

Nitrogen analogs of crown ethers

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form the asymmetric unit. This structure is consistent with all of the previously reported analytical data.

Structure 1, while without precedent for a natural product, is perfectly reasonable chemically and its dimensions are reminiscent of the closely related dipotassium salt of squaric acid, 3.³ The two crystallographically independent anions in the asymmetric unit have the same geometry and C_{2v} symmetry within experimental error. The averaged geometry is given in Table I. The anion is planar with a maximum deviation

Table I

Averaged Bond Distances			
Bond	Distance (Å)	Bond	Distance (Å)
C(1)–C(2)	1.411 (8)	C(1)–O(1)	1.243 (7)
C(1)–C(4)	1.508 (8)	C(4)–O(3)	1.209 (7)
Averaged Bond Angles			
Bond	Angle (deg)	Bond	Angle (deg)
C(1)–C(2)–C(3)	94.4 (5)	O(1)–C(1)–C(2)	137.6 (6)
C(2)–C(3)–C(4)	89.4 (5)	O(1)–C(1)–C(4)	133.0 (6)
C(3)–C(4)–C(1)	86.8 (4)	O(3)–C(4)–C(1)	136.6 (5)

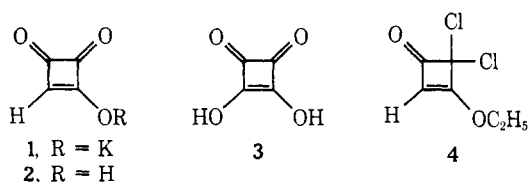
of 0.01 Å from the best least-squares plane. Oxygen atoms O(1) and O(2) formally share a negative charge, and their bond length to carbon (1.243 Å) is significantly longer than the O(3)–C(4) bond length (1.209 Å).

The coordination about the potassium cations is rather complex. K(1) is surrounded by seven oxygens at an average distance of 2.836 Å (the range is 2.721–2.990 Å) while K(1') is surrounded by eight oxygens at an average distance of 2.913 Å with a range of 2.757–3.167 Å.

The crystal structure is layered with a closest distance between layers of 3.27 Å. A similar short layer spacing was also observed in dipotassium squarate and attributed to a charge-transfer self-complex.³

The parent acid 2, 1-hydroxycyclobut-1-ene-3,4-dione, was reported several years ago;⁴ infrared, ultraviolet, and nmr spectra kindly furnished by Professor Hoffmann confirmed its identity with the acid obtained by treatment of moniliformin with trimethylsilyl chloride.

An independent synthesis was devised to provide material for biological testing. Thermal addition⁵ of dichloroketene (generated from dichloroacetyl chloride and triethylamine) to ethoxyacetylene gave adduct 4,



which could be hydrolyzed by aqueous hydrochloric acid to 2. The synthetic material was identical by ir, uv, and nmr comparison with the parent acid of moniliformin and further elicited the same physiological behavior in cockerels as moniliformin.

The biosynthetic origin of moniliformin is unknown

(3) W. M. Macintyre and M. S. Werkman, *J. Chem. Phys.*, **40**, 3563 (1964).

(4) R. W. Hoffmann, U. Bressel, J. Gehlhaus, and H. Häuser, *Chem. Ber.*, **104**, 873 (1971).

(5) N. Morita, T. Asao, and Y. Kitahara, *Chem. Lett.*, **1**, 927 (1972).

and the structure represents a novel structural type. The closest known natural compounds rhodizonic ($C_6H_2O_6$) and croconic ($C_5H_2O_5$) acids seemingly arise from microbial oxidation of myoinositol.⁶

(6) A. J. Fatiadi, H. S. Ishell, and W. F. Soger, *J. Res. Nat. Bur. Stand.*, **67A**, 153 (1963); A. J. Klugver, T. Hof, and A. J. Boczaardt, *Enzymologia*, **7**, 257 (1939); *Chem. Abstr.*, **34**, 6322 (1948); L. F. Heller, *Justus Liebigs Ann. Chem.*, **24**, 1 (1937).

(7) Camille and Henry Dreyfus Teacher-Scholar Grant Awardee, 1972–1977, and Fellow of the Alfred P. Sloan Foundation, 1973–1975.

