Synthesis of *N*-Methyl-3-aza[10]paracyclophane: A Rigid Analog of Phenethylamine

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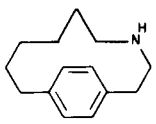
The synthesis of *N*-methyl-3-aza[10]paracyclophane is reported which represents the first example of this ring system being formed *via* an acyloin reaction. This 3-aza[10]paracyclophane ring system behaves physiochemically inbetween the normal [9]- and [10]paracyclophane ring systems. Reductive desulfurization of *N*-methyl-3-aza[10]paracyclophane-6-ethylene thioketal in ethanol provides a small amount of the title compound and an unexpected, ring-opened product, *N*-ethyl-*N*-methyl-*p*-heptylphenethylamine. A possible mechanism for the ring-opening process is suggested.

J. Heterocyclic Chem., 14, 11 (1977).

The recent publication (3) of the synthesis for 3-aza-[9]paracyclophane (**1**) as a conformationally rigid analog of phenethylamine (**2**) prompts us to report the synthesis of *N*-methyl-3-aza[10]paracyclophane (**3**).

Phenethylamine (**2**) can be viewed as the basic structure of a great number of pharmacologically active compounds, including amphetamine, epinephrine and ephedrine. Various conformationally restrained analogs (*e.g.*, **4-8**) have been synthesized and screened for their biological activities in order to assess stereochemical requirements of the drug receptor (4). Compound **3** may be used as another rigid analog of phenethylamine to aid in elucidating the topography of the receptor site. Furthermore, with the nitrogen atom above the plane of the benzene ring, the spatial arrangements of the nitrogen electron pair, away from or toward the benzene ring (5), and the possible interaction between this electron pair and the π-electron cloud of the aromatic ring might give some information concerning the interaction between drug and the receptor.

The key step for the synthesis of **3** (Scheme I) was the ring closure of the diester (**15**) *via* an acyloin reaction.



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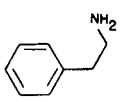

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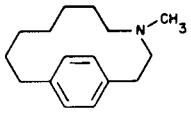

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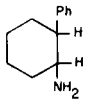

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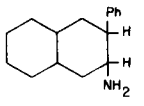

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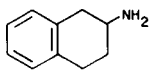

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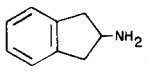

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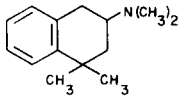

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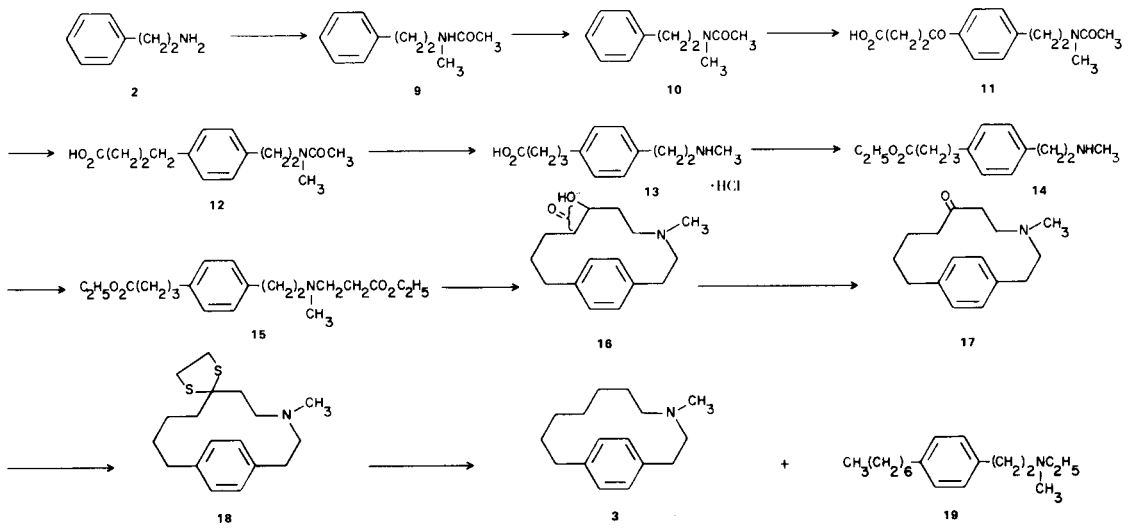
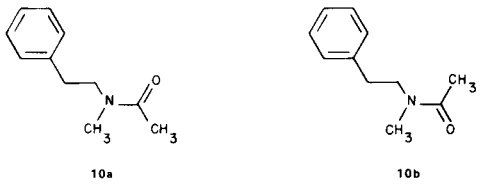
The diester was obtained in a straightforward manner through acetylation of **2**, with the resulting *N*-phenethylacetamide (**9**) being methylated (6) to yield **10**. Friedel-Crafts acylation of **10** afforded the keto acid (**11**) which was reduced to **12** by catalytic hydrogen (7). Acid hydrolysis of **12** produced the amino acid hydrochloride (**13**). Compound **13** was converted to the amino ester (**14**) and *N*-alkylated by ethyl bromopropionate to yield the diester (**15**).

