(23) J. A. Pople, D. L. Beveridge, and P. A. Dobosh, *J. Chem. Phys.*, 47, 2026 (1967).
(24) P. Claverie and R. Rein, *Int. J. Quantum Chem.*, 3, 535 (1969).
(25) R. Rein and M. Pollack, *J. Chem. Phys.*, 47, 2039 (1967).
(26) M. Pollack and R. Rein, *J. Chem. Phys.*, 47, 2045 (1967).
(27) M. Stamatiadon, T. Swissler, R. Rabinowitz, and R. Rein, *Biopolymers*, 11, 1217 (1967).
(28) J. R. Hoyland and L. B. Kier, *J. Med. Chem.*, 15, 84 (1972).
(29) L. B. Kier and H. S. Aldrich, *J. Theor. Biol.*, in press.
(30) H.-D. Höltje and L. B. Kier, *J. Pharm. Sci.*, in press.
(31) M. J. Huron and P. Claverie, *Chem. Phys. Lett.*, 4, 429 (1969).
(32) K. G. Denbigh, *Trans. Faraday Soc.*, 36, 936 (1940).
(33) R. J. W. Le Fevre, *Advan. Phys. Org. Chem.*, 3, 1 (1965).
(34) A. S. V. Burgen, *Brit. J. Pharmacol. Chemother.*, 25, 4 (1965).
(35) L. Villa and E. Grana, *Farmaco, Ed. Sci.*, 22, 502 (1967).

β-Amino Ketones. Synthesis and Some Biological Activities in Mice of 3,3-Dialkyl-1,2,3,4-tetrahydro-4-quinolinones and Related Mannich Bases†

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A series of Mannich bases, based on the α-alkyl-β-dimethylaminopropiophenone skeleton, and closely related cyclic analogs, *viz.* 3-alkyl-substituted 1-methyl-1,2,3,4-tetrahydro-4-quinolinones, was synthesized. They were screened in mice for analgetic and anticonvulsant activities. In addition, a number of these compounds were tested for sedative properties through the method involving sodium pentobarbital sleeping time potentiation.

A series of open-chain β-amino ketones and closely related 1,2,3,4-tetrahydro-4-quinolinones was previously reported to have analgetic properties[1] (Haffner tail-pinch method[2]). Sufficient biological activity was exhibited by several members in the series to warrant further investigation of a number of related compounds (Table I).

Mannich Bases. From prior studies which investigated β-dimethylaminopropiophenones, $ArCOCH_2CH_2NMe_2$, for analgetic activity, there emerged the lead compound **5** (Table I). In this particular structure, the active methylene protons were replaced by two methyl groups. Structural modification of this type of molecule was sought and a project initiated to synthesize a number of Mannich bases. The first phase of this study was to prepare compounds of type I (Table I). The aim was to detect changes in biological activity when only one alkyl group flanks the ketone in $C_6H_5COCHRCH_2NMe_2$ and assess the affect of lengthening the alkyl chain in R from CH_3 to n-C_3H_7.

These Mannich bases possess an enolizable system, -COCHR-. The possibility that the enol form may be the active species was tested by synthesizing type II Mannich bases in which enolization is impossible. These showed good analgetic activity and a series of para-substituted derivatives, type II in Table I, was planned. The para substituent in this series was designed to vary in lipophilic and electronic character (type II, Table I).

To ascertain if the ketone function was essential to these biological activities, several of these Mannich bases were reduced with $NaBH_4$ to the corresponding amino alcohol (type III, Table I). These alcohols were at least as effective as anticonvulsants, if not more so, than the corresponding ketones, type II.

Quinoline Derivatives. The analgetic effectiveness of $C_6H_5COC(CH_3)_2CH_2NMe_2$ (**5**) prompted us to synthesize several cyclic analogs, **30–32.** Rather than attempt to mono- and bisalkylate 1-methyl-1,2,3,4-tetrahydro-4-quinolinone at C-3, alternate routes to compounds of general type VI were sought.

1- and 3-substituted 4-hydroxycarbostyrils have been synthesized by reacting N-substituted anilines with alkyl- or arylmalonic esters.[3] For our needs, *N*-methylanilines were condensed with methylmalonic esters to produce **17–19.** Prior investigators had shown that 4-hydroxycarbostyrils were totally enolic, based on their uv and ir spectra, as well as chemical conversions.[3,4] We established that **17–19** existed in solution entirely as 4-hydroxycarbostyrils (instead of 4-keto lactams, type V, where R = H) since their proton magnetic resonance (pmr) spectra showed singlets between δ 2.05–2.15 and 10.15–10.30 (in DMSO-d_6) for the CH_3 and OH protons, respectively. Although meta-substituted anilines could have given mixtures of 5- and 7-substituted 4-hydroxycarbostyrils, our preparations afforded only the 7-chloro and methoxy analogs.‡

Alkylations of the potentially tautomeric compounds, 17–19, are expected to proceed *via* the corresponding ambident anions to *O*- and *C*-alkyl derivatives,[3,4,6] *viz.* **20–22** and **23–26,** respectively. Although there are claims in the literature that the ratio of isomers can be manipulated by the use of diverse solvent systems,[4,6] we found that the ratio varied little for reactions conducted in aqueous, alcoholic, or DMF media. C-Alkylation took place predominantly to furnish type V keto amides. Near the end of this investigation, we became aware of the relatively facile synthesis of dialkylmalonanilic acids, $ArNHCOCR_2CO_2H$, and their cyclization to keto amides of type V.[7] This route involved the condensation of the half acid chloride of a disubstituted malonic acid with an aniline and subsequent cyclization with polyphosphoric acid to produce V. We could not effect the direct synthesis of this quinoline system by heating a mixture of $C_6H_5NHCH_3$ with $(CH_3)_2C(CO_2CH_3)_2$.

