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AN ANTIMALARIAL ALKALOID FROM HYDRANGEA. XXI. SYNTHESIS AND STRUCTURE OF FEBRIFUGINE AND ISOFEBRIFUGINE

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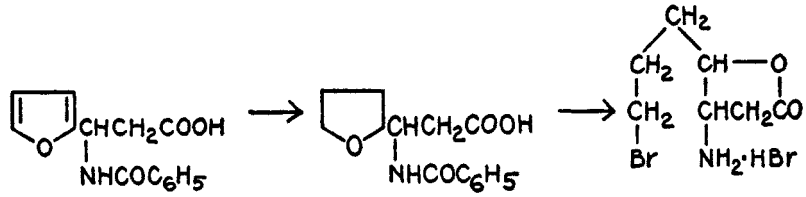
A second synthesis of the *dl*-alkaloid starting with furfural has been presented in the preceding paper (1). In this communication is described the synthesis of the naturally occurring antipode of the alkaloid (febrifugine) *via* optically active intermediates. From the filtrate of the final product was also isolated the isomeric isofebrifugine. Structures for these two isomeric compounds are proposed on the basis of infrared data.



I II III

From an economic point of view it would be best to resolve at the earliest possible step. N-Benzoyl-β-furyl-β-alanine (I) was resolved in alcohol with brucine to give a good yield of the *l*-form as the insoluble isomer. It should be noted that this molecule has only one asymmetric center, A, (see Chart I)

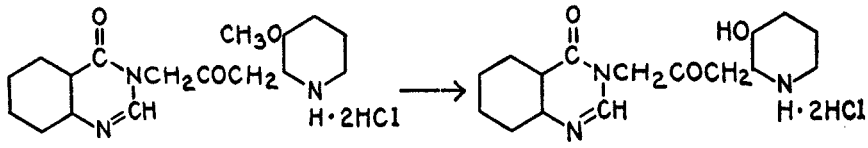
CHART I

		1	2
A + −	⟶	A + −	+ −
B ——		B + −	− +
I		II	

and that the second asymmetric center, B, is introduced by subsequent hydrogenation to II. Reduction of *dl*-I gave almost exclusively one of the two possible racemates of II (1). Whether this predominant racemate of II has configuration 1 or 2 does not matter in the following argument. If it is assumed that racemate 1 is the main reduction product, then reduction of optically active I must also give the optically active half of racemate 1, that is A (+) → AB (+,+) and A (−) → AB (−,−). This has been found to be the case. Recrystallization of crude II led to the pure optical antipode of II, $[\alpha]_D^{26}$ −15.5°. This pure antipode was converted to the optically active bromolactone (III) in 63% yield. However, a better over-all conversion of I to III (43%) was again obtained as in the *dl*-series (1) when the intermediate II was not purified.

The synthesis of the optically activn alkaloid (V) was completed in the same

manner as described in the *dl*-series (1). This compound, obtained in 59% yield by 48% hydrobromic acid hydrolysis of the methyl ether (IV), and the natural Hydrangea alkaloid (febrifugine) (2) had identical I.R. spectra, activity, and rotations. The free base of V, m.p. 158–160°, was also identical with one of the crystal forms of the alkaloid free base as were their N-carbamyl derivatives prepared with potassium cyanate (3).

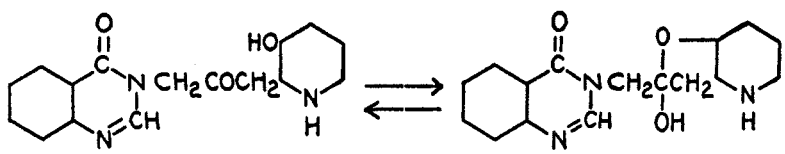


IV V

From the filtrate of V was isolated an isomeric base, m.p. 138–139°, $[\alpha]_D^{26}$ +121° ($CHCl_3$), in 13% yield. This base is identical with the isofebrifugine of Koepfli, Mead, and Brockman (4) as shown by their I.R. spectra.[1] With both febrifugine (the Hydrangea alkaloid) and isofebrifugine on hand, it becomes interesting to speculate why these two isomeric compounds are formed in the same reaction mixture and what their respective structures might be. The two important differences in properties between these bases (4) are as follows:

(a) Febrifugine will readily form ketone derivatives while isofebrifugine will not under the same conditions.

