single- and double-bond values. The C(1)—N(2) bond length of 1.350 Å, however, shows an isolated double-bond character and the N(1)—N(2) distance 1.409 Å approximates a single-bond length.

Significant out-of-plane distortions occur in the ring (Table IV). The coordinations around the nitrogen atoms are not planar but pyramidal, and the substituents on N(1) and N(2), the phenyl and methyl groups, deviate from one another in a *trans*-configuration from the least-squares plane of the ring. The phenyl ring is completely planar (Table IV), and the C—C bond lengths (1.378–1.421 Å) and the bond angles (117.5–122.2°) are those of the typical benzenoid structure. The ring is inclined by 39° with respect to the plane of the pyrazolone ring. The dimethylamino group on C(2) is also of a pyramid configuration; the C(2)—N(3) bond length of 1.421 Å is a little shorter than that of a pure single bond at 1.47 Å (5) and is perhaps affected by the conjugated system of the pyrazolone ring.

Molecular Structure of Barbital—The values of bond lengths and angles are in reasonable agreement with the corresponding values for the same molecule in the barbital crystal (Form I) reported by Craven *et al.* (6). The C—N bond lengths of 1.359–1.377 Å in the pyrimidine ring show about 20–30% of double-bond characters, and there are no significant differences among the three C—O pure double-bond lengths. The C—C bond lengths of 1.506 and 1.512 Å in the pyrimidine ring approximate that of the single bond, while the steric requirement of the ring formation leads to a slight broadening of the angle at the tetrahedrally bonded atom C(17) from the tetrahedral angle of 109.4–114.1°. In the ethyl groups, the C—C—C angles and the C—C bond lengths agree quite well with those of normal paraffin. For an isolated barbital molecule, the ring atoms should be coplanar and the hydrocarbon chain of the ethyl groups should be normal to the ring plane. Some significant deviations of the ring atoms from the plane, however, were observed in this crystal (Table IV). The pyrimidine ring is slightly folded along the C(15)—C(16) line at an angle of about 4°. Similar distortions were also found in the pyrimidine rings in barbital I (6) and in other dialkylbarbiturate crystals (7, 8), in which the foldings of the planes were observed along the N(4)—C(16) diagonals.

Crystal Structure—The intermolecular atomic distances are shown in Fig. 5, and the arrangement of the molecules in the crystals is shown in Fig. 6. The short distances between the carbonyl and the imino groups, O(1)—N(5) 2.749 Å and O(2)—N(4) 2.812 Å, suggest hydrogen bondings. The interaction between two barbital molecules with hydrogen bonds is quite similar to that in barbital crystal I, in which the molecules are arranged in infinite planar ribbons with two kinds of hydrogen bonding (6). There are no infinite chains of molecules linked by hydrogen bonds in this compound; only two aminopyrine and two barbital molecules are linked in the series of aminopyrine–barbital–barbital–aminopyrine. The hydrocarbon groups, *i.e.*, the ethyl and phenyl groups, are in contact with one another in normal van der Waals' interactions. No other unusually close contacts or overlappings of molecules, which are found in some charge-transfer complexes, were observed.

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ACKNOWLEDGMENTS AND ADDRESSES

Received September 8, 1970, from the *Faculty of Pharmaceutical Science, Kyushu University, Katakasu, Fukuoka, Japan.*

Accepted for publication December 8, 1970.

The author expresses his thanks to Professor I. Ueda and Dr. A. Okazaki for facilities for X-ray diffraction measurement, and to Professor S. Iguchi for his continued guidance and encouragement.

Synthesis and Selected Pharmacology of Anthranilamides

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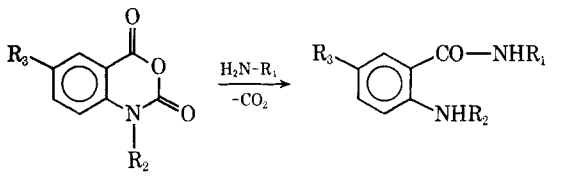
Abstract □ A series of anthranilamides of diverse structure were prepared by the nucleophilic ring opening of isatoic anhydrides. Sixteen analogs, 10 of them previously unknown in the literature, were submitted to general pharmacologic screening. Several of the compounds displayed CNS depression, anti-inflammatory–analgesic, and antitremor activities.

