Photocyclizations. III. Synthesis of 3,6-Dimethyl-8-hydroxy-3,4,5,6-tetrahydro-3-benzazocin-2(1*H*)-one

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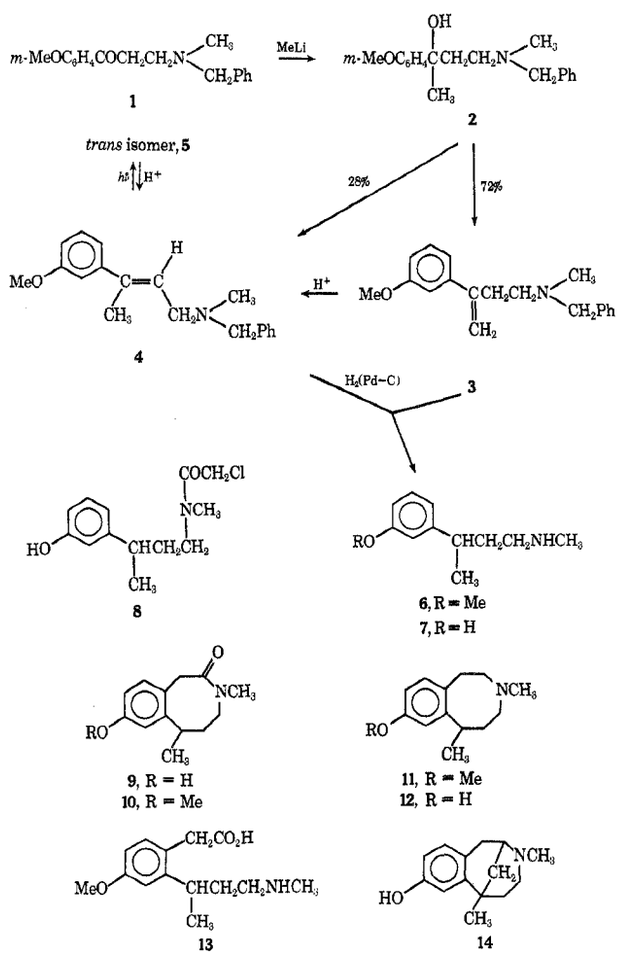
Photolysis of *N*-chloroacetyl-3-*m*-hydroxyphenyl-*N*-methylbutylamine (**8**) has given a 30% yield of benzazocinone **9**, convertible to benzazocine **12**, a demethano analog of benzomorphan **14**. The structure **9** was confirmed by conversion to amino acid **13** and by spectral data. Compound **6** was prepared from "Mannich" ketone **1** *via* carbinol **2**, dehydration of which gave vinylic compounds **3** and **4** in a ratio of 2.5:1. Irradiation of **4** produced stereoisomer **5**, which, like **3**, was isomerized to **4** by H^+. Nmr measurements served to distinguish **3**, **4**, and **5**.

(−)-2,5-Dimethyl-2′-hydroxy-6,7-benzomorphan (3,6-dimethyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-3-benzazocine, **14**) is a strong analgesic agent displaying other interesting pharmacological properties.[1] Compound **12**, 3,6-dimethyl-1,2,3,4,5,6-hexahydro-8-hydroxy-3-benzazocine, lacking the methano bridge of **14**, was desired for comparison. Recently,[2] photolytic ring closure of appropriate *N*-chloroacetyl compounds has given seven- and eight-membered nitrogen heterocycles. We now wish to report a similar success in the synthesis of benzazocinone **9**, and ultimately **12**.



