and anisotropic temperature factors for the heavier atoms converged at $R = 5.5\%$.

A crystal of **1y** suitable for X-ray analysis was obtained from the analytical sample. The crystal is orthorhombic, space group $P2_12_12_1$ (noncentrosymmetric) with $a = 15.677$ (10), $b = 11.625$ (10), and $c = 5.654$ (9) Å. For one molecule in the asymmetric unit, the calculated density is 1.45 g cm^{-3}. The observed density by flotation in bromobenzene–heptane is 1.414 g cm^{-3}. Intensity data were collected in the range $6° \leq 2\theta \leq 120°$ with Cu Kα radiation ($\lambda = 1.5418$ Å) and of the 937 reflections measured, 738 were considered observed by the criterion $I \geq 2.0\ \sigma(I)$.

The chlorine atom was located by the Patterson method and alternate structure factor and difference map calculations revealed the remaining heavier atoms. The hydrogen atoms were placed at the calculated positions and the structure refined with an anomalous dispersion correction for chlorine and anisotropic temperature factors for the heavier atoms. The refinement converged at $R = 6.0\%$.

Acknowledgment. Imides **1a,c,d,g–j,m,s,t** were originally synthesized by Patrick T. Izzo and the late Gretchen Wiegand. We acknowledge W. Fulmor, W. Gore, G. O. Morton, and group for spectral analyses and L. Brancone and group for the microanalyses. Biological tests were performed by B. Regan and G. Patel.

Supplementary Material Available: Tables X–XIII containing hydrogen coordinates and temperature parameters of **2v** and **1y** (4 pages). Ordering information is given on any current masthead page.

A Potent, New, Sedative–Hypnotic Agent: 5,7-Dihydro-5,5,7,7-tetramethyl-3-(3-nitrophenyl)furo[3,4-*e*]-*as*-triazine 4-Oxide

G. B. Bennett,* R. G. Babington, M. A. Deacon, P. L. Eden, S. P. Kerestan, G. H. Leslie, E. A. Ryan, R. B. Mason, and H. E. Minor

Chemical and Pharmacological Research, Pharmaceutical Division, Sandoz, Inc., East Hanover, New Jersey 07936.
Received May 16, 1980

A series of 3-phenylfuro[3,4-*e*]-*as*-triazines was prepared and their CNS sedative–hypnotic activity was measured. From this series, 5,7-dihydro-5,5,7,7-tetramethyl-3-(3-nitrophenyl)-furo[3,4-*e*]-*as*-triazine 4-oxide (**5b**) emerged as a potent sedative-hypnotic of unique pharmacological properties. A description of the syntheses and a discussion of the relationship between structure and CNS activity of these compounds, in particular of compound **5b**, are presented.

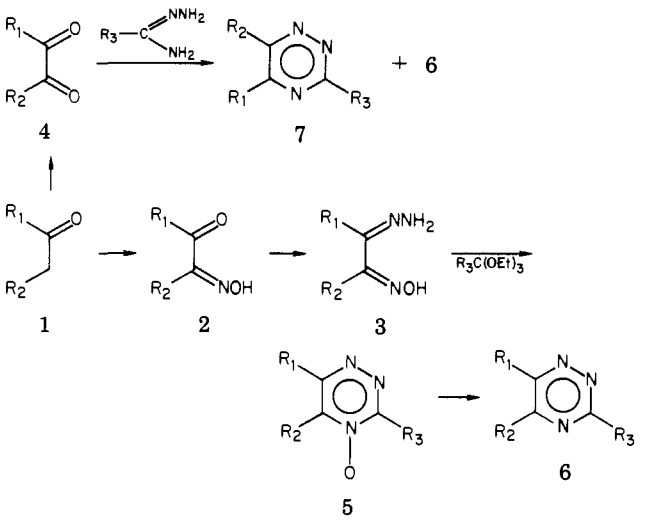
Despite the development of a number of safe and effective benzodiazepines,[1] the search for new and improved sedative–hypnotic agents continues. The longer-acting benzodiazepines tend to cause hangover, and at higher doses REM and slow-wave sleep deprivation occur, thereby affecting the quality of sleep they produce.[25] These side effects are of marginal importance, however, considered in relation to the exceptionally high safety margin the benzodiazepines display, and they are at present the safest drugs available for the induction and maintenance of sleep.[24] An ideal agent would reduce sleep latency and increase total sleep time while inducing a physiological sleep, i.e., one in which the architecture has not been skewed or disrupted.

To this end, a series of 3-phenylfuro[3,4-*e*]-*as*-triazines has been prepared and tested for sedative–hypnotic activity. From this series emerged compound **5b**, 5,7-dihydro-5,5,7,7-tetramethyl-3-(3-nitrophenyl)furo[3,4-*e*]-*as*-triazine 4-oxide, a potent sedative–hypnotic of novel chemical structure and unique pharmacological properties. A description of the syntheses and a discussion of the relationship between structure and CNS activity of these compounds, in particular of **5b**, are presented in this paper.

Chemistry. The parent compound in the series, triazine (**5a**), was prepared as part of our antiinflammatory program.[2] The synthesis via hydrazone oxime **3**, as outlined in Scheme I, was selected because of its general applicability to a variety of commercially available ketones, **1**, and diones, **4**, as well as the simple nature of the reactions. The preparation of the ketone **1** and dione **4** starting materials has been described.[3]

Pharmacology. The acute behavioral activity of these triazines as well as their ability to reinduce anesthesia were both measured in mice. The biological methods are discussed under Experimental Section. For comparison purposes, the discussion of biological activity and the compound tables use the hexobarbital reinduction ED_{50} values (mg/kg ip) as a relative measure of in vivo sedative–hypnotic activity.

Scheme I



Discussion

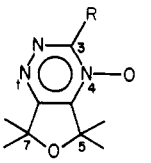
This presentation of the relationship between chemical structure and biological activity will look at the role of the 4-*N*-oxide, followed by A-ring (furan) analogues, B-ring (triazine) analogues, and finally C-3 analogues.

* Address correspondence to: Dorsey Laboratories, Lincoln, NE 68501.

