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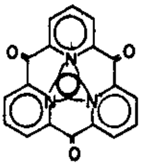
SYNTHESIS OF A NOVEL MACROCYCLIC SYSTEM: 1,3,5-TRI[2,6]PYRIDACYCLOHEXAPHANE-2,4,6-TRIONE

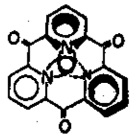
George R. Newkome*, Joe D. Sauer, Peter K. Mattschei, and
Ashutosh Nayak[1]
Department of Chemistry, Louisiana State University,
Baton Rouge, Louisiana 70803 USA

Trione (I), which possesses an unusual 6N-electron-rich cavity, has been synthesized and is the first reported member of this heterocyclic class.

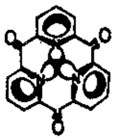
The structure and chemistry of porphyrins, metalloporphyrins, and related compounds have been extensively studied over the past seventy years.[2] Substitution of one or more of the pyrrole subunits by another electron-rich ring, such as furan and/or thiophene has been accomplished;[3] however, the substitution or incorporation of a pyridine ring has not yet been reported. We herein communicate the synthesis of 1,3,5-tri[2,6]pyridacyclohexaphane-2,4,6-trione (I)[4], which is the first example of a pyridine containing xanthoporphinogen-type model



I



IA



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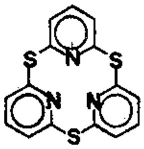


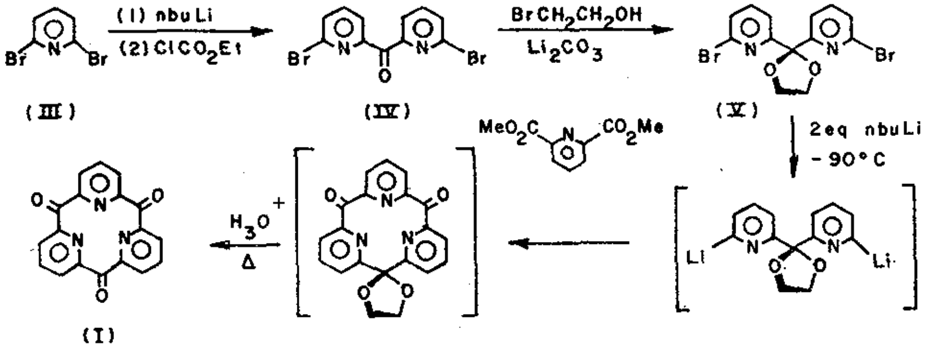
II

and a macrocycle with a highly electron rich ring cavity. The electronic and/or steric electron repulsion within the cavity should cause severe deviation from planarity; thus, two variable conformations (Ia and Ib) are possible. To date II is the only known member of this tripyridyl system and possesses a non-planar conformation as demonstrated by x-ray analysis (the internal C-S-C bond angle: 101.9°).[5] The similar N-electron interaction within the core of II may also be partially responsible for the severe distortion to planarity.

Very few tridentate chelating agents, whose donor atoms are specifically oriented in a cyclic array, are known. Busch, et al.,[6] have reported the successful synthesis of macrocyclic Schiff base complexes via condensation of 2-aminobenzaldehyde in the presence of nickel nitrate; the macrocyclic complex has an inner core similar to I, however, is non-planar.

2,6-Dibromopyridine (III) was treated with n-butyllithium in hexane at -100°C to generate 6-lithio-2-bromopyridine, which reacted smoothly with ethyl chloroformate at -90°C[7] to give IV (70%) (Scheme I). All attempted standard, acid-catalyzed, ketalizations of IV failed in our hands; however, an alternate procedure to convert electron-poor ketones to corresponding ketal was devised by treatment of IV with 2-bromoethanol and excess lithium or sodium carbonate under reflux for 6-12 hours.[8] Subsequent transmetallation of ketal V at reduced temperatures (-90°C)[9] gave the desired dilithio reagent, which was reacted with dimethyl 2,6-pyridinedicarboxylate, to afford a complex mixture of linear ketone ketals and the desired intermediary monoketal. Without further characterization, hydrolysis of this mixture gave a series of linear ketones, several of which were characterized, and in 1% yield the trione I: mp 134.5-135°C.[12]

