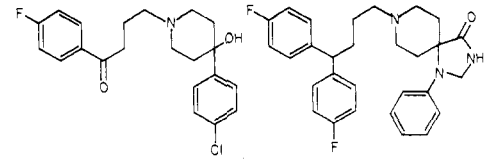
(4) G. Woolfe and A. D. MacDonald, *J. Pharmacol. Exp. Ther.*, 80, 300 (1944).
(5) F. E. D'Amour and D. I. Smith, *J. Pharmacol. Exp. Ther.*, 72, 74 (1941).
(6) W. O. Evans, *Psychopharmacologia*, 2, 318 (1961).
(7) S. S. Tenen, *Psycopharmacologia*, 12, 278 (1968).
(8) L. Grumbach in "Pain", R. S. Knighton and P. R. Dunke, Ed., Little, Brown and Co., Boston, Mass., 1966, p 163.
(9) J. D. Hardy, H. G. Wolff, and H. Goodell, "Pain Sensations and Reactions", Williams and Wilkins, Baltimore, Md., 1952, p 67.
(10) E. L. Way, H. H. Loh, and F. H. Shen, *J. Pharmacol. Exp. Ther.*, 167, 1 (1969).
(11) W. Straub, *Dtsch. Med. Wochenschr.*, 37, 1462 (1911).
(12) B. K. Koe, *Experientia*, 31, 699 (1975).
(13) A. Weissman, *Psychopharmacologia*, 12, 142 (1968).
(14) For example, haloperidol (X) and fluspirilene (XI).



X XI

(15) P. A. J. Janssen in "Modern Problems in Pharmacopsychiatry; The Neuroleptics", Vol. 5, D. P. Bobon, P. A. J. Janssen, and J. Bobon, Ed., S. Karger, Basel, 1970, p 33.

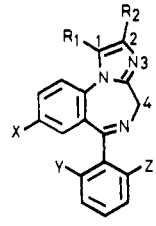
Diazepines. 5. Synthesis and Biological Action of 6-Phenyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines[1-3]

Takeshi Hara,* Yasutaka Kayama, Toshiro Mori, Kazuhiko Itoh, Hitoshi Fujimori, Tamiko Sunami, Yoshinobu Hashimoto, and Sachio Ishimoto

Teijin Institute for Bio-medical Research, Asahigaoka, Hino, Tokyo 191, Japan. *Received July 29, 1977*

A series of 6-phenyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines (**2**) has been prepared with 2-phthalimidomethylfurans (**12**) and 1-phthalimidoalkane-2,5-diones (**15**) or 2,5-dimethoxy-2-phthalimidomethyltetrahydrofurans (**16**) as the key intermediates and subsequently evaluated for CNS activity. The structure–activity data generated indicate that, in general, introduction of the methyl and/or ethyl group(s) in the pyrrole ring and a chlorine atom at the ortho position of the 6-phenyl group increases the activity and that substitution of the above chlorine atom for a fluorine atom decreases the activity. 8-Chloro-6-(2-chlorophenyl)-1,3-dimethyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (**2p**), the most potent among the compounds synthesized, was equipotent in taming and sedative activities to diazepam. The acute LD_{50} of **2p** in mice was larger than 3000 mg/kg po.

Previously we have observed that the introduction of an alkyl group (particularly the methyl and the ethyl group) at the 2 position of 6-phenyl-4*H*-imidazo[1,2-*a*][1,4]-benzodiazepines (**1**) greatly enhances the CNS activity of



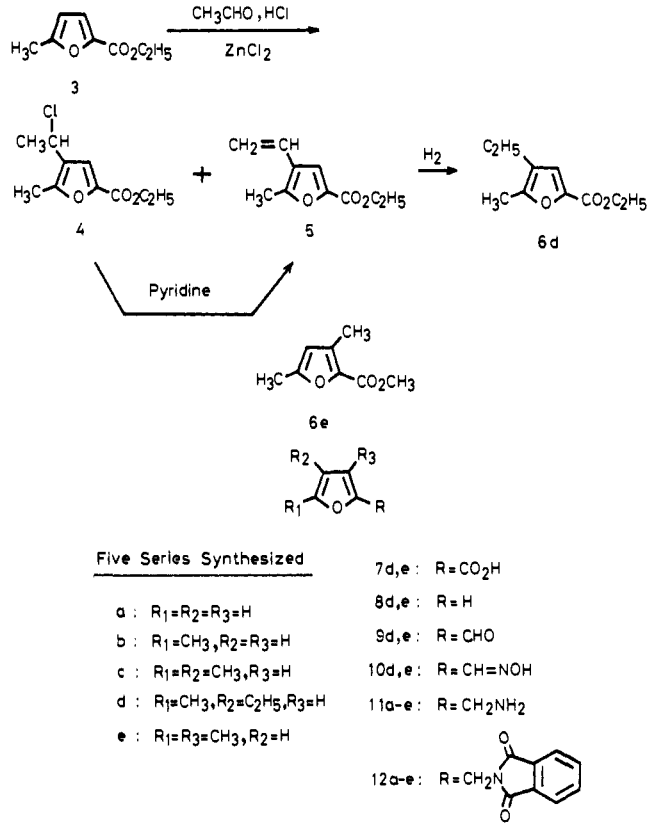
1

the compounds.[4] The present study was undertaken in order to synthesize 6-phenyl-4*H*-pyrrolo[1,2-*a*][1,4]-benzodiazepines[5] (**2**) by an efficient method and to investigate the CNS activity of the compounds particularly in terms of the effect of the alkyl group(s) on the pyrrole ring upon the pharmacological action. The potential effect of the introduction of an alkyl group at the 3 position is of interest, for compounds **1** cannot possess an alkyl group at this position.

Chemistry. The tricyclic diazepine compounds **2** were synthesized (Scheme III) with the furans **12** (Scheme I) and the 1,4-diketones **15** or the tetrahydrofurans **16** (Scheme II) as the key intermediates.