(1) L. O. Randall and B. Kappell in "The Benzodiazepines", S. Garattini, E. Mussini, and L. O. Randall, Eds., Raven Press, New York, 1973, p 27.
(2) G. B. Bennett, R. B. Mason, L. J. Alden, and J. B. Roach, *J. Med. Chem.*, **21**, 623 (1978).
(3) G. B. Bennett, W. J. Houlihan, R. B. Mason, and R. G. Engstrom, *J. Med. Chem.*, **19**, 709 (1976).

0022-2623/81/1824-0490$01.25/0

Table I

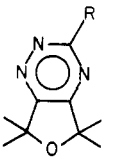


5

no.	mp or bp (mm), °C	yield, % (method)	R	emp formula	anal.	HXB ED_{50}, mg/kg
5a	154-156	91 (A)	C_6H_5	$C_{15}H_{17}N_3O_2$	C, H, N	163.1
5b	202-204	83 (E)	*m*-$NO_2C_6H_4$	$C_{15}H_{16}N_4O_4$	C, H, N	72
5c	147-148	65 (A)	*m*-$CF_3C_6H_4$	$C_{16}H_{16}N_3O_2F_3$	C, H, N	66.7
5d	81-85	73 (A)	*m*-ClC_6H_4	$C_{15}H_{16}N_3O_2Cl$	C, H, N, Cl	500[a]
5e	140-150 (0.5)	73 (A)	*m*-FC_6H_4	$C_{15}H_{16}N_3O_2F$	C, H, N	74.9
5f	183-185	41 (A)	3,5-$(NO_2)_2C_6H_3$	$C_{15}H_{15}N_5O_6$	C, H, N	500[a]
5g	160-165 (0.1)	86 (A)	*m*-$(CH_3)C_6H_4$	$C_{16}H_{16}N_3O_2$	C, H, N	150
5h	129-131	74 (A)	*p*-FC_6H_4	$C_{15}H_{16}N_3O_2F$	C, H, N	500[a]
5i	120-122	65 (A)	*p*-$(CH_3)C_6H_4$	$C_{16}H_{19}N_3O_2$	C, H, N	0
5j	110-120 (0.1)	44 (A)	3,4-$(CH_3)_2C_6H_3$	$C_{17}H_{21}N_3O_2$	C, H, N	133
5k	133-134	61 (A)	*p*-ClC_6H_4	$C_{15}H_{16}N_3O_2Cl$	C, H, N, Cl	0
5l	165-167	54 (A)	*p*-$(CH_3O)C_6H_4$	$C_{16}H_{19}N_3O_3$	C, H, N	0
5m	240-242	21 (A)	*p*-$NO_2C_6H_4$	$C_{15}H_{16}N_4O_4$	C, H, N	0
5n	205-206	6[b] (E)	*o*-$NO_2C_6H_4$	$C_{15}H_{16}N_4O_3$	C, H, N	0
5o	190-195	76 (A)	4-(CH_3O)-3-$NO_2C_6H_3$	$C_{16}H_{18}N_4O_5$	C, H, N	0
5p	196-197	82 (A)	H	$C_9H_{13}N_3O_2$	C, H, N	0
5q	87-87.5	56 (A)	CH_3	$C_{10}H_{15}N_3O_2$	C, H, N	0
5x	205-208	72 (G)	OH	$C_9H_{13}N_3O_3$	C, H, N	0

[a] Extrapolated value. [b] Byproduct in the synthesis of **5b**.

Table II



6

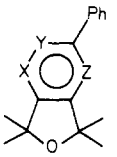
no.	mp or bp (mm), °C	yield, % (method)	R	emp formula	anal.	HXB ED_{50}, mg/kg
6a	90-91	72 (B)	C_6H_5	$C_{15}H_{17}N_3O$	C, H, N	166.6
6b	149-152	83 (C)	*m*-$NO_2C_6H_4$	$C_{15}H_{16}N_4O_3$	C, H, N	68.8
6c	73-75	88 (C)	*m*-$CF_3C_6H_4$	$C_{16}H_{16}N_3OF_3$	C, H, N	500[a]
6d	115-117	84 (B)	*p*-ClC_6H_4	$C_{15}H_{16}N_3OCl$	C, H, N, Cl	
6e	90-92	90 (C)	*p*-$(CH_3)C_6H_4$	$C_{16}H_{19}N_3O$	C, H, N	
6f	128-130	92 (C)	*p*-FC_6H_4	$C_{15}H_{16}N_3OF$	C, H, N	
6g	118-119	89 (C)	*p*-$(CH_3O)C_6H_4$	$C_{16}H_{19}N_3O_2$	C, H, N	
6h	129-131	55 (D)	3,5-$Cl_2C_6H_3$	$C_{15}H_{15}N_3OCl_2$	C, H, N, Cl	0
6i	219-221	18 (D)	*p*-$NO_2C_6H_4$	$C_{15}H_{16}N_4O_3 \cdot HCl$	C, H, N, Cl	0
6j	94-95.5	11 (D)	*p*-$NH_2C_6H_4$	$C_{15}H_{18}N_4O$	C, H, N	0
6k	237-240	33 (D)	*m*-$H_2NSO_2C_6H_4$	$C_{15}H_{18}N_4O_3S \cdot H_2O$	C, H, N, S	0
6l	120-121	89 (B)	H	$C_9H_{13}N_3O$	C, H, N	0
6m	110-111	44 (D)	3-pyridyl	$C_{14}H_{16}N_4O$	C, H, N	28.1[c]
6n	135-136	67 (D)	4-pyridyl	$C_{14}H_{16}N_4O$	C, H, N	56.2[c]
6o	138-139	78 (D)	pyrazyl	$C_{13}H_{15}N_5O$	C, H, N	100[c]
6p	oil	21 (D)	2-(4-*t*-Bu)pyridyl	$C_{18}H_{24}N_4O$	C, H, N	0[c]
6q	88-92	24 (D)	2-(5-Cl)pyridyl	$C_{14}H_{15}N_4OCl$	C, H, N, Cl	66.7[c]
6r	77-78	80 (D)	2-pyridyl	$C_{14}H_{16}N_4O$	C, H, N	21[c]
6s	150-160 (0.25)	61 (D)	2-(5-CH_3)pyridyl	$C_{15}H_{18}N_4O$	C, H, N	
6t	87-88	77 (D)	2-thienyl	$C_{13}H_{15}N_3SO$	C, H, N, S	0
6u	67-69	29 (D)	$CH_2C_6H_5$	$C_{16}H_{19}N_3O$	C, H, N	25[c]
6v	143-144	84 (D)	2-quinolyl	$C_{18}H_{18}N_4O$	C, H, N	168.1
6w	153-155	76 (D)	2-(5-nitro)thienyl	$C_{13}H_{14}N_4O_3S$	C, H, N, S	0
6x	163-165[b]	61 (D)	1-adamantyl	$C_{19}H_{27}N_3O \cdot HCl \cdot H_2O$	C, H, N, Cl	0
6y	192-194	84 (H)	2-(pyridyl *N*-oxide)	$C_{14}H_{16}N_4O_2$	C, H, N	137.5
6z	204-206.5	82 (H)	2-(5-Me-pyridyl *N*-oxide)	$C_{15}H_{18}N_4O_2$	C, H, N	0

