The *ortho* substituents could also exert a steric effect, the evaluation of which is very difficult at the present time. Finally both electronic and steric effects may play a role. It is well known that methicillin, although not susceptible to penicillinase, is much less active than benzylpenicillin and ampicillin against Gram-positive and Gram-negative microorganisms.[20] In particular, a comparative study of Barber and Waterworth[21] on the activity of 8 penicillins against 5 Gram-positive microorganisms and 15 Gram-negative ones clearly showed, as reported by Garrod,[22] that methicillin is by far the least active compound. The deviations of methicillin, cloxacillin, and dicloxacillin from the parabolic curve could mean that the enzymic system or membrane system with which the penicillins interact in the *S. aureus* and *T. pallidum* are different or that metabolism is involved in some way which causes the difference. The calculated log $1/c$ values for *S. aureus* and *T. pallidum* show that also in the case of penicillins the R_m values of the active compounds on these organisms are fairly overlapping and indicate compounds more lipophilic than those active against *E. coli*. The most active compounds against *S. aureus* and *E. coli* are benzylpenicillin ($R_m = 0.55$) and carbenecillin ($R_m = -0.46$), respectively. The products of the calculated log $1/c$ values for *S. aureus* and *E. coli* indicate that methylenampicillin and ampicillin with R_m values between the above limits are the most active against both microorganisms. This is in agreement with the literature attributing such a characteristic to ampicillin.[20]

In conclusion, both in the case of cephalosporins and penicillins there is a relationship between lipophilic character and spectrum of antibacterial activity. This could suggest that differences in the activity of a given antibiotic on different species of microorganisms may depend on its chance to cross their cell wall rather than on metabolic features of the bacterial cells. To this purpose, it was found that Gram-positive microorganisms grown under conditions of increased cellular lipid content showed also an increase in their resistance to penicillins.[23]

Acknowledgment.—We are grateful to Professor C. Hansch for his helpful suggestions.

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(21) M. Barber and P. M. Waterworth, *Brit. Med. J.*, **1**, 1159 (1962).

(22) L. P. Garrod in "Experimental Chemotherapy," R. J. Schnitzer and F. Hawking, Ed., Vol. III, Academic Press, New York and London, 1964, pp 28, 29.

(23) W. B. Hugo and J. R. Stretton, *J. Gen. Microbiol.*, **42**, 133 (1966).

Agents Acting on the Central Nervous System. XIII. 2,3,4,4a,5,6-Hexahydro-1(*H*)-pyrazino[1,2-*a*]quinolines. A New Class of Hypotensive Agents[1]

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Received October 13, 1969

The synthesis and pharmacological evaluation of a number of 3-substituted 2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino [1,2-*a*]quinolines are reported. These compounds in general show hypotensive and adrenergic-receptor blocking activity. The hypotensive activity is particularly marked in 3-β-phenethyl- and 3-γ-(*p*-fluorobenzoyl)-propyl-2,3,4,4a,5,6-hexahydro-1(*H*)pyrazino[1,2-*a*]quinolines.

N-Phenylpiperazines possess CNS and cardiovascular activities, and substitution of the second imino group greatly modulates and modifies these activities.[2] *N*-Phenylpiperazines have also served as a side chain in a number of pharmacologically important molecules.[3] In general *O*-alkyl substitution in the phenyl residue of these *N*-phenylpiperazines greatly enhances the effect on the cardiovascular activities,[4] and, in fact, a number of 1-substituted 4-*o*-tolylpiperazines are known to be strong adrenolytics.[5] It therefore seemed of interest to incorporate this molecular framework into a rigid structure such as is present in 3-substituted 2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino[1,2-*a*]quinolines (I, R = H). In this paper we report the synthesis and pharmacological activities of a number of 3-substituted derivatives of I, substituted 2-aminomethylquinolines (II), and the corresponding 1,2,3,4-tetrahydro compounds (III).[6]

(1) Communication No. 1439 from the Central Drug Research Institute, Lucknow, India.

(2) H. G. Morren, V. Bieneft, and A. M. Reyntjens, "Psycho Pharmacological Agents," Vol. I, M. Gordon, Ed., Academic Press, Inc., New York and London, 1964, p 251.

(3) (a) R. P. Muli, C. Tannenbaum, M. R. Dapero, M. Bernier, W. Yost, and G. de Stevens, *J. Med. Chem.*, **8**, 332 (1965); (b) P. C. Jain, V. Kapoor, N. Anand, A. Ahmad, and G. K. Patnaik, *ibid.*, **10**, 812 (1967).

(4) (a) V. P. Arya, G. S. Grewal, J. David, and C. L. Kaul, *Experientia*, **23**, 514 (1967); (b) G. de Stevens and R. P. Mull, French Patent, M3596 (Nov. 15, 1965); *Chem. Abstr.*, **64**, 9746 (1966).

(5) R. C. Srimal, S. Mukerjee, S. K. Chatterjee, and N. Anand, 1965, unpublished work.

(6) During the preparation of this manuscript we came across a set of patents[7] by the Ciba group describing I (R = H) and its 3-substituted derivatives.

(7) (a) A. Rossi, E. Sury (Ciba Ltd.), South African Patent, 67,05,765 (Feb. 8, 1968); *Chem. Abstr.*, **70**, 47500y (1969); (b) South African Patent 67,05,768 (Feb. 7, 1968); *Chem. Abstr.*, **70**, 47501z (1969); (c) South African Patent 67,05,766 (Feb. 7, 1968). *Chem. Abstr.*, **70**, 47502a (1969); (d) South African Patent 67,05,764 (Feb. 8, 1968); *Chem. Abstr.*, **70**, 47503b (1969); (e) South African Patent, 67,05,767 (Feb. 7, 1968); *Chem. Abstr.*, **70**, 57896w (1969).