Phthalimidomethylfurans. Compound **4** obtained by distillation in the α-chloroethylation[7] of ethyl 5-methyl-2-furoate (**3**) using acetaldehyde and hydrogen chloride with zinc chloride as the catalyst was accompanied by the olefin **5**, apparently arising from the dehydrochlorination of the α-chloroethyl derivative **4** in the distillation flask. The mixture of **4** and **5** so obtained was heated with pyridine to yield pure **5**, which was then hydrogenated over Raney nickel to give ethyl 4-ethyl-5-methyl-2-furoate (**6d**). The ester **6d** was hydrolyzed to the acid **7d**, which was

Scheme I



decarboxylated[8] to **8d** by heating in an oil bath of 250–265 °C with copper powder and quinoline. The formylation of **8d** under Vilsmeier conditions[9] afforded the aldehyde **9d**. The phthalimidomethylfuran **12d** was prepared from **9d** via the oxime **10d** and the amine **11d** according to the

0022-2623/78/1821-0263$01.00/0

Table I. 1,4-Diketones 15, Tetrahydrofurans 16, and Their Synthetic Intermediates 12-14

Compd	Mp, °C	Recrystn solvent[a]	% yield	Formula	Analyses[b]
12d	144-144.5	E	70[c]	$C_{16}H_{15}NO_3$	C, H, N
12e	114.5-115	M	89[c]	$C_{15}H_{13}NO_3$	C, H, N
13a	147.5-148[d]	MC-H	73[e]	$C_{15}H_{15}NO_5$	C, H, N
13d	127-129.5[f]	EE-H	98[g]	$C_{18}H_{21}NO_5$	H, N; C[h]
13e	142-154[i]	M	71[c]	$C_{17}H_{19}NO_5$	C, H, N
14d	100.5-101	MC-H	65[j]	$C_{16}H_{15}NO_4$	C, H, N
14e	171-171.5	MC-H	78[j]	$C_{15}H_{13}NO_4$	C, H, N
15a	136-137.5	MC-C	97[g]	$C_{13}H_{11}NO_4$	C, H, N
15d	79.5-80.5	EE-H	96[g]	$C_{16}H_{17}NO_4$	C, H, N
15e	101.5-102.5	M	98[g] 96[j]	$C_{15}H_{15}NO_4$	C, H, N
16a	113-114.5[k]	MC-H	98[g]	$C_{15}H_{17}NO_5$	C, H, N

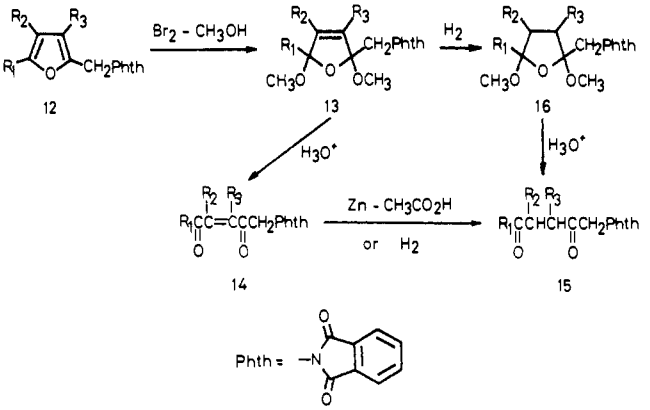
[a] E = EtOH; M = MeOH; MC = CH_2Cl_2; H = *n*-hexane; EE = ether; C = CCl_4. [b] Analyses for the elements indicated were within ±0.4% of the theoretical values unless otherwise noted. [c] Yield of recrystallized material. [d] Melting point of the less soluble isomer obtained by fractional recrystallization. [e] Yield of recrystallized material plus material obtained by silica gel column chromatography of the mother liquor. [f] Melting point of a mixture of *E* and *Z* isomers (major isomer:minor isomer = 22:1). [g] Yield of crude material identified by NMR spectroscopy. [h] C: calcd, 65.24; found, 65.69. [i] Melting point of a mixture of *E* and *Z* isomers (major isomer:minor isomer = 12.6:1). [j] Yield of material purified by silica gel column chromatography with benzene-AcOEt. [k] Melting point of one isomer obtained from the corresponding, less soluble isomer of 13a.

standard procedure.[10,11] Compounds **12a-c,e** were prepared similarly from **11a-c**[11,12] and **6e**[13] (Scheme I).

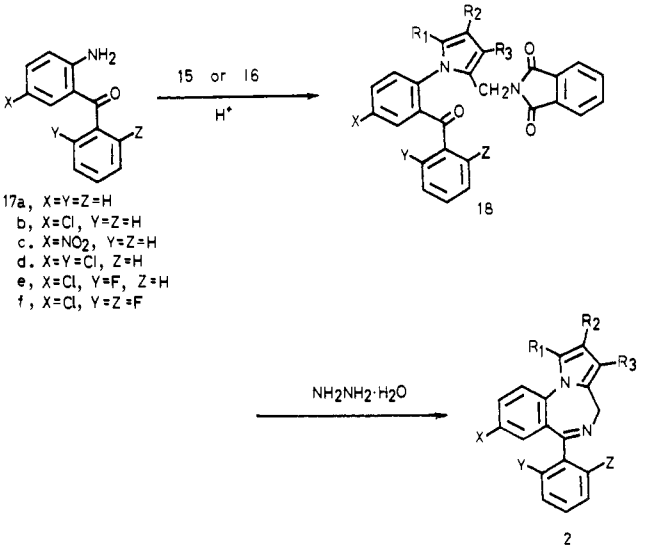
Phthalimido-1,4-dicarbonyl Compounds and Dimethoxyphthalimidomethyltetrahydrofurans. Compounds **15a-e** were prepared[14] from **12** via the dihydrofurans **13** and the unsaturated 1,4-diketones **14**. In the methoxylation of **12** to **13**, methylene chloride was used as the cosolvent of methanol because of the high solubility of **12** in methylene chloride even at the low reaction temperature of −50 to −20 °C. Compounds **13a,d,e** were, as in the cases of **13b,c**,[2,14] obtained as a mixture of *E* and *Z* isomers as indicated by two sets of the NMR signals of the methoxy groups and the methyl group at C-2 (or C-5). Hydrogenation of **13a,b** over Raney nickel proceeded smoothly under atmospheric pressure at room temperature to give **16a,b**, which on hydrolysis in a mixture of benzene and 2 N or 3 N HCl at the refluxing temperature afforded **15a,b**. This hydrolysis required stronger conditions than the conversion of **13** to **14** (Scheme II).