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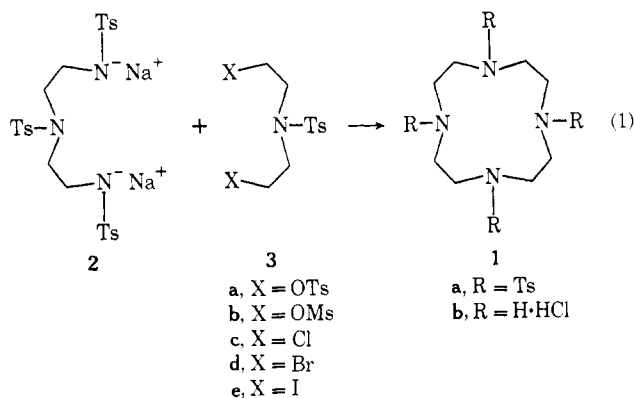
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Nitrogen Analogs of Crown Ethers

Sir:

A simple preparation of cyclic amines of medium-large ring size has long been sought. We report a simple and general synthesis of nine- to 21-membered rings containing three to seven heteroatoms. The method gives 40–90% yields and utilizes neither high dilution techniques nor template effects in the cyclization step.

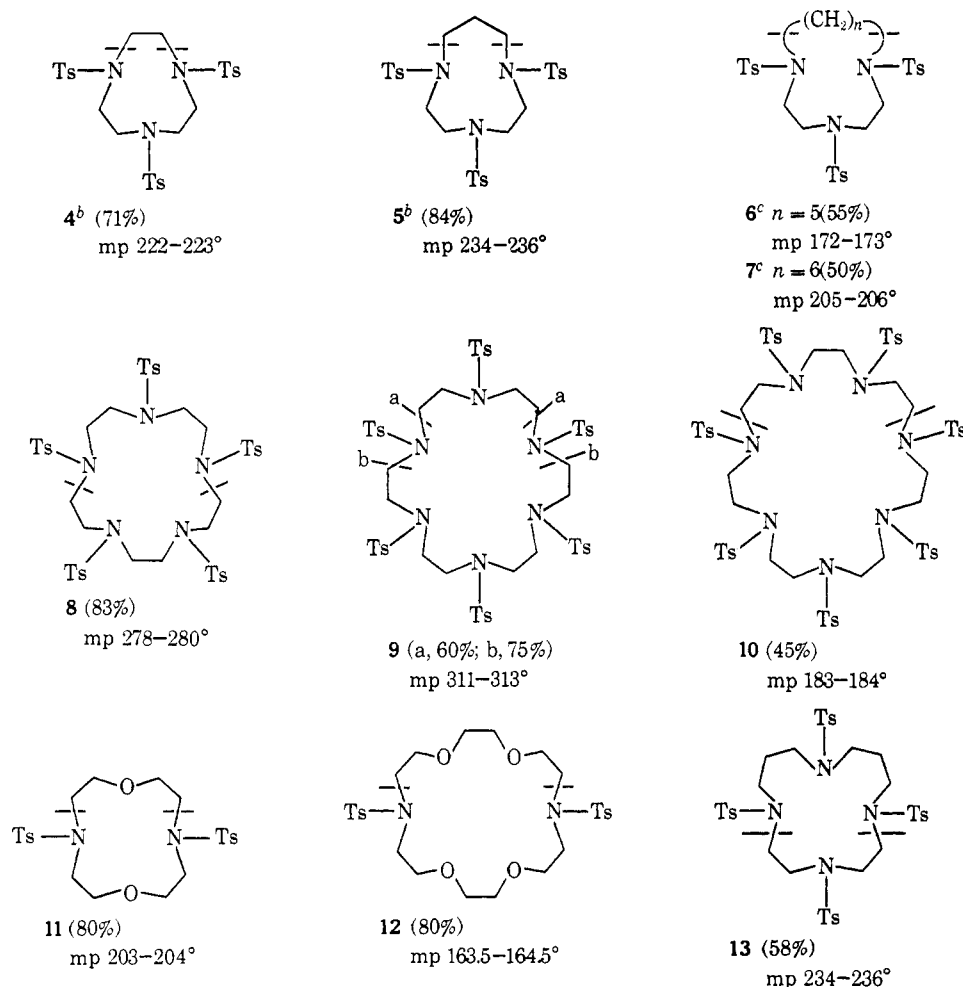
Stetter and Roos¹ reported moderate cyclization yields in the condensation of terminal dihalides with bisulfonamide sodium salts under high dilution. We have found that using preformed bisulfonamide sodium salts (e.g., 2) and sulfonate ester leaving groups in a dipolar aprotic solvent obviates the high dilution technique. Thus, large-scale preparations are now practical. For example, we have applied this method to the synthesis of "cyclen" (1,4,7,10-tetraazacyclododecane) tetrahydrochloride (1b).^{2,3}