TABLE I: PHARMACOLOGICAL ACTIVITY OF QUINOLINE DERIVATIVES

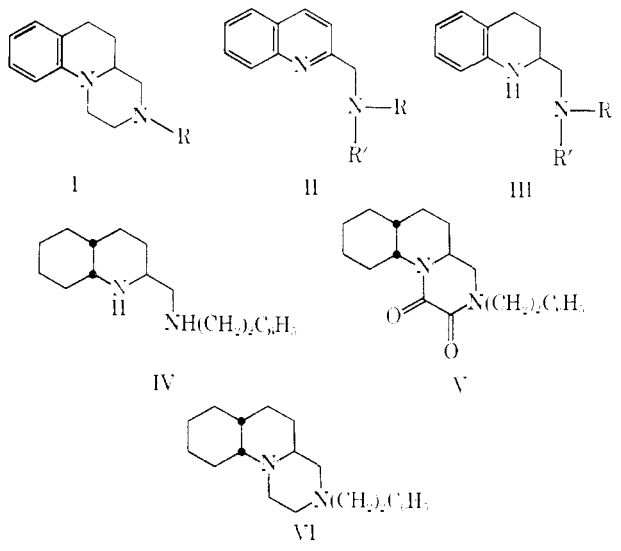
Compd[a]	LD_{50} (mice), mg/kg ip	Gross effects[b]	% reduction of amphetamine-hyperactivity at 1/5 LD_{50}	Cardiovascular activity (cat) (2.5 mg/kg iv) Effect on bp[c]	Effect on pressor response of epinephrine[d]	Remarks[e]
1	100	Stimulant	0	−12 (4)	−20	Antihistaminic (20%), anti-reserpine (antiptosis, antisedation 50% each at 1 mg/kg).
2	400	Depressant	36	0	−40	
3	200	Stimulant	0	−108 (75)	0	Potentiation of barbiturate hypnosis (56%), respiratory failure.
28	300	Depressant	25	−30 (20)	0	
29	200	Depressant	28	−50 (45)	−70	Adrenaline reversal at 5 mg/kg.
30	200	Depressant	0	−25 (35) (Tachyphylaxis)	Reversal	
4	600	Depressant	0	−64 (40)	+13	Antiacetylcholine 47%
6	100	Depressant	0	−28 (4) +20 (20)	−44	Potentiation of acetylcholine (27%) and histamine (22%).
5	100	Depressant		−20 (40)	0	
7	>800	0	0	−60 (15)	0	Histamine potentiation (10%)
11	200	Depressant	31	−46 (40) (Tachyphylaxis)	+42	
12	200	Depressant	75 20 (20 mg/kg)	−16 (10)	0	
13	300	Depressant	26	−14 (1)	0	
8	400	Stimulant	0	−30 (20)	+66	
66[f]	>800 (po)	Stimulant	0	0	0	
65	150	Depressant	0	0	0	
10	300	0	0	−30 (3)	0	Antihistaminic (33%)
23	>800	Depressant	33	−22 (1)	−40	Antihistaminic (33%)
9	600	Depressant	70	−12 (10)	−22	
17	300	Depressant	70	−90 (120)	+20	Nictitating membrane block 65%; lowering of blood pressure was observed in spinal cats also, suggesting a peripheral site of action.
18	200	Depressant	0	−36 (40)	+33	Acetylcholine potentiation 35%
19	>400	0	0	−36 (5)	−37	
16	150	Stimulant	0	−6 (5)	0	Anti-MES[g] (20%), potentiation barbiturate hypnosis (75%).
21	>800	0	64	0	0	
31	200	Stimulant	0	−18 (2)	−54	
40	165	Depressant	3	0	0	Antireserpine (antisedation 20%)
42	600	Depressant	0	0	−53	
41	200	Stimulant	0	0	0	Antireserpine (antiptotic, 25%; antisedation 25%)
59	300	Stimulant	0	+20 (3)	−15	Potentiation of acetylcholine (14%)
57	150	Depressant	18.7	0	+40	Antireserpine (antihypothermia and antisedation 25% each), antihistaminic (50%)
58	200	Depressant	27	−24 (40)	−41	Antiacetylcholine (29%), antihistamine (10%), and antireserpine (antihypothermia antiptotic and antisedation 25% each)
39	400	Depressant	0	−30 (3)	−28	Antihistamine (35%)
61	100	Depressant	0	−14 (3)	Reversal (1 mg/kg)	
47	700	Depressant	0	−12 (3)	−20	
35	150	Depressant	0	−32 (37)	−30	
49	300	Depressant	79.3	−40 (30)	−30	
51	>800	0	0	−30 (15)	0	
53	100	Stimulant	0	−40 (3)	−20	Antiacetylcholine (25%)
54	400	Depressant	54	−30 (10)	−20	
55	200	Depressant	70	−14 (3) followed by +24 (5)	Reversal (1 mg/kg)	
52	200	Depressant	0	−72 (15)	−10	Potentiation of histamine (25%)
63	200	0		−42 (2)	−29	

[a] The number implies the serial number of compounds in Tables III–V. [b] Stimulant implies alertness, straub phenomenon, excitement, hyperreflexia, preconvulsiveness, and convulsions, while depressant implies reduced spontaneous motor activity ataxia, and loss of righting reflex. [c] Millimeter rise (+) and fall (−) and the figures in parenthesis describe the duration in minutes. [d] Per cent block (−) or potentiation (+); the effect on histamine and acetylcholine, if any, is shown in the Remarks column. [e] Antireserpine anticonvulsant and effect on barbiturate hypnosis and isolated guinea pig ileum is described only for those compounds where some significant effect was observed. [f] 3-Phenethyl-1,2-dioxo-2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino[1,2-*a*]quinoline, reported by us earlier.[7] [g] MES, maximal electroshock seizures.

TABLE II
HYPOTENSIVE ACTIVITY[a] OF COMPOUND 4

State of animal (cat)	Dose mg/kg	Fall of blood pressure (mm Hg)[b,c]	Duration of hypotension (min)
Normal	1.0 i.v.	40 (11)	50
	2.0 i.v.	55 (5)	60
	5.0 i.v.	75 (2)	50
	0.05 i.a.v.[d]	20 (3)	15
	0.1 i.c.v.[e]	20 (6)	30
	0.2 i.c.v.	30 (6)	20
	0.5 i.c.v.	50 (1)	80
Spinal transected	1.0 i.v.	15 (2)	20
	2.0 i.v.	0 (1)	
Decerebrate	1.0 i.v.	40 (2)	35

[a] All experiments have been done with anesthetized cats (pentobarbital sodium). [b] Figures in parentheses indicated the number of experiments from which mean values have been derived. [c] Epinephrine potentiation 10% (11), carotid occlusion block, 50% (10), and block of nictitating membrane response 15% (7). [d] Intravertebral arterial injection. [e] Intracerebroventricular injection.



