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BENZILIC ACID REARRANGEMENT-TYPE REACTION OF PHYSALINS TO NEOPHYSALINS. STRUCTURAL REVISION OF ONE OF THE DEHYDRATION PRODUCTS OF PHYSALIN A

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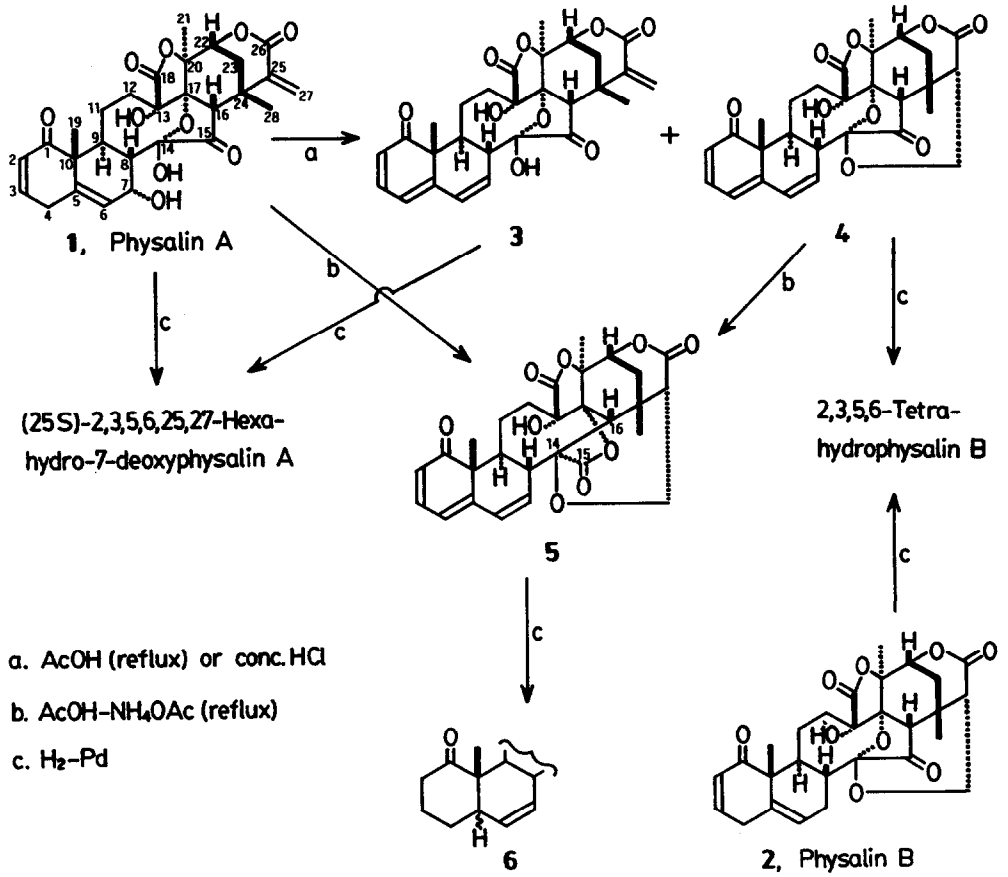
Abstract: The previously proposed structure of an acid-induced dehydration product of physalin A, a 13,14-seco-16,24-cyclosteroid, is revised as having a new carbon skeletal structure named neophysalin. The reaction from physalins to neophysalins proceed via a kind of the benzilic acid rearrangement.

Physalins are the steroidal constituents of *Physalis* plants possessing a novel 13,14-seco-16,24-cycloergostane skeleton. Since the isolation and the structure determination of physalin A (1)[1] and physalin B (2)[2] in 1969, more than a dozen physalins were isolated from Japanese *Physalis* species, *Physalis alkekengi* var. *francheti*,[3-6] and Indian *Physalis* species, *P. angulata* and *P. lancifolia*.[7-9] Acid-catalyzed dehydration products of 1 played an important role in the structural study and the chemical correlation between 1 and 2. This paper describes a correction of the proposed structure of one of the acid-treatment products of 1.

