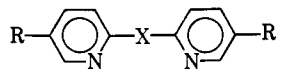
TABLE III
ACTIVITY OF



No.	Structure R	Structure X	CIST[d] at mg/kg 40	160	640
XL[a]	NO_2	S	0.1	0.3	0.7
XLI[b]	NO_2	SO_2	0.1	0.3	0.5
XLII[c]	NH_2	SO_2	0.6	0.6	1.0

[a] A. R. Surrey and H. J. Lindwall, *J. Amer. Chem. Soc.*, **62**, 1697 (1940). [b] A. Tchitchibabin and M. Bertougee, French Patent 866,482 (1941); *Chem. Abstr.*, **43**, P5050c (1949). [c] L. L. Bambas, *J. Amer. Chem. Soc.*, **67**, 668 (1945). [d] See footnote *h* of Table I.

TABLE IV
TOXICITY DATA

No.	% toxic deaths at mg/kg 160	320	640
II	0	0	40
III	0	40	80
IV	60	*a*	100
V	0	*a*	100
VI	0	20	60
X	20	20	60
XII	0	40	40
XIII	0	80	100
XVII	0	*a*	100
XXII	0	100	100
XXVI	0	*a*	100
XXXI	0	*a*	100

[a] Not tested.

these structures. It should be noted that monoacetylated DDS (X) was only slightly less toxic than DDS. A partial oxidation of NH_2 of X to NHOH of IX removed completely the toxic side effect without activity reduction. Similarly, the conversion of $NHNH_2$ (XIII) and NH_2 (XXII) into a sydnone ring (XVIII or XIX and XXV, respectively) resulted in total loss of toxicity. Reduction of the SO_2 bridge to SO or S, its replacement by the asymmetrical moieties, SO_2CH_2 or SO_2S, or substitution of α-pyridyl for Ph of III resulted in considerable (XXXII, XXXIII), or, in most cases, in total, loss of activity against *P. berghei*.

Experimental Section

4,4′-Bis(*N*-sulfinylaminophenyl) Sulfone (IV).—A suspension of 24.8 g (0.1 mole) of III and 25 g (0.35 mole) of $SOCl_2$ in 350 ml of PhMe was refluxed for 4.5 hr; most of the PhMe was distd off *in vacuo* and the residue was recrystd from PhMe to obtain 31.1 g (92%) of yellow product, mp 181–182°. When exposed to moisture it liberated SO_2. *Anal.* ($C_{12}H_8N_2O_4S_3$): C, H, N.

Ethyl *N*-[4-(*p*-Nitrophenyl)sulfonylphenyl]-*N*-acetylalaninate (XX) and *N*-[4-(*p*-Nitrophenyl)sulfonylphenyl]alanine (XXI).—A mixt of 73.8 g (0.3 mole) of 4-amino-4′-nitro(diphenyl sulfide), 55.0 g (0.3 mole) of ethyl α-bromopropionate, 42.0 g (0.3 mole) of $NaOAc \cdot 3H_2O$, and 10 ml of Carbitol was stirred for 30 hr at 150–155°. The cooled reaction mixt was poured in 1000 ml of 5% aq $NaHCO_3$ and extd (2 × 300 ml) with Et_2O. The Et_2O ext was washed with satd aq $NaHCO_3$, dried ($CaCl_2$), and evapd to obtain an oily residue which was extd with petr ether (bp 60–110°). The insol oil was subjected to vacuum (15 mm) for 30 min at 25–30° and refluxed for 2 hr with a mixt of 100 ml of glacial AcOH and 80 ml of AcOAc. A soln of 75 g of $KMnO_4$ in 700 ml of H_2O and 500 ml of AcOH was added and stirred for 1.5 hr at 35–45°. After addn of 110 g of $NaHSO_3$, the reaction mixt was poured in 800 ml of ice–water, and the resulting ppt was recrystd from C_6H_6-petr ether (bp 60–110°) to obtain 51.0 g (40%) of the acetylalaninate XX, mp 141–146°. *Anal.* ($C_{19}H_{20}N_2O_7S$): S, C, H.

A mixt of 21.0 g (0.05 mole) of XX, 50 ml of concd HCl, 20 ml of H_2O, and 200 ml of AcOH was refluxed for 4.5 hr and poured in 2 l. of H_2O. The solid product was recrystd from THF–petr ether (bp 60–110°) to obtain 13.8 g (79%) of the alanine XXI, mp 181–183°. *Anal.* ($C_{15}H_{14}N_2O_6S$): C, H, N.