(1) H. Stetter and E.-E. Roos, *Chem. Ber.*, **87**, 566 (1954).

(2) H. Stetter and K.-H. Mayer, *Chem. Ber.*, **94**, 1410 (1961).

(3) J. P. Collman and P. W. Schneider, *Inorg. Chem.*, **5**, 1380 (1966).

Chart I^a

^a The bonds formed by cyclization of ditosylates are indicated by a slash. Elemental analyses within 0.3% of theory have been obtained for all new compounds. ^b H. Koyama and T. Yoshino, *Bull. Chem. Soc. Jap.*, **45**, 481 (1972), report a synthesis of **4** and **5** in 57 and 24% yield, respectively. ^c Products resulting from 2:2 cyclization (10–15%) were observed.

A stirred solution (0.1 *M*) of **2**⁴ in dimethylformamide (DMF) at 100° was treated with 1 equiv of a 0.2 *M* solution of **3a**⁵ in DMF over 1–2 hr. Addition of water to the cooled solution gave an 80% yield of 1,4,7,10-tetratosylcyclen (**1a**).^{2,6} Hydrolysis of **1a** with 97% sulfuric acid at 100° for 48 hr, followed by work-up with 6 *N* hydrochloric acid, afforded greater than 90% yield of **1b**. This procedure can easily be run on a 0.5 mol scale and provides a convenient multigram synthesis of the hitherto elusive **1b**.^{2,3}

The additional examples in Chart I illustrate the versatility of this synthesis. Macrocyclic amines and amine ethers of up to 21 members can be readily prepared. However incorporating hydrocarbon segments longer than three methylene units, as in **6** and **7**, markedly decreases the yield of cyclization products of 1:1 stoichiometry. In these cases significant amounts of products of 2:2 stoichiometry are observed.

Changing the leaving group, X (eq 1), has a marked effect on the cyclization. The ditosylate **3a** and the

dimesylate **3b** give comparable yields of **1a**, whereas the halogenate series, **3c–e**, gives lower yields of **1a** (42, 40, and 25%, respectively). Only the dimesylate **3b** follows clean second-order kinetics for the disappearance of base.⁷

In the absence of template effects,⁸ cyclizations to medium or large rings are commonly believed to require high dilution. Clearly, this technique is essential with some cyclization methods.^{9,10} There are occasional references to high-yield cyclizations which cannot be explained by any known effect.¹¹ In the present example, neither steric nor electronic considerations suggest that **14** (the immediate precursor to **1a**) would coordinate the sodium cation. Replacing the sodium

(7) The rate expression at 39.95° is $(-d[\text{base}]/dt) = 1.1 \times 10^{-3}/M^{-1} \text{ sec}^{-1}$ [2][**3b**]. Curvature in the comparable second-order plots for **3a**, **3d**, and **3e** is evidence for competing elimination or oligomerization, which would account for the lower yields in the halogen series. Initial rates are in the order $\text{I} > \text{Br} > \text{OTs} > \text{OMs} \gg \text{Cl}$.

(8) (a) C. J. Pederson and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, **11**, 16 (1972); (b) R. N. Greene, *Tetrahedron Lett.*, 1793 (1972); (c) N. F. Curtis, *Coord. Chem. Rev.*, **3**, 3 (1968).