Photolysis of *N*-chloroacetyl derivative **8** in aqueous methanol[3] produced major product **9** (30% yield), assigned the formula $C_{13}H_{17}NO_2$ from its mass spectrum and elemental analysis. A broad, relatively low-frequency (1615 cm^{-1}) amide I band suggested hydrogen bonding with the phenolic proton. The cite of cyclization was established as para to the phenolic hydroxyl by a 100-MHz nmr spectrum of **9** showing clearly three remaining 1,2,4-distributed aromatic protons. Two of these, H_a at δ 6.55 and H_b at 7.04, were ortho coupled to each other (J_{ab} = 8.0 Hz). H_b was further split into a quartet by the third proton, H_c (J_{bc} = 2.2 Hz), located meta to H_b; H_c appeared as a doublet at δ 6.64. Signals for the alicyclic protons were not well resolved, probably a reflection of an incomplete averaging process in the (large) benzazocine system (slow rate of inversion).[4] Further proof of the structure of **9** was provided by acid hydrolysis of the methyl derivative **10**[5] to a crystalline amino acid hydrochloride whose ir and nmr spectra were consistent with **13**. Reduction ($LiAlH_4$) of the acetate of **9** gave **12**. Diborane reduction of **10** followed by *O*-demethylation with pyridine hydrochloride also afforded **12**.[6]

Amide **8** was synthesized from Mannich ketone **1** (obtained in 75% yield)[7] *via* carbinol **2** (dehydration of which with methanesulfonyl chloride[8] gave olefins **3** and **4**), debenzylated amine **6** (by Pd/C reduction of the **3**–**4** mixture), and phenol **7**, obtained by HI hydrolysis of **6**. Preparation of **8** was best achieved by O,N-bischloroacetylation of **7** followed by partial hydrolysis as described previously.[2]

The nmr spectrum of **8** (at 25°) was complex; two sets of signals were seen, corresponding to the two conformers **8a** and **8b**, interchanging slowly owing to the partial bond character of the C–N linkage.[9,10]

(1) J. H. Ager, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, **12**, 288 (1969).

(2) H. H. Ong and E. L. May, *J. Org. Chem.*, **37**, 712 (1972); **35**, 2544 (1970).

(3) O. Yonemitsu, P. Cerutti, and B. Witkop, *J. Amer. Chem. Soc.*, **88**, 3941 (1966).

(4) F. A. L. Anet and M. A. Brown, *Tetrahedron Lett.*, 4881 (1967).

(5) Acid hydrolysis of **9** gave an unstable, hygroscopic compound, difficult to purify.

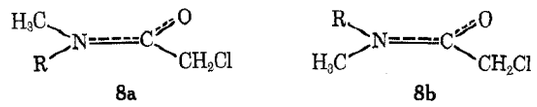
(6) Y. Sawa, T. Kato, and T. Masuda (Third International Congress of Heterocyclic Chemistry, Sendai, Japan, August 23–27, 1971) photocyclized *m*-$MeOC_6H_4C(Me)_2CH_2CH_2NHCOCH_2Cl$ to the 6,8-dimethyl homolog of **9**; B. Pecherer, F. Humiec and A. Brossi, *Helv. Chim. Acta*, **54**, 743 (1971), prepared the 6-demethyl analog of **12** by a nonphotolytic sequence. While this manuscript was in preparation, Dr. A. Brossi informed us that **12** has been prepared in the laboratories of Hoffmann-La Roche, Inc., Nutley, N. J., in continuation of their benzazocine program.

(7) Our original plan was to use *N*-chloroacetyl-3-*m*-methoxyphenylbutylamine for the photocyclization reaction, but dibenzylamine was totally inert in the Mannich reaction.

(8) A modification of the procedure of G. G. Hazen and D. W. Rosenburg, *J. Org. Chem.*, **29**, 1930 (1964), was used after numerous trials with other reagents.

(9) W. D. Phillips, *J. Chem. Phys.*, **23**, 1363 (1955).

(10) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1969, p 361.



8a 8b

R = m-HOC$_6$H$_4$CHMeCH$_2$CH$_2$

Coalescence of the signals was observed at 80°.[11] The averaged chemical shifts for the two singlets due to chloromethyl and *N*-methyl protons were δ 4.08 and 2.80, respectively.[11]

The crude product obtained in the dehydration of **2** was shown by vpc (before acid treatment) to be a 2.5:1 mixture of olefins corresponding to the formula $C_{19}H_{23}NO$ (mass spectrum, elemental analyses). Both compounds gave *m/e* 281 (M^+) with different fragmentation patterns by combined vpc–mass spectrometry (LKB 9000). Conventional efforts to separate the two olefins were unsuccessful, and, in an attempt to prepare hydrobromide salts, the predominant olefin was isomerized quantitatively to the lesser one, unambiguously assigned structure **4** from nmr data (Figure 1b).