Compounds **10-12** showed two equipotent peaks for each methyl group in the nmr spectrum, indicating the presence of two conformers for each compound. When the temperature was increased to 70°, the two resonance peaks for the acetyl methyl group coalesced. This suggested that the free rotation of the C-N bond was inhibited at room temperature and resulted in two energetically favored conformers; *e.g.*, **10a** and **10b**.

Scheme I





Distillation of **15** under reduced pressure produced **14** and ethyl acrylate. The decomposition of **15** could be avoided by distilling smaller quantities (*ca.* 20 ml.). Larger amounts apparently cause heat accumulation and thermal decomposition of **15** by a reverse Michael reaction (8).

Acyloin reaction of **15** went smoothly to afford azaacyloin (**16**) in about 50% yield. This was comparable to the 75% and 35% yields for [10]- and [9]paracyclophanes, respectively (9,10). The shorter bond length of C-N than that of C-C should make the strain energy of *N*-methyl-3-aza[10]paracyclophane inbetween those of [10]- and [9]paracyclophanes.

Clemmenson reduction of the azaacycloin (**16**) resulted in the formation of the amino ketone (**17**), which was the only isolatable product from this reaction. In contrast, [10]paracyclophane was obtained in 80-90% yield from Clemmenson reduction of the normal acyloin (9), whereas the [9]paracyclophane gave both hydrocarbon and ketone (10).

Initially, it was thought that the ketone (**17**) was a mixture of *N*-methyl-3-aza-6-keto[10]paracyclophane (**17**) and *N*-methyl-3-aza-7-keto[10]paracyclophane (**17a**). However, the relatively sharp melting point (59-61.5°) suggested a single compound, and the C-13 nmr spectrum clearly showed a single compound. Structural assignment for **17** was made after comparing with the spectrum of 5-keto[9]paracyclophane (11).

Reaction of **17** with 1,2-ethanedithiol provided the thioketal (**18**) in almost quantitative yield. However, reductive desulfurization of **18** by treatment with Raney nickel catalyst, in ethanol, afforded only small amounts of the target compound (**3**). The major product was an unexpected ring-opened *N*-ethyl-*N*-methyl-*p*-heptylphenethylamine (**19**). It has been reported that attempts to convert the ketone to a methylene group in the [9]paracyclophane ring system were unsuccessful by either Wolff-Kishner or reductive desulfurization (12). However, [10]-paracyclophane was obtained in relatively good yield from the thioketal derivative of 5-keto[10]paracyclophane by reductive desulfurization (13).

N-Methyl-3-aza[10]paracyclophane (**3**) showed the highly shielded protons at δ 0.5 in the nmr spectrum, comparable to the δ values of 0.7 and 0.4 for [10]- and [9]paracyclophanes, respectively (14). A summary and comparison of some properties of the *N*-methyl-3-aza-[10]paracyclophane series with those of [10]- and [9]-paracyclophane series is shown in Table I.

The structure determination of compound **19** was established from the following data. No shielded protons were observed in the nmr spectrum, suggesting that the ring had been opened. Two sets of triplets at δ 1.03 and 1.21 suggested that two non-equivalent ethyl groups were present. (The absence of the peak at δ 3.1 for -S-CH_2-CH_2S- indicated that the thioketal was no longer present.) Peaks at 1380 and 1390 cm^{-1} in the infrared spectrum (possibly two kinds of CH_3 bending) added another piece of evi-

Table I

Comparison of [9]-, [10]Paracyclophanes and 3-Aza[10]paracyclophane and their Derivatives

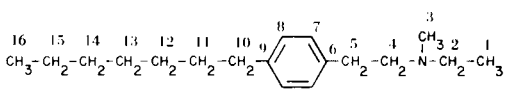
	[9]-	3-aza[10]-	[10]-
Acyloin reaction (yield)	35%	50%	75%
Clemmenson reduction of the acyloin product	hydrocarbon + ketone	ketone	hydrocarbon
Reductive desulfurization of the thioketal derivative of the ketone	0%	10% of paracyclophane + 60% of ring-opened product	70% of paracyclophane
Chemical shift of the shielded protons	0.4	0.5	0.7

dence for the presence of two kinds of ethyl groups. The molecular weight of 261 (parent peak in the mass spectrum) was equal to the sum of 231 (MW of **3**) and 30 (C_2H_5+H). The strong peak of M-15 (M-15 was absent or very weak for all cyclic compounds of this series) suggested the possible presence of $-\overset{|}{\underset{|}{N}}-CH_2CH_3$ ($-\overset{|}{\underset{CH_3}{N}}-CH_3$ was still present in the nmr spectrum), since $(M-15)^+$ usually indicates the presence of an α-methyl group (15) (CH_3 attached to the α-carbon).

