(4/1), $R_f = 0.3$). The (*R*)-1-phenyl-3-buten-1-ol was isolated as a light yellow oil (50 mg, 67 % yield) in 84 % *ee*.

Received: April 7, 1999
Revised version: June 24, 1999 [Z 13252 IE]
German version: *Angew. Chem.* **1999**, *111*, 3558 – 3561

Keywords: aldehydes · asymmetric catalysis · chromium · redox chemistry · Schiff bases

[1] a) A. Fürstner, A. Hupperts, *J. Am. Chem. Soc.* **1995**, *117*, 4468 – 4475; A. Gansäuer, *Synlett* **1998**, 801 – 809, and references therein; A. Gansäuer, H. Bluhm, M. Pierobon, *J. Am. Chem. Soc.* **1998**, *120*, 12849 – 12859; M. Bandini, P. G. Cozzi, S. Morganti, A. Umani-Ronchi, *Tetrahedron Lett.* **1999**, *40*, 1997 – 2000; b) R. Nomura, T. Matsuno, T. Endo, *J. Am. Chem. Soc.* **1996**, *118*, 11666 – 11667; c) B. Hatano, A. Ogawa, T. Hirao, *J. Org. Chem.* **1998**, *63*, 9421 – 9424; d) A. Svantoš, W. Boland, *Synlett* **1998**, 549 – 551.

[2] A. Fürstner, N. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 12349 – 12357.

[3] Y. Kishi, *Pure Appl. Chem.* **1992**, *64*, 343 – 350; L. A. Wessjohann, G. Scheid, *Synthesis* **1999**, 1 – 36; A. Fürstner, *Chem. Rev.* **1999**, *99*, 991 – 1046.

[4] For studies on the stoichiometric enantioselective Nozaki – Hiyama – Kishi reaction see: a) C. Chen, K. Tagami, Y. Kishi, *J. Org. Chem.* **1995**, *60*, 5386 – 5387; b) K. Sugimoto, S. Aoyagi, C. Kibayashi, *J. Org. Chem.* **1997**, *62*, 2322 – 2323.

[5] a) A. L. Costa, M. G. Piazza, E. Tagliavini, C. Trombini, A. Umani-Ronchi, *J. Am. Chem. Soc.* **1993**, *115*, 7001 – 7002; b) G. E. Keck, K. H. Tarbet, L. S. Geraci, *J. Am. Chem. Soc.* **1993**, *115*, 8467 – 8468; c) P. Bedeschi, S. Casolari, A. L. Costa, E. Tagliavini, A. Umani-Ronchi, *Tetrahedron Lett.* **1995**, *36*, 7897 – 7900; d) A. Yanagisawa, H. Nakashima, A. Ishiba, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 4723 – 4724; e) R. Brückner, S. Weigand, *Chem. Eur. J.* **1996**, *2*, 1077 – 1084; f) S. Casolari, P. G. Cozzi, P. Orioli, E. Tagliavini, A. Umani-Ronchi, *Chem. Commun.* **1997**, 2123 – 2124; g) C.-M. Yu, H.-S. Choi, S.-K. Yoon, W.-H. Jung, *Synlett* **1997**, 889 – 890; h) A. Yanagisawa, Y. Nakatsuka, H. Yamamoto, *Synlett* **1997**, 933 – 934.

[6] For the use of [Cr^{III}(salen)] complexes in asymmetric catalysis see: a) L. E. Martínez, J. L. Leighton, D. H. Carsten, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5897 – 5898; b) J. L. Leighton, E. N. Jacobsen, *J. Org. Chem.* **1996**, *61*, 389 – 390; c) L. E. Martínez, W. A. Nugent, E. N. Jacobsen, *J. Org. Chem.* **1996**, *61*, 7963 – 7966; d) J. F. Larrow, S. E. Schaus, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 7420 – 7421; e) S. E. Schaus, J. Brånalt, E. N. Jacobsen, *J. Org. Chem.* **1998**, *63*, 403 – 405.

