Isolation of diazacycloheptatetraenes from thermal nitrene-nitrene rearrangements

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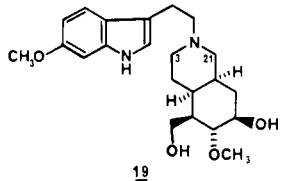
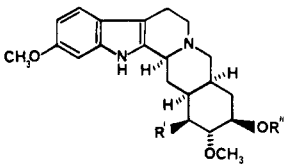
accord with the expectation that the stereoselectivity of the hydrogenation would be improved if the π system to be reduced were closer to the structural feature which induces the stereoselectivity (the cis-ring fusion), enol acetate **13**[18] provided, upon hydrogenation [H_2 (1 atmosphere), Pd/C, EtOAc], *a single diacetate* **14** (79%) along with the hydrogenolysis product **15** (14%). The stereochemistry of diacetate **14** was established by spectroscopic comparison of this compound with an authentic sample derived from (-)-reserpine, according to the degradation sequence[19] delineated in Scheme II. Thus, from the Diels-Alder adduct **4**, the introduction of all the E-ring stereocenters was achieved *with full stereocontrol.*

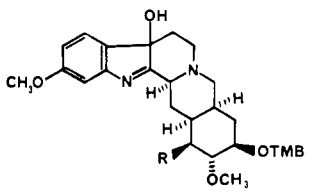
Completion of the synthesis based on **14**[20] required introduction of the methoxytryptophyl moiety and adjustment of the E-ring appendages. The former objective was accomplished by conversion of **14** with (trimethylsilyl) iodide[21] to the corresponding free amine **18** (90%), which upon alkylation with 6-methoxytryptophyl bromide[22] gave 2,3-secoreserpinediol (**19**) in 85% yield. Oxidative



19



20: R' = CH_2OH, R'' = H
21: R' = CH_2OH, R'' = TMB
22: R' = CH_2OTMB, R'' = TMB
23: R' = CHO, R'' = TMB
24: R' = CO_2CH_3, R'' = TMB



25: R = CO_2CH_3
26: R = CHO

cyclization[23] of this compound followed by $NaBH_4$ reduction produced isoreserpinediol (**20**,[24] 45%) and an isomeric diol (30%) which is presumed to be an inside reserpinediol.[25] Monoester **21** was prepared by treatment of **20** with excess 3,4,5-trimethoxybenzoyl chloride (53%) followed by selective hydrolysis (0.3 M KOH, MeOH, 25 °C, 5 min, 62%) of the resulting diester **22**. Oxidation of **21** with $Me_2SO/DCC/H_3PO_4$[26] gave aldehyde **23** (65%) and a product (20%) resulting from Pummerer rearrangement. The aldehyde, when treated with acetone cyanohydrin in the presence of triethylamine, gave in 86% yield the cyanohydrin which reacted with Me_2SO/oxalyl chloride[27] to provide, after addition of methanol, overoxidized products assigned as ester **25** (33%) and aldehyde **26** (43%). Reduction of ester **25** with $NaBH_4$ followed by treatment with acid afforded, in 85% yield, isoreserpine (**24**).[28] Since four methods are available for the conversion of isoreserpine to reserpine,[29] the described synthesis constitutes a formal, stereospecific synthesis of reserpine based on the Diels-Alder adduct **4**. Efforts to extend this method of hydroisoquinoline synthesis and to more fully exploit the advantages inherent in this general strategy for alkaloid synthesis are in progress.

Acknowledgment. We thank the National Science Foundation for support of this research (CHE-7821463).

(18) **13** was prepared by reaction of **9** with $LiN(SiMe_3)_2$ followed by quenching with excess acetyl chloride at -78 °C.

(19) Sakai, S.; Ogawa, M. *Chem. Pharm. Bull.* **1978**, *26*, 678; *Heterocycles* **1978**, *10*, 67.

(20) Due to the concomitant development of the synthetic and degradative work, all subsequent transformations were performed with material derived from (-)-reserpine.

(21) Jung, M. E.; Lyster, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 968; *J. Chem. Soc., Chem. Commun.* **1978**, 315.

