This was recrystallized twice from glacial acetic acid–absolute ethanol: wt 154 mg (Table II). Amino acid analysis gave Asp, 1.00; Pro, 1.18; Gly, 1.00; Phe, 1.08; Tyr, 1.10; Bzl-Cys, 0.96; Arg, 1.00; Glu, 1.09; NH_3, 1.80.

Deamino-8-D-arginine-vasopressin (dDAVP, 6). The protected octapeptide **5** (100 mg) was reduced, reoxidized, deionized, lyophilized, and purified as for 1 above: wt 55 mg. It was shown to be homogeneous by thin-layer chromatography and paper electrophoresis at two different pH's (Table II). Amino acid analysis gave Asp, 0.97; Glu, 0.98; Pro, 0.94; Gly, 0.95; Phe, 1.00; Tyr, 0.97; Arg, 0.96; NH_3, 2.20; cystine, 0.42; mixed disulfide of cysteine and β-mercaptopropionic acid, 0.48.

***S*-Bzl-β-mercaptopropionyl-Tyr(Bzl)-Phe-Thr(Bzl)-Asn-Cys(Bzl)-Pro-D-Arg(Tos)-Gly-NH_2 (7).** *tert*-Butyloxycarbonylglycyl resin (2.74 g, 0.68 mmol of glycine) was treated as described for the synthesis of **3** except that Boc-D-Arg(Tos) and Boc-Thr(Bzl) were used in the first and sixth incorporation steps, respectively. Upon completion of the eight-cycle procedure the protected octapeptide resin was collected and dried in vacuo over P_2O_5: wt 3.06 g. Ammonolytic cleavage of the protected octapeptide resin (2.99 g) followed by extraction with warm (50%) DMF (50 ml) and MeOH (40 ml), evaporation of the solvents, drying, and trituration with 95% ethanol (20 ml) and ether (40 ml) gave **7**: wt 244 mg; mp 207–211°. This was recrystallized from glacial acetic acid–95% ethanol: wt 151 mg (Table II). Amino acid analysis gave Asp, 0.97; Thr, 0.93; Gly, 1.00; Arg, 0.97; Pro, 1.06; Tyr, 0.78; Phe, 0.97; Bzl-Cys, 0.92; NH_3, 2.34.

Deamino[4-threonine]-8-D-arginine-vasopressin (dTDAVP, 8). The protected octapeptide **7** (100 mg) was deblocked, reoxidized, deionized, lyophilized, and purified as for 1: wt 34.1 mg (Table III). It was shown to be homogeneous by the usual methods. Amino acid analysis gave Asp, 0.98; Arg, 0.95; Thr, 0.92; Gly, 0.94; Phe, 0.96; Tyr, 0.90; Pro, 1.00; NH_3, 1.5, cystine, 0.32, mixed disulfide of cysteine and β-mercaptopropionic acid, 0.70.

Acknowledgment. This work was supported in part by research grants from the National Institute of Child Health and Human Development (No. H 606351), the National Institute of Arthritis and Metabolic Diseases (No. AM 01940), the National Heart and Lung Institute (No. HL 12738), and the National Science Foundation (No. BM 571-01238). We wish to thank Dr. John Lowbridge for helpful discussion and Miss Cindy Stanley for invaluable assistance in the preparation of the manuscript.

