proximately 3.6 times faster than in the case of **28** and the enzyme. Comparative chemical reactivities using 4-(*p*-nitrobenzyl)pyridine as the nucleophilic reagent reveal that **24** is 3.5 times more reactive than is iodoacetamide (Figure 4). It has previously been reported that when 4-(*p*-nitrobenzyl)pyridine is used as the nucleophilic reagent, the chemical reactivities of **29** and **28** relative to iodoacetamide are 3.0 and 5.6, respectively. Therefore, the increased rate of alkylation of the enzyme by **24** cannot be attributed to its increased chemical reactivity. The differences in the rates of irreversible inactivation (k_2) of adenosine deaminase by **24** and **29** may be rationalized by assuming that in the reversible E···I complex, the alkylating group of the inhibitors is juxtapositioned in a different steric orientation on the enzyme.

Irreversible Enzyme Inhibitors. CIX.[1,2] Candidate Irreversible Inhibitors of Dihydrofolic Reductase Derived from 4,6-Diamino-1,2-dihydro-2,2-dimethyl-1-phenyl-*s*-triazine. III[3]

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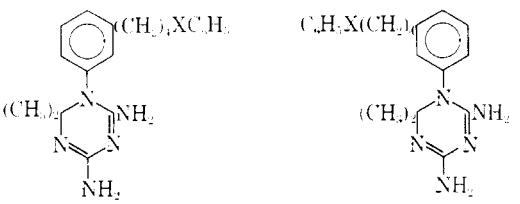
Received August 24, 1967

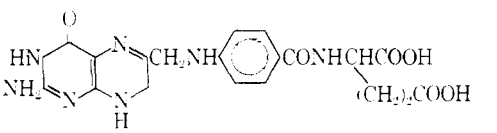
Nineteen derivatives of 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-phenyl-*s*-triazine bridged from its phenyl group to *N*-phenylbromoacetamide, maleanilic acid, and 1-chloro-2-alkanone were synthesized and evaluated as active-site-directed irreversible inhibitors of dihydrofolic reductase from pigeon liver, Walker 256 rat tumor, and L1210/FR8 mouse leukemia. Although the bromoacetamido group of most of these compounds appeared to be in contact with the enzyme surface, no irreversible inhibition occurred. These negative results were most probably due to the incapability of the juxtaposed enzymic nucleophilic group to react with these halomethyl and α,β-unsaturated carbonyl groups on the inhibitor when the inhibitor was complexed to the enzyme, since similarly positioned sulfonyl fluoride groups have been shown to inactivate the dihydrofolic reductases by the active-site-directed mechanism.

One of the major projects in this laboratory has been the design and synthesis of active-site-directed irreversible inhibitors[5,6] for dihydrofolic reductase;[7] such irreversible inhibitors that operate by the exo mechanism—that is, the inhibitor is reversibly complexed to the active site of the enzyme but covalently binds to the enzyme outside the active site—have considerable potential for species-specific or tissue-specific inhibition.[8]

Previous studies had indicated that the 1-phenyl group of dihydro-*s*-triazines such as **1** was complexed to dihydrofolic reductase by a hydrophobic interaction.[7,9,10] Furthermore, this hydrophobic bonding region[11] was not part of the active site but was just adjacent to the region on the enzyme where the 4 or 8 position of dihydrofolate (**3**), the substrate, resides.[7,12] Compounds of type **1** and **2** were then selected for investigation to determine how far the hydrophobic bonding region extended from the region where the



1a, X = CH_2 **1b**, X = CH_2
2a, X = O **2b**, X = O



3

1-phenyl group was complexed. The phenylamyl group of **1** gave a 16-fold increment in binding over the parent 1-phenyl-*s*-triazine;[13] the butyl part on **1** contributed only threefold in binding. The phenoxybutyl group of **2** had complexing ability equal to the phenylamyl group of **1**,[14] indicating that the terminal phenyl group was complexed to a relatively polar region on the enzyme.[7] With compounds of type **1**, the actual complex with the enzyme would have a preference for either conformation **1a** or **1b**, but not likely both.

When all of these studies are combined, then logical candidates for exo-type active-site-directed irreversible

(1) This work was generously supported by Grant CA-08695 from the National Cancer Institute, U. S. Public Health Service.

(2) For the previous paper in this series, see B. R. Baker, P. C. Hsiang, and A. L. Pogolatti, Jr., *J. Med. Chem.*, **10**, 1134 (1967).

(3) For the previous papers on candidate irreversible inhibitors derived from 1-phenyl-*s*-triazines see (a) B. R. Baker and G. J. Lourens, *J. Med. Chem.*, **10**, 1113 (1967), paper CV of the complete series; (b) B. R. Baker and B.-T. Ho, *J. Pharm. Sci.*, **56**, 28 (1967), paper LXX of this series.

(4) G. J. L. wishes to thank the Council for Scientific and Industrial Research, Republic of South Africa, for a tuition fellowship.

(5) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors. The Organic Chemistry of the Enzymic Active-Site," John Wiley and Sons, Inc., New York, N. Y., 1967.

(6) B. R. Baker, *J. Pharm. Sci.*, **53**, 347 (1964).

(7) For a review see ref 5, Chapter X.

(8) For a discussion of the evolutionary changes in enzymes outside the active site and utilization of such changes for chemotherapy, see ref 5, Chapter IX.

(9) For a discussion of hydrocarbon interactions with enzymes consisting primarily of hydrophobic bonding and van der Waals forces, see ref 5, Chapter II.

(10) B. R. Baker and B.-T. Ho, *J. Heterocyclic Chem.*, **2**, 335 (1965).

(11) B. R. Baker, B.-T. Ho, and D. V. Sapp, *J. Pharm. Sci.*, **54**, 1115 (1965).

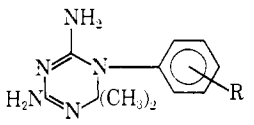
(12) (a) B. R. Baker, T. S. Selwan, J. Nowotny, and B.-T. Ho, *ibid.*, **55**, 295 (1966); (b) B. R. Baker and H. S. Shapiro, *ibid.*, **55**, 308 (1966).

(13) B. R. Baker, B.-T. Ho, and G. J. Lourens, *ibid.*, **56**, 737 (1967), paper LXXXVI of this series.

(14) B. R. Baker and G. J. Lourens, *ibid.*, **56**, 871 (1967), paper LXXXVII of this series.

TABLE I

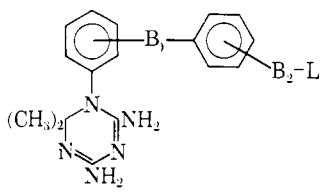
REVERSIBLE INHIBITION[a] OF DIHYDROFOLIC REDUCTASES BY



