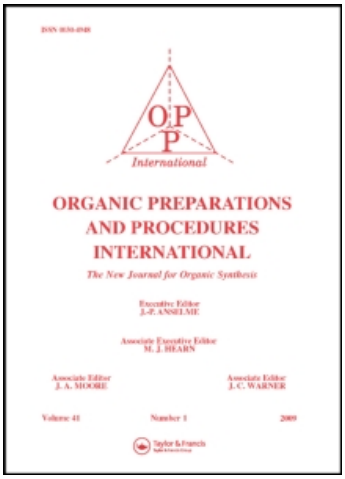

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RECENT PROGRESS IN THE SYNTHESIS AND REACTIONS OF 1,2,3- AND 1,2,4-TRIAZINES

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RECENT PROGRESS IN THE SYNTHESIS AND REACTIONS OF 1,2,3- AND 1,2,4-TRIAZINES

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RECENT PROGRESS IN THE SYNTHESIS AND REACTIONS OF 1,2,3- AND 1,2,4-TRIAZINES

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I. INTRODUCTION

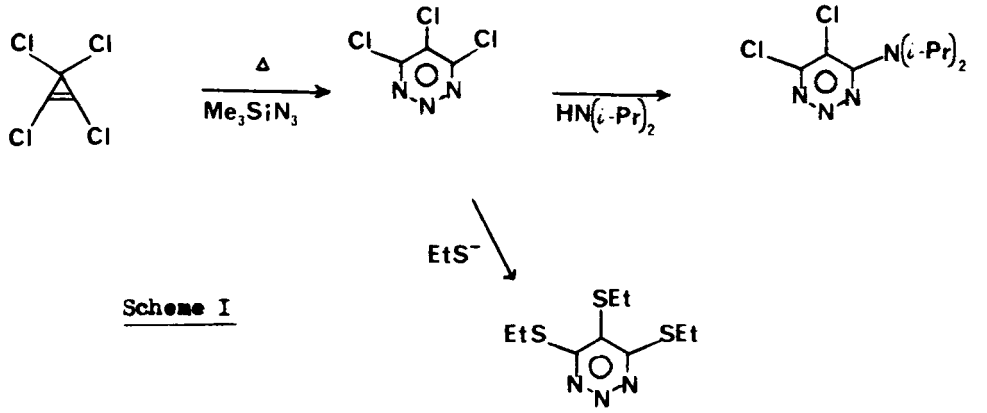
As a result of their demonstrated usefulness in many applications, there has been a rapid and sustained growth in experiments directed at the preparation of 1,2,3- and 1,2,4-triazines and at further investigation into their novel modes of reactivity. Impressive results have been obtained in the areas of medicinal chemistry[1,3,4] and agricultural chemistry,[2] spurring renewed interest in these compounds. The dramatic increase in the number of literature references pertaining to the 1,2,3- and 1,2,4-triazines has been particularly striking since the time of the last reviews.[5,6] We will limit the scope of our discussion to the preparation of triazines possessing two or more contiguous nitrogen atoms which are, in a formal sense, derivatives of hydrazine. The references encompass the literature included in ten volumes of Chemical Abstracts, volumes 82-91 inclusive. Emphasis has been placed on the more novel aspects of heterocyclic synthesis.

II. 1,2,3-TRIAZINE (v-TRIAZINE)

1. Synthesis

Many of the exciting recent results on the preparation of 1,2,3-

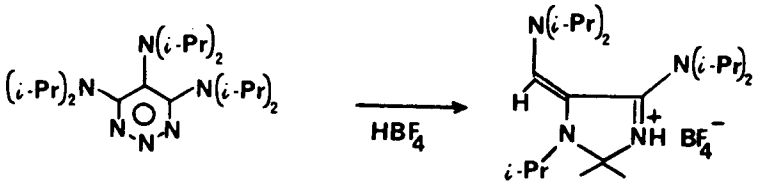
triazines have been brought about through the efforts of Gompper and coworkers,[7,8] who have exploited the facile rearrangements of cyclopropenylium perchlorates to the triazine system in the presence of alkali metal azides. The reaction may be direct or sequential. Thus tris- and bis-(dialkylamino)cyclopropenylium perchlorates react with potassium azide in methanol to give cyclopropenylium azides, which rearrange to give the corresponding 1,2,3-triazines upon warming in benzene or toluene.[9] A number of cyclopropenylium perchlorates bearing dialkylamino groups undergo the reaction to form triazines even at 25°C. 1,2,3-Triazines so formed possess one amino group in the 5-position corresponding to the largest dialkylamino group in the starting material. Yields vary from about 55% to 90%. The perchlorates are themselves formed by the amination of 3,3-dichlorocyclopropenes and subsequent treatment with perchloric acid. In related experiments,[10] it was found that tetrachloro- and tetrabromocyclopropene react with trimethylsilyl azide to give 4,5,6-trichloro and 4,5,6-tribromo-1,2,3-triazine respectively. (Scheme I.) The halogen atoms of the resulting trihalotriazines are substituted sequentially by nucleophiles at the 4-position first and next at the 6-position. With ethanethiolate, all of the chlorine atoms were rapidly replaced, as shown below.



