One-pot domino synthesis of polyvicinalamine monomers

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Abstract: Imidazole was generated *in situ via* a domino reaction between glyoxal, formaldehyde and two units of ammonia. Aqueous bicarbonate and a carboxylic anhydride or dialkyl dicarbonate were added, yielding the corresponding *N*,*N*'-diacyl or *N*,*N*'-dicarbalkoxy 2-hydroxyimidazoline. A Bamberger ring cleavage ensued, affording *cis*-1,2-di(acetamido)ethene, *cis*-1,2-di(propylamido)ethene, *cis*-1,2-di(ethoxyamido)ethene, *cis*-1,2-di(*t*-butoxyamido)ethene or *cis*-1,2-di(benzamido)ethene as easily isolable solids. The convenience and generality offered by this one-pot approach implied a cost-effective route to the routine synthesis of oligo- and polyvicinalamine precursors.

Key words: Bamberger ring cleavage, domino reaction, one-pot reaction, multi-component reaction, vicinal amine.

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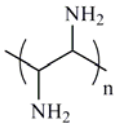
Introduction

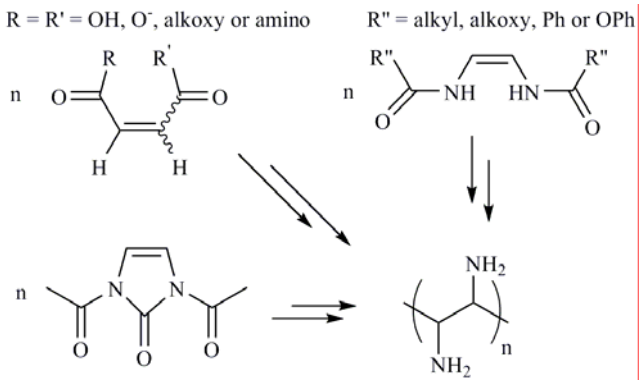
Polyamines have received much interest in view of their high amino group content, multi-interaction modes, facile tailorability and widespread applicability in products ranging from commodity chemicals for pulp processing or water treatment to specialty chemicals intended for use in pharmacy and biotechnology.[1-3]

Scheme 1. Polyamine featuring a 1:1 nitrogen-to-carbon ratio.



Recently, oligo- and polyvicinalamines with an impressive 1:1 nitrogen-to-carbon ratio have been prepared (Scheme 1). Of the three approaches portrayed (Scheme 2), the monomers utilized have been based on butenedioic acid, *cis*-1,2-diamidoethene, and 1,3-diacetyl-4-imidazolin-2-one.[1-13] The use of commercial butenedioic acid type monomers (Scheme 2, top left) introduces inconveniences related to halogenation, corrosion control and waste management. The use of *cis*-1,2-diamidoethene monomers (Scheme 2, top right) permits a relatively simpler, greener industrial process. Still, neither approach has enabled the formation of high molecular weight polyvicinalamines.[2-5] The polymerization of 1,3-diacetyl-4-imidazolin-2-one (Scheme 2, bottom left) has yielded comparatively higher molecular weight materials.[2,4] This last monomer, a cyclic analogue of *cis*-1,2-di(acetamido)ethene (**1a**, Entry 1 in Table 1), is highly reactive by virtue of the ring structure, which limits steric clutter about the double bond, and the acetyl groups, which overcome limitations inherent to polymerizing 4-imidazolin-2-one.[3] Still, the high hydrolytic stability of the polymeric intermediate formed demands harsh conditions to generate the free polyvicinalamine.[3]

Scheme 2. Monomers to prepare oligo- and polyvicinalamines: Butenedioic acid and derivatives (top, left); *cis*-1,2-diamidoethene (top, right); and 1,3-diacetyl-4-imidazolin-2-one (bottom, left).