I (R = H) was prepared according to the method described in our earlier communication.[8] Substituents were introduced at the 3 position of I (R = H) by a variety of methods, which are described in the Experimental Section. In an attempted preparation of 3-γ-10-(2-chlorophenothiazinyl)propyl derivative of I, 10-(3-chloro-propionyl)-2-chlorophenothiazine[9] was treated with I (R = H) in presence of K_2CO_3, NaI, and Me_2CO to give the corresponding amide. LAH reduction of the latter always gave back the unchanged phenothiazine. However, this compound could be prepared by the condensation of 10-(2-chlorophenothiazinyl)-propionyl chloride[10] with I (R = H), followed by LAH reduction of the amide thus obtained.

2-Substituted aminomethylquinolines II and their 1,2,3,4-tetrahydro derivatives III were prepared from quinaldine either by SeO_2 oxidation to quinoline-2-aldehyde[11] followed by condensation with an amine and $NaBH_4$ or Raney Ni reduction of the Schiff's base thus obtained, or by bromination with *N*-bromosuccinimide to 2-bromomethylquinoline[12] followed by condensation with an amine in PhMe. Hydrogenation with Rh C catalyst gave 2-substituted aminomethyl-1,2,3,4-tetrahydroquinolines III. Compounds III (R = CH_2CH-OHR′) were obtained by the condensation of 2-aminomethyl-1,2,3,4-tetrahydroquinoline,[13] with the appropriate epoxides. *N*-β-Hydroxyethyl and *N*-methyl derivatives of II (R′ = $(CH_2)_2OH$ or CH_3) were prepared from II (R′ = H) by treatment with ethylene oxide and HCHO HCO_2H, respectively. Catalytic hydrogenation of these gave III (R′ = $(CH_2)_2OH$ or CH_3).

At an early stage of our work it was found that 3-phenethyl-2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino[1,2-*a*]-quinoline (I, R = $CH_2CH_2C_6H_5$) had significant hypotensive activity. The corresponding decahydroquinoline compound VI was therefore prepared by hydrogenation[14] of II (R′ = H, R = $CH_2CH_2C_6H_5$) over Rh C, in HOAc acid at 70° to 2-phenethylaminomethyl decahydroquinoline (IV), followed by condensation with diethyl oxalate[15] to the diketo compound V and LAH reduction to VI. From the method of hydrogenation, and by analogy with previous work on the hydrogenation of 2-carboxyquinoline,[14] it is certain that A/B ring junction is *cis*. From the nmr spectrum (H-4a peak width 25 Hz) the B/C ring junction appears to be *trans*, and the relative stereochemistry of the two should be *cis-syn-trans*.

Pharmacological Activity.—Acute toxicity, gross observational effects, antagonism to sodium pentobarbital (60 mg/kg ip), amphetamine hyperactivity, electroshock seizures, and reserpine were studied in male mice at 0.5 0.2 LD_{50} and the actions on blood pressure and respiration were studied in anesthetized cats by administering 2.5 mg/kg iv by standard methods described earlier.[2,7]

The results of the testing of some selected compounds are recorded in Table I. 2,3,4,4a,5,6-Hexahydro-1(*H*)-pyrazino[1,2-*a*]quinoline (**1**), the parent member of this series had significant antidepressant activity and weak hypotensive and adrenolytic activities. These activities were greatly affected by substitution at the 3 position. 3-Acyl substituents as in **2** abolished both these activities, thus showing that basicity of N-3 was essential for these activities. Substitution by smaller alkyl radicals like CH_3 (**3**) resulted in an increase in hypotensive activity. However, this compound caused respiratory failure along with hypotension at higher doses. With increase in the bulk of the substituent on position 3 the antidepressant activity completely disappeared. Thus 3-hydroxybutyl (**29**), 3-ketobutyl (**28**), and 3-hydroxy-3-methylbutyl (**30**) analogs did not have any antidepressant activity, while maintaining their hypotensive and adrenolytic activities. With larger substituents like aralkyl the pattern of activity was changed and the compounds in gross observation acted as depressants and quite a few of these (**11**, **12**, **13**, **23**, **9**, **17**) showed antiamphetamine activity. The hypotensive activity was most marked

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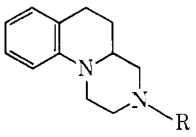
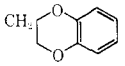
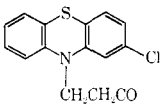
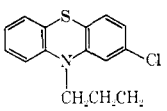
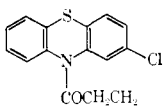
(9) A. N. Gritsenko and S. V. Zhuravlev, *Med. Prom. SSSR*, **14**, [7], 25 (1960); *Chem. Abstr.*, **55**, 9425b (1961).
(10) E. F. Godefroi and E. L. Wittle, *J. Org. Chem.*, **21**, 1163 (1956).
(11) H. Kaplan, *J. Amer. Chem. Soc.*, **63**, 2654 (1941).
(12) D. Beke, K. Leopert, J. Seress, and L. Gyermek, *Magy. Kem. Folyo.*, **61**, 190 (1955); *Chem. Abstr.*, **52**, 9124 (1958).
(13) Von H. Rupe, R. Paltzer, and K. Engel, *Helv. Chim. Acta*, **20**, 209 (1937).
(14) H. B. Sullivan and A. R. Day, *J. Org. Chem.*, **29**, 326 (1964).
(15) Von H. Rupe and W. Thommen, *Helv. Chim. Acta*, **30**, 920 (1947).