[7] Chiral ligands such as bishydrooxazoles, 2,2′-dihydroxy-1,1′-biphenyl (BINOL), $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL), sulfonamides, amino alcohols, and phosphanes afforded the homoallylic alcohol in racemic form.

[8] Bases such as pyridine and *N*-methyl imidazole were screened as well, but in these cases the homoallylic alcohol was isolated in very low yields, probably due to a complexation of the Cr species by the bases.

[9] The use of [Cr(salen)] complex following Jacobsen's protocol in the addition of allyl bromide to benzaldehyde afforded the desired homoallylic alcohol in 52 % yield and 38 % *ee*.

[10] By replacing Me_3SiCl with $ClMe_2Si(CH_2)_3CN$ or $ClMe_2SiCH_2CH_2SiMe_2Cl$ in the allylation of the benzaldehyde we obtained 76 % *ee* and 78 % *ee*, respectively.

[11] a) K. Ishihara, M. Mouri, Q. Gao, T. Muruyama, K. Furuta, H. Yamamoto, *J. Am. Chem. Soc.* **1993**, *115*, 11490 – 11495; b) K. Yamada, M. Nishida, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2301 – 2308.

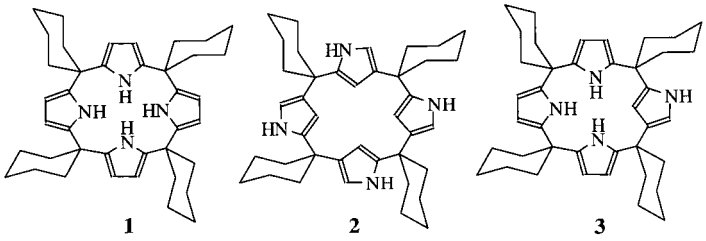
[12] Crystal structures of [Cr^{III}(salen)] complexes and related mechanistic studies were reported by Jacobsen et al. At the present, we are not able to suggest any intermediate for our reaction. However, the observed configuration of the homoallylic alcohol might derive from a mechanism involving cooperative intramolecular dimetallic catalysis: see K. B. Hansen, J. L. Leighton, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 10924 – 10925; R. G. Konsler, J. Karl, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 10780 – 10781.

N-Confused Calix[4]pyrroles**

Stefaan Depraetere, Mario Smet, and Wim Dehaen*

In recent years, calix[4]pyrroles[1] have attracted a lot of attention because of their properties as binders of anions,[2] transition metals,[3] and neutral substrates.[4] However, these compounds have been known for over a century.[5] Their synthesis is straightforward and amounts to a [4+4] cyclocondensation of pyrrole and a ketone, analoguous to the first steps of the Rothemund porphyrin synthesis. In the synthesis of porphyrins, the N-confused isomers (isomers in which one or more of the pyrrole units has the nitrogen atom at the exterior of the macrocycle) can be observed in low yields under certain conditions, as shown recently by a number of authors.[6]

There is one report in the literature[7] where the condensation of cyclohexanone and pyrrole, catalyzed by *p*-toluenesulfonic acid in benzene, was claimed to yield a mixture of the expected calix[4]pyrrole **1** and an isomer which was assigned the structure **2**. Because of the limited solubility of **2**, no NMR spectra were taken, so this assignment should be regarded as



1 **2** **3**

tentative. On the other hand, **1** was the only product claimed when hydrochloric acid was used as the catalyst in ethanol. We decided to reinvestigate this reaction in a systematic manner in order to find out the best conditions to obtain N-confused calix[4]pyrroles, which may be of importance as novel host systems.

Mixtures of equimolar pyrrole and cyclohexanone were heated for 4 h in several solvents at reflux temperature with different acid catalysts. For each reaction the mixture was evaporated to dryness, taken up in chloroform, filtered, and purified by chromatography to yield two different calix[4]pyrroles **1** and **3**. A third, chloroform-insoluble calix[4]pyrrole isomer **4** (see Figure 1) was present in some cases. The results are summarized in Table 1.