Keyphrases □ Anthranilamides—synthesis from isatoic anhydrides □ CNS depressant activity—anthranilamides □ Anti-inflammatory, analgesic potential—anthranilamides □ Antitremor activity—anthranilamides

Literature reports regarding the general pharmacology of anthranilamides are sparse. In recent years, however, numerous studies appeared on the analgesic, antipyretic, and anti-inflammatory activities of anthranilamides (*o*-aminobenzamides) (1–5). One claim was made that their physiological activity rests, at least in part, on their metabolic conversion to salicylate analogs (6).

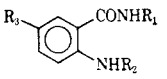
Synthetically, these compounds are obtained by nucleophilic ring opening of substituted isatoic anhydrides with amines (Scheme I). Although procedures



Scheme I

were suggested for these transformations (7, 8), an improved modification has been developed which simplifies the experimental method and enhances the yield by the use of *N*,*N*-dimethylformamide as a solvent when

Table I—Anthranilamides



Compound	R_1	R_2	R_3	Method	Yield, %	M.p. (b.p./mm. Hg)	Formula	Anal., % Calcd.	Found
I	H	H	H	—[a]		107.5–108°			
II	H	C_6H_5	H	C	81	129.0–130.5°[b]			
III	H	H	I	C	61	203–204°	$C_7H_7IN_2O$	C, 32.08 H, 2.69 N, 10.69	C, 32.09 H, 2.72 N, 10.46
IV	CH_3	H	I	C	63	163.5–164.5°	$C_8H_9IN_2O$	C, 34.81 H, 3.29 N, 10.15	C, 35.08 H, 3.31 N, 10.08
V	CH_3	H	Cl	C	75	131–132°	$C_8H_9ClN_2O$	C, 52.04 H, 4.91 N, 15.17	C, 52.33 H, 5.01 N, 14.90
VI	H	H	NO_2	C	45	234–236°[c]			
VII	C_6H_5	CH_3	Cl	A	95	179–180°	$C_{14}H_{13}ClN_2O$	C, 64.49 H, 5.02 N, 10.75	C, 64.21 H, 5.09 N, 10.66
VIII	H	H	Cl	C	58	170–172°[d]			
IX	C_6H_5	H	Cl	A	65	154–155°	$C_{13}H_{11}ClN_2O$	C, 63.29 H, 4.49 N, 11.36	C, 63.15 H, 4.21 N, 11.56
X	2—ClC_6H_4—	CH_3	Cl	A	83	139–140°	$C_{14}H_{12}Cl_2N_2O$	C, 56.96 H, 4.10 N, 9.49	C, 57.25 H, 4.35 N, 9.55
XI	$Et_2N(CH_2)_3CH(CH_3)$—	CH_3	Cl	A	81	(194–196°/2.2)	$C_{17}H_{28}ClN_3O$	C, 62.66 H, 8.66 N, 12.89	C, 62.68 H, 8.61 N, 12.87
				B	73	(194–196°/2.2)			
XII	$Et_2N(CH_2)_3$—	H	H	A	80	(159–161°/0.1)	$C_{14}N_{23}N_3O$	C, 67.43 H, 9.30 N, 16.85	C, 67.49 H, 9.42 N, 16.90
				B	67	(159–161°/0.1)			
XIII	CH_3	CH_3	Cl	C	74	104–105°[e]	$C_9H_{11}ClN_2O$	C, 54.41 H, 5.58 N, 14.10	C, 54.68 H, 5.34 N, 13.96
XIV	H	CH_3	H	C	67	161–163°[f]			
XV	$Et_2N(CH_2)_3CH(CH_3)$—	H	H	A	69	(170–171°/0.18)	$C_{16}H_{27}N_3O$	C, 69.27 H, 9.81 N, 15.15	C, 69.13 H, 9.60 N, 15.07
XVI	H	CH_3	Cl	C	78	153–154°	$C_8H_9ClN_2O$	C, 52.05 H, 4.91 N, 15.17	C, 52.19 H, 4.90 N, 15.22

[a] Commercial material from Maumee Chemical Co., purified by double vacuum sublimation, lit. m.p., 107–108°, K. Butler and M. W. Partridge, *J. Chem. Soc.*, **1959**, 2396. [b] Lit. m.p. 127.5–128.5°, M. Goodman, N. Arbiter, and G. Powell, *J. Amer. Chem. Soc.*, **55**, 4294(1933). [c] Lit. m.p. 230°, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1965, p. 176. [d] Lit. m.p. 172°, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1965, p. 101. [e] Lit. (10) m.p. 95–97°. [f] Lit. m.p. 159–160°, H. Weddige, *J. Prakt. Chem.*, **36**, 150(1887).

high boiling amines are employed as nucleophiles. The reported methods for ring opening with ammonia (9) or with methylamine (10) were used without modification. The anthranilamides were refined to analytical purity and submitted to general pharmacologic screening. Table I lists the compounds studied.