To reach the target compounds, **30–32,** directly from

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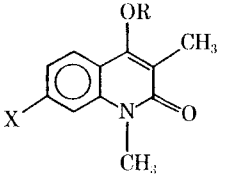
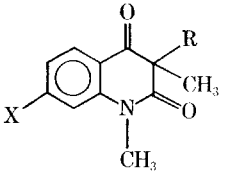
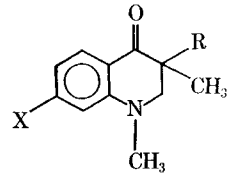
‡The structures of these 7 isomers were established by examining the pattern of the aromatic proton signals in their pmr spectra in solvents which separated the signals sufficiently to permit analysis and comparison of their chemical shifts and spin-spin coupling constants with data reported for similar 5- and 7-substituted quinoline derivatives (for noted examples, see ref 5). Attempts were made to isolate the 5 isomers of 18 and 19 by closely examining the mother liquors, but these could not even be detected (tlc, pmr spectra).

Table I

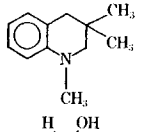
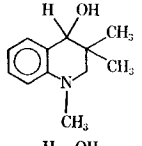
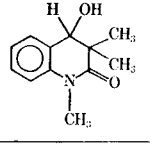
Compd no.	R	X	Bp (Torr) and/or mp, °C	Yield, %	Formula[a]	LD_{50},[b] mg/kg	Electroshock induced convulsions,[c] ED_{50}, mg/kg	Sleeping time potentiation,[d] ED_{50}, mg/kg	Anti-writhing analgetic act.,[e] ED_{50}, mg/kg
			Type I: $C_6H_5COCH(R)CH_2N(CH_3)_2$						
1	H (HCl)		146–148[f]	62		96	92		
2	CH_3 (maleate)		105–108	93	$C_{16}H_{21}NO_5$	133	63		
3	C_2H_5 (maleate)		112–115	64	$C_{17}H_{23}NO_5$	76	33		
4	n-C_3H_7 (maleate)		90–92	76	$C_{18}H_{25}NO_5$	60	31		
			Type II: p-X-$C_6H_4COC(CH_3)_2CH_2N(CH_3)_2$						
5		H	79–82 (0.4)[g]	55	$C_{13}H_{19}NO$	83[h]	43		137
6		H (maleate)	91–92		$C_{17}H_{23}NO_5$				
7		F	83–85 (0.04)	50	$C_{13}H_{18}FNO$	89	*i*		45
8		F (maleate)	116–117		$C_{17}H_{22}FNO_5$				
9		Cl	91–93 (0.1)	66	$C_{13}H_{18}ClNO$	116	65		115
10		SCH_3	212–215 (0.5)	80	$C_{14}H_{21}NOS$	145	*i*		137
11		SO_2CH_3 (HCl)	155–158	52	$C_{14}H_{22}ClNO_3S$	357	*i*		
12		t-C_4H_9	185–188 (5)	64	$C_{17}H_{27}NO$	119	68		
13		c-C_6H_{11}	140–142 (0.3)	72	$C_{19}H_{29}NO$	172	60		
			Type III: p-X-$C_6H_4CH(OH)C(CH_3)_2CH_2N(CH_3)_2$						
14		H	116–118 (0.8)	87	$C_{13}H_{21}NO$	71	34		88
15		Cl	128–132 (0.1), 37–39	86	$C_{13}H_{20}ClNO$	145	45		
16		c-C_6H_{11}	80–84	69	$C_{19}H_{32}NO$	151	34		
			Type IV: 						
17	H	H	220–222[j]	59	$C_{11}H_{11}NO_2$	464	324		
18	H	Cl	322–325	50	$C_{11}H_{10}ClNO_2$	324	*i*		
19	H	OCH_3	234–240	72	$C_{12}H_{13}NO_3$	350	*i*		
20	CH_3	H	65–67	19	$C_{12}H_{13}NO_2$	292	118	56	
21	CH_3	Cl	146–148	0.5[k]	$C_{12}H_{12}ClNO_2$				
22	C_2H_5	H	75–76	40	$C_{13}H_{15}NO_2$	293	100	56	
			Type V: 						
23	CH_3	H	58–61	52	$C_{12}H_{13}NO_2$	472	76	76	
24	CH_3	Cl	105–106	24	$C_{12}H_{12}ClNO_2$	~300	168	43	
25	CH_3	OCH_3	89–90	71	$C_{13}H_{15}NO_2$	~300	236	52	
26	C_2H_5	H	126 (0.1)	48	$C_{13}H_{15}NO_2$	~300	107		

Type VI:



27	H	H	59–61	60	$C_{11}H_{13}NO$	78	*i*	122
28	H	Cl	73–76	55	$C_{11}H_{12}ClNO$	250	134	
29	H	OCH_3	98–100	42	$C_{12}H_{15}NO_2$	300	*i*	
30	CH_3	H	123–126 (0.05), 60–62	39	$C_{12}H_{15}NO$	193	*i*	
31	CH_3	Cl	130 (0.01), 65–68	69	$C_{12}H_{14}ClNO$	350[l]	138 571[m]	
32	CH_3	OCH_3	80–82	64	$C_{13}H_{17}NO_2$	210	160	

Miscellaneous Types

33			78–83 (0.04)	46	$C_{12}H_{17}N$	400	*i*	
34			115–118 (0.05), 44–46	68	$C_{12}H_{17}NO$	192	199	
35			155–157 (0.03)	74	$C_{12}H_{15}NO_2$	152		85

[a]Analyses for N were within 0.4% of each theoretical value. The purity and structure proof of each compound were established rigorously by means of ir, pmr, and mass spectra. Most of the quinoline derivatives were purified by column chromatography and those fractions with one spot on the thin-layer chromatogram and satisfactory pmr and/or mass spectra were used for biological screening. Salts were crystallized from ethanol–ether. [b]Female Swiss mice, weighing 20–25 g, were obtained from Dolly Spring, Wis. LD_{50} and ED_{50} values were determined by intraperitoneal injections of the compound, using the method of J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96,** 99 (1949). For LD_{50}'s the mice were observed over a 24-hr period. At least five mice were used for the determination for each dose and each compound was tested at 5–7 dose levels. Whenever possible aqueous solutions were prepared. Series I, II, and III were tested as hydrochlorides or maleates in aqueous solutions. The values quoted are those based on the free base. When the free base was available (series II and III), solutions were prepared by dissolving the base in an aqueous solution containing a slight excess of HCl and adjusting the pH to 6–6.5 by the addition of $NaHCO_3$. The remainder of the compounds were tested in a suspension of 3–5% Tween 20. [c]The method utilizes the ability of the compounds (administered ip) to inhibit tonic convulsion induced by electroshock. Stimulation was applied to mice through corneal electrodes with repeated shocks of 1-msec duration at a frequency of 100 sec^{-1} and 50 mA for 0.2 sec. Untreated mice showed seizures of the tonic phase of limb flexion of roughly 10 sec and a few clonic jerks. ED_{50}'s were determined after 0.5 hr after injection. Dilantin was used as a standard and the reported ED_{50} is ~20 mg/kg, but we found the average to be 30 mg/kg. For closer description of the method, see E. S. Swinyard and J. Toman, *J. Neurophysiol.*, **9,** 231 (1946), and P. K. Kroefel and G. Lehmann, *J. Pharmacol. Exp. Ther.*, **76,** 194 (1942). [d]The method used was based on sleeping time potentiation induced by sodium pentobarbital, 60 mg/kg [W. L. Kuhl and E. F. van Maanen, *J. Pharmacol. Exp. Ther.*, **134,** 60 (1967)]. [e]The procedure is described in the Experimental Section and is based on the modification of the method of M. Anderson, G. J. de Beer, and R. Koster, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **18,** 412 (1959), with some of the modifications of D. D. Greenhouse, S. Irwin, J. K. Rendell, and R. I. Taber, *J. Pharmacol. Exp. Ther.*, **169,** 29 (1969); see also H. Ogura, *et al.*, *J. Med. Chem.*, **15,** 923 (1972). [f]Reported mp 156° [H. Heilner and C. Mannich, *Ber.*, **55,** 356 (1922)]. [g]J. Brewster and H. R. Snyder, *J. Amer. Chem. Soc.*, **71,** 1061 (1949), report bp 83–84° (1 Torr). [h]This value checks with the one reported in ref 1. [i]Inactive up to lethal dose. [j]Reference 3b reports mp 217–218°; ref 4d reports mp 221–222°. [k]Biological activities not determined due to poor yield. [l]LD_{50} determined after injecting the compound in sesame oil solution. [m]ED_{50} after 0.5 hr from a sesame oil solution of this compound.

23–25 would involve preferential reduction of the amide to the ketone group in type V compounds. Attempted reduction of **23** with $LiAlH_4$ in refluxing THF (24 hr) led to its recovery in 70% yield. A similar reaction mixture containing $AlCl_3$ (18 hr, boiling ether) effected complete reduction of **23** to **33** (15%) with 60% of **23** being recovered. Attempts to reduce the ethylene glycol ketal of **23** with $LiAlH_4$ in ether (18 hr) produced 90% of starting ketal. Again $LiAlH_4$–$AlCl_3$ reduced the ketal to **33** (30–40%). The reduction of the benzylic oxygen function to a hydrocarbon, particularly by $LiAlH_4$–$AlCl_3$, is well established.[8] As expected, **23** was reduced by $NaBH_4$ to the amide alcohol **35.**

