The First Examples of the 11*H*-[2]Benzazepino[1,2-*a*]dibenz[*b*,*f*]azocine Ring System

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The ring closure of 2-[(11,12-dihydro-6-oxodibenz[*b*,*f*]azocin-5-yl)methyl]benzoic acid in polyphosphoric acid to 16,17-dihydro-11*H*-[2]benzazepino[1,2-*a*]dibenz[*b*,*f*]azocine-4-(9*H*)-11-dione is reported. Degradation studies supporting this structural assignment for the annelation product are described.

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As part of a continuing program directed toward the synthesis of novel heterocycles for biologic evaluation, it became of interest to investigate preparative routes to the 11*H*-[2]benzazepino[1,2-*a*]dibenz[*b*,*f*]azocine ring system which has not been previously reported in the literature.

As a precursor for the dione **1**, an example of this ring system, the carboxylic acid **2** was prepared by treatment of the commerically available 12-dihydrodibenz[*b*,*f*]azocin-6-(5*H*)one (**3**) with the carbomethoxy compound **4** and subsequent alkaline hydrolysis of the intermediate ester.

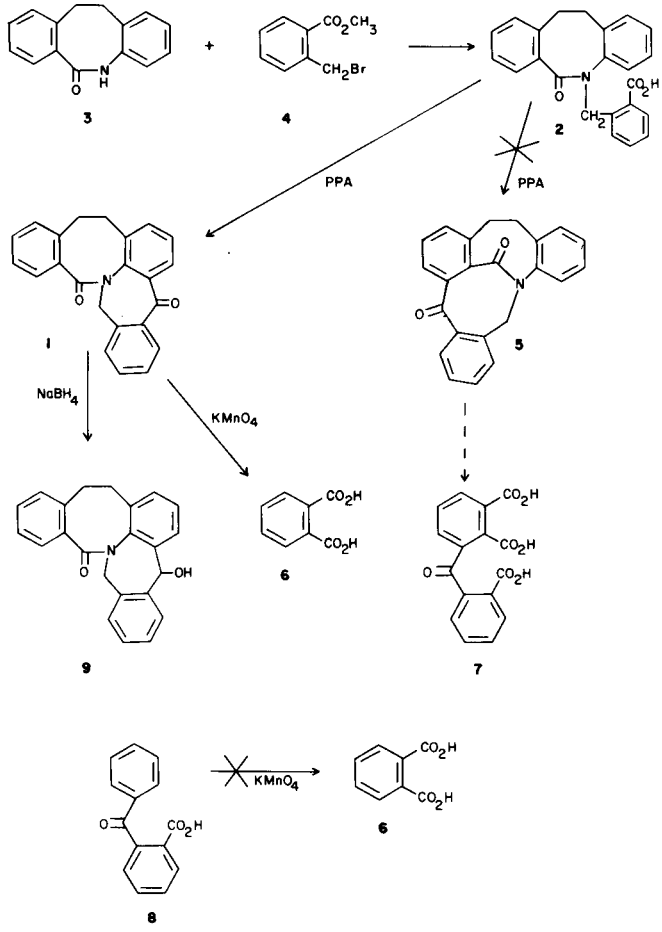
Cyclization of **2** with polyphosphoric acid at 180° gave the target compound **1**, the structure of which was supported by infrared and nuclear magnetic resonance spectra as well as elemental analysis.

Compound **5**, an alternate cyclization product of **2**, was ruled out by chemical degradation experiments. Oxidation of **1** with potassium permanganate at 100° gave o-phthalic acid **6**. Compound **5** would be expected to give the tricarboxylic acid **7** upon permanganate oxidation.

The stucture proof is based upon the hypothesis that acid **7**, if formed, was not oxidized to **6** under the conditions of the degradation. To test this hypothesis, 2-benzoylbenzoic acid **8**, a model compound, was subjected to the degradation experiments and was recovered unchanged. This suggests that **6** isolated in the degradation experiment arose from **1** and not from **7**, thus supporting the 11*H*-[2]benzazepino[1,2-*a*]dibenz[*b*,*f*]azocine structure for the cyclization product. Additional support for structure **1** in preference to product **5** is provided by the following considerations: formation of **1** would result from cyclization to a ring activated by nitrogen while **5** would arise fron annelation to a ring deactivated by a carbonyl function; formation of a seven member ring would presumably be preferred to eight member ring formation. These considerations, in addition to the described degradation data, strongly suggest the 11*H*-[2]benzazepino[1,2-*a*]dibenz[*b*,*f*]-azocine structure **1** as the cyclization product of **2**.