The C-13 nmr spectrum further supported the idea of a ring-opened structure for **19**. Its *N*-oxide derivative (**20**) showed a chemical shift of 11.85 ppm downfield for C_2,

Table II

Chemical Shifts From the C-13 Nmr Spectra of Compound **19** and its *N*-Oxide Derivatives (**20**)



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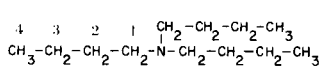
	Amine (**19**) (ppm)	*N*-Oxide (**20**) (ppm)	Difference (ppm)
1	12.24	8.83	- 3.41
2	51.40	63.25	+ 11.85
3	41.65	54.57	+ 12.92
4	57.45	68.12	+ 10.67
5	27.36	23.31	- 4.05
6	139.96	139.62	
7	127.63	127.58	
8	128.26	128.16	
9	141.28	141.33	
10	35.55	35.35	
11	31.55	31.31	
12	28.43	28.38	
13	29.51	29.16	
14	29.31 (a)	29.01 (a)	
15	27.60	26.58	
16	15.60	15.60	

(a) Assignments are uncertain.

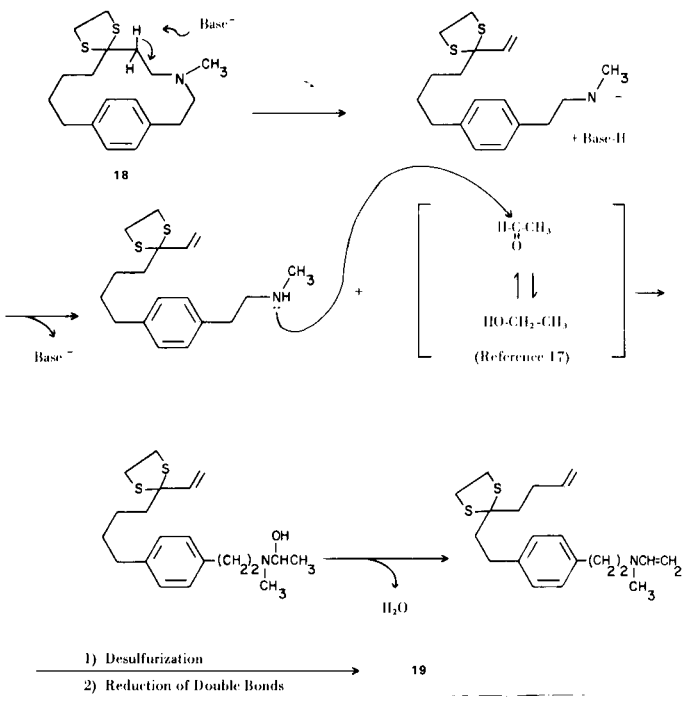
Table III

Chemical Shifts From the C-13 Nmr Spectra of Tributylamine and its Derivative



	Free amine (ppm)	*N*-Oxide (ppm)	Difference (ppm)
C_1	54.28	65.94	+ 11.66
C_2	30.28	25.16	- 5.12
C_3	20.96	20.19	
C_4	14.24	13.80	

Scheme II



12.92 ppm downfield for C_3, and 3.41 ppm upfield for C_1 from those of the corresponding carbon atoms of the free amine (see Table II), in the good agreement with those of tributylamine and its *N*-oxide derivative (16) (Table III).

A possible explanation for the unexpected ring-opening reaction may be seen in Scheme II. Since the commercial Raney nickel catalyst (W. R. Grace and Co., No. 28) was basic (*p*H *ca.* 10.5), it could serve as a base to pull off the relatively acidic proton. Future studies should consider the use of different solvents (*e.g.*, benzene), as well as Raney nickel catalyst washed sufficiently to render a *p*H near neutrality.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 467 Grating Spectrophotometer. The nmr spectra were determined on a Hitachi Perkin-Elmer R20A High Resolution nmr spectrometer using tetramethylsilane (TMS) as internal reference. However, if the compound being studied had adsorption near TMS and no absorption in the region 6.3-4.3 ppm, then methylene chloride with proton absorption at 5.28 ppm was used as internal reference. Ultraviolet spectra were determined on a Cary 118 Spectrophotometer. Mass spectra were determined on a Dupont 21-490 mass spectrometer, Department of Biochemistry, University of Georgia. C-13 nmr spectra were determined on a JEOL PFT-100 spectrometer. Elemental analyses were determined by Atlantic Microlab, Inc., Atlanta, Georgia. Tlc were performed on Eastman chromatogram sheets, type 6060 (silica gel).

N-Phenethylacetamide (**9**).

