Pergamon

Tetrahedron Letters 40 (1999) 1857–1860

TETRAHEDRON LETTERS

Structure Revision of the APHEs through Synthesis

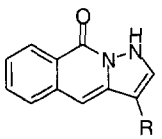
T. Ross Kelly,* Ying Fu, and Roger L. Xie

E. F. Merkert Chemistry Center, Boston College, Chestnut Hill, MA 02467, USA

Received 25 November 1998; accepted 4 January 1999

Abstract: An attempt to synthesize APHE-3 (3-methylpyrazolo[1,5-*b*]isoquinolin-9(1*H*)-one, **3**) gave the tautomer 3-methylpyrazolo[1,5-*b*]isoquinolin-9(4*H*)-one (**9**) instead, and led to a reconsideration of the structures assigned to the APHEs. The structures of the APHEs have now been reformulated as **15-18**, known natural products, whose spectra are in close agreement with those reported for the APHEs.

A series of papers[1-3] over the past several years has reported the isolation and characterization of a family of four natural products produced by the actinomycete *Streptoverticillium griseocarneum* and designated APHEs 1-4. The structures of the APHEs share in common a tricyclic pyrazoloisoquinolinone nucleus, but differ by the nature of the alkyl substituents, which form a homologous C_1 to C_4 series (**1-4**). The APHEs are the only reported naturally occurring examples of the pyrazoloisoquinolinone ring system and no synthesis of any member of the family has been recorded.



APHE-1	R = CH_2CH_3	**1**
APHE-2	R = $CH_2CH_2CH_3$	**2**
APHE-3	R = CH_3	**3**
APHE-4	R = $CH_2CH_2CH_2CH_3$	**4**

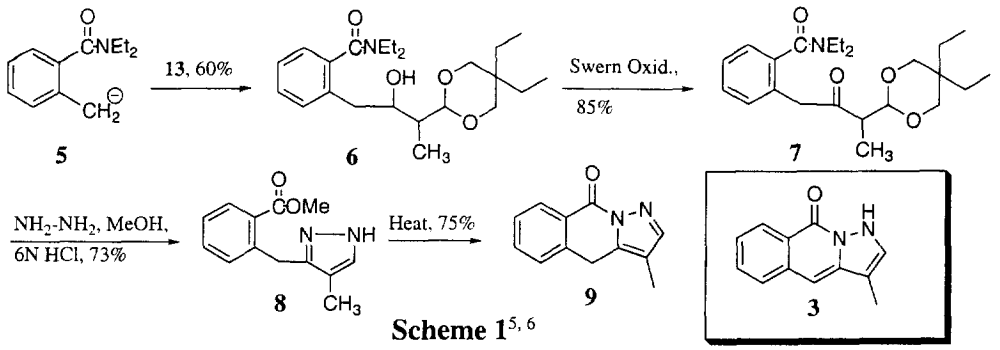
Given our continued[4] interest in the synthesis of heterocyclic natural products and the apparent absence of any synthetic activity directed toward the APHEs, we undertook the synthesis of APHE-3 (**3**), the simplest member of the family.

The synthetic approach, summarized in Scheme 1,[5,6] began with the condensation of anion **5**,[7] derived from *N,N*-dimethyl-*o*-toluamide by deprotonation with LDA, and aldehyde **13**. Aldehyde **13** was prepared from methacrolein (**10**), as indicated in Equation 1,[5,6] following an analogous sequence developed by Still and Schneider for the preparation of **14**[8] (Figure 1). The diethyldioxane ring in **13** rendered **13** less susceptible[9] to untoward side reactions than was the case with **14**. Swern oxidation[10] of alcohol **6** afforded ketone **7**. Reaction of **7** with hydrazine in methanolic HCl afforded pyrazole ester **8** directly. The latter cyclized spontaneously upon standing to give tricycle **9**, a process that could be accelerated with heat.

The cyclization of **8** to give **9** rather than APHE-3 (**3**) was puzzling. Compounds **9** and **3** are clearly distinguishable by, *inter alia*, ^{1}H NMR (the presence or absence of a 2-proton singlet

* To whom correspondence should be addressed. E-mail: ross.kelly@bc.edu

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00074-X



Scheme 1[5, 6]

for a $-CH_2-$ group is especially telltale). APHE-3 (**3**) and **9** are tautomers of each other, but **9** exhibited no tendency to tautomerize (even partially) to **3**, and there was nothing in the literature to suggest that any of the APHEs are susceptible to tautomerization to **9**-like tautomers. It is not unusual for tautomeric forms to be sufficiently kinetically stable to allow their separate isolation,[11] but the complete absence of any indication that **9** and **3** were interconvertible led us to regard both structures as suspect.