6-Phenyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines. The condensation of the 2-aminobenzophenones **17** with **15** or **16** with *p*-toluenesulfonic acid or trichloroacetic acid as the catalyst gave the pyrrolylbenzophenones **18**, which were then converted to the desired pyrrolobenzodiazepines **2** by the treatment with hydrazine hydrate (Scheme III). The transformation of **17** to **18** and then to **2** could also be operated, as a so-called one-vessel reaction, continuously without any workup of the first reaction mixture. Compounds **2** gave satisfactory IR, NMR, and mass spectra. In the NMR spectra the C-4 protons of **2**, except for **2b** and **2c**,[15] appeared as an AB quartet with δ_{AB} of about 1.0 ppm, whereas the δ_{AB} of the AB quartets of the corresponding methylene protons in **18** were smaller than or equal to 0.54 ppm. Another characteristic, NMR spectral change associated with the conversion of **18** having a methyl group at C-2′ of the pyrrole ring to the corresponding pyrrolobenzodiazepines **2** is a fairly large downfield shift (0.38-0.48 ppm in $CDCl_3$) of the methyl proton signal. These observations are consistent with the structure of **2**: the former observation is firstly due to the rigid tricyclic molecular structure retarding the flapping of the methylene group up and down the plane of the pyrrolobenzodiazepine structure considerably enough in the NMR time scale for each of the methylene protons to have a different chemical shift; the second observation is due to the anisotropic deshielding effect of the benzene ring of the benzodiazepine skeleton on the methyl group which is now close to the plane of the benzene ring. See Tables I-III.

Scheme II



Scheme III



Biological Studies. The pyrrolobenzodiazepines **2** were subjected to tests designed to measure CNS activities. In these tests the previously described methods[1] (see Experimental Section) were employed. The results are shown

Table II. 2-(2-Phthalimidomethylpyrrol-1-yl)benzophenones (18)

Compd	R_1	R_2	R_3	X	Y	Z	Mp, °C	Recrystn solvent[a]	% yield[b,c]	Method[d]	Rxn conditions[e]	Formula	Analyses[f]
18a	H	H	H	Cl	H	H	188-189.5	H	88[g]	A	TCA, 2[h]	$C_{26}H_{17}ClN_2O_3$	C, H, N
18b	H	H	H	Cl	Cl	H	237-239[i]		87[g]	A	TCA, 2[h]		IR[j]
18c	H	H	H	Cl	F	H	217.5-218	MC-C	64[g]	A	TCA, 2[h]	$C_{26}H_{16}ClFN_2O_3$	C, H, N
18d	CH_3	H	H	H	H	H	117.5-118	MC-H	92	B	TCA, 1	$C_{27}H_{20}N_2O_3$	H, N; C[k]
18e	CH_3	H	H	Cl	H	H	148.5-149.5	EE-H	93	B	TCA, 2	$C_{27}H_{19}ClN_2O_3$	C, H, N
									87	A			
18f	CH_3	H	H	NO_2	H	H	174-175	MC-H	59	B	PTS, 3.5	$C_{27}H_{19}N_3O_5$	C, H, N
18g	CH_3	H	H	Cl	Cl	H	170-170.5	MC-H	95[l]	B	PTS, 1.5	$C_{27}H_{18}Cl_2N_2O_3$	C, H, N
									80	A	PTS, 1.5		
18h	CH_3	H	H	Cl	F	H	184-185	MC-H	88	B	PTS, 1	$C_{27}H_{18}ClFN_2O_3$	C, H, N
									75	A	PTS, 1.8		
18i	CH_3	CH_3	H	H	H	H	186-187	MC-H	89	B	PTS, 1.5	$C_{28}H_{22}N_2O_3$	H, N; C[m]
18j	CH_3	CH_3	H	Cl	H	H	160-160.5	MC-H	92	B	PTS, 2	$C_{28}H_{21}ClN_2O_3$	C, H, N
18k	CH_3	CH_3	H	Cl	Cl	H	162-163	MC-H	97	B	PTS, 1	$C_{28}H_{20}Cl_2N_2O_3$	C, H, N
18l	CH_3	CH_3	H	Cl	F	H	152-153	MC-H	94	B	PTS, 1	$C_{28}H_{20}ClFN_2O_3$	C, H, N
18m	CH_3	C_2H_5	H	Cl	Cl	H	168-169.5	MC-H	65	B	PTS, 4	$C_{29}H_{22}Cl_2N_2O_3$	C, H, N
18n	CH_3	C_2H_5	H	Cl	F	H	185-186	MC-H	54[n]	B	PTS, 20	$C_{29}H_{22}ClFN_2O_3$	C, H, N
18o	CH_3	C_2H_5	H	Cl	F	F	198-199	MC-H	80	B	PTS, 24	$C_{29}H_{21}ClF_2N_2O_3$	C, H, N
18p	CH_3	H	CH_3	Cl	Cl	H	168.5-169.5	B-H	90[l]	B	PTS, 3.5	$C_{28}H_{20}Cl_2N_2O_3$	C, H, N
18q	CH_3	H	CH_3	Cl	F	H	168-168.5	MC-H	82[l]	B	PTS, 5	$C_{28}H_{20}ClFN_2O_3$	C, H, N
18r	CH_3	H	CH_3	Cl	F	F	187.5-188.5	MC-H	91[l]	B	PTS, 16.5	$C_{28}H_{19}ClF_2N_2O_3$	C, N; C[o]

[a] H = *n*-hexane; MC = CH_2Cl_2; C = CCl_4; EE = ether; B = benzene. [b] Yield of material purified, unless otherwise indicated, by silica gel column chromatography with benzene-AcOEt as the eluent; no efforts were made to optimize yields. [c] Unless otherwise indicated, compound **15** or **16** was used in a stoichiometric amount or in a small excess to **17** (1:1–1.07), and the yield is based on **17**. [d] A = reaction of **17** with **16**; B = reaction of **17** with **15**. [e] The reactions were run in, unless otherwise indicated, benzene by heating at reflux with a catalyst. The catalyst employed and refluxing time (h) are indicated: PTS = *p*-toluenesulfonic acid; TCA = CCl_3CO_2H. [f] Analyses for the elements indicated were within ±0.4% of the theoretical values unless otherwise noted. [g] Yield of material collected by filtration of the cooled reaction mixture. [h] In EtOH. [i] Of a product not recrystallized because of the very low solubility in solvents. [j] The symbol "IR" indicates that structure determination was by this method alone at this reaction step because of the very low solubility in solvents. [k] C: calcd, 77.12; found, 77.55. [l] Compound **17** was used in a small excess to 16b or **16e** (1:1.05), and the yield is based on **16b** or **16e**. [m] C: calcd, 77.40; found, 76.96. [n] 42% of **17d** was recovered. [o] C: calcd, 66.60; found, 67.07.