Scheme I

2. Reactions

Gompper and coworkers have investigated the further reactions of their triazines.[11] Protonation of 1,2,3-triazines occurs largely at N-2 although only the tetrafluoroborate salt of 5-chloro-4,5-bis(dimethylamino)triazine could be characterized. Tris(diisopropylamino)1,2,3-triazine reacts with tetrafluoroboric acid to yield 5-diisopropylamino-4-[(diisopropylamino)methylene]-3-isoprophyl-2,2-dimethyl-3,4-dihydro-2H-imidazolium tetrafluoroborate. (Eq. 1) On the other hand, 2-methyl-1,2,3-triazinium iodides were produced upon reaction with methyl iodide. (Eq. 2) Treatment of the triazinium iodides with malonitrile in triethylamine gave the corresponding adducts. The quaternary salts formed from 5-(dialkylamino)1,2,3-triazines and methyl chloroformate and picryl chloride were conveniently hydrolyzed to the related triazinones. (Eq. 3)



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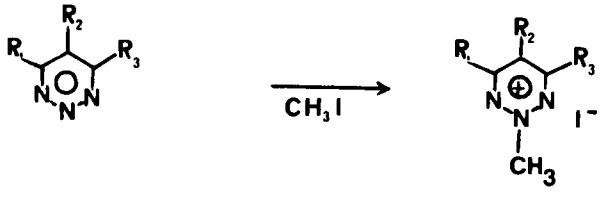

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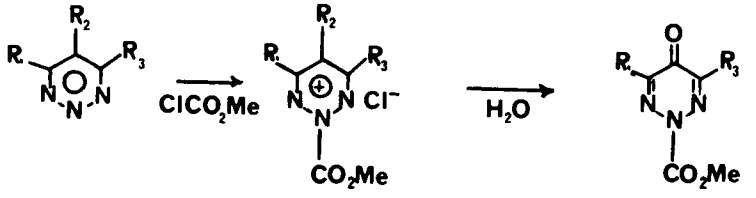

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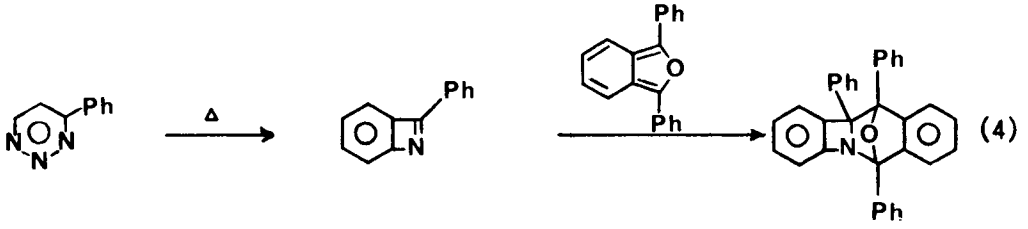
3. Synthesis of Medicinals

The medicinal chemistry of 1,2,3-triazines has recently been extensively reviewed,[12] with emphasis on the biological activity of the molecules as "masked" benzenediazonium ions. Related triazine interconversions have also been reviewed.[13]

Adger, Rees and Storr have investigated the pyrolysis reactions of a number of 1,2,3-triazines to 1-azabenzocyclobutenes.[14] (Eq. 4) Thus, heating 4-phenyl-1,2,3-triazine at 420° gave 2-phenylbenzazete, which was further characterized by its dimerization and cycloaddition reactions.



Heating 4-phenyl-1,2,3-benzotriazine 3-oxide gave 3-phenyl-2,1-benzisoxazole and acridone through the intermediacy of 2-phenylbenzazete N-oxide.