When 1 was treated with conc. HCl or heated in acetic acid under reflux, two dehydration products, 4,7-didehydro-7-deoxyphysalin A (3) and 4,7-didehydrophysalin B (4), were formed as given in Scheme 1.[3] Both of the products possessed a conjugated trienone system at the AB ring moiety, and in 4 an ether bridge was formed between C(14) and C(27) atoms. On catalytic hydrogenation 4 afforded a hexahydro derivative which was identical with the hydrogenation product of 2, namely 2,3,5,6-tetrahydrophysalin B, establishing the chemical correlation of 1 to 2. If an acetic acid solution of 1 was refluxed in the presence of ammonium acetate, another dehydration product (now proven to be 5) was formed. Since the 60 MHz ^{1}H NMR spectral data of 5 were similar to those of 4, the two compounds were originally assumed to be stereoisomers of each other and the structure epimeric to 4 at the C(8) position had been assigned to 5.[3]

Reinvestigation of the acid-dehydration products of 1 was performed using 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectroscopy. While the ^{13}C NMR spectra of 4 recorded in DMSO-d_6 solution showed two ketone carbonyl resonances at δ 205.3 (C-1) and 208.8 (C-15) and two lactone carbonyls at δ 167.2 (C-16) and 171.4 (C-18), 5 was found to exhibit only one ketone peak at δ 204.2 and three lactone carbonyls at δ 169.6, 170.1, and 172.2. This indicated that rearrangement of the carbon skeleton had occurred during the reaction from 1 to 5 and the earlier proposed structure of 5 should be revised.

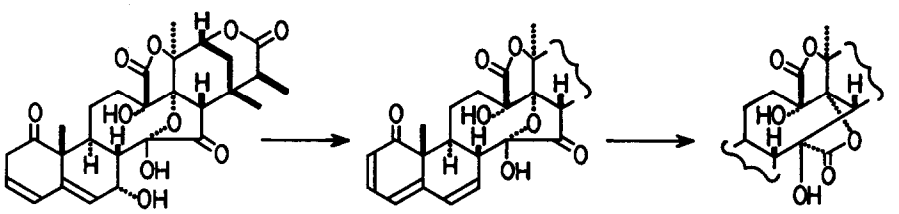
Recrystallization of 5 from methanol afforded clear yellow prisms suitable for X-ray crystallographic study. An X-ray crystal structure analysis of 5 was undertaken,[10] which established the trislactone structure of 5 having a newly formed γ-lactone ring instead of the oxacyclopentanone ring of the physalin skeleton. The carbon skeletal rearrangement from 1 to 5 involves C(15)-C(16) bond cleavage and C(14)-C(16) bond formation, accompanied



Scheme 1

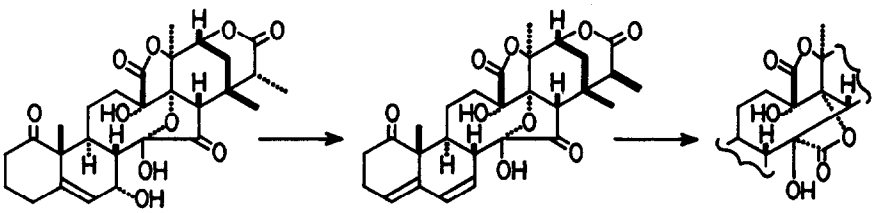
by bond migration of the ether oxygen at C(14) to the C(15) position. Since the C(15) carbon atom is that of carbonyl group and the C(14) atom in 1 is a carbonyl equivalent, this rearrangement can be considered to be a type of benzilic acid rearrangement. We propose the name "neophysalin" for this new structure formed through a benzilic acid rearrangement of a physalin. Consequently, the compound 5 can be called as 4,7-didehydroneophysalin B. The ^{1}H and ^{13}C NMR spectral data of 5 were fully analyzed based on this revised structure and are summarized in Tables 1 and 2. The structure of the tetrahydro derivative of 5[3] was also revised to 6,7-didehydro-2,3,5,6-tetrahydroneophysalin B (6).