Table III. 6-Phenyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines

Compd	R_1	R_2	R_3	X	Y	Z	Mp, °C	Recrystn solvent[a]	% yield[b]	Rxn conditions[c]	Formula	Analyses[d]
2a	H	H	H	Cl	H	H	130.5-131.5[e]	H	78	A, 1.5	$C_{18}H_{13}ClN_2$	C, H, N
2b	H	H	H	Cl	Cl	H	135.5-136.5	H	83	C, 2	$C_{18}H_{12}Cl_2N_2$	C, H, N
2c	H	H	H	Cl	F	H	123-124	MC-H	76	C, 0.5	$C_{18}H_{12}ClFN_2$	C, H, N
2d	CH_3	H	H	H	H	H	142.5-143.5	EE-H	68	A, 1	$C_{19}H_{16}N_2$	C, H, N
2e	CH_3	H	H	Cl	H	H	144-145	EE-H	65	A, 1.5	$C_{19}H_{15}ClN_2$	C, H, N
2f	CH_3	H	H	NO_2	H	H	200-201.5	MC-H	71	B, 0.5	$C_{19}H_{15}N_3O_2$	C, H, N
2g	CH_3	H	H	Cl	Cl	H	134-135.5	MC-H	87	A, 1.5	$C_{19}H_{14}Cl_2N_2$	C, H, N
2h	CH_3	H	H	Cl	F	H	99.5-100.5	EE-H	54	A, 3	$C_{19}H_{14}ClFN_2$	H, N; C[f]
2i	CH_3	CH_3	H	H	H	H	140.5-141	EE-H	67	B, 0.5	$C_{20}H_{18}N_2$	C, H, N
2j	CH_3	CH_3	H	Cl	H	H	190.5-191.5	EE-H	56	B, 0.83	$C_{20}H_{17}ClN_2$	C, H, N
2k	CH_3	CH_3	H	Cl	Cl	H	132.5-133.5	EE-H	90	B, 0.5	$C_{20}H_{16}Cl_2N_2$	H, N, C[g]
2l	CH_3	CH_3	H	Cl	F	H	182.5-183.5	MC-H	68	B, 0.33	$C_{20}H_{16}ClFN_2$	C, N; H[h]
2m	CH_3	C_2H_5	H	Cl	Cl	H	136.5-137.5	EE-H	82	B, 1	$C_{21}H_{18}Cl_2N_2$	C, H, N
2n	CH_3	C_2H_5	H	Cl	F	H	169.5-170.5	EE-H	54	B, 1	$C_{21}H_{18}ClFN_2$	C, H, N
2o	CH_3	C_2H_5	H	Cl	F	F	204.5-205	MC-H	87	B, 1	$C_{21}H_{17}ClF_2N_2$	C, H, N
2p	CH_3	H	CH_3	Cl	Cl	H	132-133	EE-H	86	B, 0.5	$C_{20}H_{16}Cl_2N_2$	C, H, N
2q	CH_3	H	CH_3	Cl	F	H	99.5-101	EE-H	48	B, 1.5	$C_{20}H_{16}ClFN_2$	C, H, N
2r	CH_3	H	CH_3	Cl	F	F	*i*		83	B, 0.83	$C_{20}H_{15}ClF_2N_2$	

[a] H = *n*-hexane; MC = CH_2Cl_2; EE = ether. [b] Yield of material purified by silica gel column chromatography with benzene-AcOEt as the eluent; no efforts were made to optimize yields. [c] The conversion of **18** to **2** with hydrazine hydrate was run by heating in a solvent or a mixture of solvents: A, heating at reflux in EtOH; B, heating at reflux in a mixture of EtOH and *N*,*N*-dimethylformamide; C, heating in an oil bath of 100 °C in *N*,*N*-dimethylformamide. Heating time (h) is indicated. [d] Analyses for the elements indicated were within ±0.4% of the theoretical values unless otherwise noted. [e] Lit.[5] mp 125–126 °C (recrystallized from *n*-hexane). [f] C: calcd, 70.26; found, 70.81. [g] C: calcd, 67.61; found, 68.23. [h] H: calcd, 4.76; found, 5.17. [i] A glassy solid obtained failed to be recrystallized.

in Table IV along with the data for diazepam.

In general, the introduction of the methyl and/or ethyl group(s) in the pyrrole ring and chlorine and/or fluorine atom(s) at the ortho position(s) of the 6-phenyl group increased the overall activities. The introduction of two alkyl groups in R_1 and R_3 (**2p** and **2q**) produced a higher activity than their introduction in R_1 and R_2 (**2k** and **2l**) or the introduction of only one in R_1 (**2g** and **2h**)—in the last case the activity is the lowest among the three. Comparison of the data of **2m** and **2n** with those of **2k** and **2l** indicates that the ethyl group at C-2 is more effective in enhancing the CNS activity than the methyl group, which is consistent with our observation[4] with the 6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepine series.

Substitution of the chlorine atom in Y for a fluorine atom decreased the overall activities (compare **2h**, **2l**, and **2q** with **2g**, **2k**, and **2p**, respectively), though the opposite is observed[16] with the bicyclic benzodiazepines. The introduction of two fluorine atoms in Y and Z (**2r**) recovered the overall activities.