A 3000 ml. round-bottomed flask was charged with 1000 g. (8.25 moles) of phenethylamine. The flask was protected with drierite and placed in an ice-bath. Acetic anhydride (850 ml., 8.99 moles) was added dropwise to the amine. After completion of the addition process, the ice-bath was removed. The contents of the reaction vessel were stirred and heated gently (*ca.* 100°) for 5 hours. The acetic acid formed from the reaction and the excess of acetic anhydride were removed *in vacuo*. The residual oil was distilled under reduced pressure to yield 1300 g. (96.6%) of colorless oil which solidified in the receiver; b.p. 135-140° (0.01 mm Hg), m.p. 50-51° [lit. (18) m.p. 44-46°]; ir (potassium bromide): 3265 (amide NH), 3080 (aromatic CH), 2940 (aliphatic CH), 1650 (amide I), 1550 (amide II), 1460, 1375, 1210, 1040, 752 and 703 (monosubstituted benzene) cm^{-1}; nmr (deuteriochloroform): δ 1.90 (s, 3H, acetyl CH_3), 2.80 (t, 2H, benzyl CH_2), 3.4 (two overlapping t, 2H, CH_2-N), 6.70 (broad band, 1H, amide NH), 7.20 (s, 4H, aromatic H's).

N-Methyl-*N*-phenethylacetamide (**10**).

Method A (6).

A three-neck, 5000 ml., round-bottomed flask, equipped with a reflux condenser, a drying tube, a mechanical stirrer, a nitrogen inlet, and a 500 ml. dropping funnel, was charged with 245 g. (1.50 moles) of *N*-phenethylacetamide (**9**) dissolved in 800 ml. of dry xylene (19). The contents of the reaction vessel were heated gently below the boiling point of the solvent. A suspension of 80 g. (1.67 moles) of 50% sodium hydride (washed three times with *n*-hexane) in 2000 ml. of dry xylene was added in small portions to the stirred solution. After the addition process was complete, the reaction mixture was heated to reflux and stirred for 20 hours. The reaction mixture was cooled slightly and the reflux condenser was replaced by a dry ice-acetone condenser. Iodomethane (500 g., 3.52 moles) was added dropwise and the reaction mixture was refluxed and stirred for another 6 hours. The hot content was chilled in a water bath, and the solid (sodium iodide) was removed by filtration and washed with xylene. The combined filtrates were concentrated *in vacuo* to yield a light yellow oil. This oily residue was distilled under reduced pressure to yield a colorless oil (235 g., 88%); b.p. 100-103° (0.015 mm Hg) [lit. (20) b.p. 165-170° (12 mm Hg)]; m.p. 38-39°; ir (neat): 3060 (aromatic CH), 2960 (aliphatic CH), 1655 (amide CO), 1500, 1470, 1415, 1370, 1315, 1270, 1210, 1140, 1085, 1040, 1010, 750 and 705 (monosubstituted benzene) cm^{-1}; nmr (deuteriochloroform): δ 1.78 and 1.98 (two s, 3H, N-CH_3), 2.85 (m, overlapped with N-CH_3, 2H, benzyl CH_2), 3.4 (m, 2H, N-CH_2), 7.20 (s, 5H, aromatic H's).

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.50; H, 8.57; N, 7.83.

Method B.

A solution of *N*-phenethylacetamide (**9**) (244.8 g., 1.5 moles) in 1000 ml. of dry *N,N*-dimethylformamide (21) was stirred mechanically with sodium hydride (81.6 g., 1.7 moles) in an ice-bath under nitrogen for 1 hour. Dimethyl sulfate (214.5 g., 1.7 moles) was added dropwise and the mixture was stirred at room temperature for 4 hours. Ammonium hydroxide (30%, 60 ml.) was added and the mixture stirred for another hour. The solid was removed by filtration and washed with benzene. The combined filtrates were concentrated *in vacuo*. Two pints of diethyl ether was added to the residue and the undissolved material was removed by filtration. The filtrate was concentrated *in vacuo* and the residual oil was distilled to yield the tertiary amide (**10**) in 86.5% yield (230 g.). This product was identical to that obtained by Method A.

Method C.

N-Methyl phenethylamide was prepared (22) by stirring a mixture of phenethyl bromide (143 g., 0.77 mole) and 600 ml. of 30% methylamine at *ca.* 70° for 5 hours (using a dry ice-acetone condenser). The mixture was allowed to cool and the aqueous layer was extracted with two 200 ml. portions of methylene chloride. The combined organic phase was dried over magnesium sulfate, concentrated *in vacuo*, and distilled to yield the desired product (68 g., 65.3%; b.p. 93° (16 mm Hg).

Acetic anhydride (79 g., 0.77 mole) was added dropwise to *N*-methylphenethylamine (76.5 g., 0.57 mole) in an ice-bath. The resulting mixture was stirred at *ca.* 100° for 4 hours. The volatile materials were removed *in vacuo* and the residual oil was distilled to yield compound **10** (97 g., 97%).

β-[*p*-(2-*N*-Acetyl-*N*-methylaminoethylbenzoyl]propionic Acid (**11**).