Sodium borohydride reduction of **1** gave the carbinol **9**.

Compounds **1** and **9** failed to elicit worthwhile activity in the CNS, antihypertensive, antibacterial or antifungal areas.



EXPERIMENTAL

Melting points were taken on a Mel-Temp apparatus in open capillary tubes and are uncorrected. The nuclear magnetic resonance spectra were taken on a Varian A-60A instrument and were compared with TMS as an internal standard. Infrared spectra were determined as Nujol Mulls on a Perkin-Elmer 137B spectrophotometer.

Methyl 2-(Bromomethyl)benzoate (**4**).

The method reported previously for the preparation of methyl 4-(bromomethyl)benzoate was employed (1). A mixture of 122 g. (0.80 mole) of methyl 2-methylbenzoate, 144 g. (0.80 mole) of *N*-bromosuccinimide, 0.20 g. of benzoyl peroxide, and 400 ml. carbon tetrachloride was stirred and refluxed for 6 hours and then stirred at ambient temperature for 15 hours. The solid was filtered and washed with 100 ml.

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carbon tetrachloride. The filtrate and washings were combined and concentrated to dryness *in vacuo* to give 179 g. (98%) of an oil that was used directly in the next step.

2-[(11,12-Dihydro-6-(5*H*)oxodibenz[*b*,*f*]azocin-5-yl)methyl]benzoic Acid (**2**).

To a suspension containing 89.2 g. (0.40 mole) of 11,12-dihydrodibenz-[*b*,*f*]azocin-6-(5*H*)one 12.0 g. of sodium iodide, and 800 ml. of toluene was added cautiously 32 g. of sodium hydride, 60% in mineral oil (19.2 g., 0.80 mole). With the reaction temperature maintained between 35-40°, a solution of 100.8 g. (0.44 mole) of **4** in 200 ml. of toluene was added over 20 minutes. The reaction mixture was stirred at ambient temperature for 20 minutes, then stirred and refluxed for 16 hours, and cooled.

The mixture was poured into a solution containing 2000 ml. of water and 200 ml. of concentrated hydrochloric acid. The toluene layer was separated and the aqueous layer was extracted with 800 ml. of toluene. The combined organic layers were washed with 800 ml. of water, decolorized, dried (magnesium sulfate) and concentrated to dryness *in vacuo* to give 159.5 g. of the crude product.

The crude product was heated with 500 ml. of 10% potassium hydroxide for 1-1/2 hours on a steam bath, then cooled and filtered. The filtrate was cooled to 15-20° in an ice bath and the *p*H of the solution was adjusted at 2 with concentrated hydrochloric acid (100 ml.). The mixture was diluted with 1000 ml. of water, stirred for 60 minutes, and filtered through a medium sintered glass funnel. The solid was air dried for 15 hours, then dried at 60° for 6 hours to give 134 g. of the crude product.

The crude product was stirred with 1000 ml. of 10% potassium carbonate for 18 hours. The mixture was filtered and the filtrate was diluted 2000 ml. of water. Acidification to *p*H 2 with 150 ml. of concentrated hydrochloric acid gave a solid which was dried at 60° for 18 hours. Recrystallization from 600 ml. of acetonitrile gave 80 g. (56%) of the product.

An analytical sample, m.p. 186-189°, was obtained by recrystallization from acetonitrile; nmr (DMSO-d_6): δ 1.75-3.27 (m, 4, $ArCH_2CH_2Ar$), 5.42 (s, 2, $ArCH_2N$), 7.00-7.92 (m, 12, aromatic CH); ir: μ 5.85, 5.92, 6.09 (C=O).

Anal. Calcd. for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.14; H, 5.42; N, 3.96.

16,17-Dihydro-11*H*-[2]benzazepino[1,2-*a*]dibenz[*b*,*f*]azocine-4-(9*H*)-11-dione (**1**).