No.	R	I_{50}[b,c] μM: Pigeon liver	Walker 256	L1210/FR8
5	m-$(CH_2)_4C_6H_5$	0.0027[d]		
6	m-$(CH_2)_4C_6H_4NHCOCH_2Br$-p	0.0092	0.0042	0.011
7	m-$(CH_2)_4C_6H_4NHCOCH_2Br$-m	0.013	0.0039	0.044
8	m-$(CH_2)_2C_6H_5$	0.024[d]		
9	m-$(CH_2)_2C_6H_4NHCOCH_2Br$-p	0.0091	0.0054	0.0043
10	m-C_4H_9-n	0.030[d]		
11	m-$CH_2NHCOCH_2Br$	0.41	0.26	0.26
12	m-$O(CH_2)_2OC_6H_5$	0.075[e]		
13	m-$O(CH_2)_2OC_6H_4NHCOCH_2Br$-$p$	0.053	0.0073	0.039
14	m-$O(CH_2)_2OC_6H_4NHCOCH_2Br$-$m$	0.045	0.022	0.076
15	m-$O(CH_2)_2OC_6H_4NHCOCH_2Br$-$o$		0.022	0.14
16	m-$O(CH_2)_3OC_6H_5$	0.11[e]		
17	m-$O(CH_2)_3OC_6H_4NHCOCH_2Br$-$p$	0.19	0.028	0.090
18	m-$O(CH_2)_3OC_6H_4NHCOCH_2Br$-$m$	0.12	0.023	0.11
19	m-$OCH_2C_6NHCOCH_2Br$-m	0.22	0.12	0.11
20	m-$OC_6H_4NHCOCH_2Br$-p	0.075	0.012	0.032
21	p-$O(CH_2)_2OC_6H_4NHCOCH_2Br$-$p$	0.053	0.020	0.057
22	p-$COCH_2Cl$	1.2[f]	0.35	0.90
23	p-$(CH_2)_2COCH_2Cl$	0.025[f]	0.012	0.036
24	m-$COCH_2Cl$	1.7[f]	0.61	1.3
25	m-$(CH_2)_2COCH_2Cl$	0.083	0.080	0.035
26	m-$(CH_2)_4COCH_2Cl$	0.025	0.080	0.027
27	m-$O(CH_2)_2OC_6H_4NHCOCH{=}CHCOOH$-$p$	0.078	0.0075	0.022
28	m-$O(CH_2)_3OC_6H_4NHCOCH{=}CHCOOH$-$p$	0.076	0.0080	0.025
29[g]	p-$(CH_2)_2CONHC_6H_4SO_2F$-p	0.070	0.020	0.080
30[g]	m-$(CH_2)_2CONHC_6H_4SO_2F$-p	0.10	0.064	0.078
31[g]	m-$CH_2CONHC_6H_4SO_2F$-p	0.31	0.046	0.30

[a] The technical assistance of Barbara Baine and Jean Reeder with these assays is acknowledged. [b] I_{50} = concentration of inhibitor necessary for 50% inhibition. [c] Assays were run in 0.05 M Tris buffer with 6 μM dihydrofolate as previously described;[3a] 12 μM TPNH was used with the pigeon liver enzyme and 30 μM TPNH with the two tumor enzymes. [d] Data from ref 13. [e] Data from ref 14. [f] Data from ref 3b. [g] Data from ref 3a.

inhibitors of dihydrofolic reductase can be summarized by **4**; if (a) the proper bridge length, B_1, between the phenyl groups and, B_2, between the outside phenyl group and the leaving group, L, exists and (b) if L is a leaving group capable of reacting with a juxtaposed nucleophilic center on the enzyme, then an active-site-directed irreversible inhibitor should emerge. Initial



4, B = bridge, L = leaving group

work was focused on the chloromethyl ketone and bromoacetamido groups for the L group of **4**, since these two groups have the electrophilic ability to react with any one of seven out of a total of fifteen different proteinic amino acids containing a third functional group. Nineteen compounds with these two leaving groups and the maleanilic group, but with varying B_1 and B_2 groups (see **4**), were synthesized and evaluated enzymatically. The results are the subject of this paper.

Enzyme Results.—Reversible inhibition with these nineteen candidate irreversible inhibitors on dihydrofolic reductase from pigeon liver, Walker 256 rat tumor, and L1210/FR8 mouse leukemia are presented in Table I; for comparison purposes some related reversible inhibitors are also collated. The following information on reversible complexing to dihydrofolic reductase can be gleaned.

(1) Introduction of the bromoacetamido group (**6**, **7**) on the m-phenylbutylphenyl-s-triazine (**5**) leads to a 3–4-fold loss in binding; this indicates that the bromoacetamido group is in contact with the enzyme, but is not complexed.

(2) The m-bromoacetamidomethylphenyl-s-triazine (**11**) is a 13-fold poorer inhibitor than the m-butylphenyl-s-triazine (**10**). Since the latter shows a threefold better inhibition than the parent phenyl-s-triazine (I_{50} = 0.11 μM),[13] the n-butyl group has some hydrophobic interaction with the enzyme; this hydrocarbon area on the enzyme could repulse the polar carboxamide group of **11**.

(3) Introduction of the bromoacetamido group (**9**) on the m-phenethylphenyl-s-triazine (**8**) gives a threefold increased binding; this result also indicates the bromoacetamido group of **9** is weakly complexed with the enzyme and therefore is in contact with the enzyme.

(4) When an amide group is substituted on the ter-

minal phenyl group of *m*-phenoxyethyloxyphenyl-*s*-triazine (**12**) to give **13**–**15** and **27**, little change in binding occurred; similarly, substitution of the bromoacetamido group (**17**, **18**, **28**) on the phenoxypropyloxyphenyl-*s*-triazine (**16**) gave little change in binding. These results indicate that these flexible side chains are unable to give a conformation that allows the amide to complex to the enzyme but can assume conformations where essentially no loss in binding occurs due to steric interaction of the bromoacetamido group with the enzyme.

The data in Table I can also be used to compare differences in reversible binding to the three vertebrate enzymes; the following information is pertinent. (1) The greatest differences in reversible binding between the pigeon liver and Walker 256 rat tumor enzymes is seen with compounds **13**, **27**, and **28** where 8–10-fold better binding occurs with the rat tumor enzyme. In only one case (with **26**) was better binding seen with the pigeon liver enzyme, and it was only threefold. (2) The greatest differences in binding between the mouse leukemia L1210/FR8 and pigeon liver was only 2–3-fold; for example, **7** was complexed slightly better to the pigeon liver enzyme, but **9** was complexed slightly better to the mouse leukemia enzyme. (3) The greatest difference in reversible binding between the rat tumor and mouse leukemia enzymes is seen with compounds **7**, **13**, and **31** where 6–10-fold better binding occurs with the rat tumor enzyme. In only two cases (**25**, **26**) was binding better to the L1210 enzyme, but only by a factor of about three.

These definite, but small, differences suggest that there is little likelihood that reversible inhibitors of dihydrofolic reductase will be of use in cancer chemotherapy unless there is some other difference between the cancer and normal tissues such as active transport[7] or rate of detoxification.[15,16]

None of the bromoacetamides, chloromethyl ketones, or maleanilic acids in Table I showed irreversible inhibition of any of three enzymes when incubated at a concentration of $5I_{50}$ by the methods previously described.[3a] The fact that the amide group of **6**, **7**, **9**, **11**, **13**–**15**, **17**, **18**, **27**, and **28** (see reversible binding discussion above) was in contact with the enzyme but did not covalently link to the enzyme to afford irreversible inhibition can be explained in one or two ways: (a) the leaving group was not juxtaposed to a nucleophilic group on the enzyme within the reversible enzyme-inhibitor complex, or (b) the juxtaposed enzymic nucleophilic group did not have the proper character to react at a detectable rate with the terminal halomethylcarbonyl or α,β-unsaturated carbonyl group on the inhibitor.

Two approaches were investigated to solve this enigma.

(1) Placement of the bromoacetamido group on a branch from the phenylalkylphenyl group was investigated; these results are reported in the paper that follows.[17] None showed irreversible inhibition of dihydrofolic reductase; however, the number of compounds investigated were not extensive since the simultaneous approach below was successful.

(2) A leaving group with the ability to react with the hydroxyl group of serine or threonine was investigated, namely the sulfonyl fluoride function; these results have been reported,[3a] but some (**29**–**31**) are included in Table I for comparison purposes. All three sulfonyl fluorides (**29**–**31**) could irreversibly inhibit the dihydrofolic reductase from pigeon liver, but only **31** could inactivate the two tumor enzymes. It is interesting to note that the irreversibly ineffective bromoacetamide (**20**) has the same total bridge distance (but different bridges) between the inside phenyl group and its leaving group as the irreversibly effective **31**; similarly, **9** and **19** have the same bridge distance as the irreversibly effective **30**.

