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ROLLINONE, A REVISION AND EXTENSION OF STRUCTURE

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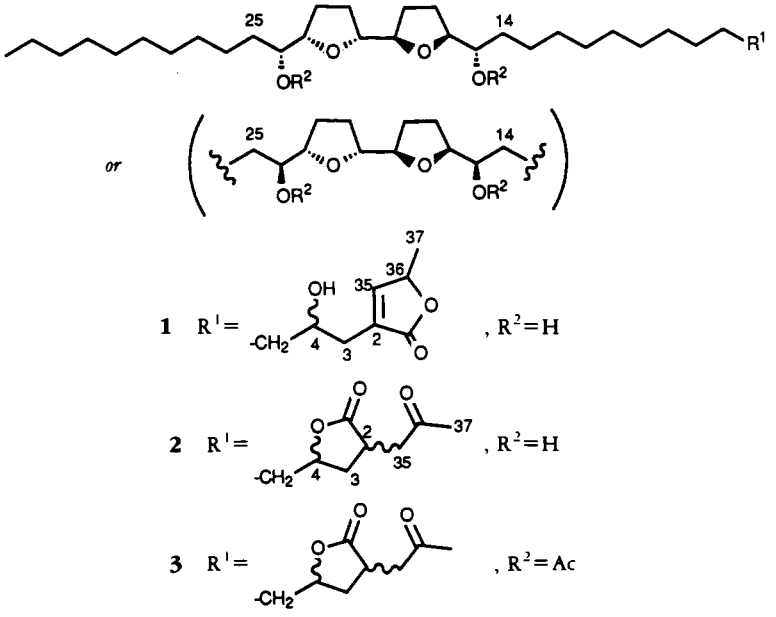
ABSTRACT.—The structure of rollinone [**2**] has been revised according to recently acquired 2D-nmr data. Instead of the previously reported terminal γ-methylbutyrolactone and 14-keto moieties, rollinone [**2**] was found to contain a butyrolactone between C-1 and C-4 with a pendant acetylmethyl moiety at C-2. The relative stereochemistry between C-15 and C-24 in rollinone [**2**] was established as erythro-cis-threo-cis-threo (or threo-cis-threo-cis-erythro) by ^{1}H-nmr experiments using the diacetate derivative. The structure was confirmed via chemical conversion of 25-desoxy-4-hydroxyneorollinicin [**1**] into **2**.

Over the past seven years, investigations of several genera of the Annonaceae have resulted in the characterization of a number of novel linear acetogenins containing one or two tetrahydrofuran rings, a terminal γ-lactone, and several hydroxyl moieties (1–13). One of the most recent reports by Yui *et al.* (11) has caused us to reexamine the structure of rollinone that we reported in 1984 (3). The original structure was proposed based upon ^{1}H-nmr (primarily at 90 MHz), ^{13}C-nmr off-resonance (at 25 MHz), and chemical ionization mass spectral data, but without the benefit of 2D-nmr correlation spectroscopy. This structure contained a terminal γ-methylbutyrolactone and a ketone at C-14, and has now proven to be an incorrect structure for rollinone.

Rollinone was reisolated during the fractionation of EtOH extracts of *Rollinia papilionella* Diels., which led to the isolation of 4-hydroxy-25-desoxyneorollinicin [**1**] (13), providing sufficient material for a reexamination of the structure. The ^{1}H-nmr spectrum of rollinone (at 300 MHz) showed a singlet at δ 2.19 due to a methyl group rather than a doublet as seen originally. Obviously, this resonance alone suggested that a change in the proposed structure of the lactone moiety was required. In addition, examination of the COSY spec-



trum of rollinone indicated that the H-15 at δ 3.42 was coupled not only to H-16 at δ 3.88 as expected but also to a methylene resonance at δ 1.4, indicating that the ketone moiety could not be located at C-14.