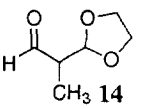
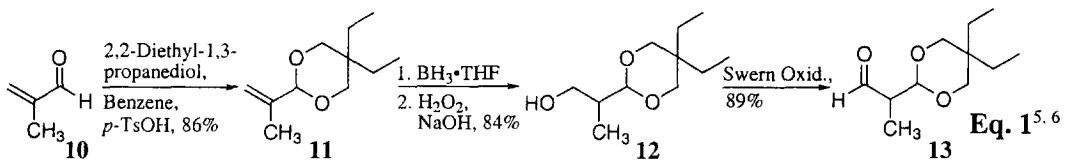
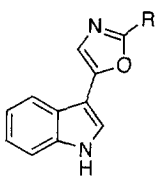


Figure 1



Eq. 1[5, 6]

An X-ray crystallographic characterization[12] of **9** fully supported the assigned structure. Accordingly, we scrutinized the structure determination of **3** and the other APHEs in greater detail. To our mind, the structures assigned to the APHEs are fully in accord with the supporting data. But while the APHEs' structures were regarded as best fits for the data,[13] that data seemed, in hindsight, also consistent with a few other putative basic structures.



Pimprinethine	$R = CH_2CH_3$	**15**
WS-30581 A	$R = CH_2CH_2CH_3$	**16**
Pimprinine	$R = CH_3$	**17**
WS-30581B	$R = CH_2CH_2CH_2CH_3$	**18**

Figure 2

A search of the *Dictionary of Natural Products*[14] was undertaken to determine if any other molecules that had been reported might fit the data recorded for any of the APHEs. Particularly rewarding was a search for molecules with the same empirical molecular formulas as the APHEs, because it identified a new tricyclic framework with the same four members (methyl, ethyl, propyl, butyl) of a homologous series of substituents (**15-18**, Figure 2).

At first glance, the different ring systems in **1-4** and **15-18** might be expected to give rise to substantially different spectra. One might expect, for instance, the presence of a carbonyl group in **3** and its absence in **17** would be evident from their ^{13}C NMR spectra. In actuality (Table 1), however, the ^{1}H and ^{13}C NMR spectra and melting points reported for the first three APHEs are, within experimental error, identical to those recorded for **15-17**. The data reported for APHE-4 and WS-30581 B are not sufficiently detailed to permit exact comparison, but there are no discrepancies. Furthermore, compounds **15-18** have been isolated from strains of microorganisms[15-19] very similar to the one that produces the APHEs.

Table 1

	APHE-1[a]	Pimprinethine[b]	APHE-2[a]	WS-30581 A[b]	APHE-3[a]	Pimprinine[b]
Mp (°C)	157-159	152-154	130-132	131-133	Not reported	202-203
^{1}H	1.42 (3H,t,J=7.5Hz)[c]	1.41 (3H,t,J=7.6Hz)[d]	1.06 (3H,t,J=7.4Hz)[c]	1.06 (3H,t,J=7.3Hz)[e]	2.52 (3H, s)[c]	2.53 (3H, s)[d]
NMR	2.90 (2H,q,J=7.5Hz)	2.87 (2H,q,J=7.6Hz)	1.90 (2H, m)	1.87 (2H, m)	7.12 (1H, s)	7.14 (1H. s)
	7.17 (1H, s)	7.14 (1H, s)	2.87 (2H,t,J=7.4Hz)	2.84 (2H,t,J=7.3Hz)	7.19-7.28 (2H,m)	7.21-7.29 (2H, m)
	7.23 (1H, m)	7.25 (2H, m)	7.19 (1H, s)	7.18 (1H, s)	7.42 (1H, m)	7.42 (1H,d,J=7.5Hz)
	7.31 (1H, m)		7.25 (1H, m)	7.21-7.31 (2H, m)	7.49 (1H,d,J=2.7Hz)	7.50 (1H,d,J=2.6Hz)
	7.44 (1H, m)	7.42 (1H, m)	7.29 (1H, m)		7.82 (1H, m)	7.82 (1H,d,J=7.7Hz)
	7.53 (1H,d,J=2.6Hz)	7.50 (1H,d,J=2.6Hz)	7.44 (1H, m)	7.43 (1H,dd,J=1.9,6.2Hz)	8.44 (1H, br s)	NH not reported
	7.83 (1H,m,J=7.3Hz)	7.83 (1H,d,J=7.7Hz)	7.53 (1H,d,J=2.6Hz)	7.52 (1H,d,J=2.6Hz)		
	8.53 (1H, br s)	8.36 (1H, br s)	7.82 (1H, m)	7.85 (1H,dd,J=2.7,6.8Hz)		
			8.44 (1H, br s)	8.93 (1H, br s)		
^{13}C	11.22	11.2	13.70	13.7	13.99	13.9
NMR	21.62	21.6	20.58	20.6	106.06	106.0
	105.82	106.1	30.70	30.1	111.47	111.4
	111.46	111.4	106.00	105.8	119.96	119.9
	119.36	119.8	111.44	111.5	120.01	120.0
	119.87	119.9	119.72	119.6	120.83	120.8
	120.79	120.7	119.92	119.9	121.44	121.3
	121.53	121.3	120.75	120.7	123.00	123.0
	122.94	123.0	121.46	121.6	124.08	124.0
	124.00	124.0	122.90	122.8	136.20	136.1
	136.14	136.1	124.06	124.1	147.31	147.2
	147.21	147.0	136.18	136.2	159.25	159.1
	163.69	163.6	147.00	147.2		
			163.40	162.7		
UV	222	224[g]	222	224[f]	222	224[f]
(MeOH)	265	266	265	266	265	266
λ_{max}(nm)	280	278	280	282	280	282
	296	295	296	298	296	298