Currently, further studies on compounds of type **31** are being pursued; by utilization of the various tenets of the bridge principle of specificity,[3] these analogs have the possibility of inactivating a given tumor enzyme with minimal effects on host tissues.

Chemistry.—The candidate irreversible inhibitors in Table I can be placed in one of five different groups dependent upon their mode of synthesis. Group I consisted of *m*-phenylalkylphenyl-*s*-triazines (**6**, **7**, **9**). The key intermediate is a diphenylalkene system (**39**, **40**) where one phenyl has an amino group to be built to a dihydro-*s*-triazine and the other phenyl has a nitro group which can be reduced at the appropriate time and converted to a bromoacetamide. The smoothest synthetic route to substituted 1,4-diphenylbutadienes or diphenylethylenes is by the Wittig reaction[18] between an appropriate benzylphosphonium salt and a nitrobenzaldehyde or nitrocinnamaldehyde.[13] In order to handle the two nitrogen functions of the diphenylalkene system, they should be dissimilar; therefore, the acetamido function on the benzylphosphonium partner (**34**) was selected.

Only two examples of catalytic hydrogenation of molecules containing a phosphonium function could be found in the literature. Raney nickel catalyst being employed in one case[19] and palladium on charcoal in the other.[20] Reduction of the nitro group of **32** was performed in HOAc with a PtO_2 catalyst; the resultant amine (**33**) was not isolated but was converted with Ac_2O to the crystalline acetamido derivative (**34**) in 50% over-all yield (Scheme I).

Wittig condensation of **34** with *m*- and *p*-nitrocinnamaldehyde (**38**) in THF in the presence of potassium *t*-butoxide afforded the desired butadienes (**36**) in only 25% yield. The reaction was much cleaner when performed in MeOH with NaOMe as the base; the products (**36**) separated directly from the reaction mixture in pure form in about 50% yield. Similarly, the required stilbenes (**35**) were synthesized from **34** by condensation with the appropriate nitrobenzaldehyde (**37**) in MeOH. The N-acetyl group of **35** or **36** was smoothly removed with a hot mixture of EtOH and concentrated HCl, the desired amine hydrochlorides (**39**, **40**) separating from the reaction mixture.

(15) Reference 5, Chapter 1.

(16) B. R. Baker, *Cancer Chemotherapy Rept.*, **4**, 1 (1959).

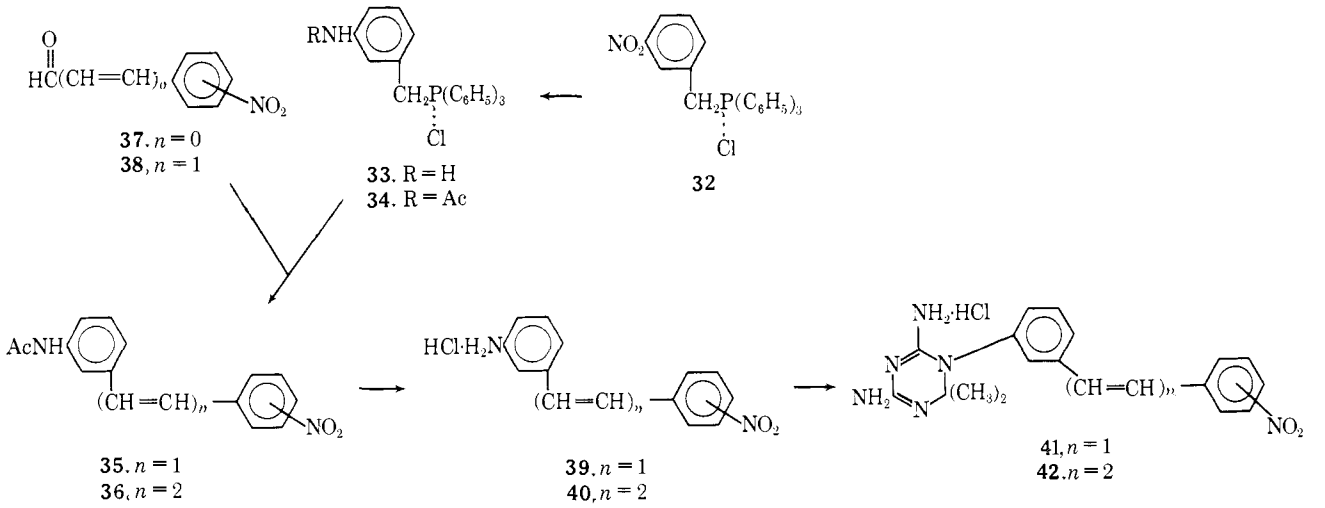
(17) B. R. Baker and G. J. Lourens, *J. Med. Chem.*, **11**, 34 (1968), paper CX of this series.

(18) For reviews on the Wittig reaction see (a) A. Maercker, *Org. Reactions*, **14**, 270 (1965); (b) R. J. Resonan, *Angew. Chem. Intern. Ed. Engl.*, **4**, 583, 646 (1965).

(19) L. Horner, H. Hoffmann, H. G. Wippel, and G. Hassel, *Chem. Ber.* **91**, 52 (1958).

(20) D. J. Maybe and C. E. Griffen, *J. Org. Chem.*, **30**, 4034 (1965).

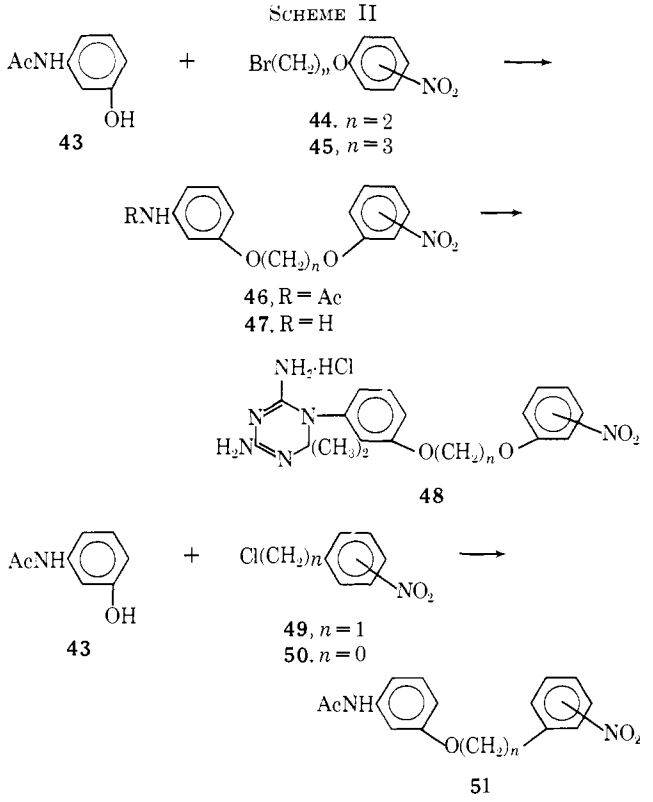
SCHEME I



The four amine hydrochlorides (**39**, **40**) were converted to the dihydro-*s*-triazines (**41**, **42**) by reaction with cyanoguanidine in Me_2CO, the three-component method of Modest.[21] Conversion of **41** and **42** to candidate irreversible inhibitors (**6**, **7**, **9**) is discussed later.