Thus at 100 MHz in $CDCl_3$, the allylic methyl protons of **4** appeared as double triplets[12] centered at δ 2.03 ($^4J_{allylic}$ = 1.3 and $^5J_{homoallylic}$ = 0.8 Hz) due to long-range coupling with the vinylic and allylic methylene protons. The three singlets at δ 2.24, 3.54, and 3.77 can be assigned to NCH_3, benzylic methylene, and OCH_3, respectively. The doublet at 3.18 (J = 6.8 Hz) is due to the allylic methylene protons,[13] and the lone vinyl proton, as expected, gave rise to a triplet of quartets (centered at δ 5.96) indicative of vicinal and long-range (allylic) coupling.

On brief irradiation (>280 mμ) of **4** in a nonpolar solvent with the aid of a photosensitizer (PhCOPh), a new isomer, **5** (readily HCl-catalyzed to **4**), was detected; vpc analysis showed a 9:1 ratio of **5** to **4** which equilibrated to 2:1 after 2 days at 0°.[14] The mass spectrum of **5** (mol wt 281) and its nmr spectrum (deduced by subtracting signals assigned to **4** from a spectrum taken on the photoisomerization mixture, Figure 1c) were consistent with structure **5**.[15,16] These assignments would suggest that **4**, with its bulkiest substituents trans to each other, should be the thermodynamically favored configuration; indeed, this is verified by experimental observation.

The structure of **3** is also based on nmr data ($CDCl_3$, 100 Mz), deduced by subtracting those signals assigned to **4** from a spectrum taken on a 2.5:1 mixture of **3** and **4** (Figure 1a). The three singlets due to NCH_3, NCH_2, and OCH_3 are similar to those of **4**; protons

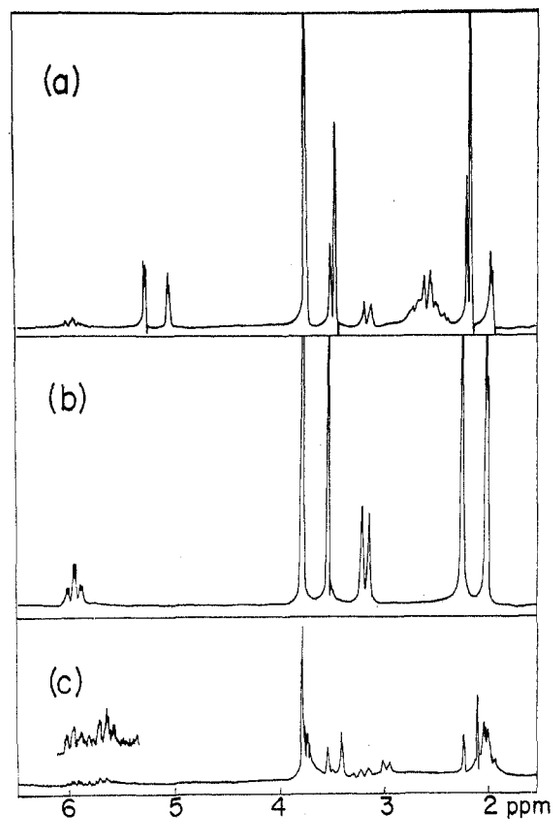


Figure 1.—Nmr spectra measured in $CDCl_3$ at 100 MHz: (a) a 2.5:1 mixture of **3** and **4**; (b) pure **4**; (c) a 1:2 mixture of **4** and **5**.

from the adjacent methylene groups gave an AA′BB′ multiplet centered at δ 2.61 and the two geminal vinyl protons appeared as a double doublet[17] at 5.07 and 5.29 (J_{gem} = 1.8 Hz). The signal at lower field is assigned to the proton cis to the *m*-methoxyphenyl radical.[15,16]

Experimental Section

General Comments.—Melting points, determined on a Kofler hot stage, are uncorrected. Ir spectra were recorded with a Perkin-Elmer Model 257 unless otherwise stated. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E double-focusing spectrometer at 70 eV. Nmr spectra were obtained either with a Varian HA-100 or an A-60 instrument (TMS, δ 0). Vpc analyses were made isothermally using an F & M instrument (Model 1609, flame-ionization detector).