[a] Extrapolated value. [b] HCl salt. [c] Toxic.

Throughout this series of compounds there would appear to be no obvious trend resulting from differences in biological activity between the *as*-triazine and its corresponding *N*-oxide (Tables I and II). With the exception of the *m*-CF_3 analogues **5c** and **6c**, the presence or absence of the *N*-oxide seems to have little effect on the biological activity.

Looking next at the relationship of A-ring structural changes to biological activity, a series of triazines (Table V) with increased steric bulk at furan positions C-5 and

Table III

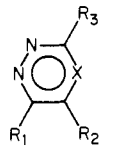


8

no.	mp, °C	yield, % (method)	X	Y	Z	emp formula	anal.	HXB ED_{50}, mg/kg
8a	152-154	23 (I)	NO	N	N	$C_{15}H_{17}N_3O_2$	C, H, N	0
8b	97-99	66 (J)	CH	N	N	$C_{16}H_{18}N_2O$	C, H, N	0
8c	151-152[b]	55 (K)	N	N	CH	$C_{16}H_{18}N_2O\cdot HCl$	C, H, N, Cl	112.5
8d	121-125[b]	12 (L)	N	CH	NO	$C_{16}H_{18}N_2O_2\cdot HCl$	C, H, N, Cl	1000[a]

[a] Extrapolated value. [b] HCl salt.

Table IV



9

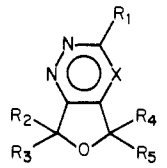
no.	mp or bp (mm), °C	yield, % (method)	R_1	R_2	R_3	X	emp formula	anal.	HXB ED_{50}, mg/kg
9a	112-114	79 (D)	$-(CH_2)_4-$		2-pyridyl	N	$C_{12}H_{12}N_4$	C, H, N	0
9b	235-237	22 (D)	$-CH(CH_3)SO_2CH(CH_3)-$		m-$NO_2C_6H_4$	N	$C_{13}H_{12}N_4O_4S$	C, H, N, S	0
9c	84-90	31 (A)	$-C(CH_3)_2NHC(CH_3)_2-$		C_6H_5	NO	$C_{15}N_{18}N_4O$	C, H, N	1000[a]
9d	115-117[b]	19 (D)	$-(C(CH_3)_2CH_2)_2S$		2-pyridyl	N	$C_{16}H_{20}N_4S\cdot HCl$	C, H, N, S, Cl	*d*
9e	124-128[b]	15 (D)	$-(C(CH_3)_2CH_2)_2S$		C_6H_5	N	$C_{17}H_{21}N_3S\cdot HCl$	C, H, N, S, Cl	31.3
9f	107-110[b]	28 (D)	$-(C(CH_3)_2CH_2)_2S$		m-$NO_2C_6H_4$	N	$C_{17}H_{20}N_4O_2S\cdot HCl$	C, H, N, S, Cl	
9g	193-194	48 (M)	$-C(CH_3)_2OH$	OH	m-$CF_3C_6H_4$	N	$C_{13}H_{11}N_3O_2F_3$	C, H, N	0
9h	180-182	55 (M)	$-C(Ph)_2OH$	OH	m-$CF_3C_6H_4$	N	$C_{23}H_{16}N_3O_2F_3$	C, H, N	0
9i	89-91	61 (M)	$-C(n\text{-}Bu)_2OH$	OH	m-$CF_3C_6H_4$	N	$C_{19}H_{24}N_3O_2F_3\cdot 2H_2O$	C, H, N	0
9j	211-213.5[b]	64 (M)	CO_2Et	OH	2-pyridyl	N	$C_{11}H_{10}N_4O_3\cdot HCl$	C, H, N, Cl	*d*
9k	164-165	46 (M)	CO_2Et	OH	m-$CF_9C_6H_4$	N	$C_{13}H_{10}N_3O_3F_3$	C, H, N	0
9l	128.5-130	24 (A)	$-C(CH_3)_2CH_2C(CH_3)_2-$		C_6H_5	NO	$C_{16}H_{19}N_3O$	C, H, N	0
9m	124.5-125.5	86 (C)	$-C(CH_3)_2CH_2C(CH_3)_2-$		C_6H_5	N	$C_{16}H_{19}N_3$	C, H, N	0
9n	124-126	29 (A)	$-CH_2C(CH_3)_2CH_2C(CH_3)_2-$		C_6H_5	NO	$C_{17}H_{21}N_3O$	C, H, N	0
9o	118-119	64 (A)	$-CH_2C(CH_3)_2OC(CH_3)_2-$		C_6H_5	NO	$C_{16}H_{19}N_3O_2$	C, H, N	121.9
9p	194-195	81 (E)	$-CH_2C(CH_3)_2OC(CH_3)_2-$		m-$NO_2C_6H_4$	NO	$C_{16}H_{18}N_4O_4$	C, H, N	500[a]
9q	82-84	10 (D)	CH_3	CH_3	2-pyridyl	N	$C_{10}H_{10}N_4$	C, H, N	*d*
9r[c]	49-52	8 (D)	n-Pr	CH_3	2-pyridyl	N	$C_{12}H_{14}N_4$	C, H, N	*d*
9s[c]	65-67	22 (D)	CH_3	n-Pr	2-pyridyl	N	$C_{12}H_{14}N_4$	C, H, N	*d*
9t	166-168	26 (D)	$-CH_2CH_2CH(CH_3)-$		2-pyridyl	N	$C_{12}H_{12}N_4$	C, H, N	0
9u	86-88	21 (D)	$-C(CH_3)_2CH_2COC(CH_3)_2-$		m-$CF_3C_6H_4$	N	$C_{18}H_{18}N_3OF_3\cdot H_2O$	C, H, N	0
9v	48-50	87 (O)	$-C(CH_3)_2CH_2CHOHC(CH_3)_2-$		m-$CF_3C_6H_4$	N	$C_{18}H_{20}N_3OF_3$	C, H, N	0
9w	55-57	82 (D)	$-C(CH_3)_2CH{=}CHC(CH_3)_2-$		m-$CF_3C_6H_4$	N	$C_{18}H_{18}N_3F_3$	C, H, N	0
9x	130-140 (0.01)	80 (P)	$-C(CH_3)_2CHOCHC(CH_3)_2-$		m-$CF_3C_6H_4$	N	$C_{18}H_{18}N_3OF_3$	C, H, N	0
9y	158-160	26 (D)	$-C(CH_3)_2CH{=}CHC(CH_3)_2-$		m-NH_2SO_2	N	$C_{17}H_{20}N_4SO_2\cdot 2H_2O$	C, H, N, S	1000[a]
9z	129-134	8 (Q)	$-C(CH_3)_2OH$	OCH_3	m-$CF_3C_6H_4$	N	$C_{14}H_{14}N_3O_2F_3$	C, H, N	0