EXPERIMENTAL

Preparation of Anthranilamides—Commercial anthranilamide (Compound I) was doubly sublimed in vacuum before biological evaluation. Other anthranilamides (Compounds II–XVI) were synthesized. Several of the required isatoic anhydrides (isatoic, *N*-methylisatoic, 5-chloro-*N*-methylisatoic, 5-chloroisatoic, and 5-nitroisatoic anhydride) were obtained as samples[1]. *N*-Phenylisatoic anhydride was prepared by a literature method (11), and 5-iodoisatoic anhydride was synthesized from 5-iodoanthranilic acid by the phosgenation technique reported for anthranilic acid (12). The 5-iodoisatoic anhydride melted with decomposition at 270–273° and was employed directly without further purification.

Method A—A solution of 20 mmoles of the required anhydride, 25–30 mmoles of the amine, and 300 ml. of anhydrous *N,N*-dimethylformamide was stirred at reflux for 4 hr. The solvent was removed *in vacuo*. If no crystallization ensued on chilling the oily mass, the product was vacuum distilled. The results of this technique with aniline, *o*-chloroaniline, 5-diethylamino-2-pentylamine ("Noval diamine"), and 3-diethylaminopropylamine are reported in Table I.

Method B—To 20 mmoles of the solid dry isatoic anhydride was added 25 mmoles of the liquid amine (5-diethylamino-2-pentylamine or 3-diethylaminopropylamine). The addition was carried out in small portions, with the resulting paste being stirred to miminize foaming (CO_2). After completion of the addition, the solution was stirred and heated at 80–90° until the evolution of gas ceased (usually 1–2 hr.). The heavy oil was cooled to room temperature, diluted with 400 ml. of chilled diethyl ether, and filtered to remove traces of insoluble solids. The filtrate was washed with 50 ml. of cold water, dried ($MgSO_4$), and concentrated to a yellow oil which was fractionated *in vacuo*.

Method C—A suspension of 25 mmoles of the anhydride and 500 ml. of 0.9 *M* aqueous amine was stirred for 12 hr. and filtered; the solid was washed with 100 ml. of a 0.9 *M* solution of the same amine. The dried solid was recrystallized from EtOH to analytical purity.

General Rat Screening—All compounds were tested and the results were analyzed according to the methods described by Malone and Carrano (13). Nonfasted albino rats (180–210 g.) were used. Injections were made intraperitoneally.

General CNS Testing—A log dose *versus* response curve was generated, using the inability of trained animals to walk a rotating wooden rod (28 mm. diameter, at 20 r.p.m.) for 1 min. as the response criterion. Six 18–22-g. nonfasted albino mice were used per group, and dosing was done intraperitoneally. The animals were tested at 0, 15, 30, 60, 90, 120, 150, and 180 min. postinjection. The time postinjection for the peak effect was determined, and the quantal response at that dose was used to plot the curve. A graphical ED_{50} was estimated. This dose and peak effect time was then used for

[1] Maumee Chemical Co., Toledo, Ohio.