A three-neck, 3000 ml., round-bottomed flask, equipped with a reflux condenser, a mechanical stirrer, and a drying tube connected to a hydrogen chloride trap made of saturated sodium hydroxide solution, was charged with 92 g. (0.52 mole) of **10**, 54 g. (0.54 mole) of succinic anhydride, and 750 ml. of double distilled *sym*-tetrachloroethane. The mixture was stirred in a warm water bath (*ca.* 40°) for one hour, then cooled in an ice-bath for another hour. Aluminum chloride (220 g., 1.65 moles) was dry transferred to the mixture in small portions over a period of 40 minutes, maintaining the ice-bath below 10°. The ice-bath was removed, and the mixture was stirred at room temperature for 4 hours,

when it became extremely difficult to stir the reaction mixture due to the increasing viscosity. During the same period, a gradual color change to dark red was also observed. The mixture was heated at 40-50° for 15 hours, then chilled in an ice-bath. One kg. of crushed ice was added to the mixture in small portions followed by 200 ml. of concentrated hydrochloride acid to decompose the complex. The mixture was transferred to a 4000 ml. separatory funnel and the aqueous layer was extracted with three 500 ml. portions of chloroform. The combined organic phase was washed with 500 ml. of dilute hydrochloric acid, followed by three 500 ml. portions of water, dried over magnesium sulfate, and concentrated on the rotary evaporator. The resulting solid was dissolved in a solution of 60 g. of sodium carbonate in 500 ml. of water and boiled for 10 minutes. The undissolved compound was removed by filtration. The filtrate was made strongly acidic by adding concentrated hydrochloric acid in an ice-bath. The yellow precipitate was collected, dried in the vacuum oven (111 g., 77%, m.p. 138-142°), and recrystallized from acetone-methanol to yield very light amorphorus crystals (m.p. 146-147°). Three recrystallizations produced a total yield of 98 g. (68%) of pure product (**11**); ir (potassium bromide): 3300-2300 (broad band, CO_2H), 1730 (carboxyl CO), 1710 (ketone CO), 1610 (amide CO), 1420, 1360, 1240, 1175, 1020, 975, 820 (*para*-disubstituted benzene) cm^{-1}; nmr (deuteriochloroform): δ 1.91 and 2.01 (two s, 3H, acetyl CH_3, due to two conformers of the compound), 2.75 and 2.94 (two s, 3H, N-CH_3, two conformers), 2.6-3.15 (m, 4H, benzyl CH_2 and CH_2 α to carboxyl), 3.3-3.8 (m, 4H, CH_2 α to N and CH_2 α to ketone), 7.3 and 8.06 (two d, 4H, aromatic H's).

Anal. Calcd. for $C_{15}H_{19}NO$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.78; H, 6.92; N, 5.08.

γ-[*p*-(2-*N*-Acetyl-*N*-methylaminoethyl)phenyl]butyric Acid (**12**).

The method of Horning and Reisner (7) was applied for preparation of this compound. A mixture of 27.7 g. (0.01 mole) of the keto acid (**11**), 3.0 g. of 5% palladium-carbon catalyst, and 200 ml. of acetic acid was shaken with hydrogen (initial pressure, 60 psi) in a Parr hydrogenation apparatus at approximately 60°. The reduction (100% absorption) was complete in about 30 minutes. No further absorption occurred on continued shaking. The catalyst was removed by filtration and washed with acetic acid. The filtrate was concentrated *in vacuo* to yield 25 g. (95%) of colorless solid (**12**). This compound was recrystallized from benzene to obtain the analytical sample; m.p. 112-113°; ir (potassium bromide): 2300-3200 (CO_2H), 1720 (carboxyl CO), 1615 (amide CO), 1520, 1440, 1360, 1240, 1165, 1020, 825 (*para*-disubstituted benzene) cm^{-1}; nmr (deuteriochloroform): δ 1.90 and 2.10 (two s, acetyl CH_3), 2.90 and 2.96 (two s, N-CH_3), 3.55 (m, 2H, N-CH_2), 1.9-3.1 (m, 14H, the above two CH_3's and all the other CH_2's), 7.16 (s, 4H, aromatic H's), 11.35 (s, 1H, CO_2H).

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.32; H, 8.07; N, 5.37.

N-Methyl-*p*-(γ-butyric acid)phenethylamine Hydrochloride (**13**).

A 500 ml. round-bottomed flask was charged with 0.1 mole of **12** and 200 ml. of 6*N* hydrochloric acid. The mixture was refluxed for 24 hours and then concentrated *in vacuo*. The residual white solid was dried in the vacuum oven overnight and utilized in the next step without further purification.

Ethyl γ-[*p*-(2-Methylaminoethyl)phenyl]butyrate (**14**).