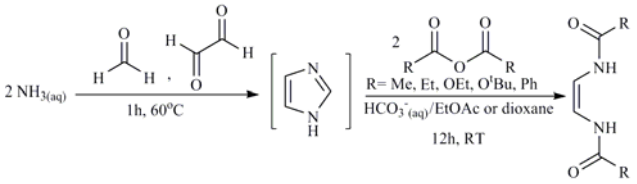


Some other factors, which influence the production feasibility of these polyamines, include the cost and commercial availability of the starting materials. While the butenedioic acid-based monomers are readily available, the *cis*-1,2-diamidoethene monomers are inevitably prepared using commercial imidazole. An even more inconvenient starting material, 1,3-diacetyl-4-imidazolin-2-one, is prepared from 4-imidazolin-2-one, a synthon that is commercially unavailable.[5] Interestingly, the related monomer 1,3-diethoxy-4-imidazolin-2-one has been prepared directly from *cis*-1,2-di(ethoxyamido)ethene (**2a**, Entry 2 in Table 1) by treatment with phosgene.[4] As this route bypassed 4-imidazolin-2-one, it followed to reason that a suitable source of imidazole, prepared very cost-effectively, could serve as a raw material of both the

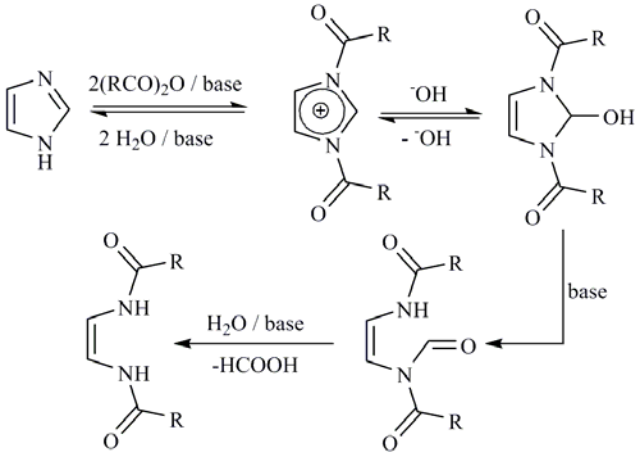
cis-1,2-diamidoethene type monomers and heterocyclic variants such as 1,3-diacetyl-4-imidazolin-2-one. The prospect was also attract-ive in that it seemed extendable to the preparation and conversion of 4-substituted and 4,5-disubstituted imidazoles.

In this work, a simple approach was envisaged to generate and utilize imidazole, affording the *cis*-1,2-diamidoethene monomers. The rationale was to prepare imidazole *in situ via* a domino synthesis,[7,13,14] and to continue directly with a Bamberger reaction (Schemes 3 and 4).[1] As implied, a key advantage of this approach was to bypass the inconveniences normally associated with isolating imidazole.[7,13] Integrating the two processes into a one-pot strategy appeared technically feasible, given that each reaction has traditionally been conducted in aqueous media. In a typical in-house procedure (Scheme 3), a mild excess of ammonia, and stoi-chiometric amounts of glyoxal and formaldehyde, were heated in a slightly oversized vessel, yielding imidazole. Unlike the classic three-hour domino synthesis,[7] the generation of imidazole was restricted to one hour; time-course trials confirmed that the yields of *cis*-1,2-di(acetamido)ethene (**1a**, Entry 1 in Table 1) were not improved by further incubation. The conditions to achieve ring cleavage were subsequently established in the same pot by modi-fying the solvent system and temperature. The workup was facili-tated by spontaneous crystallization or selective organic-phase partitioning of the *cis*-1,2-diamidoethene products. Recrystalliza-tion was conceivably optional, as the "crude" lyophilized products revealed a purity that implied their suitability as monomers.[1,2]

Scheme 3. One-pot domino reaction scheme to afford *cis*-1,2-di(alkylamido)ethene, *cis*-1,2-di(alkoxyamido)ethene and *cis*-1,2-di(benzamido)ethene from commodity materials.



Scheme 4. Bamberger ring cleavage pathway in aqueous bicarbonate. Imidazole is activated *via* carboxylic anhydride or dialkyl dicarbonate.[1] The *N*,*N*'-diacyl or *N*,*N*'-dicarbalkoxy imidazolium species formed is attacked by hydroxide at the C-2 center, affording a *N*,*N*'-diacyl or *N*,*N*'-dicarbalkoxy 2-hydroxyimidazoline. Ring fission ensues, producing a *cis*-1,2-diamido-*N*-formylethene. Hydrolytic *N*-deformylation follows, yielding the end product.