Table II—*In Vivo* Rat Screening Data for Anthranilamides

Compound	Maximum Sublethal Dose, mg./kg. i.p.	ANS Score	CNSD Score	Significant Symptomatology	Reference Drug Match
I	>1000	0.95	12.50	Decreased motor activity, slight ataxia, slight lacrimation, piloerection, decreased rectal temperature, decreased rotorod ability, decreased body tone	None outstanding
II	>1000	2.75	5.86	Slightly decreased motor activity, ataxia, piloerection, decreased body weight, decreased body tone	None outstanding
III	316	3.92	21.30	Decreased motor activity, ataxia, loss righting reflex, screen grip loss, enophthalmos, piloerection, decreased rectal temperature, decreased rotorod ability, decreased body tone	Chlordiazepoxide
IV	562	3.17	19.06	Decreased motor activity, ataxia, loss righting reflex, screen grip loss, enophthalmos, lacrimation, piloerection, decreased rectal temperature, decreased rotorod ability, decreased body tone	Phenobarbital
V	316	3.60	21.30	Decreased motor activity, ataxia, loss righting reflex, screen grip loss, enophthalmos, ptosis, slight mydriasis, piloerection, decreased skin and connective tissue elasticity, decreased rectal temperature, decreased rotorod ability, decreased body tone	Chlorpromazine, chlordiazepoxide
VI	>1000	2.86	1.62	Slight mydriasis, decreased skin and connective tissue elasticity, decreased body weight, slightly decreased body tone	None outstanding
VII	>1000	2.54	10.11	Decreased motor activity, decreased respiratory rate, enophthalmos, piloerection, decreased body weight, decreased body tone, fearfulness	None outstanding
VIII	56	2.54	8.41	Decreased motor activity, ataxia, loss righting reflex, screen grip loss, slight enophthalmos, slightly decreased rectal temperature, decreased rotorod ability, decreased body tone	Phenobarbital
IX	>1000	4.34	3.94	Mydriasis, diarrhea, decreased body weight	Indomethacin
X	>1000	2.54	7.33	Decreased motor activity, decreased respiratory rate decreased body weight, decreased body tone	None outstanding
XI	177	1.06	3.01	Decreased motor activity, slight enophthalmos, decreased body weight, decreased rotorod ability, decreased body tone	None outstanding
XII	56	3.17	2.85	Decreased motor activity, ataxia, decreased rotorod ability, decreased body tone, enophthalmos, decreased body weight	None outstanding
XIII	>1000	2.96	3.24	None	None outstanding
XIV	316	6.14	15.43	Decreased motor activity, ataxia, loss righting reflex, miosis, lacrimation, salivation, decreased skin and connective tissue elasticity, decreased rectal temperature, decreased rotorod ability, decreased body tone	None outstanding
XV	>1000	2.61	0.00	None	None outstanding
XVI	177	5.29	27.55	Decreased motor activity, ataxia, loss righting reflex, decreased body tone, decreased rotorod ability, screen grip loss, increased respiratory rate, enophthalmos, lacrimation, decreased rectal temperature	Diphenylhydantoin
Phenobarbital sodium	100	7.32	28.32	Decreased motor activity, ataxia, loss righting reflex, loss corneal reflex, screen grip loss, enophthalmos, ptosis, mydriasis, lacrimation, decreased skin and connective tissue elasticity, decreased rotorod ability, decreased body tone	Reference compound
Diphenylhydantoin sodium	316	6.46	25.74	Decreased motor activity, ataxia, loss righting reflex, screen grip loss, exophthalmos, mydriasis, piloerection, decreased skin and connective tissue elasticity, decreased rectal temperature, decreased rotorod ability, decreased body tone	Reference compound
Indomethacin	316	2.01	3.86	Slightly decreased motor activity, mydriasis, mucosal blanching, decreased body tone, diarrhea, piloerection, decreased body weight	Reference compound
Chlorpromazine hydrochloride	100	13.40	33.28	Decreased motor activity, loss righting reflex, ataxia, analgesia, loss corneal reflex, loss pinna reflex, screen grip loss, clonic convulsions, enophthalmos, ptosis, mydriasis, lacrimation, piloerection, diarrhea, decreased skin and connective tissue elasticity, decreased rectal temperature, decreased rotorod ability, decreased body tone	Reference compound
Chlordiazepoxide hydrochloride	100	6.45	35.65	Decreased motor activity, loss righting reflex, ataxia, screen grip loss, enophthalmos, miosis, lacrimation, decreased skin and connective tissue elasticity, decreased rectal temperature, decreased rotorod ability, decreased body tone	Reference compound