Table IV. Pharmacological Data[a,b]

Compd	Anticonvulsant act.		Taming act., fighting mouse	Muscle-relaxant act., inclined screen	Motor incoordinating act., rotating rod	Sedation, potentiation of thiopental
	Pentylenetetrazole	Maximal electroshock				
2a	78	>100	>100	>100	>100	44
2b	>100	>100	>100	>100	>100	18 (11.5-28.8)
2c	100	>100	39 (23.2-65.5)	>100	>100	5.2 (2.3-12.0)
2d	>100	>100	>100	>100	>100	22 (11.4-42.5)
2e	100	>100	>100	>100	>100	46
2f	≥100	>100	>100	>100	>100	5.8 (3.2-10.7)
2g	20 (15.9-25.2)	>100	11 (5.4-22.4)	>100	100	2.8 (1.1-7.1)
2h	36 (15.7-82.8)	>100	55	>100	>100	6.9 (2.9-16.2)
2i	>100	>100	>100	>100	>100	>30
2j	13.5 (7.5-24.3)	>100	≥30	>100	>100	21 (12.0-36.8)
2k	6.5 (3.0-14.3)	>100	4.8 (3.6-6.5)	>100	40	2.6 (1.7-3.9)
2l	10 (6.2-16.0)	>100	17 (12.4-23.3)	>100	>100	8.0 (1.3-49.6)
2m	3.4 (2.6-4.5)	>30	3.4 (2.2-5.2)	14 (7.8-25.2)	16.2 (4.1-64.8)	0.6 (0.3-1.1)
2n	5.5 (2.9-10.5)	>30	5.5 (2.9-10.5)	30	>100	2.2 (1.1-4.3)
2o	16.6 (5.8-47.3)	>30	12.5 (4.7-33.1)	69	>100	3.0 (1.2-7.3)
2p	1.4 (0.7-2.9)	100	1.6 (0.3-7.7)	8.2 (3.1-21.5)	15.5 (12.2-19.7)	0.34 (0.26-0.45)
2q	5.5 (2.9-10.5)	>100	8.8 (6.0-12.8)	20.5 (10.3-41.0)	>30	2.4 (1.7-3.4)
2r	2.0 (0.3-12.4)	88	1.6 (0.4-7.4)	6.4 (2.3-17.9)	16.2 (5.6-47.0)	0.7 (0.3-1.8)
Diazepam	0.6 (0.3-1.5)	8.8 (5.2-15.0)	1.6 (1.0-2.5)	0.6 (0.3-1.1)	5.4 (4.4-6.6)	0.3 (0.2-1.4)

[a] Values are ED_{50}'s expressed in mg/kg. [b] Values in parentheses are the 95% confidence limits of ED_{50}.

Compound **2p** is the most active among the compounds synthesized in the present study and is in comparison with diazepam, equipotent in taming and sedative activities, two to three times less potent in antipentylenetetrazole and motor incoordinating activities, and 11–13 times less potent in muscle relaxant activity and in preventing maximal electroshock seizure.

Compound **2p** was found to be considerably nontoxic; in an acute toxicological study the compound did not cause any death, as observed for a period of 2 weeks, to eight mice tested at a dosage of 3000 mg/kg po, the highest dosage employed.[17]

Experimental Section

Chemistry. Melting points were obtained on a Yanagimoto hot-stage apparatus and are uncorrected. Analyses were carried out by the Analytical Chemistry Laboratory of Central Research Institute, Teijin Ltd. IR spectra were recorded on a Hitachi EPI-500 spectrophotometer. NMR data were obtained on a JEOL JNM-MH-100 spectrometer with Me_4Si as an internal standard. Mass spectra were run on a LKB 9000 spectrometer at 70 eV. Although no spectral data are included in this report for compounds 4–11, all structural assignments for these compounds were unambiguously confirmed by NMR, supplemented by IR spectroscopy when necessary.

Ethyl 5-Methyl-4-vinyl-2-furoate (5). To a stirred mixture of ethyl 5-methyl-2-furoate (**3**) (45.7 g, 0.296 mol) and $ZnCl_2$ (9.6 g, 0.070 mol) in dry CH_2Cl_2 was added acetaldehyde (26.4 g, 0.599 mol) dropwise at 0 °C over a period of 45 min. To the mixture was introduced HCl gas at ca. 10 °C for 3 h. The mixture was warmed to room temperature, and stirring was continued overnight with the flask closed with stopcocks. The mixture was poured into cold water (300 mL) and extracted with CH_2Cl_2. The combined extracts were washed with water (2 × 150 mL), dried (Na_2SO_4), and evaporated. The residue was distilled, and 21.1 g of a mixture of ethyl 4-(1-chloroethyl)-5-methyl-2-furoate (**4**) and **5** (ca. 2:1) was obtained as a fraction boiling at 108–113 °C (3.7 mm).

The above mixture of **4** and **5** was heated with pyridine (20 mL) at reflux for 3 h, poured into water (800 mL), and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue was distilled to give 14.9 g (28% from **3**) of **5**, bp 73–77 °C (0.18 mm).

Ethyl 4-Ethyl-5-methyl-2-furoate (6d). Compound **5** (16.8 g, 93.2 mmol) was hydrogenated over Raney nickel in EtOH (300 mL) at room temperature to give 16.5 g (97%) of **6d**, bp 74–77 °C (0.4 mm).

4-Ethyl-5-methyl-2-furoic Acid (7d). A mixture of **6d** (27.6 g, 0.151 mol) and 20% aqueous NaOH solution (70 mL) was heated at reflux for 2 h and acidified by concentrated HCl under cooling with an ice bath. The precipitated crystals were collected by filtration and dried to give 21.1 g (91%) of **7d**.

3-Ethyl-2-methylfuran (8d). A mixture of **7d** (21.1 g, 0.137 mol), copper powder (5.1 g, 0.080 g-atom), and quinoline (50 g) was heated to boiling by raising the bath temperature gradually to 260 °C, and finally to 275 °C, during which 14.1 g (93%) of **8d** was collected as the distillate, bp 83–95 °C.

4-Ethyl-5-methyl-2-furaldehyde (9d). To a stirred mixture of *N*,*N*-dimethylformamide (10.9 g, 0.149 mol) and dry CH_2Cl_2 (25 mL) was added $POCl_3$ (19.0 g, 0.124 mol) at 0 °C over a period of 1 h. After stirring at this temperature for an additional 30 min, a solution of **8d** (13.6 g, 0.123 mol) in dry CH_2Cl_2 (35 mL) was added at 0 °C over a period of 1.5 h, and stirring was continued at 0 °C for 1 h and at room temperature for 40 min. The mixture was poured onto ice–water (250 mL), made alkaline with solid K_2CO_3, stirred at room temperature overnight, and extracted with CH_2Cl_2. The combined extracts were washed with water and

brine, dried (Na_2SO_4), and evaporated. The residue was distilled to give 15.3 g (90%) of **9d**, bp 124–128 °C (32 mm).