A 1000 ml. round-bottomed flask was charged with 70 g. of the crude amino acid hydrochloride (**13**), one pint of absolute ethanol and 2 ml. of concentrated sulfuric acid (or phosphoric acid). The mixture was refluxed in a Soxhlet extractor filled with 3A molecular sieves (23) for 15 hours. Ethanol was removed *in vacuo*, and the residual solid was dissolved in 300 ml. of water. The aqueous solution was chilled in an ice-bath and made strongly basic with 10% sodium hydroxide solution, and extracted with three 200 ml. portions of chloroform. The combined organic layer was washed with two 200 ml. portions of water, dried over magnesium sulfate, and concentrated *in vacuo*. The residual liquid was divided to three portions and distilled under reduced pressure to yield 49.5 g. (72.6% overall yield from **12**) of colorless liquid; b.p. 123-125° (0.03 mm Hg); ir (neat): 3360 (NH), 2950 (aliphatic CH), 2800 (N-CH_3), 1740 and 1200 (ester), 1520, 1455, 1380 (CH_3 bending), 1250, 1150, 1030 (C-O-C), 810 (*para*-disubstituted benzene) cm^{-1}; nmr (neat): δ 0.93 (s, 1H, NH), 1.22 (t, 3H, ethyl CH_3), 2.4 (s, 3H, N-CH_3), 2.7 (s, 4H, the ethylene group between benzene ring and nitrogen atom, these two CH_2 groups were coincidently degenerates), 4.12 (q, 2H, ethyl CH_2), 1.80-2.70 (m, 6H, all the other CH_2's), 7.18 (s, 4H, aromatic H's).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.14; H, 9.29; N, 5.64.

Ethyl γ-[*p*-(2-Methyl-*N*-β-carboethoxyethylaminoethyl)phenyl]-butyrate (**15**).

A 250 ml. round-bottomed flask was charged with 0.1 mole of **14**, 0.1 mole of dicyclohexylmethylamine, 0.1 mole of ethyl bromopropionate, and 100 ml. of benzene. The mixture was stirred and heated at *ca.* 80° for 15 hours. The precipitate (dicyclohexylmethylamine hydrobromide) was removed by filtration through Celite and washed with benzene. The filtrate was concentrated *in vacuo*, and the residue was distilled under reduced pressure to yield a light yellow oil (80-85%); b.p. 180-185° (0.02 mm Hg). The amount of compound being distilled did not exceed 20 ml. in order to avoid thermal decomposition; ir (neat): 2980, 2940 and 2840 (aliphatic CH), 2800 (N-CH_3), 1735 and 1180 (ester), 1515, 1450, 1375 (CH_3 bending), 1245, 1145, 1040, 1025 (C-O-C), 800 (*para*-disubstituted benzene) cm^{-1}; nmr (deuteriochloroform): δ 1.22 (t, 6H, two ethyl CH_3's), 4.1 (q, 4H, two ethyl CH_2's), 7.09 (s, 4H, aromatic H's), 1.5-2.9 (m, 17H, including two strong s for N-CH_3 and two degenerate CH_2's between benzene ring and N, and all the other CH_2's); uv: λ max (hexane) 263 nm (ε = 228) and 211 (7560).

Anal. Calcd. for $C_{20}H_{31}NO_4$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.62; H, 8.98; N, 4.05.

N-Methyl-3-aza-6-hydroxy-7-keto- and/or *N*-Methyl-3-aza-6-keto-7-hydroxy[10]paracyclophane (**16**).

All glassware was dried overnight in an oven (*ca.* 120°) before being used. After the high dilution apparatus (24) had been assembled, it was flamed to remove any moisture. The system was flushed with dry, oxygen-free nitrogen (25) for one hour. A 3000 ml. Morton flask was charged with 1600 ml. of dry xylene and 300 ml. of this solvent was distilled and discarded. Any possible moisture should be excluded by this process. The content in the flask was cooled somewhat. Freshly cut sodium metal (13 g., 0.56 mole) was transferred, and the mixture stirred to make a fine suspension. The diester (**15**) (44.8 g., 0.128 mole) in dry xylene was added dropwise at a speed of 30 drops per minute to the stirring (*ca.* 10000 r.p.m.) (27), refluxing sodium suspension. Color change (greyish white to yellow) was observed when the reaction was proceeding. After completion of the addition process (11-12 hours), the contents were refluxed and stirred for an additional 50 more minutes. The flask was chilled in a water bath,