[a] Extrapolated value. [b] HCl salt. [c] Prepared from a mixture of hydrazine oximes (3); separated by column chromatography. [d] Toxic.

C-7 was prepared (**10a–h**). Replacement of one or both methyls by phenyl or spirocyclohexyl, thereby increasing lipophilicity and steric bulk, led to a loss or reduction of biological activity. Changes at C-7 had a much more pronounced effect than changes at C-5 (**10d** vs. **10e**).

From Table IV we see that expansion of the A ring by one carbon improved the ED_{50} in the case of the 3-phenyl derivative **9o** (vs. **5a**) but significantly reduced the activity in the 3-NO_2 phenyl case, **9p**. Substitution for oxygen at position 6 by carbon with (**9n**,**y**) and without (**9l**,**m**,**t**) ring expansion gave products devoid of CNS activity. Substitution by either NH (**9c**) or SO_2 (**9b**) also reduced the activity. In the SO_2 case, one of the methyls at both C-5 and C-7 has been replaced by hydrogen. Expansion of ring A with inclusion of a sulfur atom (**9d–f**) led to a lower ED_{50} for the unsubstitute phenyl derivative (**9e** vs. **5a**; ED_{50} = 31.3 vs. 163.1). The total CNS profile of **9e** both in rodents and *Cebus* monkeys, however, suggested a compound of significantly weaker sedative–hypnotic activity than **5a**. Why the m-NO_2 analogue **9f** was of a lower HXB reinduction activity, especially in light of the qualitative trends discussed for the compounds of series **5** and **6** (vide infra and Tables I and II), is unclear. A series of all-carbon A-ring analogues (**9u–x**), three of which contain an A-ring oxygen [as a carbonyl (**9u**), hydroxyl (**9v**), or epoxide (**9x**)], all failed to display any CNS activity. Similarly, the open

Table V

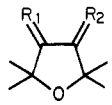


10

no.	mp or bp (mm), °C	yield, % (method)	R_1	R_2	R_3	R_4	R_5	X	emp formula	anal.	HXB ED_{50}, mg/kg
10a	145-155 (0.05)	47 (A)	C_6H_5	CH_3	CH_3	C_6H_5	C_6H_5	NO	$C_{25}H_{21}N_3O_2$	C, H, N	0
10b	150-165 (0.05)	74 (A)	CH_3	CH_3	CH_3	C_6H_5	C_6H_5	NO	$C_{20}H_{19}N_3O_2$	C, H, N	0
10c	155-158	31 (D)	m-$NO_2C_6H_5$	CH_3	C_6H_5	CH_3	CH_3	N	$C_{20}H_{18}N_4O_3$	C, H, N	800[a]
10d[b]	123-125	37 (A)	C_6H_5	CH_3	CH_3	$-(CH_2)_5-$		NO	$C_{18}H_{21}N_3O_2$	C, H, N	183.3
10e[b]	110-112	45 (A)	C_6H_5	$-(CH_2)_5-$		CH_3	CH_3	NO	$C_{18}H_{21}N_3O_2$	C, H, N	0
10f	84-85	23 (A)	CH_3	$-(CH_2)_5-$		CH_3	CH_3	NO	$C_{13}H_{19}N_3O_2$	C, H, N	0
10g	127-129	92 (C)	C_6H_5	$-(CH_2)_5-$		CH_3	CH_3	N	$C_{18}H_{21}N_3O$	C, H, N	0
10h	177-178.5	44 (A)	H	CH_3	CH_3	$-(CH_2)_5-$		NO	$C_{12}H_{17}N_3O_2$	C, H, N	0

[a] Extrapolated value. [b] Prepared from a mixture of hydrazine oximes (3). Separated by column chromatography.

