide expected from hydrolysis can be made in a few hours from the amine and the anhydride [18], and the CCR lactam acid of the same pair is accessible under neat or xylene conditions [13,52]. A mixed melting point, a co-spotted TLC plate or overlaid spectra then show at once whether the supposed oxazepine-dione is one of them. The second is care with the NMR sample. DMSO-d_6 takes up water, and an N,O-acetal that opens on standing will look like a mixture of the product and its hydrolysis products. Dry solvent, a freshly opened ampoule and a spectrum recorded soon after dissolution reduce that risk, so that a second spectrum a day later tests the compound rather than the handling.

7. TOWARDS A MINIMUM EVIDENCE SET

Taken together, the sections above suggest that most disputes can be settled with experiments already available in any department that runs a 400 MHz spectrometer. Table 4 sets them out as questions. The order matters: the first two rows ask whether the imine is gone and whether water took part, and only then does it make sense to argue about ring size.

Table 04: A minimum evidence set for imine–anhydride products, written as questions. The shift windows are those of Table 03.

Question	Experiment	Supports the N,O-acetal (oxazepine-dione)	Points to an alternative
Has the imine reacted?	FT-IR; ^{1}H NMR	loss of ν(C=N) and of the CH=N singlet	the same loss follows hydrolysis or the CCR, so the test is necessary but not sufficient
Did water take part?	^{1}H NMR in DMSO-d_6 before and after D_2O; IR 3500–2500 cm^{-1}	no exchangeable NH or CO_2H; no CHO singlet	NH and CO_2H signals (amic acid or lactam acid); CHO of the released aldehyde
How many sp^3 CH and CH_2 carbons?	^{13}C with DEPT-135; HSQC	one CH, the N,O-acetal carbon, in the acetal window	two CH and one CH_2 (lactam from succinic anhydride); no sp^3 CH (amic acid, imide)
Is the ring CH isolated?	^{1}H multiplicity; COSY	H-2 (H-3 in the benzo series) is a singlet with no COSY partner	a doublet with a COSY partner (lactam H-2/H-3)
Which carbons surround that CH?	HMBC	H-2 to both ring carbonyls and to the ipso carbon of Ar^1; no link to another sp^3 CH	H-2 to an sp^3 CH (lactam C-3) and to the CO_2H carbon
What is the formula?	HRMS; CHN	agrees with a 1:1 adduct	a lactam acid gives the same result; only hydrolysis products differ
Is the product stable in solution?	^{1}H NMR repeated after 24 h in DMSO-d_6; TLC	spectrum unchanged	growing CHO, NH or CO_2H signals (ring opening)
Is the connectivity beyond doubt?	single-crystal XRD; GIAO shifts ranked by DP4+	structure solved, or best statistical fit to the N,O-acetal	structure or best fit corresponds to another isomer

Three points deserve emphasis. DEPT-135 is probably the cheapest decisive experiment, because the phase pattern alone separates the O-route and C-route products of the succinic series. Stability should be checked, not assumed; a spectrum re-recorded after a day in DMSO-d_6 costs nothing and shows at once whether the N,O-acetal opens. And a single-crystal structure ends the argument for that compound while also calibrating the spectra of its analogues. Reports should also give the crude ^{1}H NMR spectrum, the yield of purified material and the solvent of every spectrum, since these are the details a reader needs to repeat the work.

Several open questions could be answered quickly. In situ IR or NMR monitoring might catch the iminium carboxylate, or show that the amic acid forms first. Crossover experiments with two different imines would test whether the seven-membered ring opens and re-closes under the reaction conditions. The barriers of O-closure and C-closure could be computed for the same N-acyliminium carboxylate, and the predicted shifts of each isomer compared with experiment. None of this is exotic, and each result would make the large body of oxazepine-dione work more useful to others.

8. CONCLUSION

Schiff bases and cyclic anhydrides are simple partners, but they do not have one fate. With non-enolisable anhydrides such as maleic and phthalic anhydride, N-acylation of the imine and closure of the iminium carboxylate through oxygen can give the seven-membered N,O-acetals reported as oxazepine-diones, while traces of water lead to amic acids and imides. With enolisable anhydrides a Mannich-type carbon–carbon route opens, and the Castagnoli–Cushman lactam acids that result are isomers of the claimed seven-membered rings. The CCR literature itself treats that ring as a short-lived intermediate that falls apart to an imide and an aldehyde. None of this means that the oxazepine-dione assignments are wrong. It means that infrared bands, a ^{1}H NMR singlet and a molecular ion are not enough to prove them. DEPT-135, COSY and HMBC spectra, a stability check in solution and, whenever crystals form, an X-ray structure would settle most cases. Used routinely, this evidence set would turn a large body of synthetic work into a dependable one.

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10. CONFLICT OF INTEREST

Not Declared.

11. INFORM CONSENT AND AUTHOR CONTRIBUTION

Not Applicable

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Not Declared.

13. REFERENCES

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