To 644 g. of polyphosphoric acid stirred at 60° was added 60 g. (0.168 mole) of **2**. The mixture was stirred and heated at 180° for 20 hours, cooled to 100°, and poured into 3 liters cold stirred tap water. The mixture was stirred at ambient temperature for 3 hours and the solid was filtered. The wet product was suspended in 1 liter tap water and the *p*H of the suspension was adjusted to 14 by the addition of 128 g. of solid potassium hydroxide. The mixture was stirred at ambient temperature for 2 hours and the solid was filtered through a medium sintered glass funnel. After air drying, there was obtained 68 g. of product.

Recrystallization from acetonitrile gave in three crops, 34.6 g. (61%) of the product, m.p. 138-144°. An analytical sample, m.p. 141-144°, was obtained by recrystallization from ethanol; nmr (DMSO-d_6): δ 2.88-3.27 (m, 4, $ArCH_2CH_2N$), 4.91 (s, 2, $ArCH_2N$), 7.18-7.97 (m, 11, aromatic C-H); ir: μ 5.90, 6.09 (C=O).

Anal. Calcd. for $C_{23}H_{17}NO_2$: C, 81.39; H, 5.05; N, 4.13. Found: C, 81.57; H, 5.27; N, 4.11.

Potassium Permanganate Oxidation of **1**.

To a boiling mixture of 1.70 g. (0.005 mole) of **1**, 5.0 g. (0.09 mole) of potassium hydroxide, and 140 ml. of water was added quickly 5.0 g. of potassium permanganate. The mixture was stirred and refluxed for 1.5 hours whereupon the permanganate had been consumed. Additional permanganate was added in 2.0 g. portions to the refluxing mixture until the purple color persisted for 2 hours; total amount of permanganate employed was 13 g. (0.082 mole).

The excess permanganate was destroyed with ethanol and the mixture was filtered. After the filtrate was acidified with concentrated hydrochloric acid and concentrated to dryness, the residue was extracted with 3 × 60 ml. of ether at room temperature. The ether was removed *in vacuo* and the residue was recrystallized from 20 ml. of water to give in two crops 0.52 g. (62%) of **6**, the infrared spectrum of which was identical with that of an authentic sample of the product.

Attempted Degradation of 2-Benzoylbenzoic Acid (**8**) With Potassium Permanganate.

Treatment of a boiling solution of 1.13 g. (0.005 mole) of **8**, 5.0 g. (0.09 mole) of potassium hydroxide, and 140 ml. of water with 5.0 g. (0.032 mole) of permanganate for 5 hours, destroying excess reagent with ethanol, filtration, and acidification gave 0.55 g. (49%) of unreacted **8**.

Work-up of the filtrate as described above in the degradation of **1** gave an additional 0.05 g. of **8**. No phthalic acid (**6**) was isolated from the reaction mixture.

4,9,16,17-Tetrahydro-4-hydroxy-11*H*-[2]benzazepino[1,2-*a*]dibenz[*b*,*f*]-azocin-11-one (**9**).

To a suspension of 7.0 g. (0.0206 mole) of **1** in 150 ml. of methanol stirred at 5-10°, was added over 5 minutes 2.28 g. (0.06 mole) sodium borohydride. The ice bath was removed and the mixture was stirred at ambient temperature for 2-1/2 hours. The mixture was diluted with 250 ml. of water. After a 45 minute stirring period, the solid was filtered, washed with 2 × 25 ml. of water, air dried, and dried at 60° for 18 hours to give 6.60 g. (93%) of the product, m.p. 233-235°.

Recrystallization from ethanol gave an analytical sample, m.p. 237-239°; nmr (DMF-d_7): δ 3.18 (s, 4, $Ar\text{-}CH_2CH_2\text{-}Ar$), 4.78 (s, 2, $ArCH_2N$), 6.30 (broad s, 1, $Ar_2\text{-}CH\text{-}OH$), 7.12-7.97 (m, 11, aromatic C-H); ir: μ 3.0 (O-H), 5.97 (C=O), 6.20, 6.30 (C=C).

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.91; H, 5.61; N, 4.10. Found: C, 80.80; H, 5.64; N, 4.01.

REFERENCES AND NOTES

(1) B. R. Baker and G. B. Chheda, *J. Pharm. Sci.*, **54**, 25 (1965).