then with an ice-bath with simultaneously increasing nitrogen flow to avoid any back up. Acetic acid (80 ml.) was added dropwise with moderate stirring. Water (300 ml.) was added to dissolve the formed sodium acetate, and the nitrogen flow was stopped. Potassium carbonate solution was added to basify the reaction mixture (*p*H 8-9; strong basic solution resulted in emulsion formation due to the acidic α-hydroxy ketone group). The aqueous layer was extracted with three 300 ml. portions of chloroform. The combined chloroform and xylene layer was dried over magnesium sulfate and concentrated on a rotary evaporator. The gummy, oily residue was transferred to a basic alumina column and eluted with chloroform until the eluted solution became almost colorless. Most of the polymeric material was retained on the column. The chloroform elute was concentrated by the rotary evaporator, and the residue dried by vacuum pump. The residue (gummy brown material) weighed 16.5 g. (50%). Vacuum distillation of this semi-purified material resulted in a yellow gummy oil, b.p. 157° (0.03 mm Hg). However, most of the compound was decomposed by this distillation process. This purified product solidified to a low-melting material after sitting in the refrigerator for several weeks; ir (neat): 3400 (OH), 2940, 2850 (aliphatic CH), 2800 ($N\text{-}CH_3$), 1710 (CO), 1520, 1450, 1370, 1300, 1260, 1230, 1210, 1180, 1165, 1130, 1075, 1050, 985, 960, 860, 810 (*para*-disubstituted benzene) cm^{-1}; nmr (carbon tetrachloride): δ 0.5-1.5 (m, shielded H's), 2.22 (s, $N\text{-}CH_3$), 2.85 (s, OH, which disappeared after shaking with deuterium oxide), 7.0 (m, 4H, aromatic H's), 1.5-3.1 (m, all the other H's). The ratio of the aromatic protons to the aliphatic protons was roughly 4:19; uv: λ max (hexane): 263 nm (ε = 467) and 220 (7090); Mol. wt. (MS) Calcd. 261. Found 261.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 74.28; H, 9.27; N, 5.14.

N-Methyl-3-aza-6-keto[10]paracyclophane (**17**).

A 1000 ml. round-bottomed flask was charged with 60 g. of zinc powder, 6 g. of mercuric chloride, 3 ml. of concentrated hydrochloric acid, and 80 ml. of water. The mixture was shaken for 5 minutes, and the aqueous solution was decanted. Water (40 ml.) and concentrated hydrochloric acid (60 ml.) were added to the Zn-Hg amalgum. An acetic acid solution of the semi-purified acyloin (**16**) (20 g. in 80 ml.) was added and the mixture was heated to reflux for 24 hours. In the first 10 hours, five 60 ml. portions of concentrated hydrochloric acid were added to the refluxing mixture in 2 hour intervals. After refluxing for 24 hours, the mixture was chilled in a water bath, and the insoluble material was removed by filtration and washed with dilute hydrochloric acid. The filtrate was made strongly basic by adding 10% sodium hydroxide solution. Chloroform (300 ml.) was added, and the insoluble white solid was removed by filtration and washed with chloroform. The organic layer was separated, and the aqueous solution extracted with two 200 ml. portions of chloroform. The combined organic layers were washed with water, dried over magnesium sulfate, and concentrated on the rotary evaporator. The residual yellow oil was transferred to a basic alumina column (15 g.). Fractions of 100 ml. were cut from the column eluate. Fractions 1-4 were taken with *n*-hexane and these gave only grease from evaporation. Fractions 5-9 were taken with *n*-hexane/diethyl ether (1:1 mixture). After evaporation, fraction 5 gave a trace quantity of material showing neither hydroxy nor ketone bands in the ir spectrum but decolorizing bromine in carbon tetrachloride. This possibly suggested that some kind of olefin was formed from the reaction (28). Fractions 6 and 7, after evaporation, gave 2 g. of colorless oil and showed a keto band (1710), without the appearance of a hydroxy band in the ir spectrum. Fractions 8 and 9 gave nothing after evaporation. Finally, the column was eluted with methanol and the residue, after evaporation, gave 800 mg. of hydroxy ketone (**16**). The above keto compound (**17**) was further purified by micromolecular distillation to a colorless oil which soon solidified; b.p. 110° (bath, 0.015 mm Hg); m.p. 59-61.5°; ir (neat, from column chromatograph): 2940 (aliphatic CH), 2800 ($N\text{-}CH_3$), 1710 (CO), 1520, 1450, 1370, 1280, 1270, 1235, 1170, 1130, 1120, 1090, 1070, 1060, 1030, 980, 940, 860, 840, 810 (*para*-disubstituted benzene) cm^{-1}; nmr (carbon tetrachloride): δ 0.8-1.6 (m, 4H, shielded H's), 2.23 (s, $N\text{-}CH_3$), 6.9 (s, 4H, aromatic H's), 1.9-2.8 (m, 15H, including $N\text{-}CH_3$ and all the other CH_2's); uv: λ max (hexane): 265 nm (ε = 280) and 2.19 (10650); Mol. wt. (MS) Calcd. 245. Found 245.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.39; H, 9.49; N, 5.72.

N-Methyl-3-aza[10]paracyclophane-6-ethylene Thioketal (**18**).