Table VI



11

no.	mp or bp (mm), °C	yield, % (method)	R_1	R_2	emp formula	anal.	HXB ED_{50}, mg/kg
11a	114-116	97 (F)	NOH	NNHCO(m-$CF_3C_6H_4$)	$C_{16}H_{18}N_3O_3F_3$	C, H, N	0
11b	102-103	63 (F)	O	NNH_2	$C_8H_{14}N_2O_2 \cdot 0.5H_2O$	C, H, N	133.4
11c	58-59	90 (F)	H_2	$NNHC_6H_5$	$C_{14}H_{20}N_2O$	C, H, N	162.5
11d	87-93	84 (F)	O	$NNHC_6H_5$	$C_{14}H_{18}N_2O_2$	C, H, N	0
11e	150-160 (0.05)	93 (F)	O	$NNHCH_2CH(OH)CH_2CH_3$	$C_{14}H_{22}N_2O_3$	C, H, N	0
11f	168-169	96 (F)	H_2	NNH(p-$NO_2C_6H_4$)	$C_{14}H_{19}N_3O_3$	C, H, N	0
11g	104-105	88 (F)	H_2	NNH(o-$NO_2C_6H_4$)	$C_{14}H_{19}N_3O_3$	C, H, N	1000[a]
11h	114-114.5	83 (F)	O	NNH(m-$NO_2C_6H_4$)	$C_{14}H_{19}N_3O_3$	C, H, N	0

[a] Extrapolated value.

A-ring analogues **9g–i,z** which were prepared from **9k**, as well as the all-carbon analogues **9q–s**, were all devoid of the desired biological activity. From the entire series of compounds with A-ring modifications (Tables IV and V) emerge the following qualitative relationships: a heteroatom at position 6 is necessary for activity with the order of preference being O > N or SO_2; expansion of the ring from 5 to 6 or 7 atoms lowers activity; opening of the ring eliminates activity.

We next turned our attention to modifications of the B-ring triazine (**8a–d**) (Table III). Surprisingly, 1-*N*-oxide **8a** lacked CNS activity. This is especially surprising when one considers that the presence or absence of the *N*-oxide at N-4 has little effect on biological activity. Replacement of N-4 with carbon (**8c**) provides a compound with improved HXB activity but a poorer overall CNS profile than the parent compounds **5a** or **6a**. Similar manipulations of N-2 (**8d**) or N-1 (**8b**) either reduced or eliminated CNS activity. Based on these findings, the relative order of importance of the triazine nitrogens in determining biological activity would appear to be N-1 > N-2 >> N-4. Of the open B-ring compounds (**11a–h**) (Table VI), only hydrazone **11b** and phenylhydrazone **11c** displayed significant HXB reinduction activity. Both were eliminated from further consideration on the basis of their respective CNS profile.

Looking next at the C-ring (Tables I and II), one observes that substitution for the phenyl (**5a**) by H (**5p**), CH_3 (**5q**), OH (**5x**), benzyl (**6u**), or adamantyl (**6x**) provides compounds devoid of CNS activity. The 2-thienyl analogues (**6t,w**) display no CNS activity, while the 2-quinolyl derivative's (**6v**) HXB reinduction activity is equivalent to that of the parent compound **6a**. Of the pyridyl analogues, 2-pyridyl (**6r**) was the most active. The 2-pyridyl N-oxide (**6y**) was considerably less active. Several of the other pyridine analogues, in particular 3-pyridyl (**6m**), 4-pyridyl (**6n**), and 2-(5-chloro)pyridyl (**6q**), were eliminated from further consideration because of their low LD_{50} values (toxicity). Finally, from a limited group of analogues with substituents[4] on the freely rotating phenyl ring, we can discriminate quite nicely between the physiochemical parameters relating to hydrophobic (π), electronic (σ), and steric (E_s) effects.[5] The order of substituent preparation

(4) G. B. Bennett, A. D. Kahle, H. Minor, and M. J. Shapiro, *J. Heterocycl. Chem.*, **16**, 1389 (1979).
(5) A more complete quantitative discussion of 3-aryl-substituted analogues will be published elsewhere.
(6) S. Irwin in "Pharmacologic Techniques in Drug Evaluation", J. M. Nodine and P. E. Siegler, Eds., Yearbook Medical Publishers, Chicago, 1964, p 36.
(7) L. C. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med.*, **57**, 261 (1944).
(8) C. A. Winter, *J. Pharmacol. Exp. Ther.*, **94**, 7 (1948).
(9) H. Neunhoeffer and V. Bohnisch *Tetrahedron Lett.*, 1429 (1973).
(10) J. Burdon and A. Ramirez *Tetrahedron*, **29**, 4195 (1973).

Table VII. Primary Pharmacology Results

test model	results[a] po 5b	po methaqualone	ip 5b	ip methaqualone
behavioral effects (mice)				
docility	23 ± 16	20 ± 4	100 ± 34	31 ± 6
hypomotility	50 ± 22	25 ± 4	weak @ 200	34 ± 21
righting reflex	55 ± 33	23 ± 4	123 ± 33	34 ± 11
ataxia	39 ± 22	23 ± 4	130 ± 54	29 ± 19
prehensile	54 ± 15	30 ± 3	125 ± 36	37 ± 10
behavioral effects (rats)				
ataxia	39 ± 22	23 ± 4		
hypomotility	37 ± 18	44 ± 11		
righting reflex	118 ± 56	52 ± 15		
acute toxicity (mice)				
LD_{50} 2 h	>400	>400	>400	565 ± 40
72 h	>400	>400	235 ± 29	470 ± 60
acute toxicity (rats)				
LD_{50} 2 h	>800	>800		
72 h	>800	185 ± 49		
reinduction of anesthesia (mice)			72 ± 12	19 ± 4
anticonvulsant effects (mice)				
tonic convulsions	>1000	39 ± 5	54 ± 10	25 ± 4
mortality	>1000	45 ± 5	54 ± 10	25 ± 4
rotorod motor coordination (mice)	>1000	36 ± 6	51 ± 20	25 ± 4

[a] LD_{50} ± SE, ED_{50} ± SE, or evaluations at the highest nontoxic dose used (mg/kg). Evaluations were made using a minimum of 20 animals for each drug.

was based on the procedure which applies the Hansch approach to drug design.[23]

Qualitatively certain trends or conclusions are apparent.[5] In particular: (1) ortho and para substitution lowers biological activity, independent of the electronic, steric, or hydrophobic character of the substituent, e.g., **5b** vs. **5m** or **5n**, **5d** vs. **5k**, **5e** vs. **5h**, and **5g** vs. **5i**; (2) meta substitution increases the biological activity when the substituent's electronic effect (σ) increases (except **5g**) and the hydrophobic effect (π) remains high; (3) the steric effect (E_s) of the meta substituent does not appear to play a major role in determining activity, yet (4) the aromatic C ring must retain some rotational freedom (**5b** vs. **5f** and **5n**). From this series emerged compound SaH 51-676, 5,7-dihydro-5,5,7,7-tetramethyl-3-(3-nitrophenyl)furo[3,4-*e*]-*as*-triazine 4-oxide (**5b**), a potent sedative–hypnotic of novel chemical structure and unique pharmacological properties.