γ-(*N*-Benzyl-*N*-methyl)amino-*m*-methoxypropiophenone (1) Hydrochloride.—*m*-Methoxyacetophenone (3.0 g, 20 mmol), 1.2 g (10 mmol) of $C_6H_5CH_2NHCH_3$, 1 ml of 12 *M* HCl, 1.7 ml of formalin, and 50 ml of EtOH were refluxed for 48 hr and evaporated *in vacuo*, leaving a residue which, upon trituration in Me_2CO, gave 2.4 g of hydrochloride: mp 135–138°; irregular plates from Me_2CO–EtOAc, mp 142–145°; *m/e* 283 (M^+), 268, 192 (base); ir (Nujol) 1685 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}ClNO_2$: C, 67.6; H, 6.9; N, 4.4. Found: C, 67.4; H, 7.2; N, 4.4.

Attempts to distil the free base at 0.05 mm resulted in complete polymerization above 120° (bath temperature).

4-(*N*-Benzyl-*N*-methyl)amino-2-*m*-methoxyphenyl-2-butanol (2).—To freshly prepared MeLi (1.4 g of Li wire, 15 g of MeI, and 100 ml of Et_2O) was added dropwise 28.3 g (0.1 mol) of **1** in 100 ml of dry C_6H_6. After 24 hr of reflux (stirring), the mixture was poured into 200 g of ice. The organic layer was dried ($MgSO_4$) and fractionated to give 22 g (73%) of viscous oil, bp

(11) At room temperature using DMSO-d_6 the chloromethyl protons appeared as an uneven doublet at δ 4.20 and 4.04 (relative population 2:1 in favor of the conformer resonating at lower field); the NCH_3 protons were similarly split into a 2:1 doublet at δ 2.85 and 2.71. In $CDCl_3$ the two conformers were about equal in population.

(12) The double triplets were evident only when the spectrum was expanded 20-fold (sweep width 50 Hz); otherwise, a doublet was observed.

(13) Long-range coupling was not seen, however, because of a slight broadening of lines caused by electric quadrupole relaxation of the adiacent ^{14}N: F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 21.

(14) Similar, photoinduced cis–trans isomerization has been observed for stilbene as well as for a large number of other olefins: D. C. Neckers, "Mechanistic Organic Photochemistry," Reinhold, New York, N. Y., 1967, p 198.

(15) The difference in chemical shifts observed for the two β-vinyl protons in α-methylstyrene was 0.31 ppm. The downfield signal was assigned to the proton cis to the phenyl group. See ref 10, p 224.

(16) S. W. Tobey, *J. Org. Chem.*, **34**, 1281 (1969).

(17) Long-range coupling between the two vinyl and the allylic methylene protons was not closely examined.

165–168° (0.05 mm). Ir and nmr data are consistent with structure **2**.

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.2; H, 8.4; N, 4.7. Found: C, 76.5; H, 8.5; N, 4.6.

Dehydration of 2. 4-(*N*-Benzyl-*N*-methyl)amino-2-*m*-methoxyphenyl-1-butene (3) and 4-(*N*-Benzyl-*N*-methyl)amino-2-*m*-methoxyphenyl-*cis*-2-butene (4).—Pyridine (50 ml), 20 ml of DMF, and 6.4 g (21.4 mmol) of **2** were cooled to 0° and treated dropwise with 2.4 ml of $MeSO_2Cl$ during 30 min. The mixture was left at room temperature overnight, heated (under N_2) on a steam bath for 2 hr, poured into 200 g of ice, and made basic with 40% NaOH. The slowly liberated amine was extracted exhaustively with Et_2O. The extracts were dried ($MgSO_4$) and evaporated. Distillation of the residue gave 3.1 g (51%) of oil, bp 146–148° (0.05 mm), *m/e* 281 (M^+), 266.