Since compound 4 also gives the rearranged product 5 and the neophysalin 5 was stable under the same conditions, the reaction from 1 to 5 seemed to proceed as follows: 1 ⟶ 3 ⇌ 4 ⟶ 5. In order to study whether the presence of the ether bridge C(14)-O-C(27) in 4 was essential to the rearrangement, physalin L (7), in which C(27) is a secondary methyl group unable to form an ether linkage, was refluxed in acetic acid with ammonium acetate. While acid dehydration of 7 was known to give the conjugated trienone 8,[4] the attempted rearrangement reaction really afforded the corresponding new neophysalin 9. The structure of 9 was confirmed by the ^{13}C NMR spectra exhibiting three lactone carbonyls at



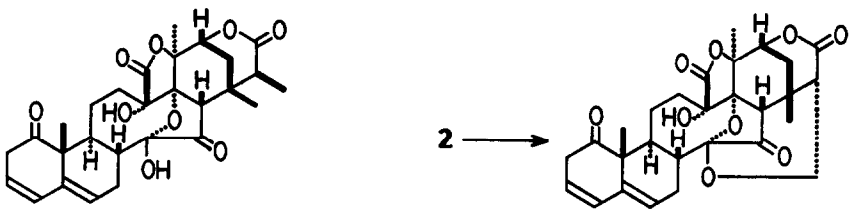
δ 172.7, 173.3, and 175.5 in addition to the trienone carbonyl at δ 204.7 as given in Table 2. Even without ammonium acetate, refluxing the acetic acid solution of 7 was found to give a mixture of 8 and 9, demonstrating that the rearrangement took place more easily for physalins lacking the C(14)-O-C(27) bridge. The result also suggested that the formation of 5 from 1 proceeded via rearrangement of 3 followed by the Michael addition of the C(14)-OH to the C(25)-C(27) double bond to form the ether bridge.

(25*R*)-2,3,25,27-Tetrahydrophysalin A (10)[3] was then subjected to acid treatment to study the contribution of the conjugated trienone moiety to the formation of neophysalins. The attempted rearrangement reaction of 10 afforded first the already known dehydration product Δ^{4}, Δ^{6}-diene 11[3] and this was then slowly converted into the corresponding neophysalin 12, namely (25*S*)-2,5,25,27-tetrahydro-4,7-didehydro-7-deoxyneophysalin A. The result indicated that the presence of conjugated trienone structure at the AB ring moiety was important but not essential to the benzilic acid-type rearrangement reaction.



10 11 12

Physalin M (13)[5] possessing a conjugated Δ^3,Δ^5-diene group, on the other hand, did not exhibit any indication of the rearrangement reaction when treated under the same conditions. Treatment of physalin B (2) also failed to give the corresponding neophysalin but resulted in the formation of the known Δ^3,Δ^5-diene compound 14.[3] Thus, while the Δ^4, Δ^6-diene compound 11, although very slowly, affords the neophysalin 12, the Δ^3,Δ^5-dienes 13 and 14 did not yield neophysalins.



13, Physalin M 2 14

Usually the benzilic acid rearrangement occurs under strongly alkaline conditions. Although the skeletal rearrangement from physalins to neophysalins is formally similar to a benzilic acid rearrangement, this conversion takes place in acidic solution. While heating the acetic acid solution of 7 under reflux yielded the neophysalin 9, under the same conditions 1 did not give the neophysalin 5 but required the presence of ammonium acetate for the rearrangement to take place. Aniline in place of ammonium acetate also enabled the formation of 5 from 1, but role of the nitrogen-containing additives is uncertain. Although no indication of the epimerization at C(8) was observed, the acidity of the methine proton at C(8) could be related to the ease of formation of neophysalins, since the ease of rearrangement was 2,4,6-trienone > 4,6-diene >> 3,5-diene. The detailed mechanism of this novel neophysalin-forming rearrangement has not been studied further.