A new strategy was explored for the conversion of **17–19** to **27–29,** and ultimately to **30–32,** respectively. Attempted $LiAlH_4$ reduction of **17,** or the *O*-methyl ether **20,** in boiling THF for 3 hr led to the recovery of starting materials in 80% yield or better. Reports of the facile reduction of disubstituted amides to tertiary amines by sodium bis(2-methoxyethoxy)dihydroaluminate, $Na[AlH_2(OCH_2CH_2OCH_3)_2]$, came to our attention.[9] The solubility of this reducing agent in benzene (sold commercially as a 70% solution in benzene,§ as Red-al) or other higher boiling solvents ensured a more homogeneous reaction mixture than was achieved with $LiAlH_4$ in ether or THF. Thus, **17–19** were reduced readily with Red-al in boiling benzene or toluene to afford 1,3-dimethyl-1,2,3,4-tetrahydro-4-quinolinones, **27–29,** in reasonable yields. Furthermore, the alkali solubility of **17–19** enabled us to recover starting 4-hydroxycarbostyrils. It would appear that Red-al forms a benzene-soluble enolate complex of these 4-hydroxycarbostyrils in which the amide function is reduced and the enolate portion remained intact. An aqueous acidic work-up hydrolyzed this enolate complex and in effect regenerated the ketone function at C-4 to give **27–29.** The nonenolic 3,3-dimethyl derivative **23** was reduced by Red-al to the expected alcohol **34.**

Methylation[10] of **27–29** in DMF with NaH and CH_3I introduced the additional alkyl group at C-3 to furnish the required cyclic amino ketones, **30–32.**

Structure–Activity Relationship. The pharmacological results for the series are recorded in Table I. The biological activities reported are toxicity, anticonvulsant activity, sleeping time potentiation, and mild (aspirin-like) analgetic activity. Generally, the open-chain Mannich bases were more toxic than the cyclic structures, as can be seen by comparing LD_{50}'s of types I and II with those of IV and V. Within the series I Mannich bases, there is a general increase in anticonvulsant activity with increased chain length. The structures of type II had similar activity to those of I. It would appear that the enol structure is not important in anticonvulsant activity. Reduction of the ketocarbonyl in type II to the secondary alcohol did not greatly improve anticonvulsant activity as can be seen with compounds **17, 20,** and **22.** Structures of type V for which sedative properties were assessed were approximately as active as sodium pentobarbital (ED_{50} = 60 mg/kg). However, these agents are effective at *ca.* one-sixth their toxic dose while the standard is effective at one-half its toxic dose.‡

Using the tail-pinch test, the mice lost muscle coordination and appeared sedated, making results from this test inconclusive. Therefore, several of the Mannich bases were examined (po) for mild analgesic activity by the writhing method. On a molar basis several of these proved to be more effective than the standard, aspirin (ED_{50} = 112 mg/kg).

Experimental Section

Melting points (capillary) and boiling points are uncorrected. Ir spectra were obtained in Nujol mulls on a Perkin-Elmer Infrared Model 700 spectrophotometer. Pmr spectra were recorded on a Varian A-60 spectrometer, using $(Me)_4Si$ as internal standard. Chemical shifts are reported only when pertinent for structure determinations.

Alumina used for chromatography was purchased from Alcoa (F-20). Petroleum ether used was the fraction, bp 30–60°.

Starting Ketones. Known ketones were either bought or prepared by literature methods.

***p*-Methylthioisobutyrophenone.** To a stirred solution (5–8°) of thioanisole (37.2 g, 0.3 mol) in CS_2 (100 ml) were added, first $AlCl_3$ (90 g, 0.675 mol) and then isobutyryl chloride (40.2 g, 0.3 mol) dropwise over 1 hr. The temperature was then permitted to rise to 25°, and the mixture was stirred 2 hr at 25° and finally refluxed for 1.5 hr. Solvents were removed *in vacuo* and the residue was poured into a mixture of crushed ice (200 g) and concentrated HCl (15 ml). The product was extracted by Et_2O; the extract was washed with 10% NaOH and then with water and dried. Distillation provided the ketone (29.0 g, 50%): bp 180–185° (2–5 Torr); mp 40–41°; pmr ($CDCl_3$) besides the AA'XX' pattern centered at δ 7.84 and 7.25, 2.84 (SCH_3) 3.47 (CH), and 1.18 (CH_3's). *Anal.* ($C_{11}H_{14}SO$) C, H.

***p*-Methylsulfonylisobutyrophenone.** To an ice-cold stirred mixture of p-$CH_3SC_6H_4COCH(CH_3)_2$ (3.88 g, 0.02 mol) in $CHCl_3$ (40 ml) and 3 *N* H_2SO_4 (100 ml) was added powdered $KMnO_4$ (4.16 g, 0.027 mol) over 0.75 hr. The mixture was decolorized with Na_2SO_3 and made basic with 10% NaOH solution. The $CHCl_3$ layer was separated, washed with H_2O, and evaporated to produce the sulfone (2.5 g, 55%): mp 73–74°; pmr ($CDCl_3$) δ 3.16 (CH_3SO_2). *Anal.* ($C_{11}H_{14}SO$) C, H.

***p*-Cyclohexylisobutyrophenone.** This ketone was prepared from pure cyclohexylbenzene (32.0 g, 0.02 mol), isobutyryl chloride (22.0 g, 0.207 mol), and $AlCl_3$ (60.0 g, 0.45 mol) in CS_2 (70 ml). Distillation provided isobutyrophenone** (4.0 g, 13%), bp 123–127° (5–10 Torr), identical commercial sample, followed by the required ketone, 20.0 g (44%), bp 124–130° (0.06 Torr). *Anal.* ($C_{16}H_{22}O$) C, H.