TABLE III

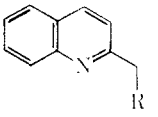


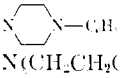
No.	R	Method	Mol formula	Mp, bp, °C	Anal
1a	H	*a*	$C_{12}H_{18}N_2 \cdot 5H_2O$[b]	120–124 (6 × 10^{-3} mm)	C, H, N
1b	H	*a*	$C_{12}H_{16}N_2 \cdot 2HCl$	151	N
2	$COCH_3$		$C_{14}H_{18}N_2O$	90[c]	C, H, N
3	CH_3	M,N	$C_{13}H_{18}N_2 \cdot HCl$[d,e]	232	N
4a	$CH_2CH_2C_6H_5$	ABCM	$C_{20}H_{24}N_2$	Oil[f,g]	C, H, N
4b	$CH_2CH_2C_6H_5$	ABCM	$C_{20}H_{24}N_2 \cdot HCl$[c]	220	C, H, N
5	$CH_2C_6H_5$	H	$C_{19}H_{22}N_2 \cdot 2HCl$[d,h]	160	N
6	$CH_2CH_2CH_2C_6H_5$	A	$C_{21}H_{26}N_2 \cdot HCl$[d,i]	182	N
7	$CH_2CHOHC_6H_5$	D	$C_{20}H_{24}N_2O$	112–113[f,j]	C, H
8	$CH_2CHOHCH_2C_6H_5$	D	$C_{21}H_{26}N_2O \cdot HCl$[d]	154	N
9	$CH_2CH_2C_{10}H_7$-α	A	$C_{24}H_{26}N_2 \cdot HCl$[d]	264	C, H, N
10	$CH_2CH_2NEt_2$	B	$C_{16}H_{29}N_3$	Oil[f]	N
11	$CH_2CHOHCH_2O_6H_5$	D	$C_{21}H_{26}N_2O_2 \cdot HCl$[d]	210	C, H, N
12	$CH_2CHOHCH_2C(p)C_6H_4COEt$	D	$C_{24}H_{30}N_2O_3 \cdot HCl$[d]	158	C, H, N
13	$CH_2CHOHCH_2O(p)C_6H_4Cl$	D	$C_{21}H_{25}ClN_2O_2 \cdot HCl$[d]	128–130	N
14	$CH_2CHOHCH_2O(o)C_6H_4$-Ac	D	$C_{23}H_{28}N_2O_3$	Oil[f]	N
15	3-NO_2-4-C_5H_3N	F	$C_{17}H_{18}N_4O_2$[k]	154	C, H
16	3-NH_2-4-C_5H_3N	F	$C_{17}H_{20}N_4$[k]	194	C, H, N
17	$(CH_2)_3COC_6H_4F$-*p*	B	$C_{22}H_{25}FN_2O \cdot 2HCl$[d]	172	N
18	$(CH_2)_2COC_6H_4F$-*p*	B	$C_{21}H_{23}FN_2O \cdot 2HCl$[d]	196	N
19		B	$C_{21}H_{24}N_2O_2 \cdot 2HCl$[l]	230	C, H
20		E	$C_{27}H_{26}ClN_3OS$[m]	186	C, H
21		E	$C_{27}H_{28}ClN_3S \cdot HCl \cdot H_2O$[d]	168	C, H, N
22		B	$C_{27}H_{26}ClN_3OS \cdot HCl$[d]	138–140	N
23	$CH_2CH_2CO_2Et$	H	$C_{17}H_{24}N_2O_2 \cdot 2HCl$[d]	165–167	N
24	$CH_2CH_2CO_2H$	H	$C_{15}H_{20}N_2O_2 \cdot H_2O$[n]	188–192	C, H
25	CHO	M	$C_{13}H_{16}N_2O$	101–102	C, H, N
26	$CH_2CH_2C_5H_4N(4)$	L	$C_{19}H_{23}N_3$	Oil[f]	N
27	$CH_2CH_2C_5H_4N(2)$	L	$C_{19}H_{23}N_3$	Oil[f,o]	C, H, N
28	$CH_2CH_2COCH_3$	I	$C_{16}H_{22}N_2O \cdot HCl$[l]	172[p]	N
29	$CH_2CH_2CHOHCH_3$	J	$C_{16}H_{24}N_2O$[q]	92[r]	N
30	$CH_2CH_2COH(CH_3)_2$	K	$C_{17}H_{26}N_2O$[s]	78–80[t]	C, H

[a] Prepared by a method reported by us earlier.[7] This compound retains moisture tenaciously and the best analysis agree with a hemihydrate. [b] Reported in literature bp 90–95° (0.001 mm),[14] 126–133° (0.3 mm).[6] [c] Prepared according to the method of Rupe and Thommen,[14] reported mp 97–98.[14,6d] [d] Crystallization from abs EtOH. [e] Literature mp 226–228°.[6d] [f] Purified by column chromatography on silica gel. [g] Literature bp 190–200° (0.5 mm).[6d] [h] Mono-HCl sinters at 203°, mp 205–207° dec, bp 173–176° (0.05 mm).[6] [i] Literature bp 200–205° (0.5 mm).[6d] [j] Literature mp 115–117°.[6e] [k] Crystallized from 95% EtOH. [l] Crystallized from EtOH–Et_2O. [m] Literature bp 160° (0.2 mm) and mono-HCl mp 180–182°.[6a] [n] Crystallized from MeOH. [o] Literature bp 190–200° (0.1 mm).[6e] [p] Literature mp 181–182°.[6c,e] [q] Crystallized from $CHCl_3$–hexane. [r] Literature mp 106–107°.[6e] [s] Crystallized from aq. MeOH. [t] Literature mp 78–79°.[6e]

in the 3-phenethyl compound **4**. Increasing the carbon chain length to 3 as in **6**, reducing it to **1** as in **5**, introducing a β-OH group in this ethyl chain (**7**), or replacing the phenethyl chain by β-hydroxy-γ-arylpropyl or β-hydroxy-γ-aryloxypropyl (**11**, **12**, **13**, **8**), caused a marked reduction in the hypotensive activity. The corresponding open chain analogs, **47**, **35**, **49**, **51**, **53**, had greatly reduced hypotensive activity as compared to **4**, thus showing that an intact pyrazinoquinoline ring structure was necessary for this activity. The necessity for both the ring nitrogens to be basic in character was shown by the lack of hypotensive activity in the **1**,2-dioxo analog **66**. Hydrogenation of the phenyl ring of the quinoline nucleus to give the perhydro compound **65** resulted in complete loss of activity. Replacement of the β-phenyl residue by a tertiary amino group as in **10** also led to reduction of activity. However, this pattern of activity was retained in compounds where