(b) Isofebrifugine is 14 times more easily extractable from water with chloroform than is febrifugine.



VI VII

There are two major possible explanations for the structures of these two easily interconvertible isomers. Koepfli, Brockman, and Moffat (5) proposed that the structure VI actually exists as the hemi-ketal (VII). This ketal has a third asymmetric center resulting in two diastereoisomers. They proposed that febrifugine and isofebrifugine were the two ketal isomers and that the open hydroxy ketone (VI) did not exist.

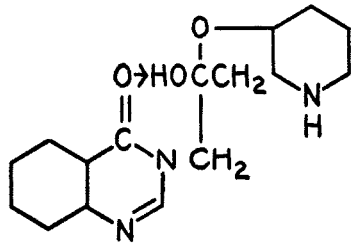
A second explanation, which they did not mention, is that febrifugine has the open hydroxy ketone structure (VI) and isofebrifugine is one of the two possible ketal isomers (VII). This can explain both properties (a) and (b)

[1] We wish to thank Dr. J. B. Koepfli for his generosity in supplying to us samples of isofebrifugine and febrifugine (m.p. 138–140°) for comparative purposes. The latter had an I.R. spectrum identical with a sample of the free base, m.p. 135–136°, prepared from the Hydrangea alkaloid (dihydrochloride) (2).

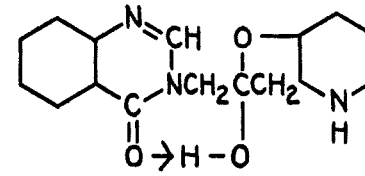
cited above as well as the ease of interconversion. These points will be discussed later.

In order to substantiate one or the other of these two hypotheses a study of the infrared spectra of the isomeric bases was made. Kuehl, Spencer, and Folkers (6) stated that febrifugine and isofebrifugine had identical I.R. spectra, but reported only a narrow range of the spectrum (6.03–6.78 μ). That these two compounds would have identical curves over a wide region (2–15 μ) of the spectrum seemed highly improbable in view of their differences in physical and chemical properties. The isomeric bases showed some similarities in their I.R. spectra, particularly in the 5.9–6.7 μ region where they were essentially identical as previously cited (6). Both had the *tert*-amide band of the 4-quinazolone carbonyl at 5.90–5.96 μ and the combined phenyl and C=N bands at 6.20 μ. However, there were many gross differences. For example, both crystal forms of febrifugine, m.p. 138–140° and 158–160°, had a ketone band at 5.79 μ which was missing in isofebrifugine. Secondly, isofebrifugine had strong bands at 9.05 and 9.48 μ not present in febrifugine. These have been assigned to a five membered cyclic ketal ring (9). Thus febrifugine must have the open hydroxy ketone structure (VI) and isofebrifugine is a hemi-ketal (VII).

The mere formation of a hemi-ketal would hardly be sufficient to stop isofebrifugine from forming ketone derivatives of febrifugine since in the sugar series carbonyl derivatives are readily formed. However, inspection of models of isofebrifugine showed that the two possible diastereoisomers, VIII and IX, could be further stabilized by hydrogen bonding of the OH to the carbonyl of the 4-quinazolone, hence decreasing the potentiality of formation of ketone derivatives and increasing the ease of extractability into organic solvents from water. It cannot be stated at this time whether isofebrifugine has structure VIII or IX. These structures require that a third isomer, the diastereoisomer of isofebrifugine, should exist. This isomer has not yet been isolated from a natural source (2, 4, 6, 8), from interconversions (4, 6), or from a synthetic reaction mixture such as described in the experimental. Secondly, either hemi-ketal, VIII or IX, should give ketone derivatives of febrifugine under the proper conditions of simultaneous interconversion.



