PHENACEIN — AN ANGIOTENSIN-CONVERTING ENZYME INHIBITOR PRODUCED BY A STREPTOMYCETE

II. ISOLATION, STRUCTURE DETERMINATION AND SYNTHESIS

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Phenacein, an inhibitor of angiotensin-converting enzyme, has been isolated from the fermentation broth of a *Streptomyces* species belonging to the *Streptomyces tanashiensis-zaomyceticus* group. The inhibitor was shown to be 3,6-dihydroxy-1-phenazinecarboxylic acid by spectroscopic, degradative and synthetic methods.

Phenacein (**1**) is a novel angiotensin-converting enzyme inhibitor with weak activity against Gram-positive bacteria that is produced by a streptomycete (ATCC 39460). The taxonomy and fermentation of the producing organism and the enzyme inhibitory and antimicrobial activity of phenacein are described in the preceding paper[1]. This paper describes the isolation, structure determination and synthesis of this inhibitor.

Phenacein was isolated as fine orange needles from fermentation broths as outlined in Fig. 1. The inhibitor is clearly an acidic substance from its extraction behavior, pH dependence during reverse-phase chromatography and from its solubility in aqueous base. The IR spectrum (Fig. 2) reveals a carboxylic acid peak at 1694 cm^{-1} which is consistent with the electrophoretic mobility (Table 1) observed under neutral and basic conditions. The UV spectrum in methanol has a strong maximum at 268 nm that shifts to 290 nm upon addition of base, indicating the presence of phenolic hydroxyl groups. The EI mass spectrum shows a molecular ion at m/z 256.

Treatment of phenacein with diazomethane gave a trimethyl derivative **2** for which the empirical formula $C_{16}H_{14}N_2O_4$ was established by high resolution mass spectrometry. Thus phenacein itself has the empirical formula $C_{13}H_8N_2O_4$ and contains three groups capable of methylation with diazomethane. These can be accounted for by the carboxylic acid and two phenolic hydroxyl groups. The UV spectrum of phenacein closely resembles the UV spectra of many phenazines[2~5], allowing the postula-

Fig. 1. Isolation of phenacein.

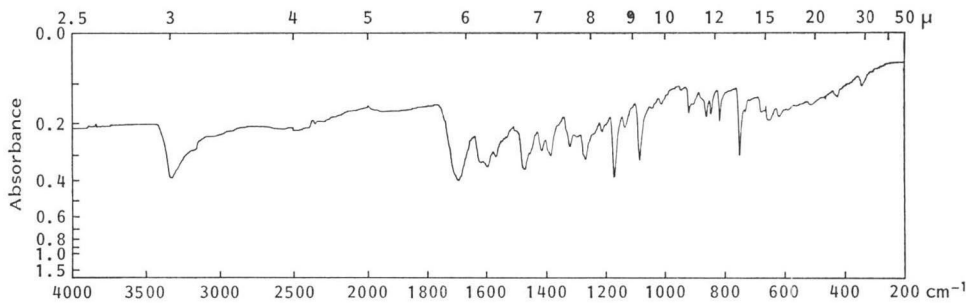
Broth supernate (10 liters)
↓ Extraction with BuOH at pH 2
Back extraction into H_2O at pH 9
Lyophilization at pH 7
6.5 g
↓ Cellulose partition chromatography in H_2O - EtOAc - BuOH
432 mg
↓ Chromatography on MCI GEL CHP20P and XAD-2 at pH 7.4 and 5.2, eluting with MeOH - H_2O
Phenacein, 2.2 mg

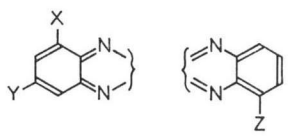
Table 1. Low voltage electrophoresis of phenacein.

System	Mobility[a]
HCO_2H - AcOH - H_2O, 1 : 3 : 36 (pH 1.8)	0.0
Sodium phosphate (0.05 M, pH 4.5)	0.0
Sodium phosphate (0.05 M, pH 7.0)	0.34 (yellow)
Sodium carbonate-bicarbonate (0.05 M, pH 9.2)	0.89 (orange-red)

[a] 250 V, 1 hour, Whatman No. 2 paper, mobility relative to vitamin B_{12} (0.00) and *p*-nitrobenzenesulfonate anion (1.00).