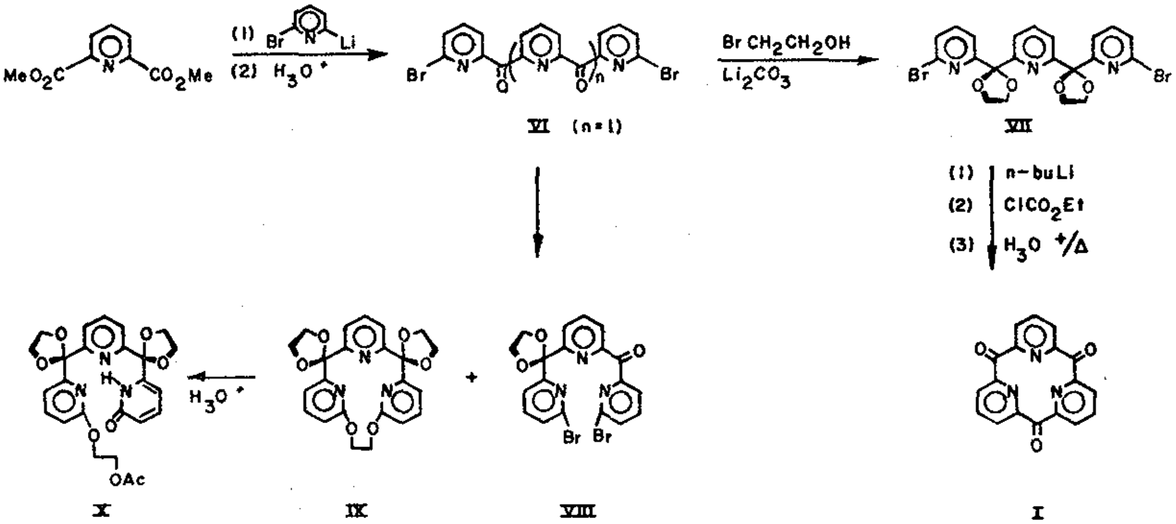
Scheme I



In an attempt to improve the yield of I, an intramolecular cyclization was utilized. Dimethyl 2,6-pyridinedicarboxylate was added quickly to two equivalents of 6-lithio-2-bromopyridine while maintaining the temperature below -80°C to afford 2,6-bis(6'-bromo-2'-picolinoyl)-pyridine (VI) (n=1) : mp 142-143°C; IR (KBr) 1680 (C=O) cm^{-1}. Base ketalization[8] of VI generated VII (67%) [mp 190-190.5°C; NMR ($CDCl_3$) δ 4.17 (s, 8H, OCH_2CH_2O)], along with unreacted starting material. In order to circumvent the tedious removal of 2-bromoethanol during the ketal workup procedure, the more volatile 2-chloroethanol was used; however, not only were the monoketal VIII and VII isolated in diminished yields, a new bis-spiro macrocycle IX [mp 209-211°C; NMR ($CDCl_3$) δ 4.0-4.2 (m, ketal CH_2), 4.35 (s, bridging $\underline{CH_2}$)] was obtained. The crystalline IX was independently synthesized from ketal VII by treatment with ethylene glycol and sodium hydride in refluxing xylene.[13] Hydrolysis of IX with 80% acetic acid afforded a ring-opened acetate X [mp 162-165°C; IR (KBr) 1660 (amide) cm^{-1}][14], in which the ketal functionality was resistant to mild hydrolytic conditions.

Diketal VII was successfully cyclized by initial conversion to the dilithio intermediate *via* carefully controlled low-temperature

Scheme II



($<-90^{\circ}C$) transmetallation, followed by treatment with ethyl chloroformate. Subsequent hydrolysis of the resultant bis-spiro ketone XI afforded the desired trione I (3.5 %)[mp 134-135°C; NMR ($CDCl_3$) δ 7.35 (t, J=9.2Hz, 4-pyr-H, 1H), 7.60 (d, J=9.2Hz, 3,5-pyr-H, 2H); IR (KBr) 1685 (C=O) cm^{-1}], along with both the hydrolyzed diketone VI (49%), and monoketal ketone VIII (18%), as well as a fourth component (26%), which was characterized as the open-chained pentaone [VI (n=4); mp 184-186°C (dec); IR (KBr) 1685 (C=0) cm^{-1}].

We are currently investigating the chemical, structural, and complexing properties of I and IX, since the disposition of N-electrons is ideally suited to generate the "perfect" proton sponge. The general procedure herein described for the construction of I is presently being applied to the synthesis of related porphyrin-type biological mimics.

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9 Metallation conditions are of paramount importance, since when metallation was conducted under standard conditions[10] (-20°C), an alternate reaction pathway was experienced, in which, one pyridine ring underwent an unexpected metallation at the 3-position, followed by a fragmentation-cyclization sequence.[11]

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14 A. Nayak, unpublished results.

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