The second and largest group of candidate irreversible inhibitors were derived from phenoxyalkyloxyphenyl-*s*-triazines, of which **13** is a member. The key intermediates were the diphenoxyalkanes substituted with an amino group on one phenyl and a nitro on the other (**47**). These were readily synthesized by alkylation of *m*-acetamidophenol (**43**) with the appropriate bromoalkoxybenzene bearing a nitro group (**44**, **45**) to **46** followed by aqueous alcoholic HCl hydrolysis to compounds **47** which were isolated as their hydrochlorides (Scheme II). The amines **46** were converted to the

SCHEME II



nitrophenylated dihydro-*s*-triazine (**48**) by the three-component method.[21]

The third group of candidate irreversible inhibitors consists of **19** and **20** (Table I). The method of synthesis was closely related to the second group in that a nitrobenzyl halide (**49**) or 4-chloronitrobenzene (**50**) was used to alkylate 3-acetamidophenol (**43**).

The fourth class consisted of candidate irreversible inhibitors synthesized by reduction of the terminal cyano group followed by bromoacetylation as represented by **11** (Table I). Three-component condensations[21] of *m*-aminobenzonitrile ethanesulfonate (**52**) with cyanoguanidine and Me_2CO afforded the dihydro-*s*-triazine (**53**) with a terminal cyano group (Scheme III). Hydrogenation of the cyano group of **53** with PtO_2 in EtOH containing **1** equiv of $EtSO_3H$ afforded the aminomethyl-*s*-triazine as its bisethanesulfonate (**54**).[22]

Similarly, alkylation of *m*-nitrophenol with ω-haloalkylnitriles afforded **55**, which were catalytically reduced to **56**, then converted to the dihydro-*s*-triazines (**57**) with a terminal cyano group. Reduction of the terminal cyano group of **57** to amino appeared satisfactory, but their bromoacetamido derivatives could not be suitably purified.

The fifth class of candidate irreversible inhibitors consisted of chloromethyl ketones **22–26**; synthesis of **22–24** has been previously reported.[3b] The key intermediates were the anilines (**63**, **64**) substituted with a terminal chloromethyl ketone function. These were synthesized by Wittig condensation[24,25] of *m*-nitrobenzaldehyde (**37**) or *m*-nitrocinnamaldehyde (**38**) with the phosphorane (**58**)[25] to give the unsaturated ketones (**59**, **60**) (Scheme IV). In order to reduce the double bonds and the nitro group to **63** and **64** without concomitant reduction of the halogen or ketone functions,[24] the ketone function was converted to a dioxolane (**61**, **62**), then reduced to **65** and **66**; the dioxolane blocking group was removed by hydrolysis with HCl in 80% aqueous *i*-PrOH. Although the resultant amine hydrochlorides (**63**, **64**) could not be crystallized,

(21) E. J. Modest, *J. Org. Chem.*, **21**, 1 (1956).

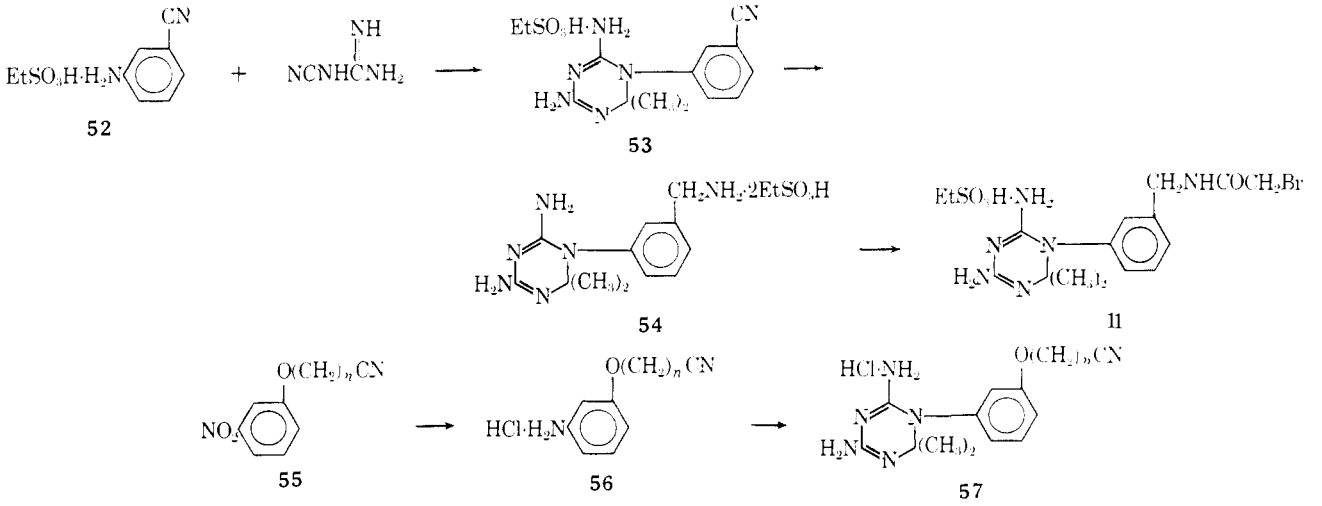
(22) The corresponding *para* isomer has been previously prepared by a similar process.[23]

(23) B. R. Baker and B.-T. Ho, *J. Heterocyclic Chem.*, **2**, 335 (1965).

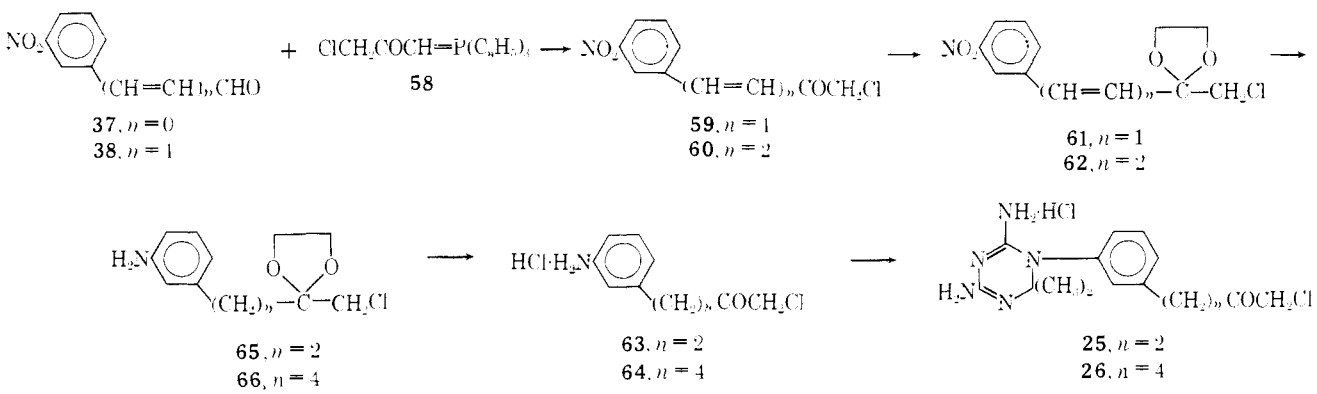
(24) B. R. Baker and J. H. Jordaan, *J. Med. Chem.*, **8**, 35 (1965).

(25) R. F. Hudson and P. A. Chopard, *J. Org. Chem.*, **28**, 2446 (1963).