Fig. 2. IR spectrum of phenacein in KBr.





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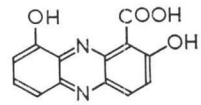

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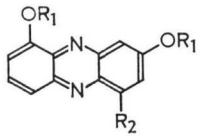
tion that phenacein is a dihydroxyphenazinecarboxylic acid. The ^1H NMR spectrum of the methylated derivative in $CDCl_3$ shows five aromatic protons between 7 and 8 ppm, and the spectrum in this region is well simulated by an AB system at δ 7.72 and 7.92 coupled by 2.8 Hz superimposed on an ABC system at δ 7.09 (J=7.4, 1.1 Hz), 7.69 (J=8.8, 7.4 Hz) and 7.87 (J=8.8, 1.1 Hz). Thus partial structures **3** and **4** can be drawn.

A sample of trimethyl derivative **2** was saponified with NaOH, and the resulting carboxylic acid **5** was decarboxylated by heating with copper powder in phenyl ether at 250°C[6] to give a dimethoxyphenazine that melted at 150~153°C. All of the dimethoxyphenazines that are consistent with partial structures **3** and **4** are known[7,8] and can be distinguished by their melting points: 1,3- mp 228°C; 1,6- mp 250°C; 1,7- mp 175°C; 1,8- mp 158°C; and 1,9- mp 260°C. It is apparent that the decarboxylation product is 1,8-dimethoxyphenazine (**6**)[9,10] and therefore that phenacein is 3,6-dihydroxy-1-phenazinecarboxylic acid (**1**).

An isomeric phenazine (**7**) differing only in the position of the carboxyl group, was reported as a metabolite of an unidentified bacterium by GERBER in 1969[11]. The location of the hydroxyl substituents was determined almost exactly as described above and the location assigned for the carboxyl group was based on the chromatographic behavior of the dimethyl ether. More recently, 2,3-dihydroxy-1-phenazinecarboxylic acid[5] and 2,6-dihydroxy-1-phenazinecarboxylic acid[12] have been reported as pseudomonal metabolites.

In order to confirm the structure and to supply material for biological studies, phenacein was prepared synthetically. The phenazine skeleton, 3,6-dimethoxy-1-methylphenazine (**8**), was assembled by the base catalyzed condensation of 4-methoxy-2-methylaniline and *o*-nitroanisole[13]. Direct oxidation of the methyl group in **8** to the carboxylic acid or aldehyde by a variety of methods was accompanied by considerable decomposition. Therefore a three-step procedure was applied. Bromination of **8** with *N*-bromosuccinimide in carbon tetrachloride initiated by azobisisobutyronitrile provided the bromide **9**. On treatment with silver tetrafluoroborate in dimethyl sulfoxide, the bromide was smoothly converted to the corresponding aldehyde **10**[14]. Oxidation of aldehyde **10** was carried out using sodium cyanide and silver (I) oxide[15]. Carboxylic acid **5** was obtained in 70% yield from **10** as orange crystals (no mp



1	R_1=H, R_2=COOH	**10**	R_1=Me, R_2=CHO
2	R_1=Me, R_2=COOMe	**11**	R_1=H, R_2=Me
5	R_1=Me, R_2=COOH	**12**	R_1=CH_2OMe, R_2=Me
6	R_1=Me, R_2=H	**13**	R_1=CH_2OMe, R_2=CH_2Br
8	R_1=R_2=Me	**14**	R_1=CH_2OMe, R_2=CHO
9	R_1=Me, R_2=CH_2Br	**15**	R_1=CH_2OMe, R_2=COOH

<250°C). Treatment of carboxyphenazine **5** with diazomethane provided the permethylated derivative **2** which was precisely identical by spectroscopic, chromatographic, and physical comparison to the compound obtained by exhaustive methylation of the natural product **1**. The structure of the microbially produced compound as 3,6-dihydroxy-1-phenazinecarboxylic acid (**1**) was therefore confirmed.