VIII



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EXPERIMENTAL

Resolution of N-benzoyl β-furyl-β-alanine (I). A hot solution of 145 g. of *dl*-I and 263 g. of anhydrous brucine in 1450 cc. of absolute alcohol was allowed to cool to room temperature After being seeded, the mixture was allowed to stand overnight. The brucine salt was collected and washed with 145 cc. of absolute alcohol; wt. 164 g., $[\alpha]_D^{28}$ −46° (1% in acetone). The rotation of a similar preparation was the same and was unchanged after recrystallization from absolute alchol.

A hot solution of 71 g. of brucine salt in 100 cc. of absolute alcohol was poured into a mixture of 500 cc. of water and 25 cc. of 12 *N* hydrochloric acid with stirring. The mixture was cooled to 0°, filtered, and the white crystals were washed with water; yield, 26.8 g. (75% over-all), m.p. 191–192°. Another preparation, m.p. 193°, gave $[\alpha]_D^{24}$ −44° (1% in acetone) and $[\alpha]_D^{24}$ −66° (0.8% in 0.1 *N* NaOH).

Anal. Calc'd for $C_{14}H_{13}NO_4$: C, 64.9; H, 5.02; N, 5.41.
Found: C, 64.9; H, 5.39; N, 5.41.

The filtrate from the brucine salt deposited additional crystals after standing several weeks. One recrystallization from absolute alcohol gave the optically pure salt of the *l*-acid and brought the yield of resolution to near quantitative.

l-β-Benzamido-β-tetrahydrofurylpropionic acid (II). A mixture of 30 g. of *l*-I, 150 cc. of Methyl Cellosolve, and 5 g. of 10% palladium-charcoal was shaken with hydrogen at 2–3 atm. and 80° until reduction was complete (one hour). The filtered solution was evaporated to dryness *in vacuo* leaving a crystalline residue in quantitative yield. Material of this purity was used in subsequent steps. Optically pure material of constant m.p. was obtained with considerable loss after five recrystallizations from 30% methanol; white plates, m.p. 182–183°, $[\alpha]_D^{26}$ −15.5° (0.8% in 0.1 *N* NaOH).

Anal. Calc'd for $C_{14}H_{17}NO_4$: C, 63.9; H, 6.46; N, 5.32.
Found: C, 64.0; H, 6.83; N, 5.23.

l-3-Amino-4-hydroxy-7-bromohepatanoic acid lactone (III). A solution of 10.9 g. of nearly optically pure *l*-II, m.p. 178–179°, in 10.9 cc. of 48% hydrobromic acid was treated as described for *dl*-III (1); yield, 7.9 g. (63%) of white crystals, m.p. 201–202° dec., $[\alpha]_D^{27}$ −36.6° (0.8% in H_2O).

Anal. Calc'd for $C_{17}H_{12}BrNO_2 \cdot HBr$: C, 27.7; H, 4.29; N, 4.62.
Found: C, 27.8; H, 4.35; N, 4.75.

For preparative purposes crude II obtained on evaporation of the hydrogenation solution was treated with 48% hydrobromic acid giving 41–43% yields over-all from *l*-I.

l-3-Hydroxypiperidine-2-acetic acid lactone hydrochloride. Cyclization of 3.0 g. of *l*-III with triethylamine as described for the *dl*-isomer (1) gave 0.93 g. (60%) of product, m.p. 234–235° dec., from absolute alcoholic hydrogen chloride. Recrystallization from methanol afforded white crystals, m.p. 238–239° dec., $[\alpha]_D^{27}$ −64.4° (0.7% in H_2O).

Anal. Calc'd for $C_7H_{11}NO_2 \cdot HCl$: C, 47.3; H, 6.75; N, 7.89.
Found: C, 47.6; H, 6.87; N, 8.13.

d-1-Benzoyl-3-hydroxypiperidine-2-acetic acid lactone (*A*). Benzoylation of 500 mg. of the preceding compound as described (1) for the *dl*-isomer, procedure *C*, gave 580 mg. (84%) of product from ethyl acetate-heptane, m.p. 110°. Recrystallization from toluene afforded white crystals of unchanged m.p., $[\alpha]_D^{31}$ +113° (1% in abs. alc.).