a) Data for APHE-1 & APHE-2 were taken from ref. 2; data for APHE-3 were taken from ref. 24; b) mp & NMR were taken from ref. 20; c) 300/75.4 MHz, $CDCl_3$; d) 400/100 MHz, $CDCl_3$; e) 250/62.5 MHz, $CDCl_3$; f) from ref. 17; g) from ref. 16.

Conclusion: The classical dictum, "synthesis is the ultimate proof of structure," continues to prevail.[25-26] Numerous syntheses and crystal structures affirm the structures assigned to **15-18**.[15-23] The present attempt to achieve the first synthesis of an APHE brings the proposed structures into question and results in the conclusion that the APHEs actually possess structures **15-18**.

Acknowledgments: We thank Drs. J. Soliveri and M. Selma Arias[1-3, 13, 24] for their extremely gracious exchange of information and spectra. We also thank Prof. W. Clark Still[8] for providing experimental details for the preparation of **14**.

References and Notes

1. Fidalgo M. L.; Alonso J. L.; Soliveri J. *J. Antibiot.* **1992**, *45*, 1753-1758.
2. Fidalgo M. L.; Arias M. S.; Soliveri J.; Arias M. E. *J. Antibiot.* **1992**, *45*, 1759-1962.
3. Cruz R.; Arias M. S.; Arias M. E.; Soliveri J. *J. Antibiot.* **1996**, *49*, 700-702.
4. Kelly T. R.; Moiseyeva R. L. *J. Org. Chem.* **1998**, *63*, 3147-3150 and earlier work cited therein.
5. **Salient experimental details** (run under N_2 as appropriate). **6**: Add over 10 min 2.45 g *N,N*-diethyl-*o*-toluamide in 20 ml THF to LDA (25.7 mmol) in 120 ml anhydrous THF at -78 °C. After 40 min at -78 °C, add dropwise 3.34 g **13** in 20 ml THF over 30 min; warm slowly to r.t.; stir overnight; quench with MeOH (10 ml); sat. aq. NH_4Cl/EtOAc workup; silica gel flash column

