cyclobutenone rapidly opens to give a vinylketene **7**, which then undergoes rapid intramolecular trapping by the acyl group in an allowed 6-electron ring closure[11] to give the observed pyrone (Scheme I).[12] While we cannot exclude the possibility that the transformation **6** → **7** occurs within the coordination sphere of the metal, it has been shown that free cyclobutenones undergo such facile openings to produce vinylketenes[12,13] and that ring opening is dramatically accelerated by the presence of phenyl groups.[14] Presumably such a mechanism is sterically disfavored for the *tert*-butyl derivative **6** because it would require an intermediate containing three coplanar *tert*-butyl groups on contiguous carbon atoms. Our results indicate that the acyl–allyl coupling step is regiospecific, occurring at the less hindered allylic terminus, and that acetyl, benzoyl, and formyl ligands all undergo this reaction. This transformation effectively involves generation of an acyl anion equivalent, followed by intramolecular attack at the allylic ligand.

This process represents a novel organometallic route to an important organic ring system,[2] in which two carbon monoxide molecules are incorporated into the product. The reaction appears to be versatile in the range of nucleophiles and substituent groups which can be employed and has the advantage of regenerating the anionic organometallic reagent, Extensions to the syntheses of biologically significant pyrones are in progress.

Acknowledgment. We are grateful to the National Science Foundation, to the donors of the Petroleum Research Fund, Administered by the American Chemical Society, and to the Air Force Office of Scientific Research (Grant AFOSR-86-0075) for generous financial support of our research.

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(12) Vinylketenes analogous to **7** have been postulated as intermediates in other pyrone syntheses.[4] Analogous ring opening of a vinylcyclobutenone, followed by electrocyclic closure to a 2,4-cyclohexadienone, has also been reported: Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1674–1676.

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Synthesis of the First Highly Potent Bridged Nicotinoid. 9-Azabicyclo[4.2.1]nona[2,3-*c*]pyridine (Pyrido[3,4-*b*]homotropane)†

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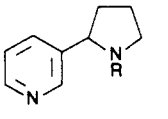
Attempts to determine the bioactive conformation of a given agonist at its receptor frequently involve the synthesis of conformationally restricted structures.[1] Significant efforts along these lines have been made in the nicotine (**1**) area.[2] Up to this time, however, there have been no reports of a bridged nicotinoid with bioactivity equaling or surpassing that of the conformationally free parent, We now report the design, synthesis, and biological activity of pyrido[3,4-*b*]homotropane (**2**)—the first highly potent bridged nicotinoid.

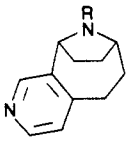
Table I

agent	IC_{50}[a] (M)	LD_{50}[b] (mg/Kg)
±-nornicotine	8×10^{-8}	1.0
±-pyrido[3,4-*b*]homotropane	5×10^{-9}	0.3

[a] Receptor binding (rat-brain membrane). IC_{50} = concentration of agent necessary to produce 50% inhibition of [^{3}H]nicotine (concentration of (-[^{3}H]nicotine in assay was 1×10^{-9}).[18] [b] Lethal dose for 50% of test animals[19] by intravenous tail injection of male mice.

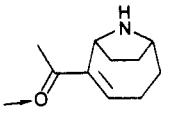


1a: R = H (nornicotine)
b: R = CH_3 (nicotine)

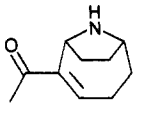


2: R = H
11: R = CH_2Ph

The semirigid alkaloid anatoxin *a* (**3**)[3] is known to possess high activity at the nicotinic acetylcholine receptor.[4] Nornicotine (**1a**),



3a (s-cis)



3b (s-trans)

a potent agonist in its own right, has an activity significantly less than that of anatoxin *a*.[4] The present work was prompted by the recognition that one of the conformers of nornicotine would position the pyrrolidine nitrogen and a hydrogen-bond acceptor in the same spacial orientation as that found in the s-cis conformation (**3a**) of anatoxin *a*. The H-bond acceptor of **2** (pyridine nitrogen lone pair) corresponds specifically to the distal lone pair on the carbonyl of *s-cis*-anatoxin *a* (see arrow). Insertion of a two-carbon bridge in nornicotine between the $C_{5'}$ of the pyrrolidine and C_4 of the pyridine would "freeze" the structure in the desired conformation to yield the novel pyrido[3,4-*b*]homotropane (**2**).