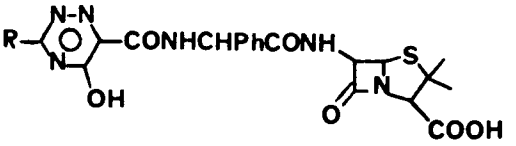
4. Advances in Understanding of Structure

A number of advances have been made in the theoretical chemistry of 1,2,3-triazines which have had significant practical consequences. Ab initio molecular orbital calculations have been performed on all the monocyclic molecules $C_nH_nN_{6-n}$ (n = 0-6).[15] It was found that the energies calculated were in better agreement with those obtained from photoelectron spectroscopy than would have been predicted by the CNDO/2, INDO and extended Hueckel methods. The MINDO/3 semi-empirical SCF molecular orbital method has also been applied.[16] A useful method has been formulated for the prediction of the ^{14}N shifts of triazine and tetrazine N-oxides.[17]

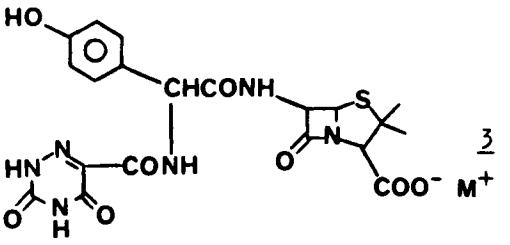
III. 1,2,4-TRIAZINES

1. Significance as Drugs

Recent interest in the 1,2,4-triazines has focussed on the antibacterial activity of certain of their β-lactam derivatives. Thus Watanabe and coworkers have made patent disclosures giving procedures for the formation of active penicillins 1 and 2 by the acylation of ampicillin and amoxicillin.[18,19] Minimum inhibitory concentrations of the new penicillins against a number of bacterial strains were detailed, with special emphasis on their utility to counter Pseudomonas aeruginosa. Penicillins 3 were also prepared from triazinecarboxylic acids via the mixed anhydride method.[20]



1, R = OH
2, R = SH



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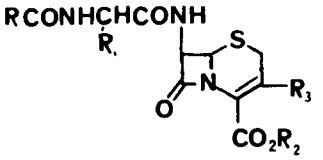
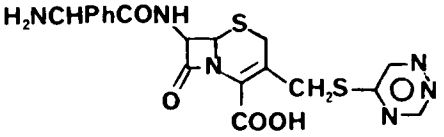
Numerous patents have appeared on triazinecephalosporins.[21-34] The search for effective antimicrobials has been successful in a number of areas, with significant bacteriostatic features incorporating substitution at the C-3 side chain as well as the acylaminoacetic acid side chain. Thus Kocsis, Peter and Bickel found that cephalosporins 4 were effective against S. aureus in mice in the range 8-100 mg/Kg s.c,[35] whereas Niato, Okumura, Kasai, Musuko, Hoshi, Kamachi and Kawaguchi obtained a compound with activity in structure 5.[36] Lunn has found minimum inhibitory concentra-

tions against E. coli in the range 6.0-130 mg/mL for compounds 6. These were prepared by treatment of the 3-acetoxymethylcephems with the triazinethiol.[37]



4, R = 1,2,4-triazino



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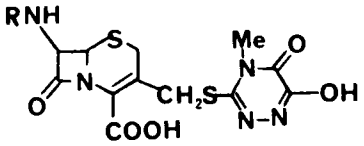

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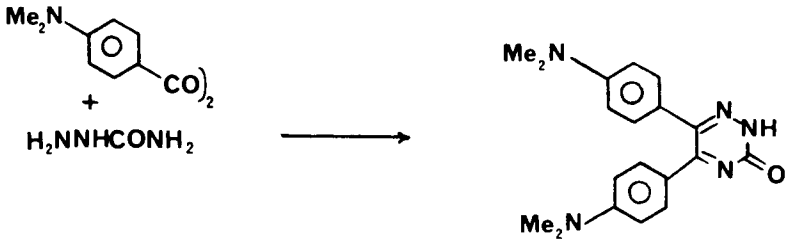
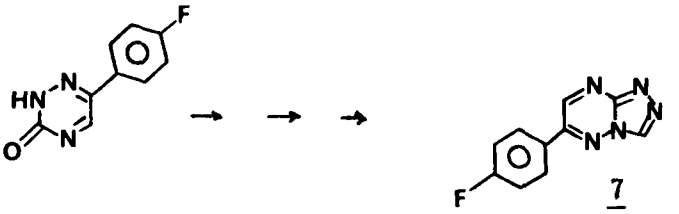
2. Cyclocondensation