chromatography (sgfcc) (4:1 EtOAc:hexanes) to give 3.0 g (60%, oil) **6**. **7**: Analogous procedure to that used for **13**; sgfcc (1:1 EtOAc:hexanes) to furnish **7** (85%, oil). **8**: To 466 mg **7** in 20 ml MeOH, add dropwise 20 ml conc. HCl. After 5 min, add 0.370 ml anhydrous NH_2NH_2; reflux for 6-7 h; H_2O/CH_2Cl_2 + solid K_2CO_3 workup; sgfcc (1:1 EtOAc:hexanes) to give 201mg (73%) **8** (oil). **9**: Upon standing, **8** cyclizes to **9**, which process can be accelerated by the following procedure. In a Kugelrohr, under high vacuum, slowly heat 250 mg **8** from r.t. to 150 °C over 1.5 h; sgfcc (1:1 Et_2O:CH_2Cl_2) to deliver 160 mg **9** (75%), "mp": ~180 °C (darkens without melting), ~275 °C (rapidly chars without melting); recrystallization (benzene) supplied colorless needle-shaped crystals good for elemental analysis and crystallography. **11**: 34.9 g methacrolein (**10**), 250 mL benzene, 65.9 g 2,2'-diethyl-1,3-propanediol and 0.33 g *p*-TsOH•H_2O refluxed 24 h using a Dean-Stark apparatus. Cool; add 0.3 g K_2CO_3; concentrate *in vacuo* and distill under vacuum to get 79.1 g **11** (86.3%), bp: 29-32 °C/0.3 torr. **12**: To 10.0 g **11** in 130 ml dry THF was added at 0 °C 35 ml of 1M BH_3/THF solution over 15 min. After 25 min add 1.53 g NaOH in 6.5 ml H_2O over 20 min; add 7.5 ml H_2O_2 (30%); stir 20 h at r.t.; evaporate THF; H_2O/Et_2O workup; distill to furnish 9.14 g **12** (83.2%), bp: 104-106 °C/1.0 torr. **13**: To 5.5 mmol oxalyl chloride in 30 ml CH_2Cl_2 at -60 °C, add 0.78 ml DMSO dropwise. After 5 min, add 1.01 g **12** in 10 ml CH_2Cl_2 over 10 min at -60 °C. After 15 min, add 3.0 ml Et_3N over 10 min; sat. aq. NH_4Cl/CH_2Cl_2 workup to deliver almost pure 0.89 g **13** (89.0%, oil).

6. **Analytical data for new compounds**. Compounds **7**, **9**, **11**, **12** and **13** gave satisfactory combustion analyses. ^{1}H NMR (400 MHz, $CDCl_3$) δ: **6**: 7.15-7.36 (m, 4H), 4.47 (d, 1H, J=7.6Hz), 2.60-3.90 (m, 12H), 2.45 (br s, 1H) 1.70 (q, 2H, J=10.4 Hz), 1.25 (t, 3H, J=10.0Hz), 1.02-1.10 (m, 8H), 0.83 (t, 3H, J=10.4Hz), 0.75 (t, 3H, J=10.4Hz); **7**: 7.16-7.35 (m, 4H), 4.53 (d, 1H, J=8.4Hz), 2.88-3.94 (m, 11H), 1.69 (q, 2H, J=10.0Hz), 1.20 (t, 3H, J=9.6Hz), 1.10 (d, 3H, 9.2Hz), 1.07 (t, 3H, J=9.6Hz), 1.04 (q, 2H, J=10.0Hz), 0.84 (t, 3H, J=10.0Hz), 0.75 (t, 3H, J=10.0Hz); **8**: 7.91 (d, 1H, J=10.4Hz), 7.42 (t, 1H, J=10.0Hz), 7.28 (t, 1H, J=10.0Hz), 7.19 (d, 1H, J=10.4Hz), 4.30 (s, 2H) 3.89 (s, 3H) 2.01 (s, 3H); **9**: 8.47 (d, 1H, J=8.0Hz), 7.77 (s, 1H), 7.66 (t, 1H, J=8.0Hz), 7.51 (t, 1H, J=8.0Hz), 7.47 (d, 1H, J=8.0Hz), 4.27 (s, 2H), 2.14 (s, 3H); **11**: 5.13 (d, 1H, J=2.0Hz), 4.97 (d, 1H, J=2.0Hz), 4.75 (s, 1H), 3.83 (d, 1H, J=11.6Hz), 3.43 (d, 1H. J=11.6 Hz), 1.79 (s, 3H), 1.73 (q, 2H, J=7.6Hz), 1.06 (q, 2H, J=7.6 Hz) 0.85 (t, 3H, 7.6Hz), 0.76 (t, 3H, 7.6Hz); **12**: 4.41 (d, 1H, J=4.4Hz), 3.60-3.85 (m, 5H) 3.37 (dd, 2H. J=1.2, 11.2Hz), 2.81 (dd, 1H, J=2.6, 3.4Hz), 1.94 (m, 1H), 1.70 (q, 2H, J=7.6Hz), 1.05 (q, 2H, J=7.6Hz), 0.93 (d, 3H, J=7.6Hz), 0.84 (t, 3H, J=7.6Hz), 0.76 (t, 3H, J=7.6Hz); **13**: 9.83 (d, 1H, J=1.6Hz), 4.65 (d, 1H, J=4.0Hz), 3.83 (m, 2H), 3.38 (m, 2H), 2.62 (m, 1H), 1.69 (q, 2H, J=7.6Hz), 1.12 (d, 2H, J=7.2Hz), 1.06 (q, 2H, J=7.6Hz), 0.84 (t, 3H, J=7.6Hz), 0.76 (t, 3H, J=7.6Hz). Selected IR (film) ν (cm^{-1}) **6**: 3396, 1607, 1104; **7**: 1720, 1629; **9**: 1716, 1604; **11**: 3081, 1665; **12**: 3421, 1036; **13**: 3458, 2861, 1734. All other data (HRMS and ^{13}C NMR) are in agreement with assigned structures.