Ethyl *N*-[*p*-(Phenylsulfonyl)phenyl]glycinate (XXIV).—A mixt of 10.0 g (0.042 mole) of the sulfone XXII, 7.2 g (0.043 mole) of ethyl α-bromoacetate, and 5.9 g (0.044 mole) of $NaOAc \cdot 3H_2O$ was refluxed for 7 hr, cooled, triturated with aq $NaHCO_3$, washed with H_2O, and recrystd from EtOH–petr ether (bp 60–110°) to obtain 7.3 g (53%) of XXIV, mp 112–114°. *Anal.* ($C_{16}H_{17}NO_4S$): C, H, N.

***N*-[*p*-(Phenylsulfonyl)phenyl]sydnone (XXV).**—A mixt of 8.0 g (0.025 mole) of the glycinate XXIV, 50 ml of concd HCl, 50 ml of H_2O, and 100 ml of AcOH was stirred and refluxed for 2 hr. A soln of 2.5 g (0.036 mole) of $NaNO_2$ in 15 ml of H_2O was added slowly to the reaction mixt at 25–35°. After 30 min at 20–25°, the mixt was poured in 500 ml of ice–water to isolate the crude *N*-nitroso-*N*-[*p*-(phenylsulfonyl)phenyl]glycine, mp 159–160° dec. It was dried (P_2O_5) at 80° *in vacuo* and refluxed for 1.5 hr in a mixt of 250 ml of Et_2O and 10 ml of $(CF_3CO)_2O$. The solid was filtered off and recrystd from acetone to obtain 5.5 g (72%) of XXV, mp 181–182° dec. *Anal.* ($C_{14}H_{10}N_2O_4S$): C, H, N.

***N*-[4-(*p*-Chlorophenyl)sulfonylphenyl]-*N*-nitrosoglycine (XXVI).**—A soln of 7.6 g (0.11 mole) of $NaNO_2$ in 15 ml of H_2O was added at 10° to 29.4 g (0.1 mole) of *N*-[4-(*p*-chlorophenyl)-sulfonylphenyl]glycine in 500 ml of AcOH and 75 ml of concd HCl and stirred for 2 hr at 10–20°. The reaction mixt was dild with 750 ml of ice–water and the ppt was recrystd from Me_2CO–petr ether (bp 60–110°) to obtain 26.6 g (77%) of XXVI, mp 158–159° dec. *Anal.* ($C_{14}H_{11}ClN_2O_5S$): C, H, N.

***N*-[4-(*p*-Chlorophenyl)sulfonylphenyl]sydnone (XXVII).**—A suspension of 14.2 g (0.04 mole) of the nitrosoglycine XXVI in 350 ml of Et_2O and 15 ml of $(CF_3CO)_2O$ was refluxed for 1.5 hr. The ppt was washed with Et_2O (3 × 75 ml) and recrystd from Me_2CO (Darco)–petr ether (bp 60–110°) to obtain 12.7 g (94%) of XXVII, mp 190° dec. *Anal.* ($C_{14}H_9ClN_2O_4S$): C, H, N, S.

4-Acetamidophenyl 4-aminobenzyl sulfone (XXVII), mp 200–201°, was obtained in 99% yield by the hydrogenation of the NO_2 analog XXXIX over Raney Ni in DMF at 4.2 kg/cm². The pure product pptd from the DMF soln upon dilution with H_2O. *Anal.* ($C_{15}H_{16}N_2O_3S$): C, H, N.

4-Aminophenyl 4-nitrobenzyl sulfone (XXXVIII), mp 292–293° (from 5:2 MeCN–DMF), was obtained in 96% yield by a 5-hr refluxing of XXXIX in 10% HCl. *Anal.* ($C_{13}H_{12}N_2O_4S$): C, H, N.