4-Ethyl-5-methyl-2-furaldehyde Oxime (10d). To a stirred mixture of **9d** (7.63 g, 55.2 mmol) and hydroxylamine hydrochloride (4.61 g, 66.3 mmol) dissolved in water (10 mL) was dropwise added a solution of Na_2CO_3 (3.81 g, 35.9 mmol) in water (16.5 mL), and the mixture was heated at reflux for 3 h and 45 min, cooled to room temperature, and extracted with CH_2Cl_2. The combined extracts were washed with water and brine and dried (Na_2SO_4). The evaporation of the solvent gave 8.28 g (98%) of **10d** as a mixture of *E* and *Z* isomers, which became an oily solid on standing at room temperature overnight.

3,5-Dimethyl-2-furfurylamine (11e). A mixture of $LiAlH_4$ (4.17 g, 0.11 mol) and dry ether (125 mL) was heated at reflux for 3 h, and to the resulting slurry was added 3,5-dimethyl-2-furaldehyde oxime (**10e**) (7.65 g, 55.0 mmol) dissolved in ether (50 mL) over a period of 1 h and 55 min at gentle reflux. The mixture was refluxed for an additional 0.5 h, cooled with an ice bath, treated with water (10.7 mL) added dropwise over a period of 35 min, stirred at room temperature for 15 min, and finally heated at reflux for 45 min. The mixture was filtered, and the solid was extracted with ether (2 × 60 mL). The combined filtrate and extracts were dried (Na_2SO_4) and evaporated to give 6.74 g (98%) of 11e as a slightly yellow liquid.

2,4-Dimethyl-5-phthalimidomethylfuran (12e). A stirred mixture of 11e (10.8 g, 86.3 mmol) and phthalic anhydride (12.8 g, 86.4 mmol) was heated in an oil bath of 120–125 °C for 1.5 h. The cooled reaction product was recrystallized from EtOH to give 18.1 g (82%) of 12e: mp 114.5–115.0 °C; IR (KBr) 1771, 1712, 1418, 1389, 1071 cm^{-1}; NMR ($CDCl_3$) δ 2.08 (s, 3 H, CH_3), 2.16 (s, 3 H, CH_3), 4.71 (s, 2 H, CH_2N), 5.74 (s, 1 H, H-3), 7.60–7.88 (m, 4 H, aromatic).

2,5-Dimethoxy-3,5-dimethyl-2-phthalimidomethyldihydrofuran (13e). To a stirred solution of 12e (4.00 g, 15.7 mmol) in a mixture of dry CH_2Cl_2 (120 mL) and absolute MeOH (8 mL) was added a solution of Br_2 (2.62 g, 16.4 mmol) in a mixture of dry CH_2Cl_2 (6 mL) and absolute MeOH (2 mL) at −40 to −50 °C over a period of 35 min. After the mixture was stirred for an additional 1.5 h at −50 to −60 °C, gaseous NH_3 was introduced to make the mixture basic. The mixture was warmed to room temperature, CH_2Cl_2 (40 mL) added, the generated solid removed by filtration, and the filtrate washed with water (2 × 50 mL), dried (Na_2SO_4), and evaporated. The residual solid (4.50 g) was recrystallized from MeOH to give 13e as colorless prisms (3.55 g, 71%), mp 142–154 °C, which was found to be a mixture of *E* and *Z* isomers (major isomer:minor isomer = 12.6:1) as determined from NMR spectroscopy: IR (KBr) 1767, 1713, 1611, 1464, 1420, 1392 cm^{-1}; NMR ($CDCl_3$) (less soluble isomer[18]) δ 1.45 (s, 3 H, CH_3), 1.89 (d, 3 H, J = 1.5 Hz, $=CCH_3$), 2.92 (s, 3 H, OCH_3), 3.10 (s, 3 H, OCH_3), 4.00 and 3.88 (AB q, 2 H, J = 13.5 Hz, CH_2N), 5.60 (q, 1 H, J = 1.5 Hz, =CH–), 7.59–7.88 (m, 4 H, aromatic); NMR (more soluble isomer[17]) δ 1.11 (s, 3 H, CH_3), 1.89 (d, 3 H, J = 1.5 Hz, $=CCH_3$), 3.27 (s, 6 H, 2 × OCH_3), 4.06 and 3.86 (AB q, 2 H, J = 13.5 Hz, CH_2N), 5.63 (q, 1 H, J = 1.5 Hz, =CH–), 7.60–7.93 (m, 4 H, aromatic).

3-Methyl-1-phthalimidohex-3-ene-2,5-dione (14e). To a solution of 13e (1.44 g, 4.54 mmol) in CH_2Cl_2 (20 mL) was added 2 N HCl (3.5 mL), and the mixture was stirred at room temperature for 4 h and treated with saturated aqueous $NaHCO_3$ solution. The CH_2Cl_2 layer was washed with brine, dried (Na_2SO_4), and evaporated. The residual solid was recrystallized from CH_2Cl_2–*n*-hexane to give 470 mg of 14e as colorless prisms, mp 171–171.5 °C. The mother liquor was concentrated and chromatographed on silica gel with benzene–AcOEt (9:1) as eluent to give additional 14e (494 mg) (964 mg in total, 78%): IR (KBr) 1769, 1714, 1689, 1614, 1464, 1414, 1390 cm^{-1}; NMR ($CDCl_3$) δ 2.06 (d, 3 H, J = 1.5 Hz, $=CCH_3$), 2.22 (s, 3 H, CH_3CO), 4.68 (s, 2 H, CH_2N), 5.21 (q, 1 H, J = 1.5 Hz, =CH–), 7.65–7.92 (m, 4 H, aromatic).

3-Methyl-1-phthalimidohexane-2,5-dione (15e). Compound 14e (423 mg, 1.56 mmol) was hydrogenated over Raney nickel in AcOEt (45 mL). The calculated amount of H_2 was absorbed in 12 min. The mixture was filtered, and the filtrate was evaporated to give 416 mg (97%) of **15e** as colorless crystals. Recrystallization from MeOH gave colorless prisms: mp 101.5–102.5 °C; IR (KBr) 1765, 1720, 1703, 1464, 1413 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (d, 3 H, J = 7.0 Hz, CH_3), 2.12 (s, 3 H, CH_3CO), 2.40–3.36 (m, 3 H, CH_2CH), 4.70 and 4.60 (AB q, 2 H, J = 18.0 Hz, CH_2N), 7.61–7.95 (m, 4 H, aromatic).