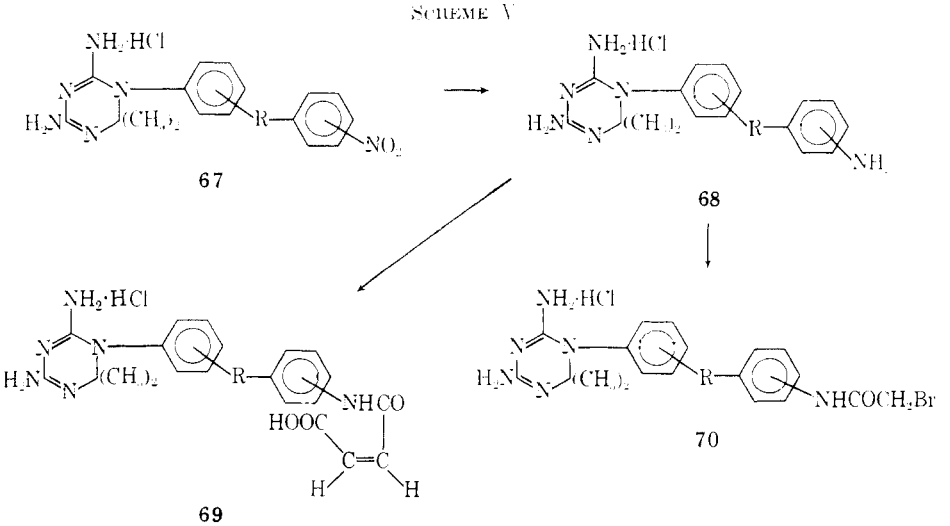
Scheme III



Scheme IV



Scheme V



the three-component method[21] gave crystalline dihydro-*s*-triazines (**25**, **26**).

All of the nitro intermediates (**41**, **42**, **48**, **51**) can be generalized by **67**. These were catalytically reduced to the amines (**68**) in EtOH with a PtO_2 catalyst; if the R bridge also contained one or more double bonds, these were reduced simultaneously (Scheme V). The amines (**68**) were treated with bromoacetic anhydride in either MeOH–Me_2CO or DMF at 0°; all of these products (**70**) were characterized[26] by a negative Bratton–Marshall test for aromatic amines, a positive 4-(*p*-nitrobenzyl)pyridine test for active halogen, and uniformity on tlc on polyamide-MN. The majority of the compounds of type **70** could be crystallized; a few could not be crystallized but were pure by the above criteria.[26] Those that did not meet these criteria were not included in Table I containing the enzyme assays.

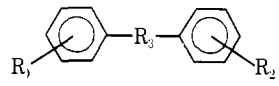
The two maleanilic acids (**69**) were obtained from the appropriate amine (**68**) by reaction[27] with maleic anhydride in MeOH.

(26) B. R. Baker, D. V. Santi, J. K. Coward, H. S. Shapiro, and J. H. Jordaan, *J. Heterocyclic Chem.*, **3**, 425 (1966).

(27) B. R. Baker and P. L. Monsolo, *J. Pharm. Sci.*, **52**, 911 (1963).

TABLE II

PHYSICAL PROPERTIES[a] OF



R_1	R_2	R_3	Method	% yield	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
m-AcNH	*p*-NO_2	$(CH{=}CH)_2$	A	72[b]	190–191	70.1	5.23	9.09	70.3	5.28	8.90
m-AcNH	*m*-NO_2	$(CH{=}CH)_2$	A	54[c]	152–153	70.1	5.23	9.09	70.0	5.17	8.98
m-AcNH	*m*-NO_2	CH=CH	A	43[c]	153–156	68.1	5.00	9.92	68.0	5.03	9.90
m-AcNH	*p*-NO_2	CH=CH	A	48[c]	182–186	68.1	5.00	9.92	67.9	5.04	9.78
m-AcNH	*p*-NO_2[d]	$O(CH_2)_2O$	B	55[c]	149–150	60.8	5.10	8.85	60.6	4.98	8.61
m-AcNH	*m*-NO_2[d]	$O(CH_2)_2O$	B	57[c]	118–122	60.8	5.10	8.85	60.5	5.16	8.51
m-AcNH	*o*-NO_2[e]	$O(CH_2)_2O$	B	67[c]	102–105	60.8	5.10	8.85	60.5	5.04	8.74
m-AcNH	*p*-NO_2[d]	$O(CH_2)_3O$	B	71[c]	129–130	60.2[f]	5.64	8.25	60.1	5.66	7.98
m-AcNH	*m*-NO_2[d]	$O(CH_2)_3O$	B	59[c]	118–119	61.2	5.49	8.48	61.5	5.39	8.58
p-AcNH	*p*-NO_2[d]	$O(CH_2)_2O$	B	53[g]	160–161	60.8	5.10	8.85	60.6	5.19	8.95
m-AcNH	*m*-NO_2	OCH_2	B	49[c]	96–97	62.9	4.93	9.78	62.8	4.99	9.73
m-AcNH	*p*-NO_2	OCH_2	B	74[c]	159–160	62.9	4.93	9.78	63.0	4.89	9.72
m-$NH_2\cdot HCl$	*p*-NO_2	$(CH{=}CH)_2$	C	53[h]	dec >210	63.5	4.99	9.25	63.4	5.29	9.09
m-$NH_2\cdot HCl$	*m*-NO_2	$(CH{=}CH)_2$	C	53[h]	dec >220	63.5	4.99	9.25	63.3	5.10	9.40
m-$NH_2\cdot HCl$	*m*-NO_2	CH=CH	C	82[h]	dec >215	60.8	4.73	10.1	60.6	4.73	9.94
m-$NH_2\cdot HCl$	*p*-NO_2	CH=CH	C	58[c]	dec >205	60.8	4.73	10.1	60.7	4.72	10.2
m-$NH_2\cdot HCl$	*p*-NO_2	$O(CH_2)_2O$	C	64[h]	dec >195	54.1	4.86	9.01	54.5	5.00	8.82
m-$NH_2\cdot HCl$	*m*-NO_2	$O(CH_2)_2O$	C	71[h]	181–182	54.1	4.86	9.01	53.9	4.92	9.20
m-$NH_2\cdot HCl$	*o*-NO_2	$O(CH_2)_2O$	C	51[h]	150–153	54.1	4.86	9.01	54.0	4.87	8.88
m-$NH_2\cdot HCl$	*p*-NO_2	$O(CH_2)_3O$	C	54[h]	172–174	55.5	5.27	8.62	55.3	5.26	8.41
m-$NH_2\cdot HCl$	*m*-NO_2	$O(CH_2)_3O$	C	94[h]	160–161	55.5	5.27	8.62	55.3	5.27	8.51
p-$NH_2\cdot HCl$	*p*-NO_2	$O(CH_2)_3O$	C	53[h]	dec >200	52.6[f]	5.04	8.76	52.5	4.98	8.78
m-$NH_2\cdot HCl$[i]	*p*-NO_2	O	C	55[j]	dec >175[k]						
m-$NH_2\cdot HCl$	*m*-NO_2	OCH_2	C	85[h]	dec >190	55.6	4.66	9.98	55.7	4.57	9.90
m-$NH_2\cdot HCl$	*p*-NO_2	OCH_2	C	98[h]	dec >200	55.6	4.66	9.98	55.6	4.68	9.97

[a] All compounds had ir and uv spectra compatible with their assigned structures. [b] Recrystallized from *i*-PrOH. [c] Recrystallized from EtOH. [d] Starting bromide prepared by method M. [e] Starting bromide prepared by method L. [f] Hemihydrate. [g] Recrystallized from Me_2CO. [h] Recrystallized from EtOH–H_2O. [i] Starting acetamido derivative, mp 137–138°, prepared according to H. E. Ungnade and E. Hansburg, *J. Org. Chem.*, **17**, 742 (1952), except NaOMe was used in place of K. [j] Recrystallized from EtOH–Et_2O. [k] K. Ikawa [*Yakugaku Zasshi*, **79**, 760 (1959); *Chem. Abstr.*, **53**, 21761 (1959)] reported mp 195°.