Table III–Results with Anthranilamides in Selected Screening Tests

Compound	Rotorod Test: Est. ED_{50}, mg./kg. i.p.	Rotorod Test: Peak Effect Time, min.	Percent Protection at the Rotorod ED_{50}: Antistrychnine Test	Antimetrazol Test	Antielectroshock Test	Antioxotremorine Test	Acetylcholine Writhing Test: Dose, mg./kg. i.p.	Acetylcholine Writhing Test: Percent Protection
I	>200	30	0	0	17	89	300	0
III	68	30	0	0	0	36	300	67
IV	172	30	0	0	0	70	300	17
V	113	30	0	0	0	83	30	0
							300	67
VII	>200	30	0	0	0	0	300	0
VIII	62.5	30	0	0	0	76	30	0
							300	33
IX	>200	30	0	0	0	6	300	17
X	>200	30	0	0	0	0	300	17
XII	180		0	0	0	72	300	50
XIII	>200	15	16	16	0	59	50	17
							100	17
							500	83
XIV	103	15	0	0	16	82	30	0
							300	83
XV	>200	30	83	0	50	3	30	17
							300	67
XVI	130	15	0	0	0	82	500	67
Indomethacin	>200	30	0	0	0	21	1	33
							3	50
							7	83
							10	100
Phenobarbital sodium	68	90	33	100	100	60	—	—
Diphenylhydantoin sodium	48	120	0	0	66	29	—	—
Chlordiazepoxide hydrochloride	40	30	0	83	66	58	—	—
Chlorpromazine hydrochloride	2	90	0	0	0	27	1	17
							5	67
							10	100

subsequent work in the antistrychnine, antimetrazol, antielectroshock, and antioxotremorine tests. In these tests, the experimental drug was injected intraperitoneally into groups of six 18–22-g. nonfasted albino mice; after the time to peak effect, strychnine sulfate (1.1 mg./kg. s.c.), pentylenetetrazole (metrazol) (70 mg./kg. s.c.), oxotremorine (350 mcg./kg. s.c.), or a 50-amp., 0.2-sec. shock was administered to each animal. The animals were observed for 30 min. for tonic extensor seizures in the antistrychnine test and for clonic seizures in the antimetrazol test. In the antielectroshock test, the animals were observed for hind-limb tonic extensor seizures. In the antioxotremorine test, tremors were subjectively rated per animal on a scale of 0–3 and the total response for the entire group was calculated and compared to that of a control group.

In each test a group of animals receiving 0.9% saline, 5 ml./kg., was run simultaneously with the experimental groups. In the acetylcholine writhing test, mice were injected orally with the experimental agent and, after an elapse of the peak effect time, challenged with a 7.0-mg./kg. i.p. injection of acetylcholine bromide. The number of animals in the experimental group that elicited a writhing response within 2 min. post the challenge was compared to that of a control group receiving 0.9% saline.

Acute Anti-Inflammatory–Analgesic Testing—Nonfasted albino rats in the weight range of 160–180 g., equally divided between sexes, were used. The experimental drugs were administered orally. A modified Randall–Selitto (14) method was used; immediately following administration of the drug, 0.1 ml. of a 1% carrageenin suspension[2] was injected into the subplantar area of the right hind paw and the control foot volume was recorded by volume displacement. The control analgesic response was then estimated by placing the injected paw between two grooved disks which were slowly forced together *via* air pressure. The amount of pressure required to cause the animal to vocalize or attempt to bite the disks was recorded. The analgesic response was again estimated at 1 and 2 hr. postinjection, and foot volume was measured at 4 hr. postinjection. A control group that received 0.9% saline in place of the experimental drug was tested simultaneously for comparison.

[2] Marine Colloids, Inc.

BIOLOGICAL ACTIVITY AND DISCUSSION

Table II summarizes some important aspects of the results of general rat screening. Several reference agents are included for comparison. The maximum sublethal dose (MSLD) is the highest dose administered at which no death occurred. No doses were made over 1.0 g./kg.; therefore, in cases where there was no death at this dosage, the MSLD is assumed to be greater than 1.0 g./kg. Also presented in the table are scores that represent the extent of general autonomic nervous system (ANS) and general CNS depressant (CNSD) activity. The absolute values of these scores between ANS and CNSD are not comparable. The significant symptomatology and results of computer-matching operations against a library of 27 reference drugs are also included.

Compounds I, III, IV, V, VII, VIII, X, XIV, and XVI produced significant CNS depression. Some of the symptomatology exhibited by these drugs would be that expected of a general CNS depressant, tranquilizer, muscle relaxant, or anticonvulsant. However, Compounds III, IV, V, VIII, IX, and XVI displayed a particular similarity to specific reference drugs, as indicated in Table II. The majority of these reference agents are CNS depressants: chlorpromazine (tranquilizer), diphenylhydantoin (anticonvulsant), chlordiazepoxide (muscle relaxant/mild tranquilizer), and phenobarbital (sedative/hypnotic). Based on these similarities, several of the drugs were screened for their CNSD potential in the tests listed (Table III).