Treatment of 1,2-oxido-5-cyclooctene[5] with benzylamine (2.0 equiv) in methanol (pot temperature 110 °C) for 3 h gave, after bulb-to-bulb distillation, an 84% yield of the *trans*-benzylamino alcohol **4**,[6,7] Aminomercuration[8] of **4** with 1 equiv of $Hg(OAc)_2$ in THF at 4 °C for 1,5 h, followed by demercuration with $NaBH_4$, yielded the bicyclic amino alcohol **5** (70% yield).[9] Jones oxidation of **5**, followed by chromatography on silica (CH_2Cl_2), yielded the

† Presented at the IXth International Symposium on Medicinal Chemistry, Berlin (West), Sept. 14–18, 1986.

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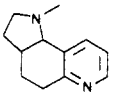
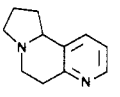
(2) Two bridged nicotines, i[4a] and ii,[4b] have been reported previously. (a)



i



ii

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(9) A 10:1 mix of the [4.2.1] and [3.3.1] bicyclic systems is obtained which may be chromatographically separated on silica with hexane/CH_2Cl_2/ether (3/3/1).

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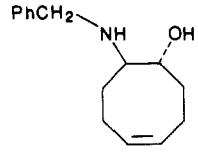
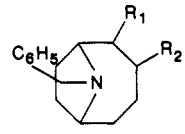
ketone **6** (45% yield). Alkylation of **6** with 1.05 equiv of allyl bromide via the boron enolate[10] (1.0 equiv of potassium hydride, 1.05 equiv of triethylborane) in THF at 0–25 °C for 3 h afforded, after chromatography on silica (CH_2Cl_2), the desired α-allyl ketone **7** (75% yield).[11]



4



5: R_1 = α-OH, R_2 = H
6: R_1 = O, R_2 = H
7: R_1 = O, R_2 = $CH_2CH{=}CH_2$
8: R_1 = CN, R_2 = $CH_2CH{=}CH_2$
9: R_1 = CHO, R_2 = $CH_2CH{=}CH_2$
10: R_1 = CHO, R_2 = CH_2CHO

Conversion of **7** to the nitrile **8** was accomplished with 2 equiv of tosylmethyl isocyanide[12] and 5 equiv of potassium *tert*-butoxide in dimethoxyethane at 45 °C for 6 h (74% yield). DIBAL reduction (1.2 equiv) in benzene at 25 °C for 5 h converted the nitrile to the aldehyde **9** (75% yield).[13] Protection of the amino functionality as the TFA salt and oxidative cleavage of the allyl group with ozone at −78 °C in CH_2Cl_2, followed by treatment with excess dimethyl sulfide and warming to room temperature, afforded the 1,5-dialdehyde **10** (75% yield). Treatment of **10** with 3 equiv of hydroxylamine hydrochloride in glacial acetic acid[15] at 100 °C for 20 min produced the desired fused pyridine **11** in 55% yield after chromatography on silica (CH_2Cl_2/MeOH 9/1). Debenzylation of **11** with $Pd(OH)_2$ on carbon[16] in EtOH and 1 equiv of HCl proceeded cleanly in the desired fashion to afford the target compound **2** (80% yield after chromatography on silica with CH_2Cl_2/MeOH/TEA 90/9.85/0.15).[17]

Pyridohomotropane was tested both in vivo and in vitro in order to determine its activity relative to nornicotine. The results (see Table I) show that the new derivative possesses 3 times the toxicological activity (intravenous mouse injection) and 16 times the receptor binding (rat brain membranes[18]) of nornicotine. Pyridohomotropane is thus the first nicotinoid to combine high activity with conformational rigidity and provides a further refinement in our understanding of the chemical and spatial requirements of the nicotinic acetylcholine receptor.