Table VIII. *Cebus* Monkey Sleep and Performance Results

criterion	effect of 5b
potency	4 to 64× the potency of methaqualone as measured by the threshold sleep-inducing dose (methaqualone threshold dose = 15-30 mg/kg)
duration of action	3 to 9 h
total sleep time	significantly increased in all monkeys (10-30% at the threshold sleep-inducing dose)
deep sleep	not significantly affected
stage REM	not affected or significantly enhanced at lower doses and significantly decreased only at doses at least 4 to 8× the threshold sleep-inducing doses
sleep latency	shortened (65-85% at the threshold sleep-inducing dose)
REM latency	shortened except at doses of 4 to 16× the threshold sleep-inducing doses where REM latencies are delayed
performance	not significantly disrupted until 8 to 64× the threshold sleep-inducing dose is administered; overall efficiency on the schedule (i.e., as measured via responses per reinforcements) was either not affected or improved

Pharmacology. Compound 5b. At the primary testing level (Table VII), compound **5b** was found to produce moderate CNS depressant activity in mice which was characterized by hypomotility, docility, ataxia, and depression of righting and prehensile reflexes. In interaction studies in the same species, compound **5b** was only moderately active in the hexobarbital reinduction test. Similarly, the compound caused only weak CNS depressant effects (hypomotility, ataxia) in rats. Despite the fact that compound **5b** did not cause profound depression, the profile of activity suggested sleep-inducing properties, and the compound was submitted for testing in *Cebus* monkeys.

(11) E. A. Braude, R. P. Linstead, and K. R. H. Wooldridge, *J. Chem. Soc.*, 3586 (1954).
(12) F. H. Case, *J. Hetrocycl. Chem.*, 7, 1001 (1970); H. Neunhoeffer, "The Chemistry of Hetrocyclic Compounds", Interscience, New York, 1978.
(13) C. L. Coon, W. G. Blucker, and M. E. Hill, *J. Org. Chem.*, 38, 4243 (1973).
(14) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", Wiley, New York, 1965, p 147.
(15) F. J. Lalor and F. L. Scott, *J. Chem. Soc., C*, 1034 (1969).
(16) T. J. Delia, M. J. Olsen, and G. B. Brown, *J. Org. Chem.*, 30, 2766 (1965).
(17) W. W. Pandler and T. K. Chen, *J. Org. Chem.*, 36, 787 (1971).
(18) P. J. Pearce, D. H. Richards, and N. F. Scilly, *J. Chem. Soc., Chem. Commun.*, 1160 (1970).
(19) M. Brugger, H. Wamhoff, and F. Korte, *Ann. Chem.*, 755, 101 (1972).
(20) H. I. Schlesinger and H. C. Brown, *J. Am. Chem., Soc.*, 75, 215 (1953).
(21) L. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, Vol. 1, 1967, p 136.
(22) B. A. Stoochnoff and N. L. Benoiton, *Tetrahedron Lett.*, 21 (1973).
(23) J. G. Topliss, *J. Med. Chem.*, 20, 463 (1977).
(24) I. Oswald, S. A. Lewis, J. Tagney, H. Firth, and I. Haider, in ref 1, pp 613-625.
(25) I. MacPhail, A. Ogilvie, and C. R. Purvis, *J. Int. Med. Res.*, 3, 49 (1975).

In *Cebus* monkeys, compound **5b** was 4 to 64 times more potent than methaqualone as a sleep inducer. However, compound **5b** did not disrupt state REM sleep until a dose 8 times the threshold sleep-inducing dose was administered and performance was not affected even at that dose level, whereas, methaqualone disrupted REM sleep at twice the threshold hypnotic dose. The effects in combined sleep and performance in three *Cebus* monkeys are summarized in Table VIII.[26]

In these experiments, compounds **5b** was active in inducing and maintaining sleep in the *Cebus* monkey, while supporting the impression that the agent will not interfere with the quality of sleep. In addition, the results from the performance portion of the experimental sessions indicate that compound **5b** will not cause the "hangover" characteristic of most marketed sleep-inducing substances.

There was some evidence of anxiolytic activity as measured in the Geller conflict procedure in rats. At an oral dose of 12.5 mg/kg, there was an increase in responding during the conflict segment of the schedule, yet there was no effect on the VI (variable interval) segment of the schedule at doses up to 50 mg/kg. The absence of an effect on VI response is an indication that compound **5b** is devoid of undesirable side effects.

In spinal studies in cats, 100 mg/kg compound **5b** given orally failed to alter segmental reflexes and exhibited no signs of toxicity. Intravenous administration of 1–4 mg/kg, on the other hand, caused respiratory failure and death, although again there were no effects on the physiological reflexes at sublethal doses.[27]

Compound **5b** in normal, free ranging cats produces CNS depression but at doses far greater than the active pharmacological doses, suggesting that the sleep-inducive effect is highly specific. Although the subjects slept if left undisturbed, they were easily aroused and were alert as long as they received attention.

Oral doses of 30, 30, and 60 mg/kg (accumulated dose of 120 mg/kg) failed to increase blood pressure or alter pulse rate in an unanesthetized *Cebus* monkey; in a second monkey, an accumulated dose of 180 mg/kg had no effect on blood pressure, pulse rate, or electrocardiogram.

Thus, in animal testing, compound **5b** appears to be an active sleep-inducing agent. It is potent, the estimated human dosage being 20–40 mg hs, and has several advantages over the currently marketed sedative–hypnotic drugs, the most important being no disruption of REM sleep. In addition, it has preclinical activity indicative of an antianxiety drug.

If these pharmacological activities are supported in clinical studies, compound **5b** would overcome some of the disadvantages of the currently marketed hypnotics.