Experimental Section

Melting points were determined on a Yanagimoto micro melting point apparatus and are not corrected. IR spectra were recorded with KBr discs on a JASCO IRA-1 spectrophotometer. NMR spectra were taken on a JEOL JNM GSX-400 spectrometer at 400 MHz for ^1H

Table 1

^{1}H NMR spectral data of neophysalins **5**, **6**, **9**, and **12** measured in DMSO-d_6[a] (Chemical shift δ in PPM, peak multiplitcity, and coupling constant in Hz)

Assignment	5	6	9	12
2	5.86 d ($J_{2,3}$=10)	2.08 m 2.66 m	5.86 d ($J_{2,3}$=9.5)	2.4 - 2.5 m (CH_2)
3	7.07 dd ($J_{3,2}$=10) ($J_{3,4}$=6)	1.9 m (CH_2)	7.11 dd ($J_{3,2}$=9.5) ($J_{3,4}$=6)	2.4 m (CH_2)
4	6.05 d ($J_{4,3}$=6)	1.64 m 1.45 m	6.07 d ($J_{4,3}$=6)	5.58 m
5	-	1.9 m	-	-
6	6.37 dd ($J_{6,7}$=10) ($J_{6,8}$=1.5)	5.82 ddd ($J_{6,7}$=11) ($J_{6,5}$=6) ($J_{6,8}$=2)	6.47 br d ($J_{6,7}$=10)	6.23 br d ($J_{6,7}$=10)
7	6.16 dd ($J_{7,6}$=10) ($J_{7,8}$=4)	5.97 dd ($J_{7,6}$=11) ($J_{7,8}$=3)	6.10 dd ($J_{7,6}$=10) ($J_{7,8}$=6)	5.93 dd ($J_{7,6}$=10) ($J_{7,8}$=4)
8	3.05 m	2.62 br d ($J_{8,9}$=8)	2.92 br t ($J_{8,7}$=6) ($J_{8,9}$=6)	2.89 m
9	1.87 m	2.28 m	1.74 ddd ($J_{9,11}$=11) ($J_{9,8}$=6) ($J_{9,11'}$=4)	2.0 m
11	1.74 m 2.57 m	1.9 m (CH_2)	1.51 m 2.58 m	1.37 m 1.81 m
12	2.27 m (CH_2)	2.13 m (CH_2)	2.20 m 2.33 m	2.12 m (CH_2)
13	6.59 s (OH)	6.49 s (OH)	6.48 s (OH)	6.47 s (OH)
14	-	-	6.14 s (OH)	6.13 s (OH)
16	3.01 s	2.91 s	2.98 s	2.96 s
19	1.16 s (CH_3)	0.91 s (CH_3)	1.12 s (CH_3)	1.10 s (CH_3)
21	1.65 s (CH_3)	1.64 s (CH_3)	1.65 s (CH_3)	1.65 s (CH_3)
22	4.59 dd ($J_{22,23'}$=6) ($J_{22,23}$=4.5)	4.56 dd ($J_{22,23'}$=4) ($J_{22,23}$=1.5)	4.42 m	4.43 m
23	1.86 m	1.87 dd ($J_{23,23'}$=15) ($J_{23,22}$=1.5)	1.59 br d ($J_{23,23'}$=15)	1.58 br d ($J_{23,23'}$=15)
	2.03 dd ($J_{23',23}$=15) ($J_{23',22}$=4)	2.05 dd ($J_{23',23}$=15) ($J_{23',22}$=4)	2.00 dd ($J_{23',23}$=15) ($J_{23',22}$=4)	2.01 dd ($J_{23',23}$=15) ($J_{23',22}$=4)
25	2.96 dd ($J_{25,27'}$=12) ($J_{25,27}$=3.5)	2.92 dd ($J_{25,27'}$=12) ($J_{25,27}$=4)	3.37 q ($J_{25,27}$=8)	3.46 q ($J_{25,27}$=7.5)
27	4.01 dd ($J_{27,27'}$=12) ($J_{27,25}$=3.5)	4.11 dd ($J_{27,27'}$=12) ($J_{27,25}$=4)	1.16 d (CH_3) ($J_{27,25}$=8)	1.17 d (CH_3) ($J_{27,25}$=7.5)
	4.26 t ($J_{27',27}$=12) ($J_{27',25}$=12)	4.28 t ($J_{27',27}$=12) ($J_{27',25}$=12)		
28	1.37 s (CH_3)	1.38 s (CH_3)	1.25 s (CH_3)	1.25 s (CH_3)