References and Notes

(1) Visiting investigator from Jozsef Attila University of Szeged, Department of Organic Chemistry, Szeged, Hungary.
(2) (a) M. Manning, L. Balaspiri, M. Acosta, and W. H. Sawyer, *J. Med. Chem.*, **16**, 975 (1973); (b) W. H. Sawyer, M. Acosta, L. Balaspiri, J. Judd, and M. Manning, *Endocrinology*, **94**, 1106 (1974).
(3) M. Manning, E. J. Coy, M. Acosta, and W. H. Sawyer, *J. Med. Chem.*, **16**, 836 (1973).
(4) M. Zaoral, J. Kolc, and F. Sorm, *Collect. Czech. Chem. Commun.*, **32**, 1242 (1967).
(5) M. Zaoral, J. Kolc, and F. Sorm, *Collect. Czech. Chem. Commun.*, **32**, 1250 (1967).
(6) R. L. Huguenin and R. A. Boissommas, *Helv. Chim. Acta*, **49**, 695 (1966).
(7) R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963).
(8) R. B. Merrifield, *Biochemistry*, **3**, 1385 (1964).
(9) M. Manning, *J. Am. Chem. Soc.*, **90**, 1348 (1968).
(10) M. Manning, E. Coy, and W. H. Sawyer, *Biochemistry*, **9**, 3925 (1970).
(11) W. H. Sawyer, *Endocrinology*, **63**, 694 (1958).
(12) W. H. Sawyer in "The Pituitary Gland", Vol. 3, G. W. Harris and B. T. Donovan, Ed., Butterworths, London, 1966, p 288.
(13) W. H. Sawyer and M. Manning, unpublished results.
(14) K. Vavra, A. Machova, V. Holocek, J. H. Cort, M. Zaoral, and F. Sorm, *Lancet*, 1, 948 (1968).
(15) W. H. Sawyer, M. Acosta, and M. Manning, *Endocrinology*, **95**, 140 (1974).
(16) J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis", W. H. Freeman, San Francisco, Calif., 1969, p 60.
(17) V. du Vigneaud, C. Ressler, J. M. Swan, P. G. Katsoyannis, C. W. Roberts, and S. Gordon, *J. Am. Chem. Soc.*, **75**, 4879 (1953).
(18) D. B. Hope, V. V. S. Murti, and V. du Vigneaud, *J. Biol. Chem.*, **237**, 1563 (1962).
(19) M. Manning, T. C. Wuu, and J. W. M. Baxter, *J. Chromatogr.*, **38**, 396 (1968).
(20) M. Manning, E. J. Coy, W. H. Sawyer, and M. Acosta, *J. Med. Chem.*, **16**, 463 (1973).

Antimalarials. 3. 1,2,4-Triazines

Louis C. March, Gurdip S. Bajwa, Jessie Lee, Khizar Wasti, and Madeleine M. Joullié*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19174. *Received July 16, 1975*

The syntheses of a number of substituted 1,2,4-triazines as potential antimalarials are described. The structural requirements for antimalarial activity are discussed with reference to the substituents of a phenyl group in the 6 position and amino groups at the 3 and 5 positions. Of the compounds tested, **2**, **5**, and **7** produced cures in mice infected with *Plasmodium berghei*. Compounds **2** [3,5-diamino-6-(4-trifluoromethylphenyl)-1,2,4-triazine], **3**, **5**, **8**, **12**, and **37** produced cures in chicks infected with *Plasmodium gallinaceum*.

3,5-Diamino-1,2,4-triazines have been reported to exhibit antimalarial activity.[1] 3,5-Diamino-6-(4'-chlorophenyl)-1,2,4-triazine (**1**) was also found to be a competitive antagonist of folic acid and folinic acid in the growth of *Lactobacillus casei*, thus confirming the suspected relationship between folic acid antagonists and antimalarial activity.[2] We, therefore, undertook the synthesis of several 6-substituted 3,5-diamino-1,2,4-triazines to examine the effect of structural changes on the antimalarial activity of this system.

Chemistry. The route employed for the synthesis of 6-aryl- and 6-thienyl-3,5-diamino-1,2,4-triazines **2–10** was previously used in the preparation of related 1,2,4-triazines.[1,3] This synthetic scheme involves the reaction of an acylnitrile with aminoguanidine bicarbonate in the presence of 8 N nitric acid and dimethyl sulfoxide. The acylnitrile aminohydrazones, obtained as nitric acid salts **2a–10a**, were cyclized with alcoholic potassium hydroxide to the desired 1,2,4-triazines **2–10**.

Some structural modifications of active 3,5-diamino-1,2,4-triazines were attempted. The reaction of **4** and **5** with *N,N*-dimethylformamide dimethyl acetal in dimethylformamide gave **11** and **12**. The reaction of **5** with phenyl isocyanate in refluxing 1,2-dimethoxyethane and **9** with *p*-toluenesulfonyl isocyanate in refluxing pyridine gave the corresponding monoureido derivatives **13** and **14**,

Table I. Antimalarial Activity against *P. berghei* in Mice[a]

Compd	Dose, mg/kg	T/C	Cures
2	640[b]	0	2
	320	0	5
	160	0	5
	80	0	5
	40	12.8	4
	20	12.8	2
	10[c]	6.8	0
5	640	15.4	3
	320	12.2	2
	160[c]	7.1	0
7	640	9.9	3

[a] Five test animals were used. [b] Toxic. [c] Active.