Results and Discussion

The one-pot process proved easy to implement and amenable to a broad selection of acylating agents (**1**-**5**, Table 1). The yields, while modest, were offset by the extremely cheap starting materials and ease of product isolation. The facility of the overall process was best illustrated by the example of acetic anhydride (**1**, Entry 1 in Table 1), which upon gradual addition, smoothly afforded **1a** *via* spontaneous crystallization.[1] The process was readily upscaled to 30L, further implying its industrial merit. The one-pot approach also confirmed the general utility of acid anhydrides, as all work on the Bamberger reaction had been focused, until recently,[1] on the use of benzoyl chloride, alkyl and aryl chloroformates, and **2**.[2,6,8-11] Validating the utility of acid anhydrides was particularly encouraging, as one of the two reported attempts to prepare a *cis*-1,2-di(alkylamido)ethene, specifically **1a**, had failed using **1**.[12] Lastly, the structural diversity offered by **1a**-**5a** (Table 1) was attractive, as stereo-electronic differences could serve to extend the utility of this monomer class. For instance, a copolymer prepared from **1a, 2a** and **3a** could potentially be prompted to selectively deblock under appropriate conditions.

Prior studies[6,9] on the Bamberger reaction provided a mechanistic basis to relate product yield to the conversion of a 2-hydroxyimidazoline intermediate. As shown in Scheme 4, ring fission is initially prompted by the stepwise *N*,*N*'-diacylation or *N*,*N*'-dialkoxyformylation of imidazole in aqueous base, forming an activated imidazolium species. Hydroxide attack ensues at the C-2 carbon, reversibly forming a *N*,*N*'-diacyl or *N*,*N*'-dicarbalkoxy 2-hydroxy-imidazoline. A general or specific base-catalyzed cleavage of the ring follows, yielding a *cis*-1,2-diamido-*N*-formylethene. The formyl group is hydrolyzed *via* base catalysis, affording the *cis*-1,2-diamidoethene product. Known to resist the activation of imi-dazole are hydrolytic pathways, which act to quench reagent and to hydrolyze any *N*-substituted and *N*,*N*'-disubstituted imidazoles. By probing the interaction of imidazole and **2** at low concen-trations, Grace *et al.* described a kinetic scenario, characterizable by the rapid accumulation of 2-hydroxy-*N*,*N*'-dicarbethoxyimida-zoline, the slow cleavage of the ring, and the pH-dependent and typically rate-determining deformylation of the C-2 carbon.[6] As all reactants of the current study were utilized at much higher initial concentrations, it was safe to conclude that the *N*,*N*'-disub-stituted 2-hydroxyimidazoline intermediate derived from each of **1**-**5** would be rapidly formed. In the mechanistic assessment of Grace *et al.*,[6] it was also clear that given enough time, the yield of *cis*-1,2-di(ethoxyamido)ethene would not reflect the deformyla-tion rate of *cis*-1,2-diethoxyamido-*N*-formylethene. Rather, it would reflect the committed conversion of 2-hydroxy-*N*,*N*'-dicarbethoxyimidazoline to *cis*-1,2-diethoxyamido-*N*-formylethene. Thus, achieving a good yield ultimately rested on establishing an extended and sufficiently high steady-state concentration of the imidazoline, a task realized by discouraging hydrolytic deactivation and optimizing the availability of **2**. A similar kinetic view applied to the current work. Namely, the yield of each of **1a**-**5a** (Table 1) reflected the extent to which an effective, prolonged conversion of the corresponding *N*,*N*'-disubstituted 2-hydroxy-imidazoline could be realized. In fact, the yield discrepancies amongst **1a**-**5a** not only reflected inherent stereo-electronic differences acting along the reaction coordinate, but presumably also some variations related to the addition of **1**-**5**. The literature yields (in parantheses, Table 1) were generally superior to the corresponding in-house process. No attempt was made to derive insight from this discrepancy, as the protocols differed notably.[2]