7. For a review on lateral lithiation reactions see: Clark R. D.; Jahangir A. *Org. React.* **1995**, *47*, 1-314.
8. (a) Still W. C.; Schneider J. A. *Tetrahedron Lett.* **1980**, *21*, 1035-1038. (b) Schneider J. A. *Ph.D. Thesis*, Columbia Univ., **1984**.
9. Walters M. A.; Shay J. J. *Encyclopedia of Reagents for Organic Synthesis*, Paquette L. A., Ed.; Wiley: NY, **1995**, vol 4, pp 2121.
10. Tietze L. F.; Eicher T. *Reactions and Syntheses in the Organic Chemistry Laboratory*, University Science Books: Mill Valley, California, **1988**, pp 93-94.
11. Elguero J.; Marzin C.; Katritzky A. R.; Linda P., *The Tautomerism of Heterocycles, Adv. Heterocylc. Chem., Suppl. 1*, **1976**.
12. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre.
13. Personal communication from Dr. M. Selma Arias.
14. *Dictionary of Natural Products*, Buckingham, J., Ed.; Chapman & Hall, London, **1994**.
15. Koyama Y.; Yokose K.; Dolby L. J. *Agric. Biol. Chem.* **1981**, *45*, 1285-1287.
16. Noltemeyer M.; Sheldrick G. M.; Hoppe H.-U.; Zeeck A. *J. Antibiot.* **1982**, *35*, 549-555.
17. Umehara K.; Yoshida K.; Okamoto M.; Iwami M.; Tanaka H.; Kohsaka M.; Imanaka H. *J. Antibiot.* **1984**, *37*, 1153-1160.
18. Bhate D. S.; Hulyalkar R. K.; Menon S. K. *Experientia*, **1966**, *16*, 504-505.
19. Joshi B. S.; Taylor W. I.; Bhate D. S.; Karmarkar S. S. *Tetrahedron* **1963**, *19*, 1437-1439.
20. Doyle K. J.; Moody C. J. *Synthesis* **1994**, 1021-1022.
21. Somei M.; Sato H.; Komura N.; Kaneko C. *Heterocycles* **1985**, *23*, 1101-1106.
22. Toshioka T.; Mohri K.; Oikawa Y.; Yonemitsu O. *J. Chem. Res. (S)* **1981**, 194-195.
23. Oikawa Y.; Toshioka T.; Mohri K.; Yonemitsu O. *Heterocycles* **1979**, *12*, 1457-1462.
24. Copies of spectra and other information about APHE-3 were kindly provided by Dr. J. Soliveri.
25. See, *inter alia*: Woodward, R. B. In "Perspectives in Organic Chemistry", Todd, A. R., Ed.; Interscience: New York, **1956**; pp 165-167. Eschenmoser, A.; Wintner, C. E. *Science (Washington, D.C.)* **1977**, *196*, 1410-1420.
26. For other papers from this laboratory where synthetic efforts have led to revisions of structures assigned to natural products see: (a). Kelly T. R.; Saha J. K. *J. Org. Chem.* **1985**, *50*, 3679-3685. (b). Kelly T. R.; Kim M. H. *J. Org. Chem.* **1992**, *57*, 1593-1597. (c). Kelly T. R.; Ma Z.; Xu W. *Tetrahedron Lett.* **1992**, *33*, 7713-7714. (d). Kelly T. R.; Kim M. H.; Curtis A. D. *J. Org. Chem.* **1993**, *58*, 5855-5857. (e). Kelly T. R.; Xu W.; Sundaresan J. *Tetrahedron Lett.* **1993**, *34*, 6173-6176. (f). Kelly T. R.; Ma Z.; Xu W. *Phytochemistry* **1994**, *36*, 253-254.