(9) (a) H. Stetter and J. Marx, *Justus Liebigs Ann. Chem.*, **607**, 59 (1957); (b) H. E. Simmons and C. H. Park, *J. Amer. Chem. Soc.*, **90**, 2428 (1968), and unpublished results.

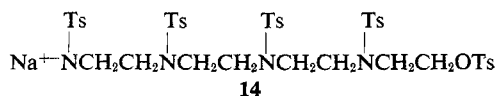
(10) B. Dietrich, J. M. Lehn, J. P. Sauvage, and J. Blanzat, *Tetrahedron*, **1629** (1973).

(11) (a) G. R. Hansen and T. E. Burg, *J. Heterocycl. Chem.*, **5**, 305 (1968); (b) A. M. Tait and D. H. Busch, *Inorg. Nucl. Chem. Lett.*, 491 (1972); (c) S. C. Tang, G. N. Weinstein, and R. H. Holm, *J. Amer. Chem. Soc.*, **95**, 613 (1973).

(4) Disodium salt **2** crystallizes in nearly quantitative yield on addition of 2 equiv of sodium ethoxide to a stirred hot slurry of *N,N*-bis(*p*-tolylsulfonamidoethyl)-*p*-tolylsulfonamide⁵ in ethanol.

(5) D. H. Peacock and U. C. Dutta, *J. Chem. Soc.*, 1303 (1934).
(6) The procedure outlined is a standardized example; **1a** can be prepared with no apparent decrease in yield by warming an equimolar solution (0.1 *M*) of **2** and **3a** in DMF at 70–100°. Dimethyl sulfoxide and hexamethylphosphoramide can also be used, but we have found DMF more convenient.

cations of **2** with tetramethylammonium cations still affords greater than 50% of **1a**; this rules out a template effect as a dominant factor.



Further observations pertaining to the mechanism of this reaction will be reported. We are investigating the preparation and chemistry of these new and highly interesting macroheterocyclic systems.

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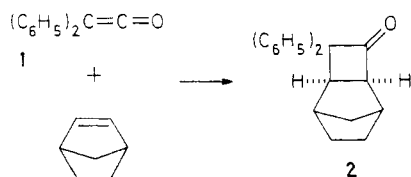
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2:1 Adducts of Diphenylketene and Norbornene

Sir:

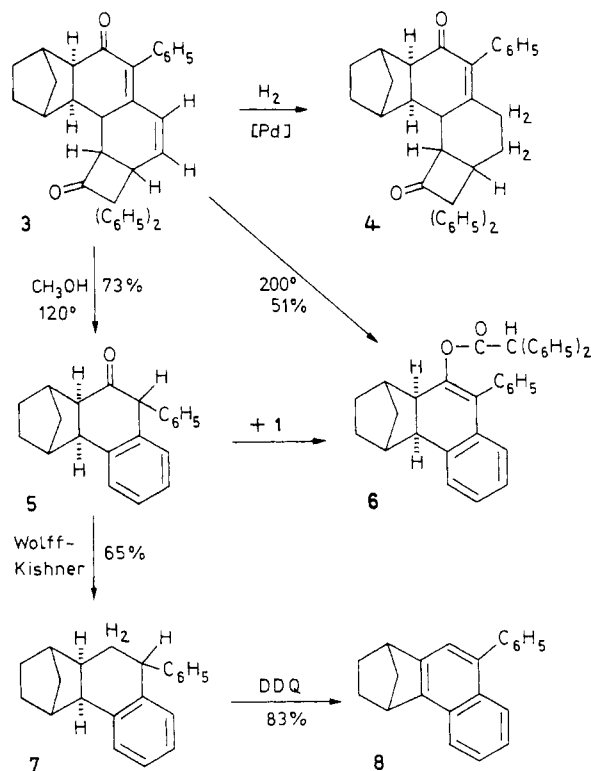
The $2 + 2 \rightarrow 4$ cycloadditions of ketenes and alkenes are concerted reactions¹ which are interpreted to be $[\pi 2_a + \pi 2_s]$ processes.² The reactions take place faster as the ketenophilic double bond becomes more electron-rich.³ Concurrent formation of 1:1 and 2:1 adducts from dimethylketene and *N*-isobutyryldialkylamines indicates a second mechanistic pathway.⁴