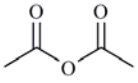
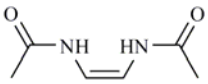
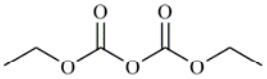
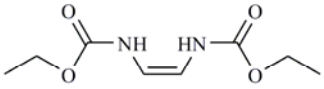
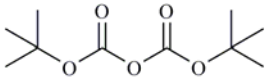
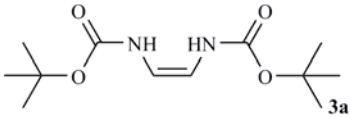
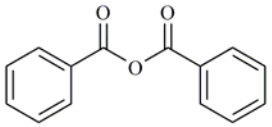
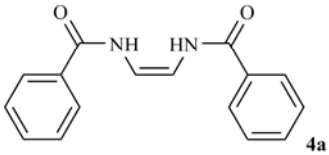
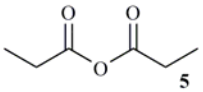
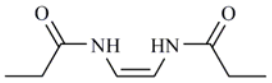
From a practical viewpoint, the yields were generally improved by strong stirring, which served to disperse **1-5**, and a moderately prolonged addition of sufficient **1-5**, to prompt the steady *N,N'*-diacylation or *N,N'*-dicarbalkoxylation of imidazole (Scheme 4). While the influence of pH on the course of reaction had not been systematically characterized at large reactant concentrations, the Bamberger reaction was reported to proceed best within the pH range of 6-7.[6] Increasing the alkalinity further was discouraged, as the half-life of the *N,N*'-diacyl or *N,N*'-dicarbalkoxy imidazolium species would drop accordingly, detracting from the accumulation and turnover of the corresponding 2-hydroxyimidazoline. Still, the findings obtained herein using alkaline bicarbonate implied a rather flexible working pH range of reaction.

As a final point, the elusive *cis*-1,2-di(formamido)ethene was targeted in view of its potential to serve as an easily polymerizable monomer.[1] Just as with prior attempts, however, no product was isolated when formic acetic anhydride was added to the *in situ*-generated imidazole, or to commercially produced imidazole as per the established method.[1] The fact that imidazole was recovered unchanged was attributed to the high accessibility and electropositive nature of the carbonyl center, which served to speed the hydrolysis of the formyl species.

To summarize, several *cis*-1,2-diamidoethene monomers were prepared by manipulating glyoxal, formaldehyde, ammonia and an acylating agent in one pot. The process precluded the purification of intermediates, the deployment of relatively expensive or vola-tile compounds like imidazole and chloroformate, and any labor-ious workup. The fact that an industrially applicable end-product was prepared and readily isolable, following a four-component transformation in the presence of many potentially interfering by-products,[7] further attested to the facility and robustness of this strategy. Finally, while *cis*-1,2-diamidoethene can serve as a mo-nomer, this class of compound may also be converted to the corresponding *N,N'*-disubstituted 4-imidazolin-2-one heterocy-cle,[4] which is known to have a much greater propensity to poly-merize.[3] All in all, it would appear that the cost-efficiency and conveniences imparted by this one-pot approach could promote the routine preparation and use of oligo- and polyvicinalamines.

Table 1

Reaction of *in situ*-generated imidazole with activating agents in alkaline media. Products: *cis*-1,2-Di(acetamido)ethene (**1a**), *cis*-1,2-di(ethoxyamido)ethene (**2a**), *cis*-1,2-di(*t*-butoxyamido)ethene (**3a**), *cis*-1,2-di(benzamido)ethene (**4a**), and *cis*-1,2-di(propylamido)ethene (**5a**).

Entry	Acylating/alkoxyformylating agent	Product	Time(h)	Solvent	Yield[a](%)	Yield[b](%)
1	 **1**	 **1a**	13	H_2O/EtOAc	35	53.8 (80[c])
2	 **2**	 **2a**	12	H_2O/EtOAc	22.4	34.5 (60[d])
3	 **3**	 **3a**	30	H_2O/1,4-Dioxane	28.7	44.1[e]
4	 **4**	 **4a**	12.5	H_2O/1,4-Dioxane	14.7	22.6 (10, 43[f])
5	 **5**	 **5a**	12	H_2O/EtOAc	39.2	60.3[e]

[a] Yields were calculated with respect to glyoxal as limiting reagent.

[b] Yields with respect to *in situ*-generated imidazole were estimated after determining a 65% yield by ^{1}H NMR. Parentheses indicate literature yields.

[c] Literature yield with imidazole as starting material and limiting reagent.[1]

[d] Literature yield with imidazole as starting material and limiting reagent, and ethylchloroformate as ethoxyformylating agent.[2]

[e] No literature preparation was available for comparative purposes.