A 100 ml. round-bottomed flask was charged with 1.5 g. of the ketone (**17**) and 3.0 g. of 1,2-ethanedithiol. The mixture was heated at 70° until solution occurred. It was chilled in an ice bath, and 4.0 g. of boron trifluoride was added. The mixture was heated again at 70° for 2 hours, chilled in an ice bath, made strongly basic by adding 10% potassium hydroxide solution, and extracted with three 100 ml. portions of diethyl ether. The organic layer was washed well with 10% potassium hydroxide solution, dried over magnesium sulfate and concentrated on the rotary evaporator to yield 1.9 g. (98%) of a colorless oil which soon solidified. The product was recrystallized from *n*-hexane to obtain colorless rhombic crystals; m.p. 82.5-84°; ir (neat, before solidifying): 2930, 2845 (aliphatic CH), 2800 ($N\text{-}CH_3$), 1520, 1450, 1360, 1275, 1210, 1120, 1050, 820 (*para*-disubstituted benzene) cm^{-1}; nmr (carbon tetrachloride): δ 0.8 (m, 4H, shielded protons), 2.18 (s, 3H, $N\text{-}CH_3$), 2.62 (s, 4H, degenerate CH_2's between benzene ring and N), 3.1 (s, 4H, $S\text{-}CH_2\text{-}CH_2\text{-}S$), 7.02 (s, 4H, aromatic H's); Mol. wt. (MS) Calcd. 321. Found 321.

Anal. Calcd. for $C_{18}H_{27}NS_2$: C, 67.24; H, 8.46; N, 4.36. Found: C, 67.27; H, 8.48; N, 4.34.

N-Methyl-3-aza[10]paracyclophane (**3**).

A 250 ml. round-bottomed flask was charged with 1.8 g. of the thioketal (**18**), 18 g. (wet weight) of active Raney nickel (W. R. Grace & Co., No. 28), and 150 ml. of ethanol. The mixture was refluxed for either 2 hours, or overnight, or just stirred at room temperature for 6 hours (These variations made no difference as far as the identifiable products were concerned). The catalyst was removed by filtration and washed with ethanol. The filtrate was concentrated on the rotary evaporator, and the residue was transferred to a basic alumina column. Fractions of 100 ml. were collected. Fractions 1 and 2 were eluted with *n*-hexane and gave nothing after evaporation. Fractions 3-6 were eluted with diethyl ether/*n*-hexane (4:96). Fraction 3 gave nothing. Fractions 4 and 5 gave 150 mg. (11.6%) of colorless liquid which was further purified by double micromolecular distillation to yield a colorless liquid for analytical purposes; b.p. 80° (bath, 0.03 mm Hg); ir (neat): 2930 (CH_2 asymmetric stretch), 2860 (CH_2 symmetric stretch), 2800 ($N\text{-}CH_3$), 1520, 1455, 1360, 1220, 1115, 1060, 1040, 1025, 1010, 815, 805 (*para*-disubstituted benzene) cm^{-1}, nmr (carbon tetrachloride): δ 2.18 (s, 3H, $N\text{-}CH_3$), 7.04 (s, 4H, aromatic H's), The other portions of this spectrum were not easily analyzed due to the consecutive line overlaps. However, the highly shielded protons were obviously seen in the spectra (centered at δ 0.5). The consecutive lines started from δ 0.1 and ended

at 2.8; Mol. wt. (MS) Calcd. 231. Found 231. The ^{13}C-nmr spectrum was consistent with the proposed structure.

Anal. Calcd. for $C_{16}H_{25}N$: C, 83.06; H, 10.89; N, 6.05. Found: C, 83.03; H, 10.89; N, 6.00.

N-Ethyl-*N*-methyl-*p*-heptylphenethylamine (**19**).

Fraction 6 from the column employed to obtain **3** (above) gave nothing after evaporation. Fractions 7-12 were taken from *n*-hexane diethyl/ether (1:1), and all of them showed similar ir spectra. About 700 mg. of the colorless liquid was obtained after evaporation. It was further purified by double micromolecular distillation to obtain the analytical sample, a colorless liquid; b.p. 80° (bath, 0.02 mm Hg); ir (neat): 2975 (CH_3 asymmetric stretch), 2930 (CH_2 asymmetric stretch), 2860 (CH_2 asymmetric stretch), 2800 (N-CH_3), 1620, 1520, 1460, 1390 and 1380 (two kinds of CH_3 bending), 1360, 1310, 1225, 1060, 1050, 820 (*para*-disubstituted benzene) cm^{-1}, nmr (carbon tetrachlorides): δ 1.04 (t, 3H, CH_3 in the heptyl group side chain), 1.22 (t, 3H, CH_3 in the amino side chain), 2.18 (s, 3H, N-CH_3), 2.2-3.5 (m, 8H, two benzyl CH_2's and two CH_2's α to N), 7.10 (s, 4H, aromatic H's), 1.36 (large s, all the other degenerate CH_2's): Mol. wt. (MS) Calcd. 261. Found 261.

Anal. Calcd. for $C_{18}H_{31}N$: C, 82.69; H, 11.95; N, 5.36. Found: C, 82.42; H, 11.93; N, 5.30.

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