2,5-Dimethoxy-2-phthalimidomethyltetrahydrofuran (16a). 2,5-Dimethoxy-2-phthalimidomethyldihydrofuran (**13a**) (21.7 g, 75.0 mmol) was hydrogenated over Raney nickel (10 mL of a MeOH suspension) in AcOEt (320 mL). The calculated amount of H_2 was absorbed in 2 h. The mixture was filtered, and the filtrate was concentrated to ca. 50 mL and allowed to stand overnight. The precipitated **16a** was collected by filtration: yield 16.8 g; colorless needles; mp 112–113.5 °C. The mother liquor was concentrated and cooled to give 1.50 g of the second crop: mp 110.5–112 °C, 18.3 g (84%) in total. Recrystallization from CH_2Cl_2–*n*-hexane afforded colorless needles: mp 112.5–114 °C;[19] IR (KBr) 1771, 1711, 1613, 1468, 1449, 1422, 1391 cm^{-1}; NMR ($CDCl_3$)[20] δ 1.72–2.41 (m, 4 H, CH_2CH_2), 3.22 (s, 3 H, OCH_3), 3.32 (s, 3 H, OCH_3), 4.05 and 3.91 (AB q, 2 H, J = 14.0 Hz, CH_2N), 5.05 (m, 1 H, OCHO), 7.64–7.91 (m, 4 H, aromatic).

1-Phthalimidohexane-2,5-dione (15b). To a solution of 2,5-dimethoxy-2-methyl-5-phthalimidomethyltetrahydrofuran (**16b**) (100 mg, 0.328 mmol) in benzene (10 mL) was added 3 N HCl (2 mL), and the mixture was refluxed for 1 h. The mixture was cooled to room temperature, washed with water, saturated aqueous $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and evaporated to give 80 mg (94%) of **15b** as colorless crystals, mp 110.5–111 °C. Recrystallization from CH_2Cl_2–*n*-hexane gave colorless prisms, mp 118–119.5 °C. The IR and NMR data of this compound were identical with those[14] of **15b** obtained by Zn–AcOH reduction of 1-phthalimidohex-3-ene-2,5-dione (**14b**).

Preparation of 2-(2-Phthalimidomethylpyrrol-1-yl)benzophenones (18) (Table II). General Method A. The preparation of 18 by the coupling of a 2-aminobenzophenone (**17**) with a 2,5-dimethoxy-2-phthalimidomethyltetrahydrofuran (**16**) is exemplified by the synthesis of **5-chloro-2′-fluoro-2-(2-methyl-5-phthalimidomethylpyrrol-1-yl)benzophenone (18h).** A stirred solution of 2-amino-5-chloro-2′-fluorobenzophenone (**17e**) (330 mg, 1.32 mmol), **16b** (422 mg, 1.38 mmol), and *p*-toluenesulfonic acid monohydrate (30 mg) in benzene (5 mL) was heated at reflux for 1.8 h. The mixture was cooled to room temperature and treated with 10% aqueous Na_2CO_3 solution, and the benzene layer was washed with brine, dried (Na_2SO_4), and evaporated. The residual material was chromatographed on silica gel with benzene–AcOEt (98:2) as eluent to give 553 mg (89%) of **18h** as pale yellow crystals. Recrystallization from CH_2Cl_2–*n*-hexane gave pale yellow prisms: mp 184–185 °C; IR (KBr) 1767, 1722, 1661, 1610, 1481, 1416, 1391 cm^{-1}; NMR ($CDCl_3$) δ 1.87 (s, 3 H, CH_3), 4.61 and 4.36 (AB q, 2 H, J = 15.0 Hz, CH_2N), 5.62 (d, 1 H, J = 3.5 Hz, H on the pyrrole ring), 5.95 (d, 1 H, J = 3.5 Hz, H on the pyrrole ring), 6.88–7.84 (m, 11 H, aromatic).

General Method B. The preparation of 18 by the coupling of 17 with a 1-phthalimidohexane-2,5-dione (**15**) is exemplified by the synthesis of **2′,5-dichloro-2-(2,4-dimethyl-5-phthalimidomethylpyrrol-1-yl)benzophenone (18p).** A stirred solution of 2-amino-2′,5-dichlorobenzophenone (**17d**) (375 mg, 1.41 mmol), **15e** (366 mg, 1.34 mmol), and *p*-toluenesulfonic acid monohydrate (30 mg) in benzene (15 mL) was heated at reflux for 3.5 h. The mixture was cooled, diluted with benzene (20 mL), washed with water, 10% aqueous Na_2CO_3 solution, and brine, dried (Na_2SO_4), and evaporated. The residual material was chromatographed on silica gel first with benzene to give 43 mg of recovered 17c and then with benzene–AcOEt (19:1) to give 608 mg (90%) of **18p**. Recrystallization from benzene–*n*-hexane gave pale yellow needles: mp 168.5–169.5 °C; IR (KBr) 1763, 1708, 1661, 1587, 1482, 1422, 1397 cm^{-1}; NMR ($CDCl_3$) δ 1.82 (s, 3 H, CH_3), 1.90 (s, 3 H, CH_3), 4.63 and 4.12 (AB q, 2 H, J = 15.5 Hz, CH_2N), 5.52 (s, 1 H, H on the pyrrole ring), 7.01–7.78 (m, 11 H, aromatic).

Preparation of 6-Phenyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines (2) (Table III). General Method. The preparation of 2 by the action of hydrazine hydrate on 18 is exemplified by the synthesis of **8-chloro-6-(2-chlorophenyl)-1,3-dimethyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (2p).** Compound **18p** (608 mg, 1.21 mmol) was dissolved by heating in *N*,*N*-dimethylformamide (2 mL). To the solution were added EtOH (8 mL) and hydrazine hydrate (0.2 mL), and the mixture was heated at reflux for 0.5 h. The EtOH was evaporated, and benzene (30

mL) was added. The mixture was heated at reflux for 5 min, cooled to room temperature, and filtered. The filtrate was washed with water and brine, dried (Na_2SO_4), and evaporated. The residual material was chromatographed on silica gel with benzene–AcOEt (49:1) as eluent to give 368 mg (86%) of **2p** as yellow crystals. Recrystallization from ether–*n*-hexane gave pale yellow prisms: mp 132–133 °C; IR (KBr) 1616, 1591, 1560, 1481, 1414 cm^{-1}; NMR ($CDCl_3$) δ 2.10 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 5.07 and 3.94 (AB q, 2 H, J = 13.0 Hz, CH_2N), 5.97 (s, 1 H, H-2), 7.06 (m, 1 H, aromatic), 7.23–7.62 (m, 6 H, aromatic).