In most cases the major product is the expected isomer **1** (up to 80 % yield, m.p. 271 – 272 °C, *m*/*z* 588). The D_4 symmetry is apparent from the ^{1}H NMR spectrum ($CDCl_3$), which is identical with that reported.[8] In all cases a significant amount (6 – 22 %) of an isomer **3**, having much lower

[*] Prof. W. Dehaen, S. Depraetere, M. Smet
Department of Chemistry
Katholieke Universiteit Leuven
Celestijnenlaan 200F
BE-3001 Heverlee (Belgium)
Fax: (+32) 16-32-79-90
E-mail: wim.dehaen@chem.kuleuven.ac.be

[**] This work was supported by the Katholieke Universiteit Leuven, the Ministerie voor Wetenschapsbeleid, and the FWO-Vlaanderen.

  1433-7851/99/3822-3359 $ 17.50+.50/0

Table 1. Results of the condensation of cyclohexanone and pyrrole at reflux temperature (4 h) in several solvents with variation of the acid catalyst. Product **1** is the normal calix[4]pyrrole, **3** the N-confused calix[4]pyrrole, and **4** the doubly N-confused calix[4]pyrrole.

Entry	Solvent	Catalyst	Yield [%]			
			total	**1**	**3**	**4**
A	ethanol	conc. HCl	74	62	12	0
B	ethanol	CH_3SO_3H	87	66	22	0
C	ethanol	$BF_3 \cdot Et_2O$	94	73	21	0
D	ethanol	CF_3COOH	97 (87)[a]	80 (77)[a]	18 (10)[a]	0 (0)[a]
E	ethanol	p-$CH_3C_6H_4SO_3H$	91	69	17	5
F	ethanol	$ZnCl_2$	44	31	13	0
G	–[b]	CH_3SO_3H	34	12	22	0
H	$CHCl_3$	CF_3COOH	87	80	3	4
I	$CHCl_3$	p-$CH_3C_6H_4SO_3H$	90 (70)[a]	53 (9)[a]	5 (4)[a]	32 (57)[a]
J	benzene	p-$CH_3C_6H_4SO_3H$	94	54	6	35
K	toluene	p-$CH_3C_6H_4SO_3H$	64	18	11	36
L	toluene[b]	CF_3COOH	90	77	16	1
M	petroleum ether	CH_3SO_3H	53	42	11	0
N	ethanol	CF_3COOH	91[c]	65[c]	26[c]	0

[a] Yields in brackets for heating at reflux for 60 h. [b] No solvent was used. Stirring became difficult because of immediate precipitation of the calixpyrrole mixture. The reaction was worked up at this point. [c] Condensation of acetone and pyrrole.

solubility in chloroform, was formed. This product (m.p. 223.2–223.6 °C, m/z 588) is clearly different from the compound found by Tsuge et al. (m.p. 302 °C).[7] The ^{1}H NMR spectrum ($CDCl_3$) and appropriate decoupling experiments showed unambiguously that only one of the four pyrrole rings was connected through the 2,4-positions, while the other three had the normal 2,5-connectivity. The fourfold symmetry, clearly present for **1**, is totally absent according to the ^{1}H and ^{13}C NMR spectra of **3**. The coupling constant beween the β- and α-hydrogen atoms of the confused pyrrole in **3** has a typical value of 1.97 Hz. Signals for the α-pyrrole hydrogen (1H) and β-pyrrole hydrogen (1H) of the 2,4-disubstituted pyrrole appear at $\delta = 6.42$ and 5.50, respectively, well apart from those of the β-hydrogens atoms (6H) of the 2,5-disubstituted pyrroles ($\delta = 6.03 - 5.82$). In the ^{13}C NMR spectrum of **3**, a new peak at $\delta = 112.8$ appears, which can be assigned (confirmed by 2D experiment) to the α-CH moiety of the confused pyrrole.