In order to obtain the natural product **1** we attempted cleavage of the methyl ethers in compound **5** by Lewis acids. Unfortunately, the reaction was accompanied by extensive degradation of the molecule, making isolation and purification of the final product extremely difficult. We therefore decided to change the protecting groups at an earlier stage. We chose the methoxymethyl ether due to its acid lability.

When **8** was heated with aluminum chloride in benzene, the diphenol **11** was obtained in 66% yield. Treatment of compound **11** with bromomethyl methyl ether and potassium carbonate in tetrahydrofuran provided the fully protected product **12**. As expected, the transformation **12** to **15** proceeded in a manner as described for **8** to **5**. The removal of the protecting groups in compound **15** was uneventful, giving synthetic **1** in 95% yield. The synthetic material was chromatographically and spectroscopically indistinguishable from the natural product and exhibited the same level of angiotensin-converting enzyme inhibition (K. BUSH, personal communication).

Experimental

Melting points were determined on Fisher-Johns and on Thomas-Hoover melting point apparatus and are uncorrected. IR and UV spectra were determined on Perkin-Elmer Model 621 and 202 instruments, respectively. NMR spectra were recorded on a Varian Associates XL-100-15 and Jeol GX-400 spectrometers; chemical shifts (δ) are given in ppm downfield from internal TMS. Mass spectra were determined with a AEI-Kratos MS-902 double-focusing mass spectrometer using electron impact ionization.

Isolation of Phenacein (**1**)

The broth filtrate from a 10-liter fermentation was extracted with two 5-liter portions of BuOH at pH 2 and the combined extract was back extracted with H_2O at pH 9. The aqsolution was adjusted to pH 7 (HCl), concentrated to 1 liter, and lyophilized, giving 6.48 g of solid. This was chromatographed on a 5×50 cm cellulose column, eluting with a linear gradient prepared from 1 liter each of H_2O-satd EtOAc and H_2O-satd EtOAc - BuOH, 1 : 1. Active fractions[1] were combined, giving 432 mg of residue. Chromatography of this material on a 2.5×26 cm column of MCI GEL CHP20P, eluting with a H_2O - MeOH gradient gave very little retention but reduced the weight to 36 mg. Repetition on Servachrom XAD-2 further reduced the weight to 25 mg. A solution of this material in 5 ml of H_2O was adjusted to pH 5.2 with HCl and mixed with a small amount of Servachrom XAD-2. The mixture was applied to a 1.5×20 cm column of Servachrom XAD-2 packed in H_2O. Elution with a H_2O -

MeOH gradient gave good retention. Active fractions were combined and concentrated, giving 2.2 mg of phenacein as fine orange needles; no mp <310°C; UV_{max} in MeOH ($E^{1\%}_{1cm}$) 218 (200), 268 (840), 385 (80), 460 nm (sh); UV_{max} in acidified MeOH 215, 268, 395, 466 nm; UV_{max} in MeOH with base 212, 293, 420, 530 nm; IR(KBr) (see Fig. 2) 3330, 1694, 1598, 1472, 1171, 1087, 751 cm^{-1}; TLC (Analtech silica gel, MeOH - $CHCl_3$, 1: 9) Rf 0.63; MS *m/z* 256 (M^+). Phenacein is soluble in dilute aq $NaHCO_3$ and DMF; slightly soluble in MeOH, $CHCl_3$, EtOAc, acetone, CH_3CN and AcOH; and insoluble in H_2O and dilute HCl.

3,6-Dimethoxy-1-phenazinecarboxylic Acid Methyl Ester (**2**)

A small sample of phenacein in methanol at 0°C was treated with excess ethereal diazomethane. After 20 minutes, the mixture was concentrated and the product purified by TLC (silica gel; $CHCl_3$ - EtOAc, 1: 1; Rf 0.67) to give **2** as yellow needles; mp 181~182°C; UV_{max} in MeOH 218, 268, 377, 425 nm; IR ($CDCl_3$) 1731 cm^{-1} (ester carbonyl); MS *m/z* 298.0928 (calcd for $C_{16}H_{14}N_2O_4$ 298.0953); ^1H NMR ($CDCl_3$) δ 4.01 (3H, s), 4.09 (3H, s), 4.17 (3H, s), 7.09 (1H, *J*=7.4, 1.1 Hz), 7.69 (1H, *J*=8.8, 7.4 Hz), 7.73 (1H, *J*=2.8 Hz), 7.86 (1H, *J*=8.8, 1.1 Hz), 7.91 (1H, *J*=2.8 Hz). The preparation of **2** from **8** was carried out by the sequence described in detail below for the conversion of **12** to **15** followed by esterification with diazomethane.