[f] Literature yields with imidazole as starting material and limiting reagent, and benzoyl chloride as benzoylating agent.[2,10]

Experimental

Technical grade starting materials were obtained from local suppliers and were used without further purification.

Typical experimental procedure

To a stirred solution of ammonium hydroxide (6.0g; 22-25wt%), a mixture of glyoxal (4.35 g; 30.0 mmol; 40wt%) and formaldehyde (2.25ml; 30.2 mmol; 37wt%) was cautiously added. The mixture was allowed to stir (60°C; 1h), generating imidazole. Subsequent-ly, distilled water (150.0ml), ethylacetate (30.0ml) and sodium bi-carbonate (25.0g) were added to the reaction. Acetic anhydride (12.0ml; 127.0mmol; 4.23 equivalents with

respect to glyoxal) was slowly added (30min) under vigorous stirring during which time effervescence was noted. The reaction vessel was lightly caped after **1** was fully added, and stirring was continued (13h; RT) to promote full deformylation. The precipitated solid was recovered by filtration, washed with distilled water (3x5.0ml), optionally triturated in distilled water (20.0ml; 80°C; 15-30min) and lyophilized to yield **1a** (1.50g; 35% with respect to glyoxal) as a white solid. Di-*t*-butyl dicarbonate (**3**) was gently warmed prior to use and administered dropwise as in the case of acetic anhydride. Unlike **1-3** and **5**, benzoic anhydride (**4**) was finely pulverized and added in one shot. 1,4-Dioxane (75.0ml) was used in place of ethylacetate (Entries 3-4). Precipitation of **4a** (Entry 4) was facilitated by adding water (250ml) during the workup. Pro-duct **5a** (Entry 5) was directly isolated by evaporating the ethyl-acetate layer. To ascertain the *in situ* yield of imidazole, an aliquot of the domino reaction (48.0µl) was dissolved in deuterium oxide (600µl) spiked with sodium acetate (24.0µg). The sample was im-mediately analyzed using ^{1}H NMR (RT; DHO presaturation; 10s interpulse delay; 256 scans). The signal corresponding to the three C-H protons of imidazole was compared against the three protons of acetate, permitting a yield calculation of the former compound.

Parameters used for characterization

NMR: Inova 500; ATR-FTIR: Bruker Equinox 55; GCMS: Gas chromatography, Agilent 6890N; GC-Column: J&W, DB5, 30m, I.D. 0.25mm; Film thickness: 0.25 µm; Carrier Gas: He; Injection: 50ng/1µl MeOH; Inj.-Temp.: 270°C; Aux-Temp.: 240°C; Temp.-Progr.: 100/5-5-260; Mass spectrometry: Sensi-TOF, Five Tech-nologies, Munich; Mass range: 40-500 amu; Ionization energy: 70eV; DSC: Netzsch 204 Phoenix; T ramp rate: 5K/min; Atmos-phere: N_2; A chemical shift of 2.5ppm (^{1}H-NMR) and 39.4ppm (^{13}C-NMR) was applied to reference DMSO-d6.[15] The melting onset temperature (T_{onset}) was estimated from the DSC profile as per ASTM stardard test procedure E794 (1994). The peak melting temperature (T_m) was obtained by direct inspection. Both values have been expressed for clarity. In **1a-5a**, the tlc runs showed one spot under UV light. All GCMS profiles yielded one peak.

Entry 1

R_f: 0.06 (EtOAc); Mp (recrys. EtOH): T_{onset} 134.8°C, T_m 136.3°C, Lit.[1] not reported; IR (neat): $\tilde{\nu}$ = 3301(w), 3211(w), 3051(w), 1708(w), 1676(m), 1637(m), 1560(m), 1356(m), 1274(m), 1164(s), 1039(m), 997(m), 744(m), 668(s); ^{1}H-NMR (500MHz, DMSO-d6): δ = 1.95 (s, 3H), 5.99 (m, 1H), 9.27 (d, 1H); ^{13}C-NMR (125.725MHz, DMSO-d6): δ = 22.61, 105.04, 166.13; GCMS: m/e 142 M^+; MS ($C_6H_{10}N_2O_2$): calcd. 142.16; found 142.09; Anal.: calcd. C, 50.69; H, 7.09; N, 19.71; found C, 48.61; H, 7.25; N, 18.60.