These results indicate that, in general, throughout the series there was significant activity in the acetylcholine writhing test, indicating potential anti-inflammatory–analgesic activity. Also, there seems to be a potential throughout the series for antitremor activity since several of the compounds (VIII, XII, XIII, XIV, XVI) had good activity in the antioxotremorine test.

Table IV—Anti-Inflammatory–Analgesic Activity of Anthranilamides

Compound	Dose, mg./kg. p.o.	Mean Percent Inhibition of Carrageenin Edema	Mean Percent Increase in Foot Pressure Pain Threshold (hr. postinjection)
II	50	0	8 (1,2)
	500	16	8 (1,2)
IX	50	16	12 (2)
	500	30	29 (2)
XII	30	0	17 (2)
	300	0	33 (2)
XIII	50	0	3 (1)
	500	13	48 (2)[a]
XIV	50	4	45 (2)
	500	12	120 (2)[b]
XVI	50	4	26 (2)
	500	9	204 (2)[b]
Indomethacin	3	39	10 (2)
	10	57	30 (1,2)
	30	51	18 (1,2)
Aspirin	100	18	16 (1)
	300	43	40 (1)
	1000	74	25 (1,2)

[a] The animals tested were slightly depressed. [b] The animals tested were moderately–markedly depressed.

Table IV summarizes the results of the acute anti-inflammatory–analgesic test for compounds selected because of their behavior in previous tests. Compound IX matched well with the reference drug, indomethacin, in the general rat screen. Compounds XII and XIII exhibited low toxicity in the general rat screen. Compounds XII, XIII, XIV, and XVI had good activity in the acetylcholine writhing test. Compound II was chosen for structure–activity relationship purposes, because it is similar in structure to known anti-inflammatory agents. None of the compounds tested exhibited outstanding anti-inflammatory activity. Compounds IX and XIV produced slight to moderate effects at 500 mg./kg. Compounds XIII, XIV, and XVI produced significant increases in pressure threshold in the analgesic portion of the test, but the animals were notably depressed.

Compounds IX, XIV, and XVI were tested intraperitoneally at 2, 10, and 50 mg./kg. for cardiovascular activity in an anesthetized cat because of the relatively high autonomic scores in the rat screen. The physical characteristics of these drugs made it impractical to test them intravenously. For all three drugs, there were no alteration in blood pressure, heart rate, or respiration and no significant effects on the responses of acetylcholine, norepinephrine, histamine, dimethylphenylpiperazinium, and sympathetic or vagal stimulation.

Compound XVI, which showed the most CNS depression in the rat screen, was found in other testing to protect significantly against amphetamine toxicity in aggregated mice at 100 mg./kg., both subcutaneously and orally. Major tranquilizer activity was indicated.

Compounds VIII and XII are the most toxic of the series, because death occurred at 56 mg./kg. in the rat screen. In general, as expected, addition of a halogen tends to increase activity and toxicity. Nitro in place of halogen seems to decrease activity and toxicity.

It seems probable that CNSD potential is related to *in vivo* binding at the *o*-amino function. Those compounds that reflected diminished basicity at this nitrogen (*i.e.*, II and VI) and those that reflected diminished steric accessibility at this site (*i.e.*, XI, XII, and XV) gave the lowest CNSD scores in the general rat screen.

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ACKNOWLEDGMENTS AND ADDRESSES

Received September 29, 1970, from the **Department of Chemistry, Lehigh University, Bethlehem, PA 18015*, and the †*Medical Research Department, Atlas Chemical Industries, Inc., Wilmington, DE 19899*

Accepted for publication December 11, 1970.

Abstracted in part from the doctoral dissertation of T. F. L., Lehigh University, 1968.

The work was supported by Atlas Chemical Industries, Inc.

The authors thank Dr. G. I. Robertson, Florham Park, N. J., for the microcombustion analyses; and Dr. K. K. Kimura, Dr. J. W. LeMaistre, Dr. D. H. McCurdy, and Dr. A. D. Miller, Atlas Chemical Industries, Inc., for their support and suggestions in the chemical and biological aspects of the project.