Experimental Section

***m*-Acetamidobenzyltriphenylphosphonium Chloride (34).**—A solution of 22.7 g (50 mmoles) of **32**[29] in 200 ml of HOAc was shaken with H_2 at 2–3 atm in the presence of 0.2 g of PtO_2 for 12 hr during which time 0.15 mole of H_2 was consumed. The filtered solution was spin-evaporated *in vacuo* leaving **33** as an oil. No attempt was made to crystallize the oil, but it was dissolved in 40 ml of Ac_2O and stirred at ambient temperature for 25 min; the product began to separate in about 10 min. The product was collected on a filter and washed with THF; yield 16.5 g (73%), mp 284–286°. Recrystallization from MeOH–Et_2O gave 11.2 g (50%) of product, mp 290–292°. For analysis a sample was recrystallized once more to give white crystals: mp 290–292°; ν_{max} 3380, 3340, 3240 (NH), 1675 (amide C=O), 1600 (C=C), 1550 (amide II), 1435 (P-phenyl), 810, 750, 725, 700, 690 cm^{-1} (phenyl CH).

Anal. Calcd for $C_{27}H_{25}ClNOP$: C, 72.7; H, 5.65; N, 3.14. Found: C, 72.5; H, 5.53; N, 3.13.

The *ortho* isomer as the bromide salt was prepared similarly in 50% yield, mp 285–286° dec.

Anal. Calcd for $C_{27}H_{25}BrNOP$: C, 66.1; H, 5.14; N, 2.86. Found: C, 66.1; H, 5.14; N, 2.89.

3-Acetamido-4′-nitrostilbene (35). Method A.—To a stirred mixture of 1.51 g (10 mmoles) of *p*-nitrobenzaldehyde and 4.90 g (11 mmoles) of **34** in 10 ml of MeOH cooled in an ice bath and protected from moisture was added a solution of 0.57 g (10.5 mmoles) of NaOMe in 5 ml of MeOH. Solution took place, then the product began to separate in about 10 min. After being stirred at 0° for 1 hr and 3 hr at ambient temperature, the mixture was chilled, then filtered. The product was washed with cold MeOH (two 10-ml portions), 20 ml of 50% aqueous MeOH, and finally 25 ml of H_2O; yield 1.36 g (48%) of product, mp 181–183°, which moved as a single spot on tlc in EtOAc. Recrystallization from absolute EtOH gave 1.21 g (43%) of yellow crystals: mp 182–186°; ν_{max} 3250 (NH), 1650 (amide I), 1600, 1550, 1500 (NH, C=C, NO_2), 1330 (NO_2), 960 (*trans* C=C), 690 cm^{-1} (C_6H_5); λ_{max} 245, 355 mμ. See Table II for analytical data and additional compounds prepared by this route.

1-(*m*-Acetamidophenoxy)-3-(*p*-nitrophenoxy)propane (46). Method B.—A mixture of 5.20 g (20 mmoles) of *p*-(3-bromopropyloxy)nitrobenzene (**45**), 3.40 g (23 mmoles) of **43**, 2.76 g (20 mmoles) of anhydrous K_2CO_3, and 30 ml of reagent Me_2CO was refluxed with stirring for 40–45 hr. Solvent was removed by spin-evaporation *in vacuo*. The residue was extracted with 50 ml of hot absolute EtOH, then the filtered solution was cooled; yield 4.85 g (71%), mp 129–130°. The compound moved as a single spot on tlc in EtOAc and had ν_{max} 3400 (NH), 1655 (amide C=O), 1600, 1545, 1500 (C=C, NH, NO_2), 1340 (NO_2), 1265 (C–O–C), 840 (*m*-C_6H_4), 690 cm^{-1} (*p*-C_6H_4). See Table II for analytical data and additional compounds prepared by this method.

1-(*m*-Aminophenoxy)-3-(*p*-nitrophenoxy)propane Hydrochloride (47). Method C.—A mixture of 6.78 g (20 mmoles) of 1-(*m*-acetamidophenoxy)-3-(*p*-nitrophenoxy)propane (**46**), 60 ml of EtOH, and 60 ml of 12 *N* aqueous HCl was refluxed with stirring for 1 hr. After being cooled to 0°, the mixture was filtered and the product was washed with cold 50% aqueous EtOH. Recrystallization from *i*-PrOH gave nearly white crystals, mp 172–174°, yield 3.5 g (54%), that moved as a single spot on tlc in MeOH and had ν_{max} 2860 (broad), 2550 (NH^+), 1600, 1590, 1525 (NH, C=C, NO_2), 1340 (NO_2), 1242, 1040 (C–O–C), 845 (*m*-C_6H_4), 685 cm^{-1} (*p*-C_6H_4). See Table II for analytical data and for additional compounds prepared by this route.

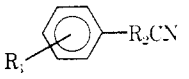
4-(*m*-Aminophenoxy)butyronitrile Hydrochloride (56, *n* = 3).

(28) Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. All analytical samples gave ir (KBr pellet) and uv spectra (EtOH) compatible with their assigned structures and each moved as a single spot on tlc. Brinkmann silica gel GF was used for tlc on all compounds except the dihydro-*s*-triazine salts where Brinkmann polyamide-MN was employed; spots were detected by visual examination under uv light.

(29) N. N. Mel'nikov, A. E. Kretov, and B. I. Mel'tzer, *J. Gen. Chem. USSR*, **7**, 461 (1937).

TABLE III

PHYSICAL PROPERTIES[a] OF

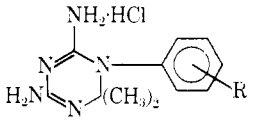


R_1	R_2	Method	% yield	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
m-NO_2	OCH_2	B	75[b,c]	91–92	53.9	3.39		54.1	3.58	
m-NO_2	$O(CH_2)_2$	*d*	38[e]	87–88						
m-NO_2	$O(CH_2)_3$	B	71[f]	50–54	58.2	4.89	13.6	58.1	4.92	13.7
m-$NH_2 \cdot HCl$	$O(CH_2)_2$	D		Oil[g]						
m-$NH_2 \cdot HCl$	$O(CH_2)_3$	D	82[h]	136–138	56.5	6.16	13.2	56.2	6.08	13.2
m-$NH_2 \cdot EtSO_3H$	...	D	71[i]	171–172	47.4	5.29	12.2	47.3	5.14	12.1

[a] All compounds gave ir spectra compatible with their assigned structures. [b] Recrystallized from C_6H_6–petroleum ether (bp 30–60°). Attempted hydrogenation by method D cleaved the ether linkage. [d] Prepared according to J. Lichtenberger, J. Core, and R. Geyer, *Bull. Soc. Chim. France*, 997 (1962), except NaOH was used as catalyst; they recorded mp 97° and a yield of 23%. [e] Recrystallized from EtOH–H_2O. [f] Recrystallized from MeOH. [g] Crude amine·HCl converted to *s*-triazine; see Table IV. [h] Recrystallized from *i*-PrOH–petroleum ether. [i] Recrystallized from absolute EtOH–petroleum ether.