Entry 2

R_f: 0.58 (EtOAc); Mp (recrys. EtOH): T_{onset} 141.3°C, T_m 143.7°C, Lit.[11] 139-141°C; IR (Neat): $\tilde{\nu}$ = 3338(w), 3316(w), 3229(w), 2976(w), 1724(m), 1668(m), 1525(s), 1455(m), 1367(m), 1308(m), 1241(s), 1149(s), 1081(s), 870(m), 765(m), 718(s), 675(m); ^{1}H-NMR (500MHz, DMSO-d6): δ = 1.19 (t, 3H), 4.06 (q, 2H), 5.69 (m, 1H), 8.78 (d, 1H); ^{13}C-NMR (125.725MHz, DMSO-d6): δ = 14.31, 60.38, 105.24, 153.18; GCMS: m/e 202 M^+; MS ($C_8H_{14}N_2O_4$): calcd. 202.21; found 202.12; Anal.: calcd. C, 47.52; H, 6.98; N, 13.85; found C, 47.23; H, 6.76; N, 13.62.

Entry 3

R_f: 0.66 (EtOAc); Mp (recrys. EtOH): T_{onset} 221.9°C, T_m 223.7°C; IR (Neat): $\tilde{\nu}$ = 3340(w), 3255(w), 3226(w), 2975(w), 1723(m), 1692(s), 1525(s), 1454(w), 1367(m), 1307(m), 1239(s), 1146(s), 1080(s), 869(m), 772(m), 717(s), 676(m); ^{1}H-NMR (500MHz, DMSO-d6): δ = 1.41 (s, 9H), 5.61 (m, 1H), 8.59 (d, 1H); ^{13}C-NMR (125.725MHz, DMSO-d6): δ = 27.92, 78.94, 104.75 , 152.29; GCMS: m/e 258 M^+; MS ($C_{12}H_{22}N_2O_4$): calcd. 258.31; found 258.23; Anal.: calcd. C, 55.80; H, 8.58; N, 10.84; found C, 54.25; H, 3.78; N, 7.18.

Entry 4

R_f: 0.48 (EtOAc); Mp (recrys. EtOH): T_{onset} 204.7°C, T_m 207.8°C, Lit.11 212-213°C; IR (Neat): $\tilde{\nu}$ = 3322(w), 3265(w), 3057(w), 1697(m), 1670(m), 1619(m), 1515(s), 1487(s), 1316(m), 1275(s), 1259(s), 1175(s), 1147(m), 1075(w), 921(m), 802(m), 693(s); ^{1}H-NMR (500MHz, DMSO-d6): δ = 6.40 (m, 1H), 7.52-7.64 (m, 2H), 7.89-7.94 (m, 3H), 10.10 (d, 1H); ^{13}C-NMR (125.725MHz, DMSO-d6): δ = 106.69, 127.17, 128.42, 131.94, 133.79, 163.81; GCMS: m/e 266 M+; MS ($C_{16}H_{14}N_2O_2$): calcd. 266.29; found 265.88; Anal.: calcd. C, 72.17; H, 5.30; N, 10.52; found C, 53.04; H, 7.53; N, 15.32.

Entry 5

R_f: 0.23 (EtOAc); Mp (recrys. EtOH): T_{onset} 138.4°C, T_m 139.6°C; IR (Neat): $\tilde{\nu}$ = 3316(w), 3199(w), 2982(w), 1706(m), 1687(m), 1635(m), 1549(s), 1507(s), 1457(s), 1420(m), 1375(m), 1280(w), 1239(m), 1202(s), 1163(s), 1085(m), 1029(m), 940(w), 758(s), 646(m); ^{1}H-NMR (500MHz, DMSO-d6): δ = 1.04 (t, 3H), 2.12 (q, 2H), 6.00 (m, 1H), 9.26 (d, 1H); ^{13}C-NMR (125.725MHz, DMSO-d6): δ = 9.41, 28.46, 104.99, 169.86; GCMS: m/e 170 M^+; MS ($C_8H_{14}N_2O_2$): calcd. 170.21; found 170.13; Anal. calcd. C, 56.45; H, 8.29; N, 16.46; found C, 54.49; H, 7.87; N, 10.19.

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