Table IV



No.	R	Method	Molecular formula	Mp, bp, °C	Anal.
31	$HNCH_2CH_2C_6H_5$	O	$C_{18}H_{18}N_2 \cdot 2HCl$[a]	193	C, H, N
32a	$HNCH_2CH_2NEt_2$	O	$C_{16}H_{23}N_3$[b]	Oil	C, H, N
32b	$HNCH_2CH_2NEt_2$	O	$C_{16}H_{23}N_3 \cdot 3HCl$	184	C, H, N
33	HNC_6H_5	O	$C_{15}H_{14}N_2$[c]	94	C, H, N
34	$HNCH_3$	O	$C_{11}H_{12}N_2 \cdot 2HCl$	202	C, H, N
35	$HNCH_2CH_2C_6H_3(OCH_3)_2$-3,4	O	$C_{20}H_{22}N_2O_2 \cdot 2HCl$[a]	183–185	N
36	$HNCH_2CH_2C_6H_4Cl$-*p*	O	$C_{18}H_{17}ClN_2 \cdot 2HCl$[a]	205	C, H, H
37	$HNCH_2CH_2C_6H_4OCH_3$-*p*	O	$C_{19}H_{20}N_2O \cdot 2HCl$[a]	200	C, H, N
38	$CH_3N \cdot CH_2CH_2C_6H_3(OCH_3)_2$-3,4	S	$C_{21}H_{24}N_2O_2$[b]	Oil	C, H, N
39		P	$C_{24}H_{21}N_3 \cdot 2HCl$[a]	161–163	C, H
40	$N(CH_2CH_2OH)CH_2CH_2C_6H_5$	T	$C_{20}H_{22}N_2O \cdot 2HCl$[a]	180–184	C, H, N
41	$N(CH_2CH_2OH)CH_2CH_2NEt_2$	T	$C_{17}H_{27}N_3O \cdot 2HCl \cdot H_2O$[a]	193	C, H, N
42	$N(CH_2CH_2OH)C_6H_5$	T	$C_{17}H_{18}N_2O$[d]	144	C, H, N
43	$N(CH_2CH_2OH)CH_3$	T	$C_{13}H_{18}N_2O \cdot 2HCl$[a]	158–160	C, H, N
44	$NHCH_2CH_2OH$	O	$C_{12}H_{14}N_2O \cdot 2HCl$[a]	164–165	C, H, N
45	$HNCH(CH_3)CH_2C_6H_5$	O	$C_{19}H_{20}N_2$[e]	Oil	C, H, N
46	$HNCH_2CH_2CH_2C_6H_5$	O	$C_{19}H_{20}N_2 \cdot HCl \cdot H_2O$[a]	168	N

[a] Crystallized from abs EtOH. [b] Purified by chromatography on silica gel column. [c] Crystallized from EtOH–Et_2O. [d] Crystallized from aq EtOH.

the phenyl ring is replaced by *p*-fluorobenzoylmethyl (**17**) or *p*-fluorobenzoyl residues (**18**). Like **4** both these compounds show epinephrine potentiation and cause marked hypotension. However, unlike **4**, compound **17** lowers blood pressure even in the spinal cat, thus suggesting a peripheral site of action.

The 2-substituted aminomethyl-1,2,3,4-tetrahydroquinolines in general showed significant adrenergic blocking activity which was most marked in **55** and **61** both of which caused a reversal of response to epinephrine.

Hypotensive Activity of 4.—Compound **4** reduces the blood pressure of an anesthetized cat by 30–60% in a dose range of 1.0–5.0 mg/kg iv (Table II). The effect of a single intravenous dose lasted for about 1 hr. The pressor response to intravenous epinephrine is potentiated and to that of carotid occlusion is blocked. Contraction of the nictitating membrane due to electrical stimulation of its preganglionic nerve is blocked by 10–20%. The compound has insignificant effect in spinal transected animals. It lowers the blood pressure of the cat when 0.05–0.1 mg is administered centrally by intracerebroventricular and intravertebral arterial injection. The predominant site of action of this compound thus appears to be in the CNS. This compound is orally effective also.

Experimental Section[16,17]

3-Substituted 2,3,4,4a,5,6-Hexahydro-1(*H*)-pyrazino[1,2-*a*]-quinolines (Table III).—The different procedures used for the synthesis of these compounds are described below.

A.—The appropriate acid chloride (15 mmol) was added to a vigorously stirred solution of I (R = H, 10 mmol) in C_6H_6 (10 ml) and aq NaOH (10 ml of 0.5 *N*). Stirring was continued for 15 hr, the C_6H_6 layer was sepd, and the aq layer extracted with Et_2O. The mixed organic layer was washed with 10% $NaHCO_3$ and H_2O. The crude amides so obtained were dried *in vacuo* and reduced with LAH in dry Et_2O or THF. The usual work-up followed by chromatography on a silica gel column gave the 3-substituted pyrazinoquinolines I which were characterized as free bases or as HCl salts.

B.—A mixture of I (R = H, 5 mmol), the appropriate alkyl halide (10 mmol), anhyd K_2CO_3 (5 mmol), and freshly dried NaI (10 mmol) in dry Me_2CO (25 ml) was stirred and refluxed for 24 hr. The reaction mixture was cooled and filtered and the residue was washed with Me_2CO. Evaporation of the Me_2CO followed by purification of the residue as the hydrochloride and chromatography of the free base obtained from the latter gave the required products. I (R = *p*-$FC_6H_4CO(CH_2)_n$, *n* = 3 or 2) were obtained by this method using I (R = H) and γ-chloro-*p*-fluorobutyrophenone[18] and β-chloro-*p*-fluoropropiophenone.[19]

C.—A mixture of I (R = H, 3 mmol), and NaH (4 mmol) in dry PhMe (25 ml) was refluxed under N_2 for 2.5 hr, the appropriate alkyl bromide (9 mmol) was then added and refluxing continued for 18 hr. The reaction mixture was washed (H_2O), and the product isolated by extn with 2 *N* HCl, followed by basification with NaOH, and extn with Et_2O.

D.—A mixture of I (R = H, 10 mmol) and the appropriate 1-substituted epoxides (12 mmol) in abs EtOH (30 ml) was refluxed for 8 hr. The solvent was evapd and the 1-β-hydroxy-β-substituted ethyl-2,3,4,4a,5,6-hexahydropyrazino[1,2-*a*]quinolines were isolated as hydrochlorides.