(22) Hydrolysis of the acetate subunits occurred under the conditions of the alkylation [6-methoxytryptophyl bromide (3 equiv)/MeOH/K_2CO_3/reflux/25 h]. 6-Methoxytryptophyl bromide was prepared by treatment of 6-methoxytryptophol with PBr_3. This alcohol was prepared by $LiAlH_4$ reduction of the methyl ester corresponding to the known[6] 2-(3-indolyl)-2-oxoacetyl chloride.

(23) (a) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1962**, *84*, 4914. (b) Morrison, G. C.; Cetenko, W.; Shavel, J., Jr. *J. Org. Chem.* **1967**, *32*, 4089. (c) Gutzwiller, J.; Pizzolato, G.; Uskokovic, M. *J. Am. Chem. Soc.* **1971**, *93*, 5908. (d) Stork, G.; Guthikonda, N. *Ibid.* **1972**, *94*, 5110. (e) Aimi, N.; Yamanaka, E.; Endo, J.; Sakai, S.; Haginiwa, J. *Tetrahedron Lett.* **1972**, 1081. (f) *Tetrahedron* **1973**, *29*, 2015.

(24) Identical by NMR with material derived from the lithium aluminum hydride reduction of (-)-isoreserpine: MacPhillamy, H. B.; Huebner, C. F.; Schlittler, E.; St. Andre, A. F.; Ulshafer, P. R. *J. Am. Chem. Soc.* **1955**, *77*, 4335.

(25) In accord with convention (cf. ref 23e,f), inside reserpinediol is that product which arises from cyclization of the iminium salt derived by oxidation of **19** at C-21.

(26) Albright, J. D.; Goldman, L. *J. Org. Chem.* **1965**, *30*, 1107.

(27) Swern, D.; Omura, K. *Tetrahedron* **1978**, *34*, 1651.

(28) Identical with an authentic sample of (-)-isoreserpine (Gaskell, A. J.; Joule, J. A. *Tetrahedron* **1967**, *23*, 4053) by NMR and IR spectroscopy, thin-layer chromatography, and melting point. A mixture melting point was undepressed.

(29) (a) Huebner, C. F.; Kuehne, M. E.; Korzun, B.; Schlittler, E. *Experientia* **1956**, *12*, 249. (b) Weisenborn, F. L.; Diassi, P. A. *J. Am. Chem. Soc.* **1956**, *78*, 2022.

(30) Fellow of the Alfred P. Sloan Foundation, 1979-1981.

(31) National Science Foundation Fellow, 1975-1978.

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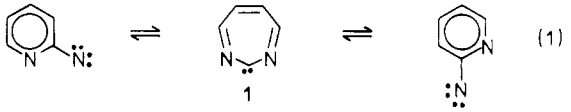
Isolation of Diazacycloheptatetraenes from Thermal Nitrene-Nitrene Rearrangements[1]

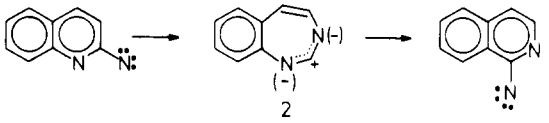
Sir:

The first examples of nitrene-nitrene rearrangements were reported in 1969, when we demonstrated the thermal gas-phase interconversion of 2-pyridylnitrenes via an intermediate which has "an arrangement of atoms as in 2,7-diazatropylidene" (**1**).[3] Since

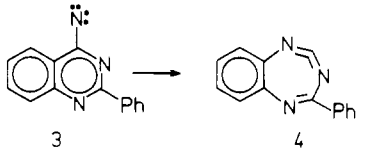


(1)

the rearrangement took place just as easily in benzo-annelated systems (quinolines and phenanthridines), we subsequently formulated the seven-membered ring intermediates as resonance forms of cyclic carbodiimides,[4,5] e.g., **2**.[4]



In 1975, we submitted evidence for the thermal ring expansion of the nitrene **3** to the carbodiimide **4**.[6] In further work, a rearranged dimer of **4** was isolated,[7] and, finally, **4** itself was



(1) Part VIII of the series "Hetarylnitrenes". Part VII: see ref 2. The financial support of the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

(2) Wentrup, C.; Thétaz, C.; Tagliaferri, E.; Lindner, H. J.; Kitschke, B.; Winter, H.-W.; Reisenauer, H. P. *Angew. Chem.* **1980**, *92*, 556-557.