A ^{13}C-nmr DEPT experiment (75 MHz) served to establish the presence of two methyl groups, as seen before. A HETCOR experiment established that the methyl resonance at 14.1 ppm was due to the terminal methyl group of the alkyl chain (C-34), and that the other methyl resonance corresponded to the singlet at δ 2.19. The COSY spectrum verified that this methyl resonance was not coupled to any other resonance, and the chemical shift and lack of coupling indicated a methyl ketone as found in bullatacinone (11). A closer examination of the ^{13}C-nmr spectrum showed that this methyl group appeared as a double resonance (29.9 and 30.0 ppm), suggesting that rollinone, like bullatacinone (11), was a mixture of two stereoisomers. This implication was strengthened by the finding that there were ten methine resonances evident in the DEPT spectrum, eight of which were oxygen-bearing carbons. Of these methine resonances, four are due to carbons 16, 19, 20, and 23 of the bistetrahydrofuran ring system (80.95, 81.1, 82.9, 83.0 ppm) and two are due to the two hydroxyl-bearing carbons (C-15 and C-24, 74.0 and 71.9 ppm, respectively). The HETCOR experiment established that two of the remaining four resonances (78.9 and 79.4 ppm) corresponded to two multiplets (each integrating for approximately 0.5 protons) at δ 4.41 and δ 4.55. (In the original spectra of rollinone, these multiplets were not distinguishable as separate resonances.) A COSY experiment established that these resonances were coupled into the methylene region between δ 1.4 and δ 2.0. Coupling from the methylene region was note to two sets of resonances, one at δ 2.62 and one at δ 3.05. The multiplet at δ 3.05 was determined, from the HETCOR spectrum, to contain resonances due to a methine proton (δ 3.01, m) and one proton of a diastereotopic methylene resonance (δ 3.10, dd, $J=4$, 10 Hz). This latter resonance was coupled to the other diastereotopic proton of the methylene at δ 2.62. In the HETCOR spectrum, the methine part of the multiplet at δ 3.01 was found to be coupled to two methine ^{13}C resonances, one at 36.7 ppm and one at 34.4 ppm, and the methylene resonances at δ 3.10 and δ 2.62 were each found to be coupled to two methylene ^{13}C resonances, one at 43.8 ppm and one at 44.2 ppm, again indicating the presence of two stereoisomers. This conclusion is also supported by the presence of two resonances for each of the carbonyls in the ^{13}C spectrum of rollinone (Table 1).

The data, summarized in Table 1, are strikingly similar to those of bullatacinone, and connection of the individual pieces indicates that rollinone has the same structure between C-1 and C-4 as bullatacinone and exists as a diastereomeric mixture that could not be

TABLE 1. Key ^{1}H- (300 MHz) and ^{13}C- (75 MHz) nmr Chemical Shifts (in $CDCl_3$) for Rollinone [2] [revised from Dabrah and Sneden (3)].

Carbon	^{1}H (δ)	^{13}C (ppm)
1	—	178.8, 181.7
2	3.01 m	34.4, 36.7
3	1.4–2.0 m	22–35
4	4.41, 4.55 m	78.9, 79.4
5	1.4–2.0	22–35
14	1.4–2.0	22–35
15	3.42 m[a]	74.0
24	3.87 m[a]	71.9
35	2.62 m	43.8, 44.2
	3.10 dd (4, 10)	
36	—	205.5, 205.6
37	2.19 s	29.9, 30.0

[a]These assignments are based on previous ^{1}H-nmr assignments for the H-15, particularly the assignments for uvaricin (1), which bears an acetoxy substituent at C-24 and a hydroxy substituent at C-15, allowing a clear distinction between the two resonances.

separated by normal chromatographic techniques. This is indicated in structure **2**, which represents the revised structure of rollinone. However, rollinone [**2**] differs from bullatacinone in the stereochemistry about the bistetrahydrofuran moiety.

The relative stereochemistry around the bistetrahydrofuran moiety of **2** was established by the method of Hoye and coworkers (14,15). The diacetate derivative **3** of rollinone [**2**] was prepared as in Dabrah and Sneden (3) and analyzed by ^{1}H nmr at 300 MHz. The acetate resonances appeared at δ 2.052 and δ 2.076, establishing one erythro and one threo relationship between the tetrahydrofuran rings and adjacent oxygenated carbons. H-16 and H-23 both were located at δ 3.95, indicating that the two tetrahydrofuran rings were either both cis or both trans. The chemical shifts of H-15 and H-24 (δ 4.89) and H-19 and H-21 (δ 3.85), by comparison with the twelve model diastereomers of Hoye and co-workers (14,15), then served to establish the relationship of the two tetrahydrofuran rings as cis-threo-cis. Thus, the relative stereochemistry between C-24 and C-15 in rollinone [**2**] is erythro-cis-threo-cis-threo as shown (or threo-cis-threo-cis-erythro, because the nmr experiment cannot distinguish between these two assignments). This is identical to the stereochemistry of 25-desoxy-4-hydroxyneorollinicin [**1**] (13).

The finding of identical stereochemistry around the bistetrahydrofuran moieties of **1** and **2** allowed a chemical confirmation of the structure of rollinone. Following the same procedure used to convert bullatacin to bullatacinone, 25-desoxy-4-hydroxyneorollinicin [**1**] was treated with 2% KOH in *t*-BuOH at room temperature for 24 h (11). After neutralization and preparative tlc over Si gel, the major product was isolated. This compound was identical to **2** by mixed tlc in three systems and by ^{1}H nmr. Thus, the revised structure of rollinone was established as **2**.

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