Refluxing of diphenylketene (**1**) with norbornene in benzene for 14 days produces the cyclobutanone **2** in 84% yield.⁵ However, on heating **1** in excess norbornene under N_2 to 70° for 20 days, one obtains 10–16% of a 2:1 adduct, $C_{35}H_{30}O_2$, mp 193.5–194.5°,⁶ along with 45–68% **2**. Our proposal of structure **3** for the 2:1 adduct rests on the following evidence. Two carbonyl frequencies at 1770 and 1650 cm^{-1} are consistent with a cyclobutanone ring and an unsaturated six-membered ring ketone ($C=C$ 1614 cm^{-1}). Besides 15 aromatic hydrogens, the nmr shows two cis coupled vinyl protons as AB spectrum at τ 3.80 and 4.33 ($J = 10.5$ Hz); in addition, the B part is split into doublets by $J \approx 2$ Hz.

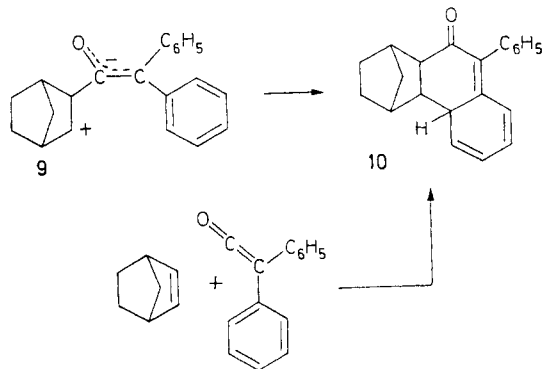
On catalytic hydrogenation the dihydro derivative **4** (mp 239–240°) is obtained. The vinylic hydrogens are lost and the uv_{max} (dioxane) of **3** at 295 $m\mu$ ($\log \epsilon$ 4.28) is shifted to 255 $m\mu$ (4.00) in **4**.

Short heating to 200° converts **3** to the isomeric 2:1



adduct **6**, mp 154–156°, 51% yield. The single $C=O$ frequency at 1743 cm^{-1} and the $C=C$ at 1668 cm^{-1} are consistent with an enol ester group. The nmr reveals 19 aromatic hydrogens and a benzhydryl proton singlet at τ 5.15. The lack of coupling between the endo protons of the norbornane system (AB at τ 6.69 and 7.17 with $J = 10.8$ Hz) with the bridgehead hydrogens is evidence for the exo ring fusion. The orange color observed during the thermal “rearrangement,” $3 \rightarrow 6$, suggests cleavage of the cyclobutanone ring of **3** with regeneration of **1** which in turn attacks the residual part of the molecule at another functional group. Indeed, methanolysis of **3** at 120° (22 hr) yields 91% of methyl diphenylacetate (**1** + CH_3OH) and 73% of **5**, mp 110–112°. The $C=O$ frequency at 1711 cm^{-1} is in accord with a β -tetralone derivative (α -tetralone 160 cm^{-1}). The enol ester **6** is prepared from **5** + **1**, even at 100°, with triethylamine as a catalyst.

The Wolff-Kishner procedure in diethylene glycol at 200° converts the ring ketone **5** into the tetraline derivative **7**, a colorless oil. Finally, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone dehydrogenates **7** to the tri-substituted naphthalene **8**. Its uv spectrum with maxima at 301.5 and 234.4 $m\mu$ ($\log \epsilon$ 3.92 and 4.69) is strikingly similar to that of 1,2-dimethyl-4-phenyl-naphthalene.



(1) R. Huisgen, L. A. Feiler, and G. Binsch, *Chem. Ber.*, **102**, 3460 (1969).

(2) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(3) R. Huisgen, L. A. Feiler, and P. Otto, *Chem. Ber.*, **102**, 3444 (1969).

(4) R. Huisgen and P. Otto, *J. Amer. Chem. Soc.*, **91**, 5922 (1969).

(5) R. Huisgen and L. A. Feiler, *Chem. Ber.*, **102**, 3391 (1969).

(6) All new compounds gave satisfactory CH analyses. Molecular weight determinations by vapor pressure osmometer or mass spectrometer.