a) Spectra were recorded at 27 °C for **5**, **9**, and **12** and at 90 °C for **6**.

Table 2

^{13}C NMR spectral data (δ/PPM)[a,b] of neophysalins 5, 6, 9, and 12 measured in DMSO-d_6

Assign-ment	5	6	9	12	Assign-ment	5	6	9	12
1	204.2	213.7	204.7	213.0	15	170.1	170.0	173.3*2	173.5*2
2	123.7	37.7	123.5	35.9	16	47.0	47.0	55.7	56.4
3	139.7	25.9	140.8	25.6	17	82.4	81.5*1	84.0*1	83.9*1
4	116.4	28.9	116.6	121.4	18	172.2	172.5	175.5*2	175.6*2
5	152.0	46.7	152.8	141.0	19	21.5	15.4	24.5	18.9
6	126.1	129.8	128.2	128.4	20	81.5	82.4	80.8*1	80.1*1
7	130.0	124.5	131.3	126.6	21	20.8	21.1	21.7	21.8
8	47.7	49.0	46.8	47.9	22	75.9	75.6	75.4	75.4
9	35.1	31.7	34.1	36.1	23	29.5	29.6	27.6	28.2
10	50.8	53.3	51.0	50.8	24	28.3	28.5	34.6	34.8
11	22.9	22.7	24.6	22.0	25	40.2	40.1	38.9	39.0
12	29.0	29.3	27.7	27.1	26	169.6	169.6	172.7*2	172.8*2
13	78.4	78.2*1	78.9*1	78.5*1	27	60.4	60.1	16.7	16.6
14	81.6	81.5	82.7*1	83.2*1	28	29.2	29.4	27.4	27.3

a) Spectra were recorded at 27 °C for 5, 9, and 12 and at 90 °C for 6.
b) *1 and *2 refer to interchangeable data.

NMR and at 100 MHz for ^{13}C NMR with DMSO-d_6 solutions. Mass spectra were recorded on a Hitachi M-2000 mass spectrometer with the electron impact ionization at 70 eV. Column chromatography was performed using Silica Gel (Merck, #7734) with chloroform as eluent. Precoated TLC plates (Merck, Silica Gel 60 F_{254}) were used for TLC analysis with the solvent system $CHCl_3$-MeOH (9:1).

4,7-Didehydroneophysalin B (5). Physalin A (1) was treated with AcOH-NH_4OAc as described in Ref. 3 to afford 5, which crystallized from MeOH as yellow prisms, mp 299-300 °C (lit.[3] 298-300 °C).