(3) Crow, W. D.; Wentrup, C. *J. Chem. Soc. D* **1969**, 1387.

(4) Wentrup, C. *Tetrahedron* **1971**, *27*, 367-374.

(5) Wentrup, C.; Thétaz, C.; Gleiter, R. *Helv. Chim. Acta* **1972**, *55*, 2633-2636.

(6) Lindner, H. J.; Mayor, C.; Thétaz, C.; Wentrup, C., paper submitted to *J. Am. Chem. Soc.* (1975). Although not rejected, this paper was found not to be publishable.

(7) Wentrup, C. *React. Intermed.* **1980**, *1*, 263-319.

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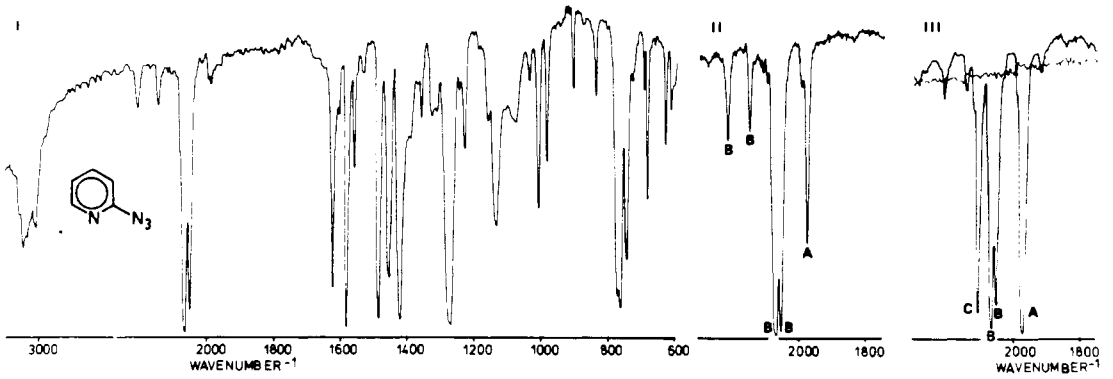
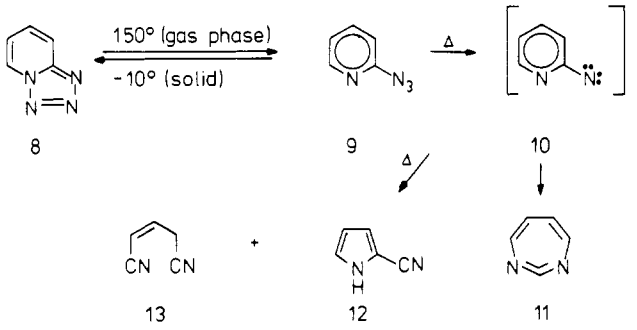
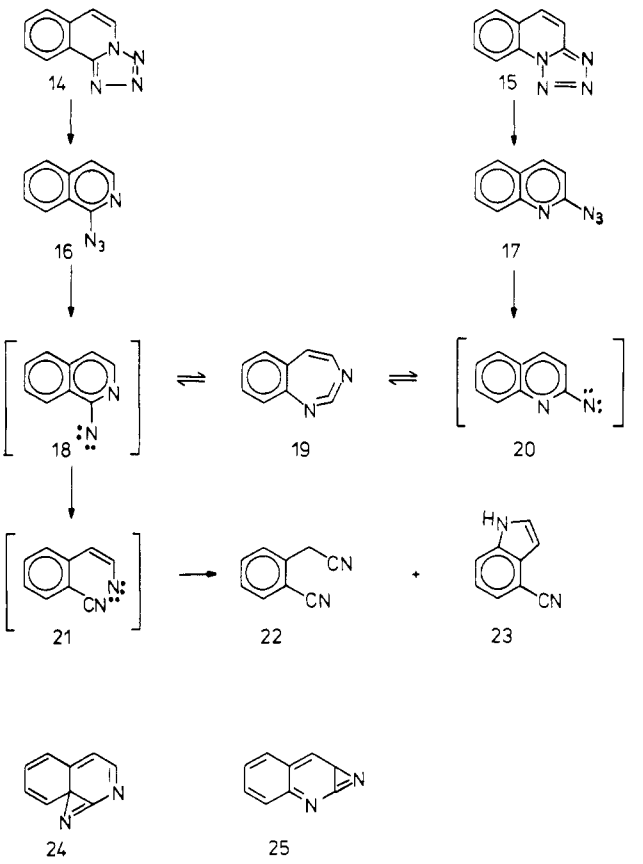