Anal. Calc'd for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.12; N, 5.71.
Found: C, 68.5; H, 6.36; N, 5.65.

(*B*). By cyclization of 33.8 g. of *l*-III with triethylamine in chloroform followed by benzoylation as described for the *dl*-isomer, procedure *D*, (1) there was obtained 20.6 g. (75%) of white crystals, m.p. 106–108°. In two more runs the yields were 66% in both cases.

d (?)-1-Benzoyl-3-hydroxypiperidine-2-acetic acid. Hydrolysis of the preceding lactone with 10% sodium hydroxide as described for the *dl*-isomer (1) gave an 82% yield of product, m.p. 156–157° dec. This material could not be further purified. In some runs the product did not crystallize in which case the oil was extracted with chloroform and carried to the next step.

d-1-Benzoyl-3-methoxypiperidine-2-acetic acid. By methylation of 10 g. of *d*-1-benzoyl-3-hydroxypiperidine-2-acetic acid as the disodium salt as previously described for the *dl*-isomer (1) there was obtained 4.8 g. (46%) of product, m.p. 149–150°, and 2.7 g. (29%) of lactone, m.p. 103–105°, was recovered. Recrystallization of a sample from ethyl acetate did not raise the m.p.: white crystals, $[\alpha]_D^{30}$ + 51° (1% in 0.1 *N* NaOH).

Anal. Calc'd for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.91; N, 5.05.
Found: C, 64.6; H, 7.19; N, 5.28.

d (?)-1-Carbethoxy-3-methoxypiperidine-2-acetic acid. By hydrolysis and carbethoxylation of 13.4 g. of the preceding benzoyl acid as described for the *dl*-isomer (1) there was obtained 9.6 g. (82%) of product as a gum.

Anal. Calc'd for $C_{11}H_{19}NO_5$: C, 53.9; H, 7.75; N, 5.71.
Found: C, 54.0; H, 7.96; N, 5.62.

After standing for some time the gum solidified. Recrystallization from benzene-petroleum ether gave a 72% recovery of white crystals, m.p. 79–80°.

d (?)-1-Carbethoxy-2-(γ-bromoacetonyl)-3-methoxypiperidine. From 7.0 g. of 1-carbethoxy-3-methoxypiperidine-2-acetic acid (m.p. 79–80°) *via* the acid chloride and diazoketone as described for the *dl*-isomer (7) there was obtained 9.0 g. (98%) of product as an oil.

d (?)-3-[β-Keto-(1-carbethoxy-3-methoxy-2-piperidyl)propyl]-4-quinazolone. Condensation of 9.0 g. of the above bromo ketone with 4-quinazolone as described for the *dl*-isomer (7) gave 5.1 g. (61%) of product, m.p. 121–122°. Recrystallization of a similar preparation from benzene-heptane afforded white crystals, m.p. 124–125°.

Anal. Calc'd for $C_{20}H_{25}N_3O_5$: C, 62.0; H, 6.46; N, 10.9.
Found: C, 62.1; H, 6.62; N, 10.8.

d (?)-3-[β-Keto-γ-(3-methoxy-2-piperidyl)propyl]-4-quinazolone dihydrochloride (IV). Hydrolysis of 5.1 g. of the preceding compound as described for the *dl*-isomer (7) gave 1.8 g. (36%) of white crystals which partially melt at 140° and decompose at 210–212°. A similar preparation was analyzed.