TABLE IV

PHYSICAL PROPERTIES[a] OF



R	Method	% yield	Mp, °C dec	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
m-$(CH{=}CH)_2C_6H_4NO_2$-*p*	E	56[b]	191–194	59.1	5.42	19.7	59.0	5.52	19.5
m-$(CH{=}CH)_2C_6H_4NO_2$-*m*	E	40[b]	176–178	59.1	5.42	19.7	58.9	5.50	19.5
m-$CH{=}CHC_6H_4NO_2$-*m*	E	86[c]	194–196	56.9	5.28	21.0	56.7	5.38	20.9
m-$CH{=}CHC_6H_4NO_2$-*p*	E	81[c]	193–195	56.9	5.28	21.0	56.7	5.69	21.1
m-$O(CH_2)_2OC_6H_4NO_2$-*p*	E	42[c]	189–190	52.5	5.33	19.3	52.2	5.43	19.3
m-$O(CH_2)_2OC_6H_4NO_2$-*m*	E	71[b]	172–174	51.7[d]	5.60	19.1	51.8	5.48	19.0
m-$O(CH_2)_2OC_6H_4NO_2$-*o*	E	69[c]	178–179	52.5	5.33	19.3	52.4	5.43	19.6
m-$O(CH_2)_3OC_6H_4NO_2$-*p*	E	55[b]	159–160	53.5	5.61	18.7	53.3	5.69	18.5
m-$O(CH_2)_3OC_6H_4NO_2$-*m*	E	69[b]	163–165	53.5	5.61	18.7	53.2	5.83	18.4
p-$O(CH_2)_2OC_6H_4NO_2$-*p*	E	74[f]	255–256	52.5	5.33	19.3	52.4	5.44	19.3
m-$OC_6H_4NO_2$-*p*	E	92[c]	194–197	52.2	4.90	21.5	52.1	4.90	21.7
m-$OCH_2C_6H_4NO_2$-*m*	E	67[e]	183–184	53.4	5.22	20.5	53.1	5.41	20.4
m-$OCH_2C_6H_4NO_2$-*p*	E	62[b]	192–193	53.4	5.22	20.5	53.2	5.42	20.7
m-CN[i]	F	65[c]	190–193	47.7	5.72	23.9	47.5	5.77	24.0
m-$CH_2NH_2 \cdot EtSO_3H$[i]	G	68[g]	Amorphous	41.2	6.48	18.0	41.4	6.73	17.8
m-$O(CH_2)_2CN$[i]	E	51[g]	193–194	52.1	5.93	26.0	52.2	6.15	26.0
m-$O(CH_2)_3CN$[i]	E	61[g]	184–185	55.5	6.28	25.0	55.3	6.40	24.8
m-$(CH_2)_4C_6H_4NHCOCH_2Br$-*p*	H	84[k]	Amorphous						
m-$(CH_2)_4C_6H_4NHCOCH_2Br$-*m*	I	73[k]	Amorphous						
m-$(CH_2)_2C_6H_4NHCOCH_2Br$-*p*	H	99[k]	Amorphous						
m-$CH_2NHCOCH_2Br$[i]	H[l]	50[c]	188–189	40.3	5.28	17.6	40.4	5.43	17.5
m-$O(CH_2)_2OC_6H_4NHCOCH_2Br$-*p*	I	70	185–186	47.1[d]	5.08	15.7	47.1	5.13	15.4
p-$O(CH_2)_2OC_6H_4NHCOCH_2Br$-*p*	H	45[c]	dec. > 180	48.0	4.98	16.0	48.3	5.20	16.0
m-$O(CH_2)_2OC_6H_4NHCOCH_2Br$-*m*	I	88[m]	121–125	48.0	4.98	16.0	47.7	4.98	15.9
m-$O(CH_2)_2OC_6H_4NHCOCH_2Br$-*o*	H	46[f]	118–120	48.0	4.98	16.0	48.3	5.35	16.0
m-$O(CH_2)_3OC_6H_4NHCOCH_2Br$-*p*	H	50[m]	210–211	48.9	5.22	15.6	48.8	5.40	15.6
m-$O(CH_2)_3OC_6H_4NHCOCH_2Br$-*m*	H	75[k]	Amorphous	45.9[n]	4.12	17.2	45.9	4.26	17.1
m-$OCH_2C_6H_4NHCOCH_2Br$-*m*	H	73[k]	Amorphous						
m-$OC_6H_4NHCOCH_2Br$-*p*	H	40[o]	210	45.6[p]	4.43	16.8	45.2	4.60	16.8
m-$O(CH_2)_2OC_6H_4NHCOCH$ ‖ *p*-HOOCCH	J	68[c]	143–146	54.9	5.41	16.7	54.8	5.54	16.6
m-$O(CH_2)_3OC_6H_4NHCOCH$ ‖ *p*-HOOCCH	J	57[c]	dec >190	55.8	5.65	16.3	55.8	5.95	16.5
m-$(CH_2)_2COCH_2Cl$	K	20[q]	139–141	50.3	5.91	19.5	50.2	5.73	19.3
m-$(CH_2)_4COCH_2Cl$	K	50[r]	156–158	52.9	6.52	18.1	53.1	6.70	17.9

[a] Each compound had ir and uv spectra in agreement with its assigned structure. Each moved as a single spot on tlc on polyamide-MN. [b] Recrystallized from absolute EtOH. [c] Recrystallized from EtOH–H_2O. [d] Hemihydrate. [e] Recrystallized from 2-methoxyethanol–EtOAc. [f] Recrystallized from *i*-PrOH–H_2O. [g] Recrystallized from absolute EtOH–petroleum ether (bp 60–110°). [h] Recrystallized from DMF–EtOH. [i] Ethanesulfonate salt. [j] Reduction of the C≡N to CH_2NH_2 followed by bromoacetylation by method G gave a mixture. [k] Amorphous product moved as a single spot on tlc, gave a positive 4-(*p*-nitrobenzyl)pyridine test for active halogen, and gave a negative Bratton–Marshall test for aromatic amine. This material contains about 15% solvent which could not be removed in high vacuum at 50° and decomposed at higher temperatures. [l] Run with triethylamine equivalent to amine salt. [m] Recrystallized from DMF–H_2O containing a trace of HCl. [n] Picrate salt, mp 161–164°, prepared in and recrystallized from EtOH. [o] Recrystallized from MeOH–H_2O. [p] Monohydrate. [q] Recrystallized from *i*-PrOH. [r] Recrystallized from *i*-PrOH–petroleum ether (bp 60–110°).

Method D.—A solution of 2.06 g (10 mmoles) of **55** (n = 3) (Table III) in 100 ml of EtOH was treated with 0.2 g of decolorizing carbon, then filtered. After the addition of 0.2 g of PtO_2, the mixture was shaken with H_2 at 2–3 atm until 30 mmoles of H_2 was consumed (about 30 min). The mixture was filtered through a Celite pad, then 1 ml of 12 *N* HCl was added to the filtrate. The solution was spin-evaporated *in vacuo*. Two recrystallizations from *i*-PrOH–petroleum ether (bp 30–60°) gave 1.74 g (82%) of product, mp 136–138°, that moved as a single spot on tlc in MeOH; ν_{max} 2850, 2600, 1950 (NH^+), 2210 (C≡N),

1620, 1590, 1550 (C=C, NH), 1250, 1040 (C–O–C), 840 cm^{-1} (*m*-C_6H_4). See Table III for additional data.

4,6-Diamino-1,2-dihydro-2,2-dimethyl-1-{*m*-[γ-(*p*-nitrophenoxy)propoxy]phenyl}-*s*-triazine Hydrochloride (48). Method E.—A mixture of 406 mg (1.25 mmoles) of 1-(*m*-aminophenoxy)-3-(*p*-nitrophenoxy)propane hydrochloride (**47**), 109 mg (1.35 mmoles) of cyanoguanidine, and 3 ml of reagent Me_2CO was refluxed with stirring for 20 hr; during this time the product separated. The product was collected on a filter and washed with Me_2CO. Two recrystallizations from absolute EtOH gave 312 mg (55%) of white crystals: mp 159–160°; λ_{max} 244, 284, 307 mμ; ν_{max} 3400, 3250, 3100 (NH), 1650 (C=NH^+), 1600, 1570, 1520, 1500 (NH, C=C, C=N, NO_2), 1320 (NO_2), 1240 (C–O–C), 810, 750, 705 cm^{-1} (phenyl CH). See Table IV for additional data.

Method F was the same as E, but the ethanesulfonic acid of the amine was employed.