Synthesis of Mannich Bases.[12] The ketone (0.1 mol), dimethylamine hydrochloride (0.32 mol), and paraformaldehyde (0.28 mol) in 2-propanol (60 ml) were refluxed for 24 hr.†† Solvents were removed in a rotating flash evaporator at 70–90° (20–30 Torr) and the residue was partitioned between water and ether. Work-up of the ether extract led to the recovery of the starting ketone.

The aqueous phase was cooled below 10° and made alkaline by the addition of ice-cold 50% aqueous NaOH solution. The base was extracted into ether (3 × 50 ml), and when stability permitted, the base was distilled *in vacuo*. It was converted to a maleate by adding an ether solution of maleic acid to the base in ether. Pmr and mass spectra were used to determine the purity of these compounds. Their physical properties are listed in Table I.

1-(*p*-Methylsulfonylphenyl)-2,2-dimethyl-3-dimethylamino-1-propanone Hydrochloride (11). A solution of **10** (5.0 g, 0.024 mol) in $CHCl_3$ (50 ml) and 3 *N* H_2SO_4 (100 ml) was stirred at 5° while $KMnO_4$ (6.0 g, 0.038 mol) was added slowly over 0.5 hr. The mixture was decolorized by Na_2SO_3, made alkaline with 10% NaOH, and filtered. The inorganic precipitates were washed twice with $CHCl_3$ and the combined $CHCl_3$ extracts were washed with water. After removal of solvents, the sulfone remained as a yellow oil which was converted in ethanol–ether to the hydrochloride (1.2 g, see Table I).

1-Aryl-2,2-dimethyl-3-dimethylamino-1-propanols, Type III. The reduction of the corresponding ketone (0.01 mol) was accomplished by stirring with $NaBH_4$ (0.02 mol) in methanol (25 ml) at 25° (4 hr). The amino alcohols were isolated by diluting the reaction mixture with water, ether extraction, and subsequent distillation (Table I).

§Aldrich Chemical Co., Milwaukee, Wis. The solution was stored in a refrigerator.

‡Quoted from Merck Index.

**Gc analysis (enrichment method) of freshly distilled cyclohexylbenzene clearly indicated the absence of benzene in the starting arene. Isobutyrophenone can be created in this reaction if cyclohexylbenzene undergoes a retro-Friedel–Crafts reaction to create benzene and cyclohexyl products *or* from dealkylation of any one of the isomeric cyclohexylisobutyrophenones possibly formed during the reaction. This type of reaction is discussed by March[11a] and Dlamini, *et al.*[11b]

††We found 2-propanol a most useful solvent for our reactions.

Synthesis of 4-Hydroxycarbostyrils. One typical experiment is described. *m*-Chloroaniline was converted by means of formic acid to *m*-chloroformanilide.‡‡ Best results for the $LiAlH_4$ (2 mol equiv) reduction were attained at room temperature for 24 hr to furnish *N*-methyl-*m*-chloroaniline (73%). The amine (14.1 g, 0.1 mol) and ethyl methylmalonate (22.7 g, 0.13 mol) were heated until the slow distillation of EtOH (through a Vigreux column) ceased (2–3 hr). The residue was cooled and the product recrystallized from EtOH (Table I): pmr (DMSO-d_6) δ 2.05 (CCH_3), 3.55 (NCH_3), 7.21–7.46 (m, H-6, H-8), 7.91 (d, H-5), 10.20 (s, OH).

Alkylation of 1,3-Dimethyl-4-hydroxycarbostyrils. The most pertinent details are provided. A solution of **17** (18.9 g, 0.1 mol) in NaOH solution (5.0 g, 0.125 mol, in 250 ml of water) was stirred with MeI (14.2 g, 0.1 mol) at 35–37° for 12 hr. More MeI (14.2 g) and NaOH (5.0 g, in 50 ml of water) were added, and the mixture was stirred 2 days longer. Extraction with $CHCl_3$ provided a yellow oil (9.2 g, 70%). The aqueous layer was acidified to provide 34% starting material. The contents of the $CHCl_3$ extract were shown by pmr to consist of a mixture of *O*- and *C*-methyl derivatives and the ratio was obtained by integration of the methyl singlets. The isomers could not be separated by distillation.[4d] They were separated by chromatography on a column of Al_2O_3 (20 times their crude weight) prepared in benzene. The *C*-methyl ketone was obtained pure in a fraction eluted by benzene–acetone (5:2). The yields and other data are given in Table I.

Using this procedure, ethylation of **17** with ethyl iodide at 60° produced the isomers *O*- and *C*-ethyl derivatives.

A change in the alkylation procedure in DMF is indicated by the following method. A stirred solution of **17** in DMF (0.05 mol in 250 ml) was treated with K_2CO_3 (0.05 mol) and alkyl iodide (0.1 mol) at 60° for 24 hr. The solution was cooled and filtered, and solvents were removed *in vacuo*. The residue was dissolved in 200 ml of $CHCl_3$ and washed with 0.5 *N* NaOH solution (2 × 25 ml) and then water (50 ml); $CHCl_3$ was distilled off and the residue chromatographed.