Anal. Calc'd for $C_{17}H_{21}N_3O_3 \cdot 2HCl \cdot 2H_2O$: C, 48.1; H, 6.39; N, 9.90; CH_3O, 7.29.
Found: C, 47.8; H, 5.91; N, 10.1; CH_3O, 6.81.

d-3-[β-Keto-γ-(3-hydroxy-2-piperidyl)propyl]-4-quinazolone (the Hydrangea alkaloid, febrifugine) (V). A solution of 1.8 g. of IV in 18 cc. of 48% hydrobromic acid was refluxed for ten minutes, then evaporated to dryness *in vacuo*. The residue was twice dissolved in 18 cc. of 6 *N* hydrochloric acid and evaporated to dryness *in vacuo*. A solution of the residue in 18 cc. of absolute alcohol was again evaporated to dryness *in vacuo*. The semi-crystalline residue was heated to boiling with 18 cc. of absolute alcoholic hydrogen chloride for about five minutes. After being cooled to 0° for one hour, the mixture was filtered and the solid washed with two 4-cc. portions of absolute alcoholic hydrogen chloride, then with acetone; yield, 1.05 g. (59%) of white crystals of febrifugine dihydrochloride, m.p. 218–220° dec. with some shrinkage at 200°. Recrystallization from 10 cc. of 95% methanol by the addition of 30 cc. of saturated absolute alcoholic hydrogen chloride raised the m.p. to 232–233° dec., $[\alpha]_D^{25}$ +12.8° (0.8% in H_2O). This compound had an I.R. spectrum and antimalarial activity identical with the natural Hydrangea alkaloid for which a micro m.p. 223–225° and $[\alpha]_D^{31}$ +12.8° (0.8% in H_2O) have been recorded (2).

Anal. Calc'd for $C_{16}H_{19}N_3O_3 \cdot 2HCl$: C, 51.3; H, 5.68; N, 11.2.
Found: C, 51.5; H, 6.15; N, 11.2.

The *N-carbamyl* derivative, prepared with potassium cyanate (3), formed white crystals from dilute methanol, m.p. 239–241°. It gave no depression in m.p. when mixed with the N-carbamyl derivative of the natural alkaloid, m.p. 238–240°, and both had identical I.R. spectra.

Anal. Calc'd for $C_{17}H_{20}N_4O_4$: C, 59.3; H, 5.85; N, 16.3.
Found: C, 59.3; H, 6.13; N, 16.2.

When a sample of the synthetic dihydrochloride was converted to the high-melting form of the free base, white crystals from chloroform-petroleum ether were obtained, m.p. 158–160°, $[\alpha]_D^{29}$ +16° (0.8% in abs. alc.).

Anal. Calc'd for $C_{16}H_{19}N_3O_3$: N, 14.0. Found: N, 14.0.

Koepfli, Mead, and Brockman (4) have recorded m.p. 154–156° for the high-melting dimorph, 139–140° for the low-melting dimorph, and the same rotation for both, $[\alpha]_D^{25}$ +28° (0.5% in alc.). Kuehl, Spencer, and Folkers (6) have reported $[\alpha]_D$ + 21° (1.5% in alc.) for the low-melting dimorph.

The filtrate from the 1.05 g. of febrifugine dihydrochloride was evaporated to dryness *in vacuo*. The residue (500 mg.) was dissolved in 10 cc. of water, the solution basified with potassium carbonate, and then extracted with 3 10-cc. portions of chloroform. Dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo* (bath 30°) leaving 340 mg. of a gum. Crystallization from 3 cc. of acetone was complete after ½ hour at room temperature; yield, 175 mg. (13%) of white needles, m.p. 138–139°, $[\alpha]_D^{26}$ +121° (0.4% in $CHCl_3$). This compound had an I.R. spectrum identical with that of isofebrifugine.[1]

Anal. Calc'd for $C_{16}H_{19}N_3O_3$: C, 63.8; H, 6.40; N, 14.0.
Found: C, 63.6; H, 6.63; N, 13.5.

The following constants have been recorded for isofebrifugine: m.p. 129–130°, $[\alpha]_D^{25}$ +131° (0.4% in $CHCl_3$) (4) and m.p. 131–132°, $[\alpha]_D^{25}$ +120° (0.8% in $CHCl_3$) (6).

SUMMARY

The syntheses of optically active febrifugine (the Hydrangea alkaloid) and isofebrifugine starting with *l*-N-benzoyl-β-furyl-β-alanine have been described. The structures of these alkaloids have been elucidated from their respective infrared spectra.

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