1,8-Dimethoxyphenazine (**6**)

A solution of 1.1 mg of **2** in MeOH - 1 N NaOH, 9: 1, was warmed gently until none of the ester was detectable by TLC. The solution was acidified (HCl), extracted with $CHCl_3$, and the extract concentrated giving 1.0 mg of carboxylic acid dimethyl ether **5**. This was heated with $CuSO_4$ in quinoline at 200°C for 3 hours[16] which gave incomplete reaction. Unreacted starting material was recovered by TLC and treated with Cu powder in phenyl ether at 250°C for 2.5 hours, a procedure[8] that appeared to give faster decarboxylation. The decarboxylation product was purified by TLC (silica gel, EtOAc, yellow band Rf 0.6~0.7), dissolution in 4 N HCl, precipitation with NH_4OH and recrystallization from H_2O containing a little MeOH to give 95 μg of **6** as very fine yellow needles, mp 150~153°C, *m/z* 240.

3,6-Dimethoxy-1-methylphenazine (**8**)

A mechanically stirred mixture of 66.0 ml (0.51 mol) of freshly distilled 4-methoxy-2-methylaniline, 50.5 ml (0.41 mol) of freshly distilled *o*-nitroanisole, 189 g (3.37 mol) of finely powdered KOH, and 945 ml of toluene was heated to reflux (initially exothermic) for 1 hour. The mixture was then cooled to room temperature, filtered, and the filter cake washed with toluene, 1% MeOH in CH_2Cl_2, and CH_2Cl_2. The solvent from the combined filtrate and washings was removed *in vacuo* to yield 86 g of black solid. The black material was then flash filtered through silica gel eluting with ether and the fractions containing the desired phenazine (Rf 0.22 on silica gel, CH_2Cl_2) were combined, concentrated and purified by flash chromatography, eluting with CH_2Cl_2. A final chromatography on a Waters Model 500 preparative chromatograph (silica gel; hexane - acetone, 6: 1) followed by recrystallization from a hexane - toluene mixture afforded 12.3 g (9.4%) of compound **8** as yellow needles: mp 201~202°C; ^1H NMR ($CDCl_3$) δ 2.85 (3H, broad s), 3.97 (3H, s), 4.16 (3H, s), 7.34 (1H, dd, *J*=2.7, 1.2 Hz), 7.44 (1H, d, *J*=2.7 Hz), 7.65 (1H, dd, *J*=8.9, 7.6 Hz), 7.83 (1H, dd, *J*=8.9, 1.2 Hz).

Anal Calcd for $C_{15}H_{14}N_2O_2$: C 64.96, H 5.77, N 8.91.
Found: C 64.64, H 5.77, N 8.77.

6-Methyl-1,8-phenazinediol (**11**)

A magnetically stirred mixture of 0.509 g (2 mmol) of compound **8**, 1.0 g of $AlCl_3$ (7.5 mmol), and 20 ml of benzene was heated at reflux for 18 hours. The mixture was cooled to room temperature and concentrated. The residue was treated with crushed ice and the resulting mixture was taken up in 1 N NaOH and washed with CH_2Cl_2. The combined CH_2Cl_2 layers were back extracted with 1 N NaOH and the combined aqlayers were acidified to pH 4~5. This solution was extracted with CH_2Cl_2 containing a trace of MeOH. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed to yield 1.06 g of a brown solid. Flash chromatography on silica gel with toluene - acetone (6: 1) yielded 0.38 g of yellow solid. This was recrystallized from toluene to yield 298 mg (66%) of **11** as orange crystals: mp >256°C (dec), ^1H NMR ($CDCl_3+CF_3CO_2D$) δ 2.90 (3H, s), 7.53 (1H, dd, *J*=6.6, 0.9 Hz), 7.54 (1H, broad s), 7.59 (1H, broad d, *J*=2.4 Hz), 7.83 (1H, dd,

J=8.9, 7.9 Hz), 8.03 (1H, dd, J=8.9, 0.8 Hz).