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.1; H, 8.3; N, 5.0. Found: C, 80.7; H, 8.0; N, 4.9.

Although tlc of the distilled oil showed only one spot,[18] vpc analysis[19] revealed two components, **3** and **4** (2.5:1 ratio, retention times 5.5 and 7.8 min, respectively). Individual mass spectra of **3** and **4** were obtained with an LKB 9000 spectrometer[20] fitted with a vpc column.[19] Major peaks for **3** were at 281 (M^+), 266, and 136 (base) and for **4**, 281 (M^+), 266 (base), 190, 161, 160, and 146. The nmr spectrum of the distillate also indicated approximately a 7:3 mixture of **3** to **4**.

Isomerization of 3 to 4.—Ether (50 ml) and 200 mg of the distillate above (2.5:1 mixture of **3** and **4**) were treated with ethereal HBr to strong congo red acidity. The precipitate was separated by decantation and warmed (steam bath) with 10 ml of EtOAc for 30 min to give 178 mg of crystals: mp 146–148° (from Me_2CO–Et_2O); mass spectrum *m/e* 281 (M^+), 266, 190, 161, 160, 146; nmr (DMSO-d_6, 100 MHz) δ 2.08 (s, 3, $CH_3C{=}CH$),[21] 2.71 (s, 3, $-NCH_3^+$), 3.80 (s, 3, OCH_3), 4.00 (d, $C{=}CHCH_2-$, J = 7.8 Hz), 4.45 (broad s, 2, $ArCH_2N-^+$), 6.04 (t, 1, $-C{=}CH-$, J = 7.8 Hz), 6.85–7.80 (m, 9, aromatic H).

Anal. Calcd for $C_{19}H_{23}NO\cdot HBr$: C, 63.0; H, 6.7; N, 3.9. Found: C, 62.9; H, 6.7; N, 3.6.

Treatment of this hydrobromide with 1 *N* NaOH and ether gave, after distillation at 10^{-3} mm, 110 mg of oil which proved (vpc analysis) to be pure **4**. The combined filtrates above gave an additional 45 mg of pure **4** base.

Photoisomerization of 4 to 4-(*N*-Benzyl-*N*-methyl)amino-2-*m*-methoxyphenyl-*trans*-2-butene (5).—EtOAc (100 ml), 50 mg of **4**, and 10 mg of PhCOPh were irradiated under N_2 for 1 hr with a 200-W, high-pressure Hg lamp and a Pyrex filter. Immediate vpc analysis[19] of the solution revealed a new compound, **5**, retention time 3.6 min, and a 9:1 ratio of **5** to **4**; at 0° and 48 hr later, this ratio was 2:1. The mass spectrum of **5** (LKB 9000 combined with gas chromatography as described before)[19,20] gave *m/e* 281 (M^+), 280, 266, 161, 146; the nmr spectrum of **5** was determined from the 2:1 photoisomerization solution of **5** and **4** (*cf.* Figure 1c). Assignments were consistent with structure **5**, especially that for the vinyl proton as stated before. Conversion of **5** to **4** was easily effected with HCl.

3-*m*-Methoxy-*N*-methylbutylamine (6).—The 2.5:1 mixture of **3** and **4** (9 g, 32 mmol), 100 ml of glacial HOAc, 3 ml of 12 *N* HCl, and 3 g of 10% Pd/C were hydrogenated at room temperature and pressure to absorption of *ca.* 0.1 mol of H_2 to give, after the usual work-up, 6.2 g (82%) of chromatographically pure **6**, *m/e* 193 (M^+), 163 (base).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.5; H, 9.9; N, 7.2. Found: C, 74.4; H, 9.9; N, 7.4.

3-*m*-Hydroxyphenyl-*N*-methylbutylamine (7).—Compound **6** (6.2 g, 32 mmol) and 5 ml of 47–50% HI were refluxed together for 2 hr and evaporated to dryness *in vacuo*, and the residue was made basic with dilute NH_4OH. The liberated base was dried in CH_2Cl_2, evaporation of which left 4.5 g (79%) of an oil which solidified on cooling. Recrystallization from ether–ligroin (bp 30–60°) gave prisms, mp 103–104°, *m/e* 179 (M^+). Nmr data ($CDCl_3$–D_2O, 100 MHz) were consistent with structure **7**.