Under the conditions of Tsuge et al.[7] (entry J in Table 1) and other conditions (entries E, H–L) we found next to **1** and **3** (total 13–86%) small to fair amounts (1–36%) of a third isomer **4** (m.p. 312–313 °C, m/z 588), which is, as reported, highly insoluble in common organic solvents. We assume this product to be identical with the Tsuge product (m.p. 302 °C). A ^{1}H NMR spectrum of **4** could be taken at low concentration using [D_6]DMSO as the solvent. This showed the structure to correspond to a "doubly N-confused" calix[4]pyrrole **4** (see Figure 1) and not to the "all-confused" calix[4]pyrrole **2** as assigned by Tsuge et al. The signals for the α-pyrrole hydrogen atom (2H at $\delta = 6.35$) are again well separated from those for the β-hydrogen atoms (6H, $\delta = 5.70 - 5.54$). The NH protons appear as two groups of signals (each 2H) corresponding to the 2,4- and 2,5-connected pyrroles. Although the concentration of **4** in [D_6]DMSO was too weak to obtain a satisfactory ^{13}C NMR spectrum, the two signals at $\delta = 112.8$ and 113.2, corresponding to the α-CH carbon atoms, are another proof for a doubly N-confused structure. There are five different possible ways **4a–e** in which the 2,4- and 2,5-substituted pyrroles can be connected (Figure 1), and indeed the ^{1}H NMR spectrum may correspond to a mixture of isomers, with most of the signals overlapping. However, due to the extremely low solubility of **4**, it is not possible to determine which isomers **4a–e** are formed or to separate them at this point. The pyrrole parts ($\delta = 10.2 - 5.4$) of the

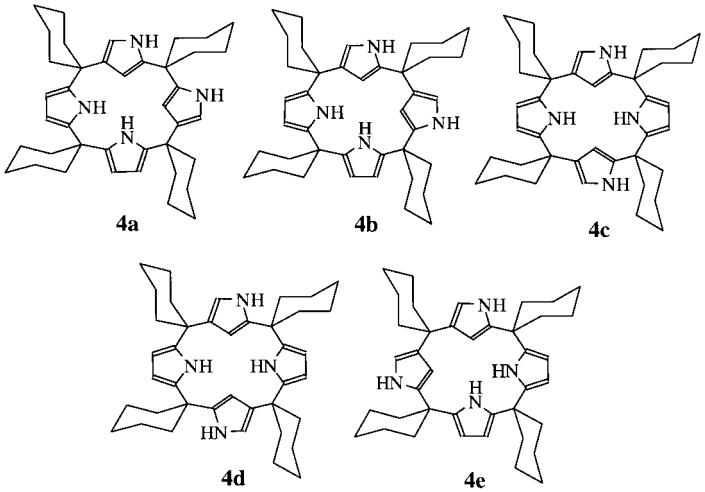


Figure 1. Schematic representation of the different ways in which the 2,4- and 2,5-connected pyrroles can be arranged in **4.**

^{1}H NMR spectra of compounds **1**, **3**, and **4** (all taken in [D_6]DMSO for comparison) are compiled in Figure 2.

When the reaction is run for longer times (entries D and I in Table 1), the total yield decreases. The amount of the N-confused isomer **3** decreases, whereas that of the less soluble **4** increases (up to 57% when p-toluenesulfonic acid is used as the catalyst, entry I). These findings indicate that the reactants and products are in equilibrium, and displacement of the equilibrium may occur owing to the lower solubility of **4**. The N-confused calixpyrroles **3** and **4** have a free pyrrole α-position, which makes these products unstable in solution. In particular we have noticed that the singly N-confused **3**