E. 3-γ-10-(2-Chlorophenothiazinyl)propyl-2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino[1,2-*a*]quinoline (21).—A solution of 10-(2-chlorophenothiazinyl)propionylchloride (10 mmol), in dry $CHCl_3$ (10 ml) was added under stirring to a soln of I (R = H, 20 mmol) in $CHCl_3$ (25 ml). The reaction mixture was stirred and refluxed for 10 hr and filtered. The filtrate was evapd to dryness and the residue crystallized from MeOH to give amide **20** which was reduced with LAH in THF by the usual method to give **21** isolated as its hydrochloride.

F. 3-(3-Amino-4-pyridyl)-2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino[1,2-*a*]quinoline (16).—A mixture of I (R = H, 10 mmol), 4-chloro-3-nitropyridine[20] (10 mmol), Et_3N (12 mmol) in dry PhMe (25 ml) was heated at 100° for 8 hr. $Et_3N \cdot HCl$ was filtered, the filtrate was evapd to dryness and the residue crys-

(16) Melting points were determined in an H_2SO_4 bath and are uncorrected. The various compounds were routinely checked by ir and nmr spectroscopy on a Perkin-Elmer Infracord and Varian A-60D instrument, nmr values being expressed as τ using TMS as internal reference. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

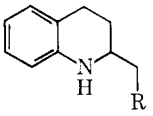
(17) The Roman numerals refer to the types of compounds, while the Arabic numerals refer to the specific compounds as they appear in the text.

(18) C. V. de Westeringh, P. Hermans, F. Paey-maekers, and C. V. der Eycken, *Ind. Chim. Belge*, **25**, 1073 (1960); *Chem. Abstr.*, **55**, 6428 (1961).

(19) J. Kenner and F. S. Statham, *J. Chem. Soc.*, 301 (1935).

(20) S. Kruger and F. C. Mann, *ibid.*, 4516 (1954).

TABLE V



No.	R	Method	Mol formula	Mp, bp, °C	Anal.
47a	$HNCH_2CH_2C_6H_5$	Q	$C_{18}H_{22}N_2$	210–212 (0.5 mm)	N
b	$HNCH_2CH_2C_6H_5$	Q	$C_{18}H_{22}N_2 \cdot HCl$[a]	196	C, H, N
48	$HNCH_2CH_2NEt_2$	Q	$C_{16}H_{27}N_3$	174 (1 mm)	C, H
49	$HNCH_2CH_2$-3,4-$C_6H_3(OCH_3)_2$	Q	$C_{20}H_{26}N_2O_2 \cdot 2HCl$[b]	182	C, H, N
50	$HNCH_2CH_2C_6H_4Cl$-*p*	Q	$C_{18}H_{21}ClN_2$[c]	164	C, H, N
51	$HNCH_2CH_2C_6H_4OCH_3$-*p*	Q	$C_{19}H_{24}N_2O \cdot H_2O$[c]	152	C, H, N
52	$N(CH_3)(CH_2)_2$-3,4-$C_6H_3(OCH_3)_2$	Q	$C_{21}H_{28}N_2O_2$[d]	Oil	C, H, N
53	$HNCH(CH_3)$-$CH_2C_6H_5$	Q	$C_{19}H_{24}N_2 \cdot 2HCl$[b]	234	C, H, N
54	$HN(CH_2)_2$-3,4-$C_6H_3(OH)_2$		$C_{18}H_{22}N_2O_2 \cdot 2HBr$[b]	252	C, H, N
55	$HN(CH_2)_2$-3,4-$(CH_3)_2C_6H_3$	Q	$C_{20}H_{26}N_2 \cdot HCl$[c]	202	C, H, N
56	$HN(CH_2)_3C_6H_5$	Q	$C_{19}H_{24}N_2$[c]	115–120	C, H, N
57	$HNCH_2CHOHC_6H_5$	R	$C_{18}H_{22}N_2O \cdot HCl$[c]	223	C, H, N
58	$HNCH_2CHOHCH_2OC_6H_5$	R	$C_{19}H_{24}N_2O_2 \cdot 2HCl H_2O$[b]	174	C, H, N
59	$N(CH_2)_2OH(CH_2CH_2C_6H_5)$	Q	$C_{20}H_{26}N_2O$[d]	Oil	C, H, N
60a	$HN(CH_2)_2OH$	Q	$C_{12}H_{18}N_2O \cdot 2HCl$[b]	182	C, H, N
b	$HN(CH_2)_2OH$	Q	$C_{12}H_{18}N_2O$[e,f]	103	C, H, N
61	—N⟨ ⟩NC_6H_5	Q	$C_{20}H_{25}N_3$[d]	Oil	C, H

Crystallized from: [a] H_2O. [b] EtOH–Et_2O. [c] EtOH. [d] Purified by column chromatography on silica gel. [e] Crystallized from EtOAc. [f] Reported by Rupe and Thommen,[14] mp 103°.

tallized from EtOH to give 3-(3-nitro-4-pyridyl)-2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino[1,2-*a*]quinoline (**15**).

The nitro compound obtained as above was reduced in EtOH with H_2 at 2.5 atm pressure in presence of Raney Ni to give the amino compound which was crystallized from EtOH.

G. 3-(β-Carboxyethyl)-2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino[1,2-*a*]quinoline (24).—A mixture of I (R = H, 5 mmol) and ethyl acrylate (6 mmol) was heated on the steam bath for 3 hr; the 3-β-ethoxycarbonylethyl compound **23** was then isolated as its hydrochloride.

A mixture of the above ester hydrochloride (0.32 g) was dissolved in min EtOH and NaOH (3 ml of 4%) was added. The mixture was refluxed for 30 min and then just neutralized with HCl, evapd to dryness, and finally dried at 80° (0.1 mm). The residue was extd with hot MeOH and filtered from inorg salts. Concentration of filtrate gave **24**.

H. 3-Benzyl-2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino[1,2-*a*]quinoline (5).—A mixture of I (R = H, 5 mmol) $PhCH_2Cl$ (5 mmol) and $NaHCO_3$ (5 mmol) in H_2O–EtOH (25 ml, 1:1 v/v) was refluxed on steam bath for 20 hr. The oily product which sepd was taken up in Et_2O and converted into its hydrochloride.