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.7; H, 9.6; N, 7.8. Found: C, 73.8; H, 9.3; N, 7.7.

***N*-Chloroacetyl Derivative (8) of 7.**—To a mixture of 0.6 g (3.3 mmol) of **7**, 100 ml of CH_2Cl_2, and 0.25 g of $NaHCO_3$ was added dropwise during 30 min (stirring) (1.1 g (10 mmol) of $ClCH_2COCl$. After 2 hr the mixture was poured into 100 g of ice water; the organic layer was separated and evaporated to dryness *in vacuo*. After addition of 20 ml of 1 *N* NaOH to the residue, a clear solution was gradually obtained. Acidification with 12 *M* HCl and extraction with CH_2Cl_2 afforded, after drying and evaporation of solvent, 0.69 g (82%) of oily **8** as prisms from ether–ligroin, mp 77–79°, *m/e* 255 (M^+), 220, 206. Nmr and ir spectral data were consistent with structure **8**.

Anal. Calcd for $C_{13}H_{18}ClNO_2$: C, 61.0; H, 7.1; 5.5. Found: C, 60.8; H, 7.4; N, 5.3.

3,6-Dimethyl-8-hydroxy-3,4,5,6-tetrahydro-3-benzazocin-2-(1*H*)-one (9).—Nitrogen was "bubbled" through a solution of 1.0 g (4 mmol) of **8** in 600 ml of 50% MeOH while the solution was irradiated[3] with a 200-W, high pressure, Hg-immersion lamp equipped with a Vycor[22] filter (water cooling of the quartz well). After 6 hr,[23] the solution was lyophilized or evaporated to dryness at 35°. Trituration of the residue in 2 ml of Me_2CO, then cooling overnight at 0° gave 192 mg of **9**, mp 223–225°. Thick layer chromatography of the filtrate (2-mm Brinkman plates, 95:5 $CHCl_3$–MeOH) gave an additional 67 mg (total yield 30%) of **9**: R_f 0.43; ir (KBr) 3250, 1615 cm^{-1} (broad);[24] *m/e* 219 (M^+), 204 (base); nmr (DMSO-d_6–D_2O, 100 MHz) δ 1.29 (d, 3, CH_3CH-, J = 7.0 Hz), 2.70 (broad s, 3, NCH_3) (*cf.* text for aromatic proton signals).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.1; H, 7.8; N, 6.4. Found: C, 71.2; H, 7.5; N, 6.5.

Methyl Ether 10 of 9.—Methanol (20 ml), **9** (910 mg, 4.1 mmol), and excess ethereal diazomethane (from 10 g of *N*-methyl-*N'*-nitrosoguanidine) were left overnight. Molecular distillation (10^{-4} mm, 150°) of the product gave 920 mg (95%) of a viscous, chromatographically pure oil,[24] *m/e* 233 (M^+), 218, 190, 176, 175.

Anal. Calcd for $C_{14}H_{19}NO_2$: N, 6.1. Found: N, 5.7.

3,6-Dimethyl-1,2,3,4,5,6-hexahydro-8-methoxy-3-benzazocine (11) Hydrobromide.—Borane (25 ml of 1 *M*, THF) was added to 920 mg (3.8 mmol) of **10** in 50 ml of THF. The solution was refluxed overnight, cooled slightly, and refluxed with 50 ml of 6 *N* HCl for 2 hr. Evaporation *in vacuo* left a semisolid which was made basic with 1 *N* NaOH. The liberated base was dried (K_2CO_3) in Et_2O and converted to 1.0 g (90%) of **11** HBr (ethereal HBr) as irregular prisms from Me_2CO–Et_2O, mp 169–170°, *m/e* 219 (M^+), 204, 176, 162.

Anal. Calcd for $C_{14}H_{22}BrNO$: C, 56.0; H, 7.4; N, 4.7. Found: C, 56.0; H, 7.7; N, 4.5.