  1433-7851/99/3822-3360 $ 17.50+.50/0

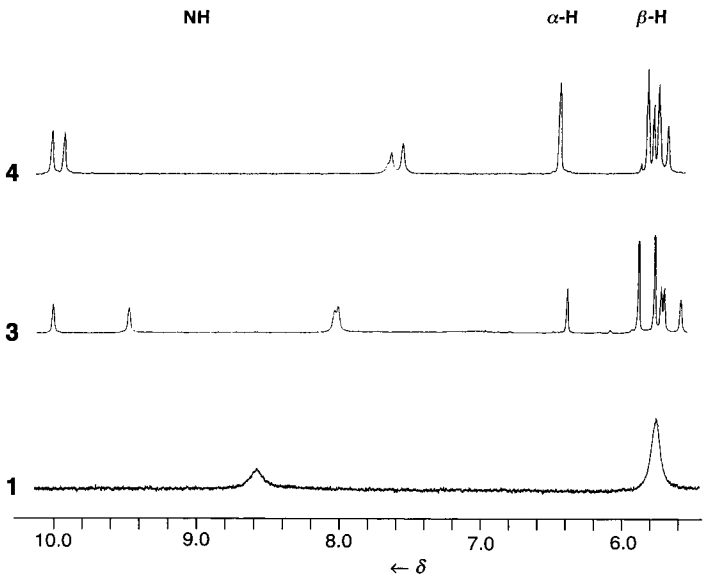


Figure 2. The pyrrole region of the ^{1}H NMR spectrum (400 MHz, [D$_6$]DMSO) of calix[4]pyrrole **1**, N-confused calix[4]pyrrole **3**, and doubly N-confused calix[4]pyrroles **4a–e**.

deteriorates in chloroform, giving a darkly colored, complex mixture. This may have been the reason why **3**, which is present in appreciable amounts in the reaction mixtures leading to calix[4]pyrroles, has so far remained undetected. However, the compounds **3** and **4** are perfectly stable in the solid phase.

From our systematic study we can conclude that trifluoroacetic acid/ethanol is the best catalyst/solvent system (total yield of 97%, entry D in Table 1). The condensation of acetone and pyrrole under these conditions (entry N) gives the octamethyl analogues of **1** and **3** in a total yield of 91%.

Experimental Section

General procedure for the condensation reactions: To a solution of pyrrole (15 mmol) and cyclohexanone (15 mmol) in the solvent of choice (5 mL) is added the appropriate acid catalyst (typically around 1 mmol) in a dropwise manner or with a spatula. In most cases an exothermic reaction results. The mixture was heated at reflux for a further 4 h and evaporated. The residue was taken into chloroform, and the solution filtered and purified by chromatography over silica gel with chloroform as the eluent to give **1** and **3**. The residue from the filtration contains **4a–e**.

1: M.p. 271–272 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.47$ (m, 24H; cyclohexyl), 1.92 (m, 16H; cyclohexyl), 5.90 (d, ^4J(H,H) = 3 Hz, 8H; pyrrole β-H), 7.04 (br, 4H; pyrrole NH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 22.8$, 26.0, 37.2, 39.6, 103.4 (pyrrole β-CH), 136.4 (pyrrole α-CH); MS (70 eV, %): *m*/*z* 589 ([*M*H]$^+$, 100).

3: M.p. 223.2–223.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 1.20–1.60 (m, 24H, cyclohexyl), 1.70–2.10 (m, 16H, cyclohexyl), 5.50 (br, 1H; pyrrole β-H), 5.82 (m, 2H; pyrrole β-H), 5.97 (br, 2H; pyrrole β-H), 6.03 (br, 2H; pyrrole β-H), 6.42 (d, ^3J(H,H) = 1.97 Hz, 1H; pyrrole α-H), 7.10 (br, 2H; pyrrole NH), 7.44 (br, 1H; pyrrole NH), 7.63 (br, 1H, pyrrole NH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 22.8$, 25.9, 26.0, 26.4, 36.6, 37.2, 37.5, 37.7, 38.4, 39.4, 39.8, 39.9, 101.3, 102.2, 103.9 (3 × pyrrole β-CH), 112.8 (pyrrole α-CH), 130.1 (pyrrole β-C), 133.7, 134.6, 136.5, 137.8, 139.1, 140.3 (pyrrole α-C); MS (70 eV, %): *m*/*z* 589 ([*M*H]$^+$, 100).

4a–e: M.p. 312–313 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta = 1.20$–1.60 (m, 24H; cyclohexyl), 1.70–2.10 (m, 16H; cyclohexyl), 5.54 (br, 1H; pyrrole β-H), 5.60–5.70 (m, 5H; pyrrole β-H), 6.35 (br, 2H; pyrrole α-H), 7.51 (br, 1H pyrrole NH), 7.96 (br, 1H; pyrrole NH), 9.98 (br, 1H; pyrrole NH), 10.07 (br, 1H; pyrrole NH), MS (70 eV, %): *m*/*z* 589 ([*M*H]$^+$).