Analgetic and Anticonvulsant Activity of Some 2- and 4-Pyridyl Ketones[1]

E. FRANK, J. GEARIEN,* M. MEGAHY, AND C. POKORNY

Department of Chemistry, College of Pharmacy, University of Illinois at the Medical Center, Chicago, Illinois 60612

Received December 17, 1970

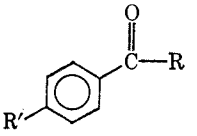
Previous investigations have shown that certain substituted 2,3-dihydro-4-quinolones[2] and their open chain analogs, the substituted β-aminopropiophenones,[3] possess analgetic activity. Compounds in the open chain series were more potent. With the hope that such simple compounds might provide information concerning structural requirements for analgetic activity, we wished to examine the biological activity of compounds in which the amino and carbonyl groups had a more

(1) This investigation was supported in part by the Institute of Arthritis and Metabolic Diseases, National Institute of Health, Public Health Service Grant AM 06432-05.

(2) M. Atwal, L. Bauer, S. Dixit, J. Gearien, and R. Morris, *J. Med. Chem.*, **8**, 566 (1965).

(3) M. Atwal, L. Bauer, S. Dixit, J. Gearien, M. Megahy, R. Morris, and C. Pokorny, *ibid.*, **12**, 994 (1969).

TABLE I: SUBSTITUTED PHENYL PYRIDYL KETONES



R	R′	Reaction solvent[a]	Mp or bp, °C	Crystn solvent	Yield, %	Formula	LD_{50}
2-C_5H_5N	H	A	130–131 (18)		61	$C_{12}H_9NO$	475
3-C_5H_5N	H	A	120–122 (19)		55	$C_{12}H_9NO$	460
4-C_5H_5N	H	A	69–71 (18)		70	$C_{12}H_9NO$	520
2-C_5H_5N	OCH_3	C	93–95 (20)	B	46	$C_{13}H_{11}NO_2$	>1000
3-C_5H_5N	OCH_3	C	95–96 (21)	B	47	$C_{13}H_{11}NO_2$	1375
4-C_5H_5N	OCH_3	C	118–119	D	66	$C_{13}H_{11}NO_2$	750
2 C_5H_5N	OC_2H_5	C	87–89 (20)	B	29	$C_{14}H_{13}NO_2$	>500
3 C_5H_5N	OC_2H_5	C	86–88	B	58	$C_{14}H_{13}NO_2$	>1000
4-C_5H_5N	OC_2H_5	C	57–58	A	51	$C_{14}H_{13}NO_2$	490
2-C_5H_5N	OH	C	103–104	D	53	$C_{12}H_9NO_2$	780

[a] Solvents for reactions and recrystn, A = anhyd Et_2O, B = cyclohexane C = THF, D = cyclohexane–benzene (1:1). [b] Compds whose physical constants were not previously reported were analyzed for C, H, and N and anal. results for those elements were within ±0.4% of the theor value.

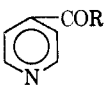
definite spatial relationship to each other. The commercially available 2-, 3-, and 4-benzoylpyridines were selected for biological evaluation since they appeared to meet this requirement. While 2-benzoylpyridine, when subjected to evaluation by the Hafner tail pinch method,[4] demonstrated analgetic activity (ED_{50}, 200 mg/kg), the other isomers did not. However, 4-benzoylpyridine was shown to protect mice from convulsions induced by electroshock when evaluated using the procedure of Toman and Swinyard.[5]

The analgetic activity of 2-benzoylpyridine prompted the synthesis of a number of substituted 2-benzoylpyridines (Table I). All of these were devoid of analgetic activity. Reduction of 2-benzoylpyridine yielded (±)-2-pyridylphenylmethanol. This compound had an ED_{50} for analgesia of 135 mg/kg. Separation of the racemic mixture yielded 2 optical isomers each possessing ED_{50}'s equal to that of the racemic mixture. It is interesting to note that while the analgetic activity of 1-methyl-2,3-dihydro-4-quinolone is increased by placing a MeO group in conjugation with C=O, similar substitution in the 2-benzoylpyridine series was accompanied by loss of activity. A further lack of correlation between these series is found when the C=O is reduced. Reduction of 1-methyl-2,3-dihydro-4-quinolone results in an inactive compound, while reduction of 2-benzoylpyridine to (+)-2-pyridylphenylmethonol yielded a more active compound.

Because of the anticonvulsant activity of 4-benzoylpyridine, a series of analogs in which the Ph group is replaced by various alkyl groups was prepared. The physical properties and anticonvulsant activity of these compounds are reported in Table II.