Experimental Section

Biological Methods. Acute Behavioral and Toxicity Studies in Mice and Rats. Acute toxicities were determined intraperitoneally and orally with Royal Hart male mice, 20–25 g, and orally with Wistar male rats, 130–160 g. Behavioral analyses were conducted for 2 h after ip administration to mice and at 1–2 and 4 h after ip administration to rats. A modification of the method of Irwin[6] was used. All LD_{50} and ED_{50} values (mg/kg) were estimated by probit analysis according to Miller and Tainter.[7]

Reinduction of Anesthesia in Mice. A modification of the method of Winter[8] was used. Reinduction was defined as the ability of a compound when administered ip to reinduce anesthesia in mice (Royal Hart males, 20–25 g) which were awakening (regaining their righting reflex) from anesthesia previously induced by hexobarbital, 70.0 mg/kg iv. ED_{50} values (mg/kg) (defined as that dose of drug which reinduced anesthesia, i.e., loss of righting reflex for 10 min in 50% of mice) were estimated by probit analysis.

Anticonvulsant Effects in Mice. Seizures were evoked in groups of five male Royal Hart mice, 20–25 g, by SaH 41-178 (50.0 mg/kg, ip).[28] Test substances were administered intraperitoneally or orally 1 h prior to administration of SaH 41-178. ED_{50} values for antagonism of tonic convulsions or death (defined as those doses which prevented these effects in 50% of the animals) were estimated by probit analysis.

Effects on Motor Coordination in Mice. A modification of the rotarod method of Dunham and Miya[29] was used. Groups of five male Royal Hart Mice, 20–25 g, were trained to ride a revolving rod (15 rpm) covered with corrugated paper for 60–90 s. Ability of the mice to remain on the rod was tested again at 30 and 60 min after intraperitoneal or oral administration of drug or saline. Rotarod times for control and treated groups were compared to determine the percent change. ED_{50} values were defined as that dose of drug which decreases the rotarod time by 50% and were estimated by probit analysis.

Effects on Sleep Patterns of *Cebus* Monkeys. To study the effects of drugs on sleep, the animals were implanted under sterile conditions with both cortical (monopolar) and subcortical (bipolar) electrodes. Stainless-steel screws were inserted over the superior orbital ridges of both eyes for electrooculograms (EOG), and Nichrome wires bared at their tips were inserted in the dorsal neck muscles for electromyograms (EMG). All subjects were allowed at least 2 weeks to recover before any recordings were obtained.

For recording purposes, the monkeys were restrained via neck and waist plates in chairs, which were placed within sound-attenuated cubicles. Five channels of data per animal were recorded. Sessions began with dosing of the monkeys at 5:00 p.m. each night. EEG data were recorded for 13.5 h, Monday thru Thursday, and were scored using visual analysis. One decision (sleep epoch) was made per 50 s of data (one page), with the stage of sleep occupying the majority of the time per epoch, being scored as the stage of sleep for the total epoch. The exception was deep sleep, for which 10 s per epoch was sufficient to score the epoch as deep sleep.

Nine hours after the onset of each experimental session, an audible tone signified the start of a 90-min operant conditioning task. The tone reoccurred every 5 min until the monkey was awakened and a lever press occurred. This lever press was immediately reinforced with a banana-flavored pellet and also initiated a DRL (differential reinforcement of low rate of responding) 60-s schedule. According to the contingencies of the DRL-60, each lever press reset a timer to zero. However, if 60 s elapsed between lever presses, the monkey was automatically reinforced with a banana-flavored pellet. The number of reinforcements were recorded, and interresponse time, i.e., the times between lever presses, were counted.

Each animal served as its own control, with each parameter of sleep and performance being statistically compared to the last 15 control days. Each control night, the subjects were dosed intragastrically with a carboxymethylcellulose placebo suspension. Drugs were administered per os. Computerized statistical readouts were obtained for all control sessions in order to determine any drug rebound and/or carry-over effects on sleep patterns and to ensure control stability between drug administrations.

Effects on Experimentally Induced Conflict in Rats. In the Geller conflict test,[30] brief sessions of an approach–avoidance paradigm (conflict) were interposed upon a food-reinforced behavioral schedule (variable interval, VI). The primary activity of antianxiety drugs was demonstrable during the conflict trials as an increase in responding. Secondary activities, or side effects, were demonstrable as disruptions of the VI portion of the schedule.

(26) *Cebus* monkey sleep and performance data are available from the authors upon request.

(27) The observed toxicity after iv administration in the spinal cats preparation is most probably due to the interaction of the surgical anesthetic and compound **5b**.

(28) L. C. Iorio, E. A. Ryan, and J. H. Gogerty, *Arch. Int. Pharmacodyn. Ther.*, **206**, 282 (1973).

(29) N. W. Dunham and T. S. Miya, *J. Am. Pharm. Assoc.*, **46**, 208 (1957).

(30) I. Geller and J. Seifler, *J. Psychopharmacol.*, 1, 482 (1960).

Overt Behavior in Normal, Free Ranging Cats. Three cats administered compound **5b** were tested for gross behavioral changes. After the animals were dosed, they were simply handled and observed for the ensuing 4–6 h and overt changes in behavior were noted.

Effects on Gross Spinal Reflexes in Cats. The effects of compound **5b** were studied on monosynaptic (patellar) and polysynaptic (flexor) spinal reflexes in intact-chloralose anesthetized cats. The monosynaptic reflex was elicited by tapping the patellar tendon with a solenoid-controlled hammer, and the ensuing knee jerk was recorded. The flexor reflex was recorded as contractions of the tibialis anticus muscle elicited by electrical stimulation of the popliteal nerve.

Cardiovascular Effects in *Cebus* Monkeys. Blood pressure was recorded from two *Cebus apella* monkeys via polyethylene catheters inserted into a carotid artery of each subject. Following surgical implantation of the catheters, the subjects were placed in restraining chairs and allowed to accommodate for 2.5–3.0 h before drug administration. In addition to blood pressure, an EEG was monitored in one subject and an EKG was recorded in the second.