I. 3-(3-Oxobutyl)-2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino[1,2-*a*]quinoline (28).—A mixture of I (R = H, 20 mmol), and methyl vinyl ketone (22 mmol) in PhH (20 ml) was stirred at room temp for 24 hr, the solvent was evapd *in vacuo*, and the oily product was purified as the hydrochloride.

J. 3-(3-Hydroxybutyl)-2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino[1,2-*a*]quinoline (29).—Powdered $NaBH_4$ (0.8 g) was added to a solution of the above ketone I (R = $(CH_2)_2COCH_3$, 1.5 g) in abs MeOH (25 ml) cooled to 0°. The reaction mixture was stirred at room temp for 16 hr, and worked up in the usual manner.

K. 3-(3-Hydroxy-3-methyl)butyl-2,3,4,4a,5,6-hexahydro-1-(*H*)-pyrazino[1,2-*a*]quinoline (30).—A solution of ketone I [R = $(CH_2)_2COCH_3$, 1.5 g] in dry Et_2O (25 ml) was added to MeMgI (from 0.45 g of Mg and 3 g of MeI) in dry Et_2O (50 ml). The reaction mixture was refluxed for 3 hr and stirred at 25° for 20 hr and then the complex was decomposed by the addition of a solution of NH_4Cl (5 g in 50 ml) and worked up as usual.

L. 3-β-(2- or 4-Pyridylethyl)-2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino[1,2-*a*]quinoline (26 and 27).—A solution of 2- or 4-vinylpyridine (11 mmol), glacial AcOH (10 mmol), and I (R = H, 10 mmol) was refluxed[21] for 20 hr and worked up as usual.

3-Methyl-2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino[1,2-*a*]quinoline (3).—This was prepared by two methods.

M.—A mixture of I (R = H; 5 mmol) and ethyl formate (50 mmol) was refluxed for 48 hr. Excess HCO_2Et was evapd *in vacuo* and residue was filtered through a column of silica gel and eluted with C_6H_6. The *N*-formyl product **25** thus obtained was reduced with LAH in a mixture of dioxane and Et_2O in the usual manner.

N.—2-Methylaminomethyl-1,2,3,4-tetrahydroquinoline [prepared according to method Q (20 mmol)] and diethyl oxalate (20 mmol) was heated on the steam bath for 16 hr. and then diluted with EtOAc to give 3-methyl-1,2-dioxo-2,3,4,4a,5,6-hexahydro-1(*H*)-pyrazino[1,2-*a*]quinoline (**62**), mp 182°. *Anal.* ($C_{13}H_{14}N_2O_2$) C, H, N. The diketo compound was reduced with $LiAlH_4$ in the usual manner to give **3** (I, R = CH_3).

2-Substituted Aminomethylquinolines (II, R′ = H) (Table IV).

O.—A mixture of quinoline-2-aldehyde (0.05 mol) and the appropriate primary amine (0.05 mol) in dry C_6H_6 (50 ml) was azeotroped till no more H_2O sepd. C_6H_6 was evapd under reduced pressure and the crude Schiffs base was dissolved in abs EtOH (50 ml) and reduced with $NaBH_4$ (0.2 mol). The usual work-up gave 2-substituted aminomethylquinolines II which were isolated either as free bases or as hydrochlorides.

P.—A mixture of quinaldine (0.2 mol) and NBS (0.22 mol) in dry CCl_4 (150 ml) was refluxed for 4 hr. The reaction mixture was then cooled in ice, filtered, and the filtrate evapd to dryness under reduced pressure. The crude 2-bromomethylquinoline so obtained was dissolved in dry PhMe (200 ml) and the appropriate amine (0.2 mol) added, and the mixture heated at 100° for 10 hr. The reaction mixture was filtered to remove amine·HBr. The filtrate on evapn gave the 2-substituted aminomethylquinolines, which were isolated as their hydrochlorides.

2-Substituted Aminomethyl-1,2,3,4-tetrahydroquinolines (III, R′ = H) (Table V).

Q.—II HCl (6.0 g) in abs EtOH (250 ml), concd HCl (4 ml), and 5% Rh–C (0.5 g) was hydrogenated under 2.5 atm of H_2. The usual work-up gave the tetrahydro compounds III, which were either isolated as free bases or as hydrochlorides.

R. 2-β-Hydroxy β-Substituted Ethylaminomethyl-1,2,3,4-tetrahydroquinoline.—Compounds III (R′ = H, R = CH_2CHOHR'') were obtained by refluxing a solution of 2-aminomethyl-1,2,3,4-tetrahydroquinoline (0.1 mol) and the corresponding 1-substituted epoxy compounds (0.11 mol) in abs EtOH (100 ml) for 20 hr. The usual work-up gave the required compounds.

2-(*N*-Methyl-*N*-3,4-dimethoxyphenethyl)aminomethylquinoline (38).

S.—A mixture of 2-(3,4-dimethoxyphenethyl)aminomethylquinoline (II, R′ = H, R = $(CH_2)_2$-3,4$(OCH_3)_2C_6H_3$, 0.3 g), CH_2O (0.35 ml of 37% solution), and HCO_2H (0.36 ml, 98–100%) was heated on a steam bath for 7 hr. Ice-cold H_2O was added and the reaction mixture made strongly alkaline with NaOH and the product isolated by extraction with EtOAc,

(21) J. E. Robertson, J. H. Beil, T. F. Mitchell Jr., W. K. Moya, and H. A. Leiser, *J. Med. Chem.*, **6**, 805 (1963).

purified by chromatography on alumina in C_6H_6 and eluted with C_6H_6 with increasing proportions of EtOAc, when the product was obtained as an oil.

2-(*N*-β-Hydroxyethyl-*N*-substituted)aminomethylquinoline (II) (R′ = $(CH_2)_2OH$). T.—A mixture of 2-substituted aminomethylquinoline (II, R′ = H, 0.03 mol) and ethylene oxide (0.04 mol) in EtOH (50 ml) was stirred at 30° for 18 hr, solvent was evapd to dryness and the products were isolated as hydrochlorides.