TABLE II

ANTICONVULSANT ACTIVITY OF ALKYL 4-PYRIDYL KETONE



R	Mp or bp, °C	Yield, %	Formula[a]	ED_{50}, mg/kg	LD_{50}, mg/kg
C_6H_5	130–131 (1.0)		$C_{12}H_9NO$	35[b]	450[b]
CH_3	125–127 (40)[c]	52	C_7H_7NO	150	1400
C_2H_5	135–138 (17)[d]	46	C_8H_9NO	200	680
n-C_3H_7	59–63 (0.07)[e]	44	$C_9H_{11}NO$	99	270
n-C_4H_9	65–69 (0.06)	43	$C_{10}H_{13}NO$	75	260
n-C_5H_{11}	85–88 (0.04)	33	$C_{11}H_{15}NO$	149	325
n-C_6H_{13}	77–82 (0.02)[f]	43	$C_{12}H_{17}NO$	87[b]	345[b]
n-C_7H_{15}	40–42[g]	42	$C_{13}H_{19}NO$	225[b]	>500[b]
c-C_6H_{11}	63–66 (0.05)	18	$C_{12}H_{15}NO$	98	175

[a] Because of discrepancies in boiling points, all compds were analyzed, and structures verified by ir and pmr spectroscopy. Anal. for C, H, and N were within 0.4% of the theoretical values. [b] Sesame oil solns of these compds were employed for biological evaluation. Other compds were suspended in tragacanth soln. [c] C. C. Chu and P. C. Teague, *J. Org. Chem.*, **23,** 1578 (1958), reported bp 104–105° (20 mm). [d] C. C. Chu and P. C. Teague, in reference *c* reported bp 104–106° (10 mm). [e] Bp 104–106° was reported by J. Cejka, M. Ferles, S. Chlodek, J. Labsky, and M. Zelinky, *Collect. Czech. Chem. Commun.*, **26,** 1429 (1961). [f] C. C. Chu and P. C. Teague in reference *c* reported bp 124–125°. In order to obtain the reported yield of this comp a 4:1 ratio of Grignard reagent was employed. [g] The compd is a solid and the value reported is its mp.

Experimental Section

All melting points were determined using a Hoover-Thomas melting point apparatus. Optical rotations were determined using a Rudolph and Sons No. 283 polarimeter. 2-, 3-, and 4-benzoylpyridines were purchased from Aldrich Chemical Company, Milwaukee, Wis. Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Pyridyl Ketones.—All ketones were synthesized by the reaction of the appropriate Grignard reagent in either Et_2O or THF with 2-, 3-, or 4-cyanopyridine following the procedure reported here for the synthesis of *n*-butyl 4-pyridyl ketones.

To a stirred suspension of 3.75 g (0.15 g-atom) of Mg turnings in 50 ml of anhyd Et_2O, a soln of 20.85 g (0.15 mole) of BuBr in 50 ml of anhyd Et_2O was added dropwise. When the addn was complete, the soln was heated at reflux temp for 45 min. After cooling in an ice bath to 15°, a soln of 7.8 g (0.075 mole) of 4-cyanopyridine was added dropwise with constant stirring. After the addn was completed, the resulting soln was heated at reflux temp for 24 hr and then treated with 50 ml of H_2SO_4 (1:1). The Et_2O soln was sepd, and the aq soln was extd 3 times with 50-ml portions of Et_2O. The aq soln was then made basic (pH 8.0) with 20% NaOH and extd 5 times with 50-ml portions of Et_2O. The Et_2O ext of the basic soln was dried (Na_2SO_4), and the Et_2O was removed by distn. The resulting oil (5.7 g, 43%) boiled at 65–69° (0.06 mm).

(+)-2-Pyridylphenylmethanol.—2-Benzoylpyridine (18.3 g, 0.1 mole) was dissolved in 100 ml of MeOH and hydrogenated under an initial pressure of 3.37 kg/cm² at 25° until the theor amt of H_2 for the reduction of C=O was absorbed (560 g of H_2 in 1 hr). The catalyst was removed by filtration, and the solvent was evapd under reduced pressure. A few drops of anhyd Et_2O was added, and the soln was kept in the refrigerator for 12 hr at which time crystals sepd. The solid was removed by filtration,

(4) C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9,** 28 (1954).
(5) J. Toman and E. Swinyard, *J. Neurophysiol.*, **9,** 231 (1946).

washed with petr ether, and recrystd from 2-PrOH–petr ether (bp 30–60°), mp 76–78° (lit.[6] 82°, 78°).