Chemistry. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Silica gel (0.063–0.2 mm) was used in preparing column chromatograms, and analytical thin-layer chromatography was conducted on precoated 40 × 80 mm plastic sheets of silica gel G with fluorescent indicator. In all workup procedures, the drying process involved swirling over $MgSO_4$ and filtering prior to evaporation. Starting materials 1–4 were prepared according to literature methods.[2,3] Compounds of type 5, 6, and 8–11 were prepared according to literature methods A,[9] B,[9,10] C,[11] D,[12] E,[13] F,[14] G,[15] H,[16] I,[17] J,[2] M,[18] N,[19] O,[20] P,[21] and Q.[22] The pertinent data are summarized in Tables I–VI.

Method K. Preparation of 3-Phenyl-5,7-dihydro-5,5,7,7-tetramethylfuro[3,4-*c*]pyridazine Hydrochloride (8c). Using a condenser equipped with a Dean–Stark trap, a mixture of 4-hydroxy-4-(phenylethynyl)-2,5-dihydro-2,2,5,5-tetramethylfuran-3(2*H*)-one (2.58 g, 10 mmol), hydrazine (0.32 g, 10 mmol), and $pTsOH \cdot H_2O$ (0.19 g, 1 mmol) was heated in refluxing toluene (50 mL) for 18 h. After cooling and neutralization with $NaHCO_3$, the solution was evaporated in vacuo and the resulting residue dissolved in Et_2O. Recrystallization of the solid resulting from HCl gas addition to the Et_2O solution from CH_2Cl_2–hexane gave 1.60 g (55%) of pyridazine **8c** as a yellow solid, mp 151–152 °C.

Method L. Preparation of 2-Phenyl-5,7-dihydro-5,5,7,7-tetramethylfuro[3,4-*b*]pyrazine 1-Oxide Hydrochloride (8d). A solution of 1-aminoacetophenone hydrochloride (1.71 g, 10 mmol) in toluene (50 mL) was neutralized with concentrated NH_4OH. To the mixture was added 2,2,5,5-tetramethylfuran-3,4-dione monooxime (1.71 g, 10 mmol), and the resulting mixture was heated at reflex for 18 h using a Dean-Stark trap to remove azeotroped water. Evaporation of the solvent and chromatography of the residue over silica gel gave a brown oil. Dissolution in Et_2O and HCl gas addition provided 0.37 g (12%) of pyrazine **8d**, mp 121–125 °C.

Acknowledgment. The services provided by the Physical Chemistry Section of Preclinical Research are greatfully acknowledged. The authors also thank Dr. S. Barcza for many helpful discussions.

New Analgesic Drugs Derived from Phencyclidine[1]

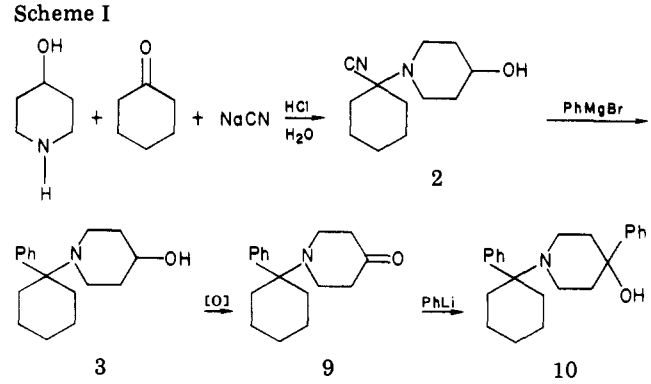
Yossef Itzhak, Asher Kalir,* Ben Avi Weissman, and Sasson Cohen

Department of Physiology and Pharmacology, Tel-Aviv University, Sackler School of Medicine, and Israel Institute for Biological Research, Ness-Ziona, Israel. *Received August 14, 1980*

Several esters of 1-(1-phenylcyclohexyl)-4-piperidinol (**3**), 1-(1-phenylcyclohexyl)-4-phenyl-4-piperidinol (**10**) and its propionate (**11**), and 1-(1-phenylcyclohexyl)-4-phenylpiperidine (**13**) were prepared and characterized. The new compounds, which are derived from phencyclidine, exerted analgesic activity in mice. The most potent is **10**, which is twice as active as morphine. The antinociceptive activity of **10**, **11**, and **13** could be well correlated with their potency in the mouse vas deferens bioassay, and both were completely reversed by naloxone.

Phencyclidine [1-(1-phenylcyclohexyl)piperidine, PCP], now a major drug of abuse,[2] held intially the promise of a safe general anesthetic. Indeed, the drug is unique in its lack of depressant effect on the heart and respiration.[3a,b] Its use, precluded in man on account of the acute psychotic syndrome it precipitates, is still practiced with success in veterinary medicine.[4,5] PCP has also been accredited with the exertion of analgesia,[6,7] but no precise data are available on this particular aspect. We assumed that a proper manipulation of the PCP structure might change the balance between its antinociceptive and psychotomimetic properties in favor of the former. This is not unreasonable, in view of the successful precedence offered by ketamine,[8]

Scheme I



(1) Taken from the Ph.D. dissertation of Y.I., 1980.
(2) R. C. Petersen and R. C. Stillman, "Phencyclidine: A Review", National Institute of Drug Abuse: Washington, D.C., May, 1978.
(3) (a) F. E. Greifenstien, M. Devault, J. Yoshitake, and J. E. Gajewski, *Anesth. Analg. (Cleveland)*, **37**, 283 (1958); (b) M. Johnstone, Y. Evans, and S. Baigel, *Br. J. Anesth.*, **31**, 433 (1959).
(4) E. F. Domino, D. A. McCarthy, and G. A. Deneau, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **28**, 1500 (1969).
(5) G. Chen and J. Can, *Anaesth. Soc.*, **20**, 180 (1973).
(6) E. C. Maybe, and H. J. Baker, *J. Am. Vet. Med. Assoc.*, 147, 1068 (1965).
(7) A. M. Harthoorn, *Nature (London)*, **198**, 1116 (1963).
(8) R. A. Myres, *J. Am. Vet. Med. Assoc.*, **162**, 835 (1973).

0022-2623/81/1824-0496$01.25/0