Acid-treatment of Physalin L (7). a) A solution of 7 (101 mg) in AcOH (20 mL) was refluxed for 5 h. TLC analysis indicated that the product was a mixture of the two components (R_f 0.65 and 0.55) in the ratio of approximately 2 : 1. Column chromatographic separation gave 8 (R_f 0.65, 64 mg) and 9 (R_f 0.55, 24 mg). **(25*S*)-25,27-Dihydro-4,7-didehydro-7-deoxyphysalin A (4,7-didehydro-7-deoxyphysalin L, 8)**, yellow plates from AcOEt-hexane, mp 238-241 °C (lit.[4] 197-234 °C); ^1H NMR δ 0.95 (m, H-11β), 1.14 (s, Me-19), 1.15 (d, J=7 Hz, Me-27), 1.29 (s, Me-28), 1.62 (d, J=15 Hz, H-23), 1.74 (s, Me-21), 1.92 (m, H-11β), 2.09 (dd, J=15 and 3.5 Hz, H-23'), 2.1 (m, H-12α), 2.7 (m, H-8, H-12α, and H-25), 2.79 (s, H-16), 3.34 (m, H-9), 4.46 (br d, J=3.5 Hz, H-22), 5.82 (d, J=10 Hz, H-2), 6.03 (d, J=6 Hz, H-4), 6.28 (dd, J=10 and 2.5 Hz, H-7), 6.36 (dd, J=10 and 2 Hz, H-6), 6.40 (s, OH), 6.99 (s, OH), 7.02 (dd, J=10 and 6 Hz, H-3); ^{13}C NMR δ 16.6 (C-27), 18.2 (C-19), 20.9 (C-21), 22.2 (C-12), 25,5 (C-23), 25.7 (C-28), 28.7 (C-11), 34.0 (C-9), 34.5 (C-

24), 41.0 (C-25), 47.3 (C-8), 50.6 (C-10), 53.3 (C-16), 76.6 (C-22), 79.3, 82.5, and 83.0 (C-13, C-17, and C-20), 101.0 (C-14), 118.1 (C-4), 124.9 (C-2), 128.2 (C-7), 131.1 (C-6), 139.8 (C-3), 153.2 (C-5), 171.6 and 171.9 (C-18 and C-26), 205.3 (C-1), 214.8 (C-15).

b) A mixture of 7 (106 mg), NH_4OAc (200 mg) in AcOH (40 mL) was heated under reflux for 5 h. The resulting yellow solution showed a main spot (R_f 0.55) on TLC and column chromatographic purification afforded **(25*S*)-25,27-Dihydro-4,7-didehydro-7-deoxyneophysalin A** (**4,7-didehydro-7-deoxyneophysalin L**, **9**), 80 mg, yellow needles from acetone, mp 273-275 °C; IR 1790 (two γ-lactones), 1730 (δ-lactone), 1660 (conjugated C=O), 1630 and 1540 cm^{-1} (conjugated C=C); ^1H and ^{13}C NMR (Tables 1 and 2); MS calcd for $C_{28}H_{30}O_9$ m/z 510.1888, found 510.1899.

Acid-treatment of (25*R*)-2,3,25,27-Tetrahydrophysalin A (10). A mixture of **10** (63 mg), AcOH (20 mL), and NH_4OAc (100 mg) was heated under reflux and the proceeding of reaction was monitered by TLC. After 5 h the starting material **10** dissapeared and (25*S*)-2,3,25,27-tetrahydro-4,7-didehydro-7-deoxyphysalin A (**11**, R_f 0.8) was a main product but presence of a new compound (**12**, R_f 0.75) in small quantity was observed. The second product **12** became a major component after 10 h and the initial product **11** almost disappeared after 20 h. Column chromatography of the product yielded **(25*S*)-2,3,25,27-tetrahydro-4,7-didehydro-7-deoxyneophysalin A** (**12**), 28 mg, colorless needles from MeOH, mp 293-295 °C; IR 1785 (two γ-lactones), 1725 (δ-lactone), 1710 cm^{-1} (cyclohexanone); ^1H and ^{13}C NMR (Tables 1 and 2); MS calcd for $C_{28}H_{32}O_9$ m/z 512.2044, found 512.2066.

Acid-treatment of Physalin M (13). A mixture of **13** (154 mg), AcOH (30 mL), and NH_4OAc (300 mg) was heated under reflux for 24 h. TLC and ^1H NMR spectrum of the product indicated that no reaction had occurred.

Acid-treatment of Physalin B (2). A mixture of **2** (151 mg), AcOH (60 mL), and NH_4OAc (300 mg) was heated under reflux for 25 h. ^1H NMR spectral analysis of the reaction product revealed it to be an almost 1:1 mixture of starting material **2** and 3,4-didehydro-2,3-dihydrophysalin B (**14**).

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