Table II. Antimalarial Activity against *P. gallinaceum* in Chicks[a]

Compd	Dose, mg/kg	T/C	Cures
2	640	9.9	3
	480[b]	9.9	1
	240	6.4	1
3	320	2.2	3
	240	1.5	3
4	320[c]	7.0	0
5	320	3.2	3
	160	3.2	3
	80	1.7	2
12	480	1.5	3
36	640[b]	4.4	2

[a] Five test animals were used. [b] Toxic. [c] Active.

respectively. The structures of **13** and **14** were assigned by analogy to previous reports in the literature that 3-amino-1,2,4-triazines react readily with phenyl isocyanates at ambient temperature to give 1-phenyl-3-[3-(1,2,4-triazinyl)]ureas.[4] It was not possible to determine whether reaction had occurred at the 3 or 5 position on the basis of the spectral properties obtained (ir and ^{1}H NMR).

The synthesis of 3-amino-1,2,4-triazines has been previously reported.[5-8] Both 6-methyl- (**15**) and 6-phenyl-3-amino-5-hydroxy-1,2,4-triazine (**16**) were similarly prepared by the cyclization of aminoguanidine bicarbonate with the appropriate α-keto acid. Compound **17** was obtained by treating **15** with phosphorus pentasulfide in refluxing anhydrous pyridine. 3-Amino-5-(2-diethylaminoethylamino)-6-methyl-1,2,4-triazine (**18**) was prepared from **17** and refluxing diethylaminoethylamine.

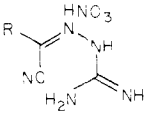
Several 3-amino-1,2,4-triazines **19** and **20** were synthesized from aminoguanidine bicarbonate and the corresponding dicarbonyl compounds in refluxing benzene. Other 3-amino-substituted 1,2,4-triazines **25–30** were prepared by the reaction of 5,6-disubstituted 3-(methylthio)-1,2,4-triazines with amines or hydrazine. The intermediate triazines **23** and **24**[9,10] were obtained by the methylation (sodium ethoxide, methyl iodide) of 5,6-disubstituted 3-thio-1,2,4-triazines **21** and **22** which, in turn, were prepared from benzil or a substituted benzil and thiosemicarbazide in refluxing acetic acid.

Several 6-substituted 3-thio-2,5-dihydro-1,2,4-triazin-5-ones **31–34** were synthesized via cyclization of the thiosemicarbazone of an α-keto acid in ethanolic sodium ethoxide. The reaction of **31** with ethanolic sodium ethoxide and methyl iodide afforded 6-methyl-3-(methylthio)-4,5-dihydro-1,2,4-triazin-5-one (**35**) as the sodium salt. Treatment of 6-methyl-3,5-dithio-1,2,4-triazine (**36**) with sodium ethoxide and methyl iodide gave the 3,5-bis(methylthio) derivative **37**. The reaction of **37** with ammonia in methanol at room temperature resulted in the displacement of the 5-thio group to give **38**. The structural assignment for compound **38** is based upon the previously reported reaction of 6-methyl-3,5-dithio-1,2,4-triazine with ammonia in alcohol[11] and the fact that **17** was shown to undergo facile displacement of the 5-thio group when treated with diethylaminoethylamine. When **37** was treated with 2-phenylethylamine at 200° for 4 h, two products (**39** and **40**) were obtained. The major product was the monosubstituted compound **39**.

Biological Results. The antimalarial tests were performed at the Leo Rane Laboratory, University of Miami, and supplied to us by the Walter Reed Army Institute of Research. The tests were based upon the relative response of *Plasmodium berghei* malaria in mice[12] to each of the submitted compounds as expressed by the mean survival time of treated animals (MSTT) and the mean survival time of controls (MSTC). A single dose of the test compound was administered subcutaneously 72 h after the mice were infected with trophozoites of *P. berghei*. Untreated animals died within 6–8 days and had a mean survival time (MSTC) of 6.1 days. Treated animals were kept under observation for 60 days. The prolongation of life for 2.5 days was deemed statistically significant. A minimum mean survival time of 12 days was required for the compounds to be considered active. Animals which survived for 60 days and showed no parasitemia were considered cured. Compounds **2–17**, **4a–8a**, **19–28**, **31–37**, **39**, and **40** were so tested. All compounds were examined at a maximum dose of 640 mg/kg with the exception of compound **2** (320 mg/kg). Compounds **2**, **4**, **5**, and **7** displayed the highest degree of activity against *P. berghei* in mice. These compounds were 1,2,4-triazines that possessed free amino groups in the 3 and 5 positions and a phenyl group at the 6 position which was substituted with one or two electron-withdrawing atoms or groups. The compounds shown in Table I were curative.