Pharmacology. Methods. CNS Actions. Male ddY mice weighing 18–24 g were used for all studies reported here. The test compounds were suspended in 5% arabic gum solution and administered orally to a group of six mice per dose. The compounds were examined suitably at three or four dosage levels selected from 100, 30, 10, 3, 1, 0.3, and 0.1 mg/kg. The ED_{50} values were calculated by the method of Litchfield–Wilcoxon.[21] Procedures for measuring the activities of the test compounds—antipentylenetetrazole activity, antimaximal electroshock activity, taming activity in fighting mice induced by electrofootshock, muscle relaxant activity using an inclined wooden board, motor incoordinating activity, and potentiation of thiopental—have been described previously.[1]

Acute Toxicity. Male ddY mice weighing 18–24 g were used. The test compounds were suspended in 5% arabic gum solution and administered orally to a group of four mice at a dosage of 1000 and 2000 mg/kg and to a group of eight mice at a dosage of 3000 mg/kg.

Acknowledgments. The authors wish to thank Miss K. Muramoto for technical assistance in biological studies, Mr. M. Asano for mass spectral measurement, Miss A. Mineo for NMR spectral measurement, and Misses N. Igarashi, K. Tatebe, N. Hashiguchi, N. Nagasawa, and M. Sasaki for elemental analyses. Particular appreciation is expressed to Dr. T. Noguchi for his advice and support during the course of this investigation.

References and Notes

(1) For paper 4 in this series, see T. Hara, H. Fujimori, Y. Kayama, T. Mori, K. Itoh, and Y. Hashimoto, *Chem. Pharm. Bull.*, **25**, 2584 (1977).
(2) A part of this work has been reported as a communication; Y. Kayama, T. Hara, K. Itoh, and T. Sunami, *J. Heterocycl. Chem.*, 14, 171 (1977).
(3) Presented at the 97th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1977, Abstract No. 7C10-1.
(4) T. Hara, T. Mori, K. Itoh, and N. Itoh, unpublished results. For the synthesis of compounds 1, see T. Hara, K. Itoh, and N. Itoh, *J. Heterocycl. Chem.*, **13**, 1233 (1976), and ref 6.
(5) The synthesis of 8-chloro-6-phenyl-4*H*-pyrrolo[1,2-*a*]-[1,4]benzodiazepine (**2a**) has been reported by a route different from that reported herein [E. E. Garcia, J. G. Riley, and R. I. Fryer, *J. Org. Chem.*, **33**, 1359 (1968)].
(6) J. P. Maffrand, G. Ferrand, and F. Eloy, *Tetrahedron Lett.*, 3449 (1973); *Eur. J. Med. Chem.-Chim. Ther.*, **9**, 539 (1974).
(7) A. L. Mndzhoyan and A. A. Aroyan, *Dokl. Akad. Nauk Arm. SSR*, **25**, 267 (1957).
(8) D. M. Burness, *Org. Synth.*, **39**, 46, 49 (1959).
(9) J. P. Kutney, H. W. Hanssen, and G. V. Nair, *Tetrahedron*, **27**, 3323 (1971).
(10) A. L. Mundzhoyan, V. G. Afrikyan, and G. V. Khorenyan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauki*, 14, 363 (1961).
(11) J. C. Sheehan, D. W. Chapman, and R. W. Roth, *J. Am. Chem. Soc.*, 74, 3822 (1952).
(12) A. L. Mndzhoyan, R. A. Oganesyan, T. R. Akopyan, and L. G. Khachatryan, *Arm. Khim. Zh.*, **23**, 528 (1970).
(13) M. Elliott, N. F. Janes, and B. C. Pearson, *Pestic. Sci.*, **2**, 243 (1971).
(14) H. Fujimori, Y. Kayama, T. Hara, K. Itoh, and T. Sunami, *J. Heterocycl. Chem.*, 14, 235 (1977).
(15) The C-4 protons of **2b** and of **2c** exhibited one broad singlet and two broad singlets at ambient temperature, respectively.
(16) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lehr in "Drugs Affecting the Central Nervous System", Vol. 2, A. Burger, Ed., Marcel Dekker, New York, N.Y., 1968, p 237.
(17) No death was observed at the lower dosages. In a control experiment, LD_{50} of diazepam was determined to be 930 mg/kg (mice, po).
(18) Although the pure isomer was not obtained, data assignment was done by analysis of the spectral change through recrystallization.
(19) Of a mixture of *E* and *Z* isomers (major isomer:minor isomer = 22:1).
(20) Of the less soluble isomer.
(21) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).

Synthesis and Antitumor Activity of Halogen-Substituted 4-(3,3-Dimethyl-1-triazeno)quinolines

Ai Jeng Lin* and Ti Li Loo

Department of Developmental Therapeutics, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, Texas 77030. *Received July 22, 1977*

Halogenated 4-(3,3-dimethyl-1-triazeno)quinolines were synthesized as potential antitumor agents on the basis of the biochemical pharmacological properties of existing triazenes, their structural–activity relationships, and the high melanin binding of chloroquine and iodoquine in vivo and in vitro. They were synthesized by diazotization of appropriate halogen-substituted 4-aminoquinolines in fluoboric acid at −5 °C followed by coupling with dimethylamine. Among these new compounds, 8-chloro-4-(3,3-dimethyl-1-triazeno)quinoline produces significant antitumor activity against both P-388 and L1210 murine leukemias. Although only marginally active or inactive against P-388, the other chloro, bromo, or iodo analogues show activity against L1210 comparable to that of dacarbazine (DIC). However, none of these compounds is active against B-16 melanoma. Compared with DIC these new agents demonstrate a higher in vitro affinity for melanin; however, this affinity is apparently not correlated with their antitumor activity.

Although metastatic melanoma is only one of the many varieties of malignant tumors, its virulence and high mortality have stimulated studies over the ages. It comprises about 2% of all cancers, and about 80–90% of them arise in the skin.[1] 5-(3,3-Dimethyl-1-triazeno)-imidazole-4-carboxamide (DIC) is by far the most useful single agent against melanoma in man. However, it has produced only temporary responses in 19% of the patients with this disease.[2] The lack of effective agents against melanoma justifies the continuous search for better new agents. A large number of triazenes with diverse structures have been synthesized and tested in experimental systems.[3]

0022-2623/78/1821-0268$01.00/0