A column of alumina (200 g in a 2.5 × 61 cm column) was prepared using heptane to form a slurr. It was treated with a soln of (±)-tartaric acid (3 g in 10 ml of MeOH), and the column was washed with an addl liter of heptane. A soln of the racemic carbinol (9.25 g, 0.05 mole) and (+)-tartaric acid (7.5 g, 0.05 mole) in 20 ml of MeOH was applied to the column and eluted with heptane (2 l.). The eluent was collected in 200-ml fractions. Elution was contd with *i*-PrOH (2 l.) in 200-ml fractions. Finally 1 l. of EtOH was passed through and collected in 1 portion. All the fractions were evapd under reduced pressure to give oily residues. The solids were completely sol in anhyd Et_2O indicating the presence of the alcohol as the free base. The opt activities of the different fractions indicated that the (+) isomer was eluted by heptane while the (−) isomer was eluted in *i*-PrOH. Tartaric acid was eluted by EtOH. The (+) isomer had mp 64–65°, α_{589}^{20} +17.2 (0.154 g in 10 ml of $CHCl_3$). The (−) isomer had mp 60–62, α_{589}^{26} −17.3 (0.1209 g in 10 ml of $CHCl_3$).

The HCl salts of both enantiomorphs were prepd by passing HCl gas through their Et_2O soln. (+)-Phenyl-2-pyridylcarbinol·HCl had mp 179–180°. *Anal.* ($C_{12}H_{12}ClNO$) C, H, N, Cl. (−)-Phenyl-2-pyridylcarbinol·HCl had a mp of 174–176°. *Anal.* ($C_{12}H_{12}ClNO$), C, H, N, Cl.

2-(*p*-Hydroxybenzoyl)pyridine.—A soln of 2.0 g (0.0094 mole) of 2-(*p*-methoxybenzoyl)pyridine in 20 ml of 48% HBr was heated at 140° for 4 hr. After cooling and the addn of 20 ml of H_2O, the reaction mixt was chilled to 10° and neutralized with solid K_2CO_3. The resulting ppt, after recrystn from H_2O and then cyclohexane–PhH (1:1), melted at 103–104°; yield 1.0 g (53%). *Anal.* ($C_{12}H_9NO_2$) C, H, N.

(6) A. Tschitschibabin, *Ber.*, **37**, 1371 (1904).

Central Nervous System Depressive Activity of Some Amides of Tryptamine[1]

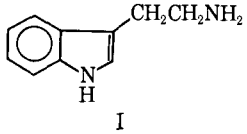
BENG T. HO,* RONG AN, MICHAEL B. NOEL, AND L. WAYNE TANSEY

Texas Research Institute of Mental Sciences, Houston, Texas 77025

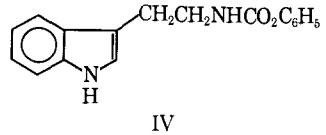
Received January 21, 1971

During our investigation of the inhibitory activity of a series of *N*-acyltryptamines on hydroxyindole-*O*-methyltransferase (HIOMT),[2] several compounds were found to cause sedation in rats. This led us to synthesize other substituted amides, benzenesulfonamide, and ureido derivatives of tryptamine for evaluation of their CNS-depressive activity.

All the acyl and benzenesulfonyl derivatives of tryptamine (I) except **10** were prepared by treating I in



I

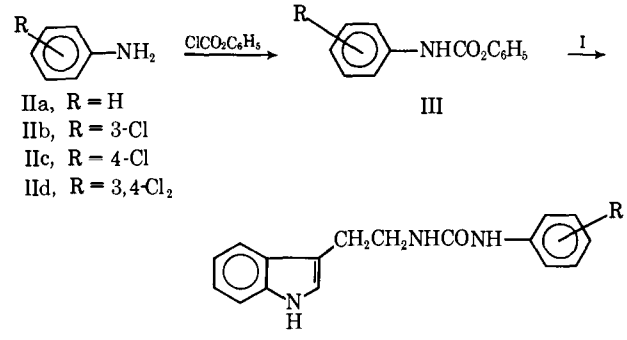


IV

$CHCl_3$ or CH_2Cl_2 with the appropriate acid chloride in the presence of Et_3N (in the case of **13** pyridine was used). Compound **10** was obtained by Schotten–Baumann reaction between I and $PhSO_2Cl$.