Compounds differing only by the absence of one electron-withdrawing atom or group in the 6-phenyl substituent exhibited diminished activity. Compound **19**

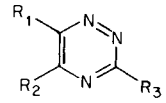
Table III. Acylnitrile Aminohydrazones



No.	R	Yield, %	Mp, °C	Crystn solvent	Formula	Analyses[a]
4a	3,4-$(CH_3O)_2$-C_6H_3	54	180.5-181	EtOH	$C_{11}H_{14}O_5N_6$	C, H, N
5a	3,4-OCH_2O-C_6H_3	91	204-205	Me_2SO	$C_{10}H_{10}O_5N_6$	C, H, N
6a	2-Thienyl	53	170-172	EtOH	$C_7H_8O_3N_6S$	C, H, N
7a	3-Cl-4-CH_3-C_6H_3	73	200-201	DMF-EtOH	$C_{10}H_{11}O_3N_6Cl$	C, H, N, Cl
8a	4-CH_3SO_2-C_6H_4	*b*				
9a	3,4-$(C_2H_5O)_2$-C_6H_3	*b*				
10a	3,4-$(CH_3)_2$-C_6H_3	*b*				

[a] Analytical results are within 0.3% of the theoretical values. [b] Crude product used in next step.

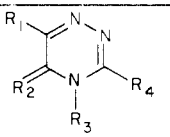
Table IV. 3,5,6-Substituted 1,2,4-Triazines



No.	R_1	R_2	R_3	Yield, %	Mp, °C	Crystn solvent	Formula	Analyses[a]
3	m-CF_3-C_6H_4	NH_2	NH_2	39	199-201		$C_{10}H_8N_5F_3$	C, H, N
4	3,4-$(CH_3O)_2$-C_6H_3	NH_2	NH_2	91	279-280	Me_2SO	$C_{11}H_{13}O_2N_5$	C, H, N
5	3,4-OCH_2O-C_6H_3	NH_2	NH_2	81	215-215.5	Me_2SO	$C_{10}H_9O_2N_5$	C, H, N
6	2-Thienyl	NH_2	NH_2	85	275-276	Me_2SO-H_2O	$C_7H_7N_5S$	C, H, N
7	3-Cl-4-CH_3-C_6H_3	NH_2	NH_2	63	225-226	EtOH	$C_{10}H_{10}N_5Cl$	C, H, N
8	4-$CH_3SO_2C_6H_4$	NH_2	NH_2	33	316-318	Me_2SO	$C_{10}H_{11}N_5O_2S$	C, H, N
9	3,4-$(C_2H_5O)_2$-C_6H_3	NH_2	NH_2	78	245-246	1. Me_2SO 2. EtOH	$C_{13}H_{17}N_5O_2$	C, H, N
10	3,4-$(CH_3)_2$-C_6H_3	NH_2	NH_2	32[b]	198-198.5	EtOH	$C_{11}H_{13}N_5$	C, H, N
11	3,4-$(CH_3O)_2$-C_6H_3	N=CHN$(CH_3)_2$	N=CHN$(CH_3)_2$	90	198-199	Acetone	$C_{17}H_{23}N_7O_2$	C, H, N
12	3,4-OCH_2O-C_6H_3	N=CHN$(CH_3)_2$	N=CHN$(CH_3)_2$	79	230-231	Acetone	$C_{16}H_{19}N_7O_2$	C, H, N
13	3,4-$(CH_3O)_2$-C_6H_3	NH_2	NHCONHC_6H_5[c]	49	243-244	1. C_5H_5N 2. Acetone	$C_{17}H_{14}N_6O_3$	C, H, N
14	3,4-OCH_2O-C_6H_3	NH_2	$NHCONHSO_2C_6H_4$-4-CH_3[c]	7	240-243.5[d]	EtOH	$C_{21}H_{24}N_6O_5S$	C, H, N
18	CH_3	$NH(CH_2)_2N(C_2H_5)_2$	NH_2	55	137-138	C_6H_6	$C_{10}H_{20}N_6$	C, H, N
19	CH_3	CH_3	NH_2	21	203-205[d]	EtOH	$C_5H_8N_4$	
20	C_6H_5	C_6H_5	NH_2	64	172-173[e]	EtOH	$C_{15}H_{12}N_4$	
21	C_6H_5	C_6H_5	SH	50	228-230[f]	EtOH-H_2O	$C_{15}H_{11}N_3S$	
22	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4	SH	55[g]	248-250	HOAc	$C_{17}H_{15}N_3O_2S$	
23	C_6H_5	C_6H_5	SCH_3	85[h]	118-119	EtOH	$C_{16}H_{13}N_3S$	
24	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4	SCH_3	55[i]	135-137	EtOH	$C_{18}H_{17}N_3O_2S$	
25	C_6H_5	C_6H_5	$NHCH_2C_6H_5$	82	190-191	EtOH	$C_{22}H_{18}N_4$	C, H, N
26	C_6H_5	C_6H_5	$NHCH_2C_6H_4$-4-Cl	34	175-177	EtOH	$C_{22}H_{17}N_4Cl$	C, H, N
27	C_6H_5	C_6H_5	$NHCH_2C_6H_3$-2,4-Cl_2	62	178-179	EtOH	$C_{22}H_{16}N_4Cl_2$	C, H, N
28	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4	$NHNH_2$	57	171-173	MeOH	$C_{17}H_{17}N_5O_2$	C, H, N
29	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4	$NHCH_2C_6H_4$-3-Cl	51	192-193	EtOH	$C_{24}H_{21}N_4O_2Cl$	C, H, N
30	C_6H_5	C_6H_5	$NHCH_2CH_2C_6H_5$	70	144-146	EtOH	$C_{23}H_{20}N_4$	C, H, N
36	CH_3	SH	SH	56	217.5-219	H_2O	$C_4H_5N_3S_2$	C, H, N
37	CH_3	SCH_3	SCH_3	47	78-79.5	EtOH	$C_6H_9N_3S_2$	C, H, N, S
38	CH_3	NH_2	SCH_3	28	174.5-175	1. EtOH-C_6H_6 2. EtOH-H_2O 3. H_2O	$C_5H_8N_4S$	C, H, N, S
39	CH_3	$NH(CH_2)_2C_6H_5$	SCH_3	47	142-143	1. EtOH-H_2O 2. Chromatography	$C_{13}H_{16}N_4S$	C, H, N
40	CH_3	$NH(CH_2)_2C_6H_5$	$NH(CH_2)_2C_6H_5$	20	147-148	1. EtOH-H_2O 2. Chromatography	$C_{20}H_{23}N_5$	C, H, N