Acknowledgment. We acknowledge Drs. Michael Broadhurst, Charles Chavdarian, Karl Fisher, and William Haag and Prof. Henry Rapoport for useful discussions. We also thank William Callahan and Rose Chan for technical assistance.

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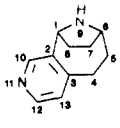

^{13}C NMR (100 MHz; $CDCl_3$, 77.0 ppm) δ 149.2 (C_2, 148.5 (C_{12}), 148.1 (C_{10}), 142.6 (C_3), 125.5 (C_{13}), 60.5 (C_1), 58.2 (C_6), 33.5 (C_5), 31.7 (C_4), 31.4 (C_8), 29.8 (C_7); ^1H NMR (400 MHz; $CDCl_3$, 7.24 ppm) δ 8.3 (d, H_{12}), 8.2 (s, H_{10}), 7.0 (d, H_{13}), 4.4 (dd, H_1), 3.8 (dddd, H_6), 3.1 (ddd, $H_{4\alpha}$), 2.7 (ddd, $H_{4\beta}$), 2.4 (dddd, $H_{8\beta}$), 2.1 (dddd, $H_{7\beta}$), 1.8 (dddd, $H_{5\alpha}$), 1.8 (dddd, $H_{7\alpha}$), 1.8 (dddd, $H_{8\alpha}$), 1.6 (dddd, $H_{5\beta}$); measured coupling constants (Hz) $J_{12\text{-}13}$ = 4.9; $J_{1\text{-}8\alpha}$ = 2.3; $J_{1\text{-}8\beta}$ = 9.8; $J_{8\beta\text{-}8\alpha}$ = 13.3; $J_{8\beta\text{-}7\alpha}$ = 2.8; $J_{8\beta\text{-}7\beta}$ = 13.2; $J_{8\alpha\text{-}7\beta}$ = 2.0; $J_{7\beta\text{-}7\alpha}$ = 18; $J_{7\beta\text{-}6}$ = 6.7; $J_{6\text{-}5\beta}$ = 2.9; $J_{5\beta\text{-}5\alpha}$ = 13.6; $J_{5\beta\text{-}4\alpha}$ = 13.7; $J_{5\beta\text{-}4\beta}$ = 3.5; $J_{5\alpha\text{-}4\beta}$ = 3.8; $J_{5\alpha\text{-}4\alpha}$ = 3.5; $J_{4\beta\text{-}4\alpha}$ = 15.7. HRMS: *m/e* calculated for $C_{11}H_{14}N_2$ (M^+) 174.1157, found 174.1136.
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Topological Control of Reactivity by Interfacial Orientation: Excimer Fluorescence and Photodimerization of 4-Stilbazolium Cations in Aerosol OT Reversed Micelles[1]

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Photocycloaddition and cyclodimerization reactions have been the subject of extensive study. Although widely used, their employment in solution frequently is limited by a lack of stereochemical or regiochemical selectivity or control. In contrast, many photodimerization reactions occur in crystals; these are frequently selective with often only a single product resulting.[3-9] Several studies have shown correlation between monomer packing in the crystal and photodimer structure;[3-5,11] while such topological control appears general for solids,[3-7] it is often difficult to predict or control the packing of different substances so as to generally utilize this property.[8-11] The ability of microheterogeneous media such as micelles, vesicles, films, or microemulsions to provide an environment of variable order and properties intermediate between solid and solution suggests an opportunity to control or at least obtain some selectivity in these photoreactions. Indeed, several investigations in micellar media have shown both high yields of photodimers and some selectivity in product distribution;[12-20] for a number of reactions including photodimerizations many of the

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