2-(3,4-Dihydroxyphenethyl)aminomethyl-1,2,3,4-tetrahydroquinoline (54). U.—2-(3,4-Dimethoxyphenethyl)aminomethyl-1,2,3,4-tetrahydroquinoline (2.0 g) and HBr (20 ml of 48%) were refluxed 20 hr. Excess HBr was evapd *in vacuo* and the residue crystallized from EtOH–Et_2O to give the HBr salt of the dihydroxy compound.

2-Phenethylaminomethyldecahydroquinoline (IV) (63).—2-Phenethylaminomethylquinoline (II, R′ = H, R = $(CH_2)_2C_6H_5$, 2.9 g) in AcOH (50 ml) and 5% Rh–C (1 g) at 70–80° were hydrogenated under 5 atm of H_2. The usual work-up gave the free base, which was purified by chromatography and obtained as an oil: yield, 2.7 g; nmr (CCl_4) showed only one singlet (2.8 δ, C_6H_5) in the aromatic region. *Anal.* ($C_{18}H_{22}N_2$) N.

3-Phenethyl-1,2-dioxoperhydro-1(*H*)-pyrazino[1,2-*a*]quinoline (V) (64).—IV was converted into V by the action of diethyl oxalate as described earlier: crystallized from EtOAc–hexane, mp 210°; yield, 75%. *Anal.* ($C_{20}H_{26}N_2O_2$), N.

3-Phenethylperhydro-1(*H*)-pyrazino[1,2-*a*]quinoline (VI) (65) was obtained by LAH reduction of V as described earlier, and purified by chromatography: mp 55–60°, yield 70%; nmr (CCl_4) 2.85 (s, C_6H_5), 7–8.8 (m, 25 protons); VI·2HCl, crystallized from EtOH, mp 220°. *Anal.* ($C_{20}H_{30}N_2$) C, H.

Acknowledgment.—We wish to express our thanks to Dr. B. N. Dhawan for his interest in this work, to Mr. R. M. Saxena, G. Shanker, and P. S. Gupta for technical assistance, and to Riker Laboratories, Northridge, Calif., for a supply of chemicals. The assistance of Mr. B. B. P. Srivastava and Mr. J. Saran and his associates for nmr and microanalyses is gratefully acknowledged.

Benzo[*g*]quinolines. II. Novel Synthesis and Pharmacological Evaluation of *cis*-1-Alkyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolines[1]

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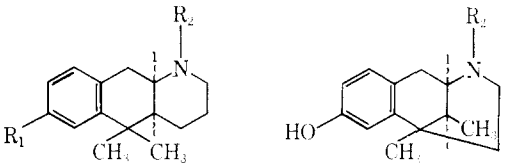
Received November 7, 1969

Cyclization of N derivatives of *trans*-2-(*p*-methoxybenzyl)-α,α-dimethyl-3-piperidinemethanol gives derivatives of mixtures of *cis*- and *trans*-1,2,3,4,4a,5,10,10a-octahydro-7-methoxy-5,5-dimethylbenzo[*g*]quinoline, the product ratios depending on the N substituent. Cyclization of the *cis* alcohols gives the *cis* products exclusively. A possible explanation involving olefinic intermediates is discussed, along with the application of this phenomenon to the synthesis of *cis*-1-alkyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolines and their evaluation as narcotic antagonists.

In our previous paper,[2] it was established that certain *N*-alkyl derivatives of *cis*-1,2,3,4,4a,5,10,10a-octahydro-5,5-dimethylbenzo[*g*]quinolin-7-ol (**1b**) possessed approximately 0.05 the narcotic antagonist activity (*vs.* meperidine) of the correspondingly *N*-substituted β isomer of 2′-hydroxy-5,9-dimethyl-6,7-benzomorphan (**2**). Our basic premise was that these alkyl derivatives of **1b** probably owe their activity to the fact that they can assume a conformation in which much of the



1a, R_1 = H
b, R_1 = OH

2

molecule is superimposable on the corresponding *N*-alkyl derivative of **2**. If such be the case, then one might conclude that the mechanisms of action of the two different types of molecules are the same, or at least very similar.[3] A necessary (but not sufficient) condition for the validity of this interpretation is that removal of the C7-OH function of **1b** to give **1a** should lead to decreased activity in this series, since the corresponding change in the series of **2** derivatives results in such a decrease.[4] With this idea in mind, synthetic approaches to the efficient production of **1a** (R_2 = H) were explored.

Chemistry.—The general synthesis of compounds in the **1b** series found only limited applicability to the preparation of **1a** (R_2 = H **9**) = (Scheme I). Acylation of diethyl 2-cyanoethylmalonate with phenylacetyl chloride using NaH afforded **3**. Catalytic reduction of this ketonitrile over Pt gave **4**. Carbobenzoxylation of **4** gave **5** which was saponified to half-acid ester **6**. Decarboxylation of **6** gave **7a** as a mixture of stereoisomers. However, unlike the mixture **7b** from which the *cis* isomer crystallized readily, mixture **7a** could not be separated. Treatment of mixture **7a** with MeMgI followed by hydrogenolysis of the carbobenzoxy group gave a mixture of **8a** isomers, also inseparable. Cyclization of mixture **8a** with hot 1:5 H_2SO_4–AcOH gave a mixture of approximately 60% **9** and 40% **10** as determined by nmr.[2,5] This mixture could be separated through the use of dry column chromatography[6] on alumina; however, only small quantities of the mixture could be separated at any one time.

The difficulties attending the separation of stereoisomers in Scheme I made it desirable to find an alternative route to the large scale preparation of **9**.

(1) Taken in part from the Ph.D. thesis of W. F. Michne, Rensselaer Polytechnic Institute, Troy, New York, June, 1968.

(2) W. F. Michne and N. F. Albertson, *J. Med. Chem.*, 12, 402 (1969).

(3) For a discussion of the implications of such a comparison, see P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966).

(4) N. F. Albertson, unpublished results.

(5) Since the **8b** isomers cyclize without losing their configurations, it can be assumed that the **8a** isomers behave similarly. Hence, the composition of mixture **8a** is probably 60% *cis* and 40% *trans*.

(6) B. Loev and M. M. Goodman, *Chem. Ind.*, 2026 (1967).