[a] Analytical results are within 0.3% of the theoretical values. [b] From ketonitrile. [c] The assignments of the substituents at positions 3 and 5 (R_2 and R_3) are tentative. [d] Lit. mp 221-212°: J. G. Erickson, *J. Am. Chem. Soc.*, 74, 4706 (1952). [e] Lit. mp 175°: J. Thiele and R. Bihan, *Justus Liebigs Ann. Chem.*, 302, 299 (1898). [f] Lit. mp 220°: B. A. Gingras, T. Suprunchuk, and C. H. Bayley, *Can. J. Chem.*, 40, 1053 (1962). [g] Lit.[10] mp 255°. [h] Lit.[10] mp 119-120°. [i] Lit.[10] mp 154°.

Table V. 3,4,5,6-Substituted 1,2,4-Triazines



No.	R_1	R_2	R_3	R_4	Yield, %	Mp, °C	Crystn solvent	Formula	Analyses[a]
15	CH_3	O	H	NH_2	100	>300[b]	H_2O	$C_4H_6N_4O$	
16	C_6H_5	O	H	NH_2	30	335-338	H_2O	$C_9H_8N_4O \cdot H_2O$	C, H
17	CH_3	S	H	NH_2	9	>315 dec	H_2O	$C_4H_6N_4S$	C, H, N, S
31	CH_3	O	H	SH	59	217.5-218.5	H_2O	$C_4H_6N_3OS$	C, H, N, S
32	$(CH_2)_2CO_2H$	O	H	SH	100	212-213.5	H_2O	$C_6H_7N_3O_3S$	C, H, N, S
33	$CH_2C_6H_4$-4-OH	O	H	SH	61	230-231.5	EtOH-H_2O	$C_{10}H_9N_3O_2S$	C, H, N, S
34	C_6H_5	O	C_2H_5	SH	20	205-206	EtOH-H_2O	$C_{11}H_{11}N_3OS$	C, H, N, S
35	CH_3	O	Na	SCH_3	33	299-300 dec	Acetone	$C_5H_6N_3OSNa$	C, H, N, S