Neither method was productive in obtaining more than trace amounts of the *O*-methyl ether of the 7-methoxy-4-hydroxycarbostyril.

Reduction of 4-Hydroxycarbostyrils with Red-Al. A typical experiment is described. To a stirred suspension of 1,3-dimethyl-4-hydroxy-7-chlorocarbostyril (**18**, 6.7 g, 0.03 mol) in toluene (100 ml) was added Red-al (18.2 g, 0.06 mol, in 18 ml of benzene) and the mixture boiled for 1.5 hr. After cooling, water (21 ml) was added; the hydrocarbon layer was separated and washed with water (2 × 30 ml). Solvents were removed *in vacuo* and the residue was characterized (Table I): ir (Nujol) 1680 (γ C=O); pmr ($CDCl_3$) δ 1.22 (d, $CHCH_3$), 3.22 (s, NCH_3), 2.84–3.74 (m, NCH_2CH), and signals due to the aromatic protons.

1,3,3-Trimethyl-1,2,3,4-tetrahydroquinoline (33). A stirred mixture of 1,3,3-trimethyl-1,2,3,4-tetrahydro-2,4-quinolinedione (6.0 g, 0.03 mol), ethylene glycol (3.70 g, 0.06 mol), 50 ml of benzene, and 0.2 ml of methanesulfonic acid (70%) was refluxed, using a Dean-Stark apparatus to remove water as it was formed during the course of reaction (24 hr). The mixture was cooled to 25° and was neutralized with K_2CO_3. Inorganic materials were filtered off. Benzene was removed *in vacuo* to give 5.8 g of a viscous yellow oil (5.8 g), which was distilled to produce the ketal (3.2 g, 43%), bp 138–145° (0.05 Torr). The distillate was dissolved in boiling petroleum ether and gave on cooling 3.1 g (42%) of white crystals: mp 65–68°; ir (film) 1675 cm^{-1} (amide, C=O); pmr ($CDCl_3$) δ 1.15 (s, 6, *gem*-dimethyl), 3.37 (s, 3, NCH_3), 4.05 [s, 4, $(OCH_2)_2$], 6.83–7.50 (m, 4, aromatic H's). *Anal.* ($C_{14}H_{17}NO_3$) N.

The reducing solution was prepared by adding granular anhydrous $AlCl_3$ (3.39 g, 0.03 mol) to a stirred suspension of $LiAlH_4$ (1.14 g, 0.03 mol) in ether (75 ml) within 15 min at 0–5°. The mixture was stirred for 30 min at 25°. To this suspension was added a solution of the ketal (3.0 g, 0.012 mol) in 15 ml of ether at such a rate to cause gentle reflux (30 min). The mixture was stirred for 18 hr at 25°. The unreacted hydride was decomposed at 5° by the careful addition of water (30 ml). The mixture was filtered and the precipitate was washed well with ether (2 × 25 ml). Distillation of the ether extracts yielded the product (0.75 g, 46%): bp 78–83° (0.04 Torr); pmr ($CDCl_3$) δ 0.93 (s, 6, *gem*-dimethyl), 2.53 (s, 2, benzylic H's), 2.90 (s, 2, NCH_2), 2.96 (s, 3, NCH_3), 6.40–7.25 (m, 4, aromatic H's). The second fraction consisted of 0.7 g (23%) of recovered ketal, bp 135–138° (0.04 Torr).

‡‡ The formanilides were prepared by literature methods; see ref 13.

1,3,3-Trimethyl-1,2,3,4-tetrahydro-4-quinolinol (34). A stirred solution of **23** (3.78 b, 0.02 mol) in benzene (50 ml) was treated dropwise with Red-al (12 ml) over 0.5 hr. The mixture was then heated under reflux for 1.5 hr and water (21 ml) was added. The benzene layer was separated and the inorganic precipitate washed with warm benzene (2 × 40 ml). The combined benzene extracts were washed with water (2 × 30 ml) and the product was purified by chromatography on Al_2O_3. It was eluted first by C_6H_6 and then by CH_2Cl_2: pmr ($CDCl_3$) δ 0.80 (s, CH_3), 1.00 (s, CH_3), 1.73 (s, OH), 2.88 (s, NCH_3), 2.55–3.26 (m, NCH_2), 4.07 (s, benzylic H), 6.50–7.18 (m, arene H's) (Table I).

1,3,3-Trimethyl-1,2,3,4-tetrahydro-4-quinolinol-2-one (35). To a stirred solution of **23** (2.04 g, 0.01 mol) in CH_3OH (50 ml) was gradually added $NaBH_4$ (0.76 g, 0.02 mol). After heating 18 hr under reflux, the mixture was diluted by water (12 ml) and the product extracted into ether. The product was distilled *in vacuo* (Table I).