Figure 1. (I) Infrared spectrum of 2-pyridyl azide (**9**) at −196 °C, obtained by pyrolysis of tetrazolo[1,5-*a*]pyridine (**8**) at 200 °C. (II and III) Partial infrared spectra (−196 °C) of the pyrolysates of **8** at 370 and 480 °C, respectively. The bands labeled A, B, and C are due to the carbodiimide **11**, the azide **9**, and 2-cyanopyrrole (**12**), respectively.

Scheme I



Scheme II



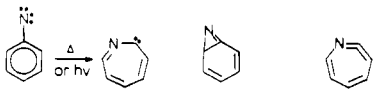
matrix-isolated in argon at 10 K.[2,8] We now report direct spectroscopic evidence for the formation of relatively stable cyclic carbodiimides in thermal nitrene rearrangements.

Flash vacuum pyrolyses were carried out at 10^{-5}–10^{-4} torr in an apparatus allowing the direct IR spectroscopic observation of the products at −196 °C.[11] The sublimation of tetrazolo[1,5-*a*]pyridine (**8**) through this apparatus at 150–200 °C caused complete transformation into 2-pyridyl azide [**9**: IR (−196 °C) 2130 (vs), 2100 (vs) [$\nu_{as}(N_3)$], 1625 (s), 1580 (s), 1485 (s), 1455 (s), 1420 (s), 1275 (vs) [$(\nu_{sym}(N_3)$], 1135 (m), 770 (s), 750 (s) cm^{-1}] (Figure 1). The weak absorptions at 2300 and 2420 cm^{-1} belong to the azide. All previous attempts at a direct observation of **9** in solution or in the solid state at elevated temperatures had failed, although the existence of **9** in the gas phase had been deduced from mass spectrometric measurements.[12] It can now be asserted that the equilibrium between **8** and **9** lies strongly to the side of **8** in the solid state and in solution; in contrast, once formed, the azide **9** is more stable than **8** in the gas phase. The sample of **9** deposited from the gas phase was permanently stable at −196 °C but disappeared when warmed to −10 °C, being transformed back into the tetrazole **8**.

When the pyrolysis of **8** was carried out at 480 °C, the IR spectrum of the product [Figure 1 (III)] still showed the presence of the azide **9**, together with a new, sharp absorption at 2220 cm^{-1} due to 2-cyanopyrrole (**12**), but the strongest peak in the spectrum was a sharp band at 1975 cm^{-1}, which we identify as the carbodiimide **11** (Scheme I)(unstrained carbodiimides absorb at 2155–2100 cm^{-1}). The 1975-cm^{-1} band disappeared when the product was warmed to −70 °C. No change in the nitrile absorption occurred under these conditions. After warm-up to room temperature, 2-cyanopyrrole (**12**) and a small amount of glutaconitrile (**13**) were isolated as described previously.[3]

Pyrolysis of **8** at 370 °C caused formation of **9** and **11** only, the nitriles **12** and **13** being absent [Figure 1 (II)]. Pyrolysis of **8** at progressively higher temperatures above 480 °C resulted in a gradual disappearance of **11** and increased formation of **12** and **13** together with 3-cyanopyrrole. The latter is a thermolysis product of **12**.[3,10] The mechanism of formation of **12** and **13** has been discussed elsewhere.[7,10,13]

(8) (a) Both the thermal and photochemical rearrangements of phenyl azide have been interpreted in terms of ring expansion of phenylnitrene to azacycloheptatrienylidene (**5**),[8b] although several other authors have preferred the azabicycloheptatriene intermediate **6**. During the last 2 years, Chapman and co-workers have shown that the stable intermediate formed by matrix photolysis of phenyl azide is, in fact, the ketenimine **7**.[9] Thus, a strong analogy exists between the thermal[7,8b,10] and photochemical[9] rearrangements of aromtic carbenes and nitrenes. (b) Wentrup, C. *Tetrahedron* **1974**, *30*, 1301–1311.