[a] Analytical values are within 0.3% of the theoretical values. [b] Lit.[8] mp >300°.

which had no phenyl group in the 6 position and only one amino group showed reduced activity. When one or both of the free amino groups were derivatized or protected, activity was diminished as in compounds **11**–**14**. Compounds **3**, **4**, **10**, **12**, and **19** increased the mean survival time of the test mice (IMST) by 4.6 (640 mg/kg), 11.7 and 10.1 (640 and 320 mg/kg), 4.9 (640 mg/kg), 5.9 (640 mg/kg), and 4.2 days (640 mg/kg), respectively. The remaining compounds were inactive. Compounds **8**, **20**, **31**, **36**, **37**, and **6a** were toxic and, of these, five contained sulfur. Compounds **12** (48 mg/kg, maximum dose), **8**, **19**, **31**, **32** (100 mg/kg), **5**, **5a**, **37** (160 mg/kg), **3**–**5**, **7**, **15**, **34** (320 mg/kg), and **2** (480 mg/kg) were tested against *Plasmodium gallinaceum* in chicks as described for *P. berghei* in mice. Several of the compounds were active (Table II).

All other compounds were inactive. Compounds **2**, **3**, **5**, and **8** possessed free amino groups in the 3 and 5 positions and a phenyl group at the 6 position substituted with electron-withdrawing atoms or groups. Compound **12** was similar to **5** but possessed dimethylformamidino groups instead of amino groups at the 3 and 5 positions. While this compound displayed reduced activity in mice, it exhibited the same curative ratio (3/5) as **5** in chicks. Compound **37** produced 2/5 cures but was toxic. The remaining compounds were inactive.

Experimental Section

General Procedures. Melting points were determined with a Mel-Temp or Thomas-Hoover apparatus and are uncorrected. Microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind., or Galbraith Laboratories, Knoxville, Tenn. Analytical results (C, H, N, X) were within 0.3% of the theoretical values. Melting points, recrystallization solvents, percentage yields, and analytical results are given in Tables III–V.

The structures assigned were supported by ir spectra recorded on Perkin-Elmer 137 or 521 spectrophotometers and NMR spectra recorded on Varian A-60A or HA-100D spectrometers.

Acknowledgment. This work was supported by the U.S. Army Medical Research and Development Command, Contract DADA 17-71-C1065. This is Contribution No. 1372 in the U.S. Army series of publications on malaria research. The authors wish to thank Dr. Edgar A. Steck for his encouragement and Ms. Joan Miller, Mr. David Pennes, and Mr. Walter Tsou for their assistance with the synthetic work.

References and Notes

(1) R. W. A. Rees, P. B. Russell, T. J. Foell, and R. E. Bright, *J. Med. Chem.*, **15**, 859 (1972).
(2) E. A. Falco, G. H. Hitchings, P. B. Russell, and H. Vanderwerf, *Nature (London)*, **164**, 107 (1949).
(3) J. A. Settepani and A. B. Borkovec, *J. Heterocycl. Chem.*, **3**, 188 (1966).
(4) A. J. Basso and R. C. O'Neill (to Merck and Co., Inc.) U.S. Patent 2762743 (Sept 11, 1956).
(5) E. H. Rodd, Ed., "The Chemistry of Carbon Compounds", Vol. IVC, Elsevier, Amsterdam, 1960, p 1561.
(6) W. W. Paudler and J. M. Barton, *J. Org. Chem.*, **31**, 1720 (1966).
(7) W. W. Paudler and R. E. Herbener, *J. Heterocycl. Chem.*, **4**, 224 (1967).
(8) T. Ueda and M. Furukawa, *Chem. Pharm. Bull.*, **12**, 100 (1964).
(9) M. Polonovski, M. Pesson, and P. Rajzman, *C. R. Hebd. Seances Acad. Sci.*, **238**, 1134 (1954).
(10) M. Polonovski and M. Pesson, *C. R. Hebd. Seances Acad. Sci.*, **232**, 1260 (1951).
(11) E. A. Falco, E. Pappas, and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 1938 (1956).
(12) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).