Received: June 2, 1999 [Z13512IE]
German version: *Angew. Chem.* **1999**, *111*, 3556–3558

Keywords: calixarenes · cyclizations · isomers · NMR spectroscopy

[1] P. A. Gale, J. L. Sessler, V. Kral, *Chem. Commun.* **1998**, 1–8.
[2] a) P. A. Gale, J. L. Sessler, V. Kral, V. Lynch, *J. Am. Chem. Soc.* **1996**, *118*, 5140–5141; b) P. A. Gale, J. L. Sessler, W. E. Allen, N. A. Tvermoes, V. Lynch, *Chem. Commun.* **1997**, 665–666; c) J. L. Sessler, P. A. Gale, J. W. Genge, *Chem. Eur. J.* **1998**, *4*, 1095–1099.
[3] a) D. Jacoby, C. Floriani, A. Chiesy-Villa, C. Rizolli, *J. Chem. Soc. Chem. Commun.* **1991**, 790–792; b) C. Floriani, *Chem. Commun.* **1996**, 1257–1263; c) C. Floriani, E. Solari, G. Solari, A. Chiesi-Villa, C. Rizolli, *Angew. Chem.* **1998**, *110*, 2367–2369; *Angew. Chem. Int. Ed.* **1998**, *37*, 2245–2248; d) L. Bonomo, E. Solari, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *J. Am. Chem. Soc.* **1998**, *120*, 12972–12973.
[4] a) W. E. Allen, P. A. Gale, C. T. Brown, V. M. Lynch, J. L. Sessler, *J. Am. Chem. Soc.* **1996**, *118*, 12471–12472; b) Y. Furusho, T. Aida, *Chem. Commun*. **1997**, 2205–2206.
[5] A. Baeyer, *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 2184; M. Dennstedt, J. Zimmermann, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 850–857.
[6] a) P. J. Chmielewski, L. Latos-Grażyński, K. Rachlewicz, T. Głowiak, *Angew. Chem.* **1994**, *106*, 805–808; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 779–781; b) H. Furuta, T. Asano, T. Ogawa, *J. Am. Chem. Soc.* **1994**, *116*, 767–768; c) P. J. Chmielewski, L. Latos-Grażyński, K. Rachlewicz, *Chem. Eur. J.* **1995**, *1*, 68–73; d) P. J. Chmielewski, L. Latos-Grażyński, *J. Chem. Soc. Perkin Trans. 2* **1995**, 503–509; e) G. G. Qiao, M. W. Wong, C. Wentrup, *J. Org. Chem*. **1996**, *61*, 8125–8131; f) K. Ariga, T. Kunitake, H. Furuta, *J. Chem. Soc. Perkin Trans. 2* **1996**, 667–672; g) P. J. Chmielewski, L. Latos-Grażyński, T. Głowiak, *J. Am. Chem. Soc.* **1996**, *118*, 5690–5701; h) P. J. Chmielewski, L. Latos-Grażyński, *Inorg. Chem*. **1997**, *36*, 840–845; i) Y. Ishikawa, I. Yoshida, K. Akaiwa, E. Koguchi, T. Sasaki, H. Furuta, *Chem. Lett.* **1997**, 453–454; j) L. Latos-Grażyński, P. J. Chmielewski, *New J. Chem*. **1997**, *27*, 691–700; k) G. R. Geier, J. S. Lindsey, *J. Org. Chem*. **1999**, *64*, 1596–1603.
[7] O. Tsuge, M. Tashiro, Y. Kiryu, *Org. Prep. Proc. Int.* **1975**, *7*, 39–42.
[8] A. H. Corwin, A. B. Chivvis, C. B. Storm, *J. Org. Chem.* **1964**, *29*, 3702–3703.

  1433-7851/99/3822-3361 $ 17.50+.50/0