1-(*m*-Aminoethylphenyl)-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazine Bisethanesulfonate (54). (Method G).—A mixture of 705 mg (2 mmoles) of **53** (Table IV), 100 ml of absolute EtOH, 225 mg (2.04 mmoles) of ethanesulfonic acid, and 100 mg of PtO_2 was shaken with H_2 at 2–3 atm for 90 min when reduction was complete. The filtered solution was spin-evaporated *in vacuo*. Two recrystallizations from absolute EtOH–petroleum ether, the first with the aid of decolorizing carbon gave 634 mg (68%) of hygroscopic white crystals with no definite melting point: λ_{max} 3350, 3150 (NH), 1650 (C=NH^+), 1560–1500 (NH, C=C, C=N), 1190, 1030 (SO_3^-), 740 cm^{-1} (phenyl CH). See Table IV for additional data.

1-{*m*-[γ-(*p*-Bromoacetamidophenoxy)propoxy]phenyl}-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazine Hydrochloride (17). Method H.—A mixture of 898 mg (2 mmoles) of **48** (n = 3), 100 ml of absolute EtOH, and 100 mg of PtO_2 was shaken with H_2 for 70 min when reduction was complete. The filtered solution was spin-evaporated *in vacuo* leaving the crude amine (**68**); yield 637 mg (76%). To a solution of 105 mg (0.25 mmole) of the crude amine in 0.5 ml of DMF stirred in an ice bath was added 98 mg of bromoacetic anhydride. After 20 min at 0°, the mixture was diluted with 5 ml of ether. The solvent was decanted from the gummy product which was then triturated with fresh ether until it solidified. The product was crystallized from aqueous DMF containing a few drops of 12 *N* HCl; yield 90 mg (66%) of off-white crystals, mp 210–211° dec. The compound moved as a single spot on tlc on polyamide-MN in EtOH–$CHCl_3$ (3:2), gave a negative Bratton–Marshall test for aromatic amine, and gave a positive 4-(*p*-nitrobenzyl)pyridine test for active halogen;[26] λ_{max} 248, 272 (infl) mμ; ν_{max} 3400, 3250 (NH), 1660, 1625 (C=NH^+, C=O), 1605, 1580, 1525, 1500 (NH, C=C, C=N), 1220, 1050, (C–O–C), 830, 790, 750, 700 cm^{-1} (phenyl CH). See Table IV for additional data.

Method I was the same as method H except the bromoacetylation was run in 0.2 ml of MeOH and 1.5 ml of Me_2CO. See Table IV for additional data.

Method J was the same as method H using a 50% excess of maleic anhydride in cold MeOH. The product separated from the reaction mixture; it was collected on a filter, washed with MeOH, then recrystallized. See Table IV for additional data.

1-Chloro-6-(*m*-nitrophenyl)-3,5-hexadien-2-one (60).—A mixture of 5.32 g (30 mmoles) of *m*-nitrocinnamaldehyde (**38**),[30] 10.6 g (30 mmoles) of chloroacetonyltriphenylphosphorane (**58**),[26] and 50 ml of MeOH was stirred in a bath at 55° for 40 hr. The cooled mixture was filtered, and the product was washed with cold MeOH. Recrystallization from 2-methoxyethanol gave 4.00 g (53%) of yellow crystals, mp 144–146°, that moved as a single spot on tlc in 1:4 EtOAc–petroleum ether. The compound had λ_{max} 317 mμ; ν_{max} 1700 (C=O), 1615, 1600 (C=C), 1520, 1450 (NO_2), 1000 (*trans*-diene), 775, 735, 690 cm^{-1} (phenyl CH).

Anal. Calcd for $C_{12}H_{10}ClNO_3$: C, 57.3; H, 4.00; N, 5.57. Found: C, 57.1; H, 3.91; N, 5.50.

2-Chloromethyl-2-[4-(*m*-nitrophenyl)-1,3-butadien-1-yl]-1,3-dioxolane (62).—A mixture of 3.78 g (15 mmoles) of **60**, 10 ml of $HOCH_2CH_2OH$, 30 ml of C_6H_6, and 100 mg of $EtSO_3H$ was refluxed under a Dean–Stark water trap for 12 hr. The cooled mixture was diluted with 50 ml of C_6H_6, then washed with ice H_2O (two 50-ml portions). Dried with $MgSO_4$, the solution was spin-evaporated *in vacuo*. Two recrystallizations from 2-methoxyethanol gave 2.81 g (63%) of yellow crystals, mp 102–108°, that moved as a single spot on tlc in 1:4 EtOAc–petroleum ether. The compound had λ_{max} 280 mμ; ν_{max} 1650, 1620, 1575 (C=C), 1525, 1455 (NO_2), 1040 (C–O–C), 805 740, 680 cm^{-1} (phenyl CH).

Anal. Calcd for $C_{14}H_{14}ClNO_4$: C, 56.9; H, 4.77; N, 4.74. Found: C, 57.0; H, 4.80; N, 4.62.

1-[*m*-(1-Chloro-2-hexanon-6-yl)phenyl]-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazine Hydrochloride (26). Method K.—A solution of 1.47 g (5 mmoles) of **62** in 25 ml of EtOAc and 75 ml of EtOH was shaken with H_2 at 2–3 atm in the presence of 50 mg of PtO_2 for 18 hr during which 25 mmoles of H_2 was consumed. The mixture was filtered through a Celite pad, then the filtrate was spin-evaporated *in vacuo*. The residual oily amine (**66**) gave a single spot on tlc in 1:9 MeOH–C_6H_6: it was refluxed in a solution of 20 ml of *i*-PrOH, 4 ml of H_2O, and 1 ml of 12 *N* HCl for 20 min to remove the dioxolane blocking group. The solution was spin-evaporated *in vacuo*. Me_2CO was added and the spin-evaporation *in vacuo* was repeated three times. The crude ketone, which gave a postive 4-(*p*-nitrobenzyl)pyridine test,[26] was dissolved in 20 ml of Me_2CO. After the addition of 421 mg (5 mmoles) of cyanoguanidine, the solution was refluxed with magnetic stirring for 21 hr. The hot solution was clarified by filtration, then chilled. The product was collected and recrystallized from *i*-PrOH–petroleum ether to give 970 mg (50%) of white crystals: mp 156–158°; λ_{max} 246 mμ; ν_{max} 3300, 3120 (NH), 1725 (C=O), 1660–1500 (multiple bands C=NH^+, C=N, NH, C=C), 800, 710 cm^{-1} (phenyl CH). See Table IV for additional data.

2-Bromoethyl *o*-Nitrophenyl Ether. Method L.—A mixture of 24.6 g (0.125 mole) of sodium *o*-nitrophenoxide and 94 g (0.5 mole) of 1,2-dibromoethane was refluxed with stirring in 100 ml of H_2O for 40 hr. The cooled mixture was extracted with 100 ml of $CHCl_3$. The extract was washed with 5% NaOH (two 100-ml portions), then dried ($MgSO_4$). The solvent was removed *in vacuo* and the hot residual oil was dissolved in 25 ml of EtOH, then chilled. The crude product was collected on a filter. The solid was dissolved in about 25 ml of absolute EtOH at 55°, then filtered from some insoluble 1,2-(*o*-nitrophenoxy)ethane. The filtrate was clarified with decolorizing carbon, then chilled. The resultant product was recrystallized twice more from absolute EtOH; yield 14.2 g (46%) of yellow crystals, mp 36–38°, that moved as one spot on tlc in 1:1 C_6H_6–petroleum ether; ν_{max} 1600 (C=C), 1570, 1340 (NO_2), 1240, 1060 (C–O–C), 770, 740 cm^{-1} (phenyl CH).

Anal. Calcd for $C_8H_8BrNO_3$: C, 39.1; H, 3.27. Found: C, 39.2; H, 3.38.

Method M was the same as method L except 30 ml of DMF was used in place of H_2O and the reaction was run at ambient temperature for 70 hr; the reaction can be stopped in less than 70 hr if the red color of sodium nitrophenoxide has been discharged to yellow.

(30) Prepared by the method of S. G. Waley, *J. Chem. Soc.*, 2008 (1948), used for the *para* isomer.