Anal Calcd for $C_{13}H_{10}N_2O_2$: C 69.02, H 4.45, N 12.38.
Found: C 69.08, H 4.50, N 12.18.

3,6-Bis(methoxymethoxy)-1-methylphenazine (**12**)

A stirred suspension of compound **11** (113 mg, 0.5 mmol), finely ground potassium carbonate (690 mg, 5.0 mmol) and 18-Crown-6 (catalytic amount) in anhydrous THF (4 ml) was cooled to 0°C (ice bath) and treated with bromomethyl methyl ether (156 mg, 1.25 mmol, dropwise addition) under argon. After stirring at 0°C for 30 minutes, the reaction was allowed to warm to room temp and stirring was continued for 5 hours. The suspension was filtered through a Celite pad and the solid was washed with $CHCl_3$. Solvent evaporation provided a yellow solid that was recrystallized from CH_2Cl_2 - ether to give yellow needles (119 mg). The mother liquor was purified by preparative TLC (1% MeOH in CH_2Cl_2) to give 11 mg of additional product for a combined yield of 130 mg of **12** (83%): mp 157~158°C; ^{1}H NMR ($CDCl_3$) δ 2.88 (3H, s), 3.54 (3H, s), 3.62 (3H, s), 5.36 (2H, s), 5.58 (2H, s), 7.40 (1H, dd, J=2.8, 1.5 Hz), 7.47 (1H, dd, J=7.6, 1.2 Hz), 7.65 (1H, dd, J=8.9, 7.6 Hz), 7.69 (1H, d, J=2.7 Hz), 7.90 (1H, dd, J=8.9, 1.2 Hz); IR (KBr) 1630, 744 cm^{-1}.

Anal Calcd for $C_{17}H_{18}N_2O_4$: C 64.96, H 5.77, N 8.91.
Found: C 64.84, H 5.77, N 8.77.

1-(Bromomethyl)-3,6-bis(methoxymethoxy)phenazine (**13**)

A reaction mixture containing compound **12** (188 mg, 0.6 mmol), recrystallized *N*-bromosuccinimide (120 mg, 0.7 mmol) and azobisisobutyronitrile (5 mg, 0.03 mmol) in CCl_4 (6 ml, dried over alumina) was heated at reflux under argon while illuminating it with a sun lamp. After 1 hour, the reaction was cooled to room temp, diluted with CH_2Cl_2 and washed with H_2O. After drying ($MgSO_4$), the solvent was removed to give a brown residue. Purification by flash chromatography on silica gel eluting with CH_2Cl_2 provided 20 mg of recovered starting material and 127 mg (55% yield) of **13**: mp 167~168°C (from CH_2Cl_2 - ether); ^{1}H NMR ($CDCl_3$) δ 3.54 (3H, s), 3.61 (3H, s), 5.27 (2H, s), 5.37 (2H, s), 5.58 (2H, s), 7.50~7.90 (5H, m); IR (KBr) 1630, 747 cm^{-1}.

Anal Calcd for $C_{17}H_{17}N_2O_4Br$: C 51.92, H 4.36, N 7.12, Br 20.32.
Found: C 51.81, H 4.30, N 7.08, Br 20.46.