3,6-Dimethyl-1,2,3,4,5,6-hexahydro-8-hydroxy-3-benzazocine (12). A. From 9.—Ac_2O (2 ml) and 500 mg (2.3 mmol) of **9** were warmed to homogeneity (2 hr) on the steam bath, and reagent was evaporated *in vacuo*. The residue was dissolved in ether, washed with dilute $NaHCO_3$, dried ($MgSO_4$), and reduced with 1.0 g of $LiAlH_4$ in 50 ml of THF (4-hr reflux). After the usual work-up, 390 mg (83%) of **12** crystallized from Me_2CO in needles, mp 206–207.5°, *m/e* 205 (M^+), 190, 162.

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.0; H, 9.3; N, 6.8. Found: C, 75.8; H, 9.4; N, 6.7.

The hydrobromide crystallized from EtOH–Et_2O as prisms, mp 205° dec.

Anal. Calcd for $C_{13}H_{20}BrNO$: C, 54.6; H, 7.0; N, 4.9. Found: C, 54.5; H, 7.3; N, 4.8.

B. From 11.—Pyridine HCl[25] (1.5 g) and 150 mg (0.7 mmol) of **11** were fused at 200–210° under N_2 for 30 min and treated with 20 ml of H_2O. Basification (aqueous K_2CO_3), extraction with CH_2Cl_2, and evaporation of the extract *in vacuo* gave a brown oil which was molecularly distilled (10^{-4} mm, bath temperature 150°). Trituration of the distillate in cold Et_2O gave 82 mg (57%) of **12**, mp 205–207°, identical with that obtained by procedure A.

3-(2-Carboxymethyl-5-methoxyphenyl)-*N*-methylbutylamine (13) Hydrochloride.—Refluxing **10** (100 mg) and 10 ml of 4 *N* HCl for 3 hr, vacuum distillation to dryness, and trituration of the residue in 1 ml of EtOAc afforded 92 mg (72%), of prisms: mp 157–159° (from EtOH–Et_2O); ir (Nujol) 1715 cm^-; nmr

(18) Silica gel plates: system I, BuOH–HOAc–H_2O (4:1:1), R_f 0.72; system II, $CHCl_3$–MeOH (40:1), R_f 0.51.

(19) On a 6-ft, 1% ECNSS-S (on Gas-Chrom Q) column, 160°.

(20) Electron energy 70 eV, separation temperature 285°, ion source 295°.

(21) Long-range couplings were too small to be measured.

(22) When a Corex filter was used, no **9** was formed.

(23) Optimal time because of competitive cleavage and/or polymerization of **9**.

(24) Perkin-Elmer 421. This amide I band was shifted to 1650 cm^{-1} (Nujol) and sharpened in the methyl ether **10**.

(25) M. Gates and T. A. Montzka, *J. Med. Chem.*, **7**, 127 (1964).

(D_2O, 60 MHz)[26] δ 1.26 (d, 3, CH_3CH, J = 7.0 Hz), 1.84–2.48 (m, 2, $ArCHCH_2$), 2.70 (s, 3, NCH_3), 2.77–3.22 (m, 3, ArCH and CH_2N), 3.74 (s, 2, CH_2CO_2H), 3.88 (s, 3, OCH_3), 6.89 (1, 1, aromatic H, J_{ortho} = 8.5 and J_{meta} = 2.5 Hz), 7.01 (d, 1, aromatic H, J_{meta} = 2.5 Hz), 7.26 (d, 1, aromatic H, J_{ortho} = 8.5 Hz).

Anal. Calcd for $C_{14}H_{22}ClNO_3$: C, 58.4; H, 7.7; N, 4.9. Found: C, 58.6; H, 7.7; N, 4.6.

Registry No.—**1**, 37436-85-4; **1** HCl, 37436-86-5; **2**, 37436-87-6; **3**, 37436-88-7; **4**, 37440-18-9; **4** HBr, 37440-19-0; **5**, 37440-20-3; **6**, 37436-89-8; **7**, 37436-90-1; **8**, 37436-91-2; **9**, 37436-79-6; **10**, 37436-80-9; **11**, 37436-81-0; **11** HBr, 37436-82-1; **12**, 37436-83-2; **12** HBr, 37567-13-8; **13** HCl, 37436-84-3; *m*-methoxyacetophenone, 586-37-8; *N*-methylbenzylamine, 103-67-3.