(9) Chapman, O. L.; Le Roux, J.-P. *J. Am. Chem. Soc.* **1978**, *100*, 282–285. Chapman, O. L.; Sheridan, R. S.; Le Roux, J.-P. *Ibid.* **1978**, *100*, 6245. Chapman, O. L.; Sheridan, R. S. *Ibid.* **1979**, *101*, 3690–3692. Chapman, O. L.; Sheridan, R. S.; Le Roux, J.-P. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 334–337. Chapman, O. L. *Pure Appl. Chem.* **1979**, *51*, 331–339.

(10) Wentrup, C. *Top. Curr. Chem.* **1976**, *62*, 173–251.

(11) Winter, H.-W.; Wentrup, C. *Angew. Chem.*, in press.

(12) Wentrup, C. *Tetrahedron* **1970**, *26*, 4969-4983.

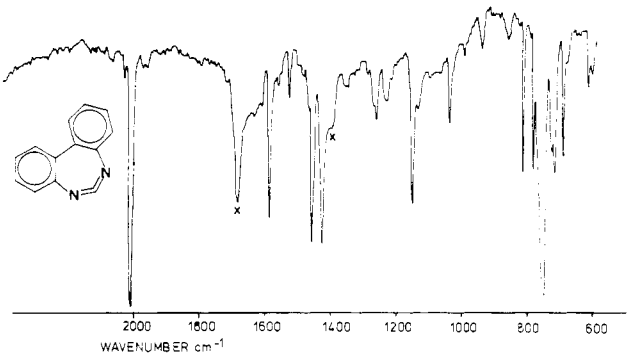


Figure 2. Infrared spectrum of dibenzo[*d*,*f*]-1,3-diazacyclohepta-1,2,4,6-tetraene at −196 °C. Bands marked X are due to impurities.

In view of these results, the stable intermediate in the interconversion of 2-pyridylnitrenes (eq 1) should now be formulated as the carbodiimide **11**, rather than the carbene **1**. The question whether **1** is formed at all, or whether it is in thermal equilibrium with **11** in the gas phase, cannot be answered at this time.[14]

The identification of the stable intermediate as the carbodiimide **11** receives strong support from the observation of a common intermediate in the pyrolyses of tetrazolo[5,1-*a*]isoquinoline (**14**) and tetrazolo[1,5-*a*]quinoline (**15**) (Scheme II). Sublimation of these compounds at or above 150 °C gave the previously unknown azides **16** and **17**, respectively, identified by their IR spectra at −196 °C and by the fact that they reverted to **14** and **15**, respectively, when warmed to −10 to 0 °C [**16**: IR 2140 (s), 2120 (s), 1350 (s) cm^{-1}. **17**: IR 2130 (vs), 2110 (s), 1330 (s) cm^{-1}]. The intensities of the azide absorptions increased with the pyrolysis temperature until ca. 380 °C, when a new and strong absorption at 2000 cm^{-1} appeared. The latter absorption increased in intensity till ca. 500 °C; the azide absorptions decreased over the same temperature interval. Above 500 °C, the 2000-cm^{-1} band started disappearing again, and new nitrile absorptions at 2225–2250 cm^{-1} appeared in its place. The latter absorptions remained unchanged at room temperature, and isolation and chromatographic separation of the material allowed their assignment to the two nitriles **22** and **23**, which had been identified previously.[4]

An optimal pyrolysis temperature for the observation of the 2000-cm^{-1} absorption was found at 490 °C. Under these conditions, only traces of the azides (**16** or **17**) remained, and only weak bands due to the end products **22** and **23** were present. The spectra recorded at −196 °C, following pyrolysis of either **14** or **15** at 490 °C, were identical, and we therefore assign them to a common intermediate, the carbodiimide **19**. When the matrix was warmed to ca. −55 °C, the carbodiimide band at 2000 cm^{-1} disappeared, and the nitriles **22** and **23** did *not* appear. Instead, a new compound, $C_{18}H_{12}N_4$, corresponding to a dimer of **19** was isolated. The two dimers formed from **14** and **15** were identical.[15]

These observations are summarized and interpreted in Scheme II. The formation of the common intermediate **19** demonstrates that both 1-isoquinolylnitrene (**18**) and 2-quinolylnitrene (**20**) undergo ring expansion under rather mild conditions, i.e., the activation energies cannot be significantly higher than those required for thermolysis of the azides **16** and **17**. It would be difficult to interpret the observed spectra in terms of the fused azirines **24** and **25** (Scheme II). These molecules would be expected neither to absorb at 2000 cm^{-1} nor to have identical IR spectra, or to give identical dimers. Furthermore, **24** and **25** are predicted to be unstable relative to the triplet nitrenes **18** and **20**,[16] and force-field–SCF calculations on the all-carbon analogues indicated that the heat of formation of **24** is 17 kcal/mol higher than that of **25**.[17] We therefore reinforce our original conclusion[6] that the seven-membered ring intermediates are more stable than the bicyclic azirines.