3,6-Bis(methoxymethoxy)-1-phenazinecarboxaldehyde (**14**)

To a solution of silver tetrafluoroborate (359 mg, 1.86 mmol) in anhydrous DMSO (15 ml) was added the bromide **13** (600 mg, 1.53 mmol), and the resulting suspension was stirred overnight at room temp under argon. It was then treated with triethylamine (0.5 ml) and the stirring continued for 30 more minutes. The reaction mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was thoroughly washed with H_2O, brine and dried ($MgSO_4$). Concentration provided a yellow solid that was taken up in dry CH_2Cl_2 (5 ml) and added to a solution of pyridinium chlorochromate (130 mg, 0.6 mmol) in CH_2Cl_2 (2 ml). After stirring for 3 hours, the reaction was worked up in standard fashion (ether quench) to give an orange solid. Purification by flash chromatography on silica gel eluting with $CHCl_3$ gave the pure aldehyde, **14**, (406 mg, 80%) as yellow needles from $CHCl_3$ - ether: mp 148~150°C; ^{1}H NMR ($CDCl_3$) δ 3.54 (3H, s), 3.62 (3H, s), 5.41 (2H, s), 5.59 (2H, s), 7.46~8.22 (5H, m), 11.48 (1H, s); IR (KBr) 1693, 1625, 737 cm^{-1}.

Anal Calcd for $C_{17}H_{16}N_2O_5$: C 62.19, H 4.91, N 8.53.
Found: C 61.85, H 5.04, N 8.43.

3,6-Bis(methoxymethoxy)-1-phenazinecarboxylic Acid (**15**)

A suspension of aldehyde **14** (400 mg, 1.22 mmol) and Ag_2O (1.6 g, 13 mmol) in MeOH (30 ml) was treated with sodium cyanide (300 mg, 6.1 mmol) and the reaction mixture was heated (85°C bath) under argon for 6 hours. The reaction was allowed to cool to room temp and was then filtered through a Celite pad. The filtrate was concentrated to 20 ml and treated with 2 N KOH (6 ml) in order to hydrolyze the ester formed. After stirring at room temp for 1~2 hours, the reaction mixture was diluted with H_2O (20 ml) and excess MeOH was removed under reduced pressure. The resulting aq solution was stirred with $CHCl_3$, and 2 N HCl was carefully added to the two-phase solution until the pH approached 3. The organic layer was separated, and the aq phase was reextracted with $CHCl_3$.

The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated to give a yellow solid. Recrystallization from $CHCl_3$ - ether provided the pure acid **15** (320 mg) as yellow needles. The mother liquor was purified by preparative TLC on silica gel (2% MeOH in CH_2Cl_2, run twice) to give an additional 10 mg of the product for a combined yield of 330 mg (79%): mp 178~180°C; ^1H NMR ($CDCl_3$) δ 3.54 (3H, s), 3.63 (3H, s), 5.43 (2H, s), 5.61 (2H, s), 7.58 (1H, dd, J=7.6, 1.2 Hz), 7.81~7.89 (2H, m), 8.16 (1H, d, J=3.1 Hz), 8.70 (1H, d, J=2.7 Hz); IR (KBr) 1742, 1623, 753 cm^{-1}.

Anal Calcd for $C_{17}H_{16}N_2O_6 \cdot \frac{1}{2}H_2O$: C 57.79, H 4.85, N 7.93.
Found: C 57.87, H 4.67, N 7.97.

3,6-Dihydroxy-1-phenazinecarboxylic Acid (Phenacein, **1**)

A solution of acid **15** (327 mg, 0.95 mmol) in THF (15 ml) and 70% TFA (20 ml) was stirred at room temp for 5 hours and then heated at 70°C for 2 hours. The solution was cooled to ambient temp, diluted with H_2O (10 ml), and the solvent was removed *in vacuo* to give a yellow residue that was suspended in acetone - ether (1 : 2) and filtered. The solid was washed with the same solvent mixture and dried *in vacuo* at 50°C for 10 hours to give 240 mg (95%) of **1**: no mp <300°C; ^1H NMR ($CDCl_3+CF_3CO_2D$) δ 7.72 (1H, d, J=7.9 Hz), 8.09 (1H, d, J=8.7 Hz), 8.15 (1H, d, J=2.4 Hz), 8.22 (1H, dd, J=9.1, 7.5 Hz), 8.91 (1H, d, J=2.8 Hz).

Anal Calcd for $C_{13}H_8N_2O_4 \cdot \frac{1}{2}H_2O$: C 58.87, H 3.42, N 10.56.
Found: C 58.63, H 3.45, N 10.52.

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