1,3,3-Trimethyl-1,2,3,4-tetrahydro-4-quinolinones (30–32). Sodium hydride (1.0 g, 50% in oil, 0.02 mol) was washed with dry petroleum ether (3 × 25 ml), and the upper layer was decanted. Freshly distilled DMF (40 ml) was added and the suspension was stirred vigorously for 0.5 hr at 25° to obtain a fine suspension of NaH (appearance, light gray). The mixture was cooled to 10°, a solution of the appropriate 1,3-dimethyl-1,2,3,4-tetrahydro-4-quinolinone, **27** and **28** (0.01 mol), in distilled DMF (15 ml) was added dropwise within 15 min, and the mixture was stirred at 25° for 3 hr. Then, MeI (3.0 g, 0.021 mol) was added in 3–5 min. The reaction mixture was stirred for 18 hr at 25°. Unreacted NaH was decomposed first by the careful addition of water (2 ml), followed by more water (300 ml). The product was extracted into ether (3 × 25 ml). The ether extracts were washed with water (5 × 75 ml) to remove DMF and dried. Evaporation of ether gave the product, which was purified by column chromatography on Al_2O_2. The product was eluted usually either with hexane, a mixture of benzene–hexane (1:1), and benzene. Final purification was effected by distillation (Table I).

Evaluation of Mild Analgetic Activity by the Writhing Method. The procedure utilized was essentially that described by Koster, *et al.*, as modified by modifications of Taber, *et al.* In the screening procedure, groups of five fasting (18–24 hr) male CD-1 mice, weighing 20–25 g (from the Charles River Farms, Willimantic, Mass., were injected intraperitoneally with 10 mg/kg of 0.6% aqueous acetic acid solution and then placed into observation jars. The compound or vehicle was administered by gavage 30 min prior to the administration of the acetic acid solution.

Five minutes following the acetic acid injection, the total number of writhes exhibited by the given mice was counted during a 10-min period. Each day one control (vehicle-treated) and several test groups were studied. The compounds were dissolved in water or suspended in 5% Acacia in water depending upon their solubility characteristics. The number of writhes exhibited by the test group was compared to that of the control group to determine per cent reduction.

Initially, all compounds were administered at a dose of 800 mg/kg. If any animal died, the dose was halved and the test repeated. When it had been determined by preliminary experimentation that a compound inhibited writhing to the extent of 50% or more, at the 800 mg/kg level or less, ED_{50} values were determined. In this instance, five groups of five mice each were studied. One group was treated with vehicle, and the other four groups received graded doses of the compound. The number of writhes exhibited in the 10-min periods by the drug-treated group was calculated as a per cent of the number of writhes exhibited by the control group. From these data a dose–response curve was plotted on double-cycle, semilog paper with per cent response as the ordinate and log dose as the abscissa. The ED_{50} value was then determined by the least-squares method and these are in Table I. The mean ED_{50} value is also reported for aspirin for purposes of comparison (ED_{50}, 112 mg/kg).

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References

(1) M. S. Atwal, L. Bauer, S. N. Dixit, J. E. Gearien, M. Meg-

ahy, R. Morris, and C. Pokorny, *J. Med. Chem.*, **12**, 994 (1969).
(2) C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954).
(3) (a) R. E. Bowman, A. Campbell, and E. Tanner, *J. Chem. Soc.*, 444 (1959); (b) R. E. Bowman, T. F. Grey, D. Huckle, I. M. Lockhart, and M. Wright, *ibid.*, 3350 (1964); (c) L. F. Wiggins, J. W. James, and R. W. Temple, U. S. Patent 3,133,928 (May 19, 1864); (d) R. S. Sagitullin, A. N. Kost, and N. N. Borisov, *Chem. Heterocycl. Compounds (USSR)*, **9**, 1207 (1970); (e) R. H. Prager and K. Y. Ting, *Aust. J. Chem.*, **25**, 1229 (1972); (f) R. Storer and D. W. Young, *Tetrahedron Lett.*, 1555 (1972); (g) R. A. Corral, O. O. Orazi, and I. A. Benages, *Tetrahedron*, **29**, 205 (1973); (h) J. F. Collins, G. A. Gray, M. F. Grundon, D. M. Harrison, and C. G. Spyropoulos, *J. Chem. Soc., Perkins Trans. 1*, 94 (1973); (i) T. Sekiba, *Bull. Chem. Soc. Jap.*, **46**, 577 (1973); (j) R. Storer, D. W. Young, D. R. Taylor, and J. M. Wagner, *Tetrahedron*, **29**, 1721 (1973).
(4) (a) F. Arndt, L. Ergener, and O. Kutlu, *Chem. Ber.*, **86**, 951 (1953); (b) T. Kappe, P. F. Fritz, and E. Zeigler, *ibid.*, **106**, 1927 (1973); (c) T. Kappe and E. Ziegler, *Monatsh. Chem.*, **99**, 1943, 1950 (1968); (d) U. Hoerlein and W. Geiger, *Arch. Pharm. (Weinheim)*, **304**, 131 (1971); (e) R. Storer and D. W. Young, *Tetrahedron*, **29**, 1215 (1973).
(5) G. S. Bajwa and M. M. Jouillie, *J. Heterocycl. Chem.*, **10**, 1403 (1972); A. Rosowsky and E. J. Modest, *J. Org. Chem.*, **30**, 1832 (1965); G. H. Douglas, H. Smith, and C. R. Walk, *Experientia*, **20**, 418 (1964).
(6) W. J. Le Noble and H. F. Morris, *J. Org. Chem.*, **34**, 1969 (1969); W. J. Le Noble, *Synthesis*, 1 (1970).
(7) H. Nishimura, Y. Nagai, T. Suzuki, and T. Sawayama, *Yakugaku Zasshi*, **90**, 818 (1970).
(8) H. A. Davis and R. K. Brown, *Can. J. Chem.*, **51**, 361, 2563 (1973); E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Amer. Chem. Soc.*, **84**, 2371 (1962).
(9) J. Malek and M. Cerny, *Synthesis*, 217 (1972); *Collect. Czech. Chem. Commun.*, **35**, 2030, 3079 (1970); M. Cerny, J. Malek, M. Capka, and V. Chvalovsky, *ibid.*, **34**, 1033 (1969).
(10) K. Pfister and M. Sletzinger, U. S. Patent 3,169,971 (1965); *Chem. Abstr.*, **62**, 9234g (1965).
(11) (a) J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N. Y.,1968, p 433; (b) A. T. Dlamini, H. J. Williams, and R. G. Shotter, *Tetrahedron*, **29**, 1327 (1973).
(12) J. V. Greenhill and M. D. Mehta, *J. Chem. Soc. C*, 1549 (1970); A. M. Kulier, M. S. Guseinov, S. A. Sardarova, and T. Yu Iskenderova, *J. Org. Chem. USSR*, **8**, 1301 (1972).
(13) E. Froehlich and E. Wedekind, *Ber.*, **40**, 1009 (1907); F. Reverdin and A. de Luc, *ibid.*, **47**, 1537 (1914).