(26) 3-(Trimethylsilyl)propanesulfonic acid sodium salt was the internal standard.

Acknowledgments.—The nmr measurements and some interpretations are due to Dr. Herman Yeh and most of the mass spectra were performed by Mr. William Landis, both of this laboratory. Dr. H. M. Fales of the National Heart and Lung Institute, NIH, made available the LKB-9000 instrument for combined gas chromatography–mass fragmentography.

Reaction of Aromatic Amine Oxides with Acid Halides, Sulfonyl Halides, and Phosphorus Oxychloride. Stereochemical Configuration of Substituents in the 1 Position of 12,13-Benzo-16-chloro[10](2,4)pyridinophanes[1]

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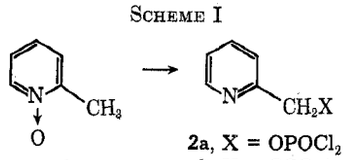
The reaction of 12,13-benzo-16-chloro[10](2,4)pyridinophane *N*-oxide (**3**) with benzoyl chloride, *p*-toluenesulfonyl chloride, phosphorus oxychloride, phosphorus thiotrichloride, and one hydrazidic bromide are described. Reactions of **3** with organic anhydrides or acid chlorides give mixtures of syn and anti esters; reaction with *p*-toluenesulfonyl chloride gives exclusively the syn tosylate **4d**. Reaction of **3** with phosphorus oxychloride is the first example in which a stable phosphate ester is formed; evidence is presented that alkyl chlorides, usually formed when alkylpyridine *N*-oxides react with *p*-toluenesulfonyl chloride or phosphorus oxychloride, are secondary products derived from intermediate esters. A new procedure has been developed to determine whether derivatives of type **4** or **5** have the syn or anti configuration at C-1 which is based on the chemical shifts observed for the methinyl proton when **4** or **5** is converted into the corresponding *N*-oxide.

Reactions of heterocyclic amine oxides with reagents such as acid anhydrides, sulfonyl halides, and acid chlorides have been intensively investigated and reviewed.[3–5] While there is a great deal known about these synthetically useful reactions, a number of points remain obscure. Among these, and of particular interest to us, is the question as to whether chlorides such as **2c**[6,7] (Scheme I), generally formed from appropriately

SCHEME I



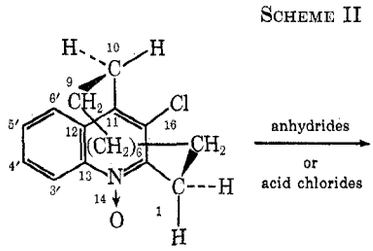
1

2a, X = $OPOCl_2$
b, X = OSO_2Ar
c, X = Cl

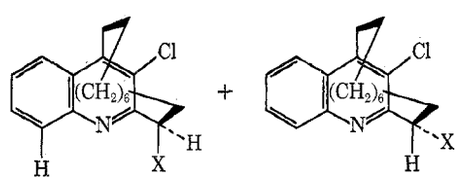
substituted *N*-oxides such as **1** by reaction with *p*-toluenesulfonyl chloride or phosphorus oxychloride, are primary products or whether they are derived in secondary reactions involving intermediate phosphate (**2a**) or sulfonate (**2b**) esters with the hydrogen chloride liberated.

The availability of metacyclophanes of type **3** (Scheme II) is of particular interest in this regard, since

SCHEME II



3



4a, X = $OCOCH_3$
b, X = OH
c, X = $OCOC_6H_5$
d, X = $OSO_2C_6H_4CH_3$
e, X = $OPOCl_2$
f, X = $OPO(OC_2H_5)_2$
g, X = Cl
h, X = Br
j, X = OCH_2CH_3
k, X = H

5a, X = $OCOCH_3$
b, X = OH
c, X = $OCOC_6H_5$
d, X = $OSO_2C_6H_4CH_3$
j, X = OCH_2CH_3

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