The general route (Scheme I) for the synthesis of

SCHEME I



IIa, R = H
IIb, R = 3-Cl
IIc, R = 4-Cl
IId, R = 3,4-Cl_2

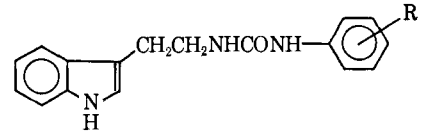
III

6–9

urea derivatives **6–9** started with the reaction of phenyl chloroformate with aniline (IIa) or substituted anilines (IIb–IId) to give *N,O*-diphenylcarbamate (IIIa) or its substituted analogs (IIIb–IIId), followed by replacement of phenoxy group of III by I forming the ureas. Table I lists the physical constants of the 4 ureas. A previous attempt to prepare the ureas by the treatment of $PhNH_2$ or the substituted anilines with *N*-β-3-indolylethyl phenylcarbamate (IV) in refluxing dioxane was unsuccessful. Compound IV was made from I and phenyl chloroformate in a basic medium.

TABLE I

SUBSTITUTED *N*-β-3-INDOLYLETHYL-*N'*-PHENYLUREA



Compd[a]	R	Yield, %	Recrystn solvent	Mp, °C	Formula
6	H	75	MeOH	185–187	$C_{17}H_{17}N_3O$
7	3-Cl	83	MeOH–H_2O	148.5–150.5	$C_{17}H_{16}ClN_3O$
8	4-Cl	82	EtOH–H_2O	198–200	$C_{17}H_{16}ClN_3O$
9	3,4-Cl_2	84	50% MeOH	150–151.5	$C_{17}H_{15}Cl_2N_3O$

[a] The corresponding starting materials, substituted phenyl phenylcarbamates, were prepared by treating aniline or substituted $PhNH_2$ with $ClCO_2Ph$, according to the procedure of D. G. Crosby and C. Neimann (*J. Amer. Chem. Soc.*, **76**, 4458 (1954); mp's: *N,O*-diphenyl carbamate, 125–127° (C_6H_6); substituted phenyl phenylcarbamates, 3-Cl, 74–76° (C_6H_6); 4-Cl, 150–152° (C_6H_6); 3,4-Cl_2, 131–133° (C_6H_6).

Of the 13 compounds tested, five (**3**, **4**, **5**, **8**, **13**) have shown a significant effect in reducing the spontaneous motor activity of mice (Table II). The ED_{50} values of the two most active compounds (**5**, **3**) were 19 ± 3.8 and 12 ± 3.2 mg per kg, respectively. Although **5** is also the best HIOMT inhibitor thus far found,[3] no correlation can be established between the enzyme inhibitory activity and the effect on spontaneous motor activity of mice.

Experimental Section[3]

***N*-β-3-Indolylethyl-*m*-nitrobenzenesulfonamide** (11).—To a soln of 6.4 g (40 mmoles) of tryptamine (I) and 4.04 g (40 mmoles) of Et_3N in 100 ml of CH_2Cl_2 was added with cooling a soln of 8.86 g (40 mmoles) of *m*-nitrobenzenesulfonyl chloride in 25 ml of CH_2Cl_2. The mixt was stirred for 3 hr and then washed successively with H_2O (two 100-ml portions), 10% HCl (two 100-ml

(1) This work was supported in part by Grant MH-11168, U. S. Public Health Service, Bethesda, Md.

(2) (a) B. T. Ho, W. M. McIsaac, and L. W. Tansey, *J. Pharm. Sci.*, **58**, 130 (1960); (b) B. T. Ho, W. M. McIsaac, L. W. Tansey, and P. M. Kralik *ibid.*, **57**, 1998 (1968); (c) B. T. Ho, W. M. McIsaac, and L. W. Tansey, *ibid.*, **58**, 563 (1969); (d) B. T. Ho, M. B. Noel, and W. M. McIsaac, *ibid.*, **59**, 573 (1970).

(3) Melting points were taken on a Mel-Temp apparatus and are corrected. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for these elements or functions were within ±0.4% of the theoretical values. Ir spectra of all the compounds were compatible with the assigned structures.