Since annelated benzene rings appeared to stabilize the cyclic carbodiimides, 9-azidophenanthridine (**26**) was also investigated.

26 27

26 was obtained by pyrolysis of tetrazolophenanthridine at 150–300 °C. At 490 °C, this azide had entirely disappeared, and an almost pure sample of the carbodiimide **27** was obtained, characterized by a strong absorption at 2010 cm^{-1} (Figure 2). **27** was stable in the solid state until ca. −40 °C, where rapid dimerization to a colorless, crystalline material occurred.[15] Pyrolyses of **26** at higher temperatures (700–800 °C) resulted in the formation of 4- and 9-cyanocarbazoles as previously described.[4,5]

In conclusion, we have shown that heteroarylnitrenes rearrange to diazacycloheptatetraenes in the gas phase under relatively mild conditions. The diazacycloheptatetraenes are remarkably stable and can even be prepared in quantity by deposition at −196 °C. These results open the possibility of a new chemistry of cyclic carbodiimides and related compounds.

(13) Harder, R.; Wentrup, C. *J. Am. Chem. Soc.* **1976**, *98*, 1259.

(14) (a) It is relevant to note that the chemistry of the all-carbon analogue of **1**, cycloheptatrienylidene, is usually rationalized in terms of carbene character, although indications of an equilibrium with cycloheptatetraene have appeared.[14b] Quantum-chemical calculations indicate that cycloheptatetraene is the most stable or even exclusive structure in this system.[14c] (b) Jones, W. M. *Acc. Chem. Res.* **1977**, *10*, 353–359. Mayor, C.; Jones, W. M. *J. Org. Chem.* **1978**, *43*, 4498–4502. (c) Tyner, R. L.; Jones, W. M.; Öhrn, Y.; Sabin, J. R. *J. Am. Chem. Soc.* **1974**, *96*, 3765–3769. Dewar, M. J. S.; Landman, D. *Ibid.* **1977**, *99*, 6179–6182.

(15) The X-ray structures of the dimers of **19** and **27** will be reported in the full paper. The dimer of **27** is a normal carbodiimide dimer, consisting of two units of **27** joined by an almost square four-membered ring. We thank Dr. W. Massa for the structure determination.

(16) See ref 10, 196–199.

(17) Lindner, H. J.; Wentrup, C., to be published.

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A Stereocontrolled Synthesis of (+)-Thienamycin

Sir:

The recent discovery of thienamycin (**1**)[1] and related, naturally occurring, carbapenem antibiotics has provided impetus for considerable synthetic activity due to both the novel chemical structure[1,2] and the unprecedented and highly desirable antibiotic

(1) *Thienamycin.* Isolation: J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, D. Hendlin, S. Mochales, S. Hernandez, and H. B. Woodruff, 16th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 1976, Abstr. 227; J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff, and J. Birnbaum, *J. Antibiot.*, **32**, 1 (1979). Structure: G. Albers-Schonberg, B. H. Arison, E. Kaczka, F. M. Kahan, J. S. Kahan, B. Lago, W. M. Maiese, R. E. Rhodes, and J. L. Smith, 16th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 1976, Abstr. 229; G. Albers-Schonberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 6491 (1978). Biological Activity: H. Kropp, J. S. Kahan, F. M. Kahan, J. Sundelof, G. Darland, and J. Birnbaum, 16th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 1976, Abstr. 228; F. P. Tally, N. V. Jacobus, and S. L. Gorbach, *Antimicrob. Agents Chemother.*, **14**, 436 (1978); S. S. Weaver, G. P. Bodey, and B. M. LeBlanc, *ibid.*, **15**, 518 (1979).

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