Antifungal Activity of Bischelates of 5-, 7-, and 5,7-Halogenated 8-Quinolinols with Copper(II). Determination of Approximate Dimensions of the Long and Short Axes of the Pores in the Fungal Spore Wall

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The effect on antifungal activity of simultaneously varying the substituents on the 5,5′ and 7,7′ axes of the Cu(II) bischelate of 8-quinolinol was studied. Calculations of approximate long and short dimensions of the pores of the spore walls of four fungi were made based on the geometry of the molecules in conjunction with their fungitoxicities. They were found to be: *A. niger*, 15.0, 10.8 Å; *T. viride*, 16.6, 10.7 Å; *A. oryzae*, 15.0, 10.8 Å; *T. mentagrophytes*, 16.6, 10.7 Å.

In a hypothesis proposed by Gershon, *et al.*,[1] it was suggested that the fungal spore wall behaved as a barrier with respect to certain potential antifungal agents. If the geometry and distribution of charge around a molecule are incompatible with the geometry and charge distribution around the peripheries of the pores in the fungal spore wall, penetration of the wall by the agent cannot take place, and toxic reactions within the spore do not occur. A further consequence of this hypothesis is that by altering the sizes and shapes of the toxicant molecules, and relating these geometrical forms with antifungal activity, it should be possible to arrive at an approximation in two dimensions of the appearance of the pores in the fungal spore wall.

In these studies[1,2] which are concerned with five fungi it was shown by fungitoxicity studies with Cu(II) bischelates of 5-substituted 8-quinolinols that the minimal long dimensions of the pores of the spore wall in each species are as follows: *Aspergillus niger*, 15.0 Å; *Trichoderma viride*, 16.6 Å; *Aspergillus oryzae*, 15.0 Å; *Myrothecium verrucaria*, 16.6 Å; and *Trichophyton mentagrophytes*, 16.6 Å. If the hypothesis is sound, and the explanation of the nontoxicity of certain compounds is due to the long axes being greater than the major axes of the pores, alteration of a secondary axis of the compound should not cause the derivative to become toxic. This was found to be true by means of studies with the Cu(II) bischelates of 5-nitro-7-substituted 8-quinolinols.[3] It was further deduced from the dimensions and angles between the 5,5′ and 7,7′ axes of Cu(II) bischelates of 5-substituted 8-quinolinols and 5-substituted 7-nitro-8-quinolinols that the pores in the spore walls are not circular but may be elliptical or hexagonal.[2,4,†]

The present work is concerned with the effect on antifungal activity of simultaneously varying the substituents on the 5,5′ and 7,7′ axes of the Cu(II) bischelate of 8-quinolinol from H to F to Cl to Br to I. Based on these data, calculations can be made of approximate lengths of axes at the midpoint and perpendicular to the major axes of the pores in the fungal spore walls.

Of the ligands employed for preparing the chelates listed in Table II, compounds Ia, IIIa,c, IVa,d, and Va,e were commercially available. The remaining compounds were synthesized according to published methods as follows: Ib,[5] Ic,d,[6] Ie,[7] IIa,[8] IIb–d,[9] IIe,[8] IIIb,[9] IIId,[10] IIIe,[11] IVb,[9] IVc,[12] IVe,[9] Vb,[9] Vc,[11] and Vd.[9] The bischelates with Cu(II) were prepared by the methods described by Hollingshead.[13] The Cu(II) bischelates of the commercially available 8-quinolinols have been adequately reported in

†It was found that what was believed to be 5-bromo-7-nitro- and 5-iodo-7-nitro-8-quinolinols in ref 2 was incorrect. The corresponding compounds with correct structures were reported in ref 5 and 6. The data in ref 4 on the bis(5-halo-7-nitro-8-quinolinolato)copper(II) complexes were obtained with the new compounds, and it should be mentioned that bis(7-nitro-8-quinolinolato)copper(II) does not inhibit *T. mentagrophytes* below 1000 ppm as reported in ref 4 where inhibition was obtained with a decrepitated culture of the organism.