Certain of the 1,2,4-triazinones have been prepared for investigation of their antacid properties,[38] and the 1,2,4-triazine moiety has been incorporated in the structures of peripheral vasodilator, analgesic andanti-inflammatory benzodioxolylmethylpiperazines.[39] Aminoaryl-1,2,4-triazines have been made as useful analgesic agents and for the treatment of rheumatism.[40] The preparation of the latter compounds is illustrative of the cyclocondensation method, which continues to be the most widely applicable synthesis of the 1,2,4-triazine framework. Thus the appropriate benzils condense and cyclize when treated with semicarbazide as shown below. Subsequent N-alkylation yields the medicinal substance.



In the synthesis of 6- and 7-aryl-1,2,4-triazolo (4,3-b)-1,2,4-triazines as anxiolytic agents, Albright has made use of a similar sequence, starting with the benzil, as noted below.[41] In one example, 4-fluoroacetophenone was oxidized to the glyoxal, which was selectively oximated at the aldehyde function. Conversion of the keto group to the semicarbazone was followed by heating in acid to yield 6-(4-fluorophenyl)-1,2,4-triazin-3(2H)-one. Further treatment with phosphorus oxychloride, hydrazine and ethyl orthoformate produced the bicyclic ring system 7.



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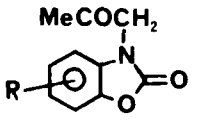
3. Mechanistic Studies

That the course of the cyclocondensation may well be subject to the nature of the reaction conditions is a fact underscored by recent work,[42] in which ketones 8 reacted with hydrazine hydrate to produce compounds 9, 10, or 11, depending on the ratio of hydrazine to ketone and the reaction temperature.



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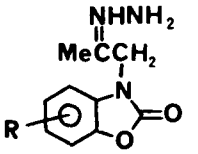

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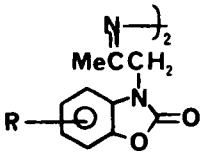

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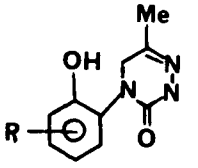

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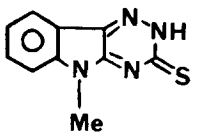
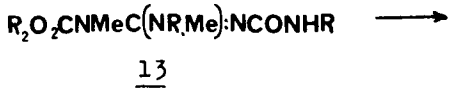
Tomchin and Lepp have investigated the effect of acidity on the formation of the triazine ring system 12 in isatin 3-thiosemicarbazones.[43]



12

Base-catalyzed cyclocondensation in the liquid phase has been the subject of a recent patent specification for the preparation of herbicidal triazines. The large scale batch process method developed by Cummins[44] for the preparation of the sym-triazine 14 from 13 may have use in scaling up cyclocondensations in the as-triazine series as well



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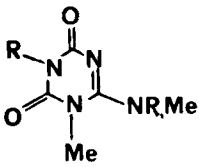
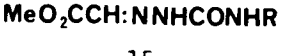


14

Yields in excess of 80% were obtained for the azauracil compounds 16 by Beranek and Hrebabecky.[45] The syn-isomers of the hydrazones 15 were cyclized by sodium methoxide.



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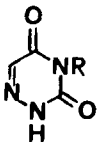

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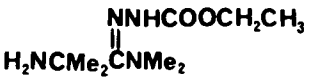
3-Dimethylamino-2,2-dimethyl-2H-azirine reacted with semicarbazide to give the condensation product 17, which could be isolated. Cyclization readily followed to give the dimethylamino triazinone 18.[46]



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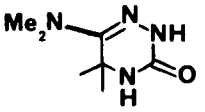

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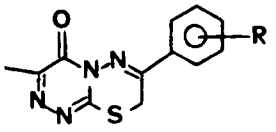
Where the product triazine itself contains more than one nucleophilic center, further cyclocondensation reactions are possible to produce more complex heterocyclic systems. In searching for new fungicides, it was found that reaction of 4-amino-3-mercapto-6-methyl-1,2,4-triazin-5(4H)-one with phenacyl halides yielded compounds 19 in which the benzene moiety was variously substituted.[47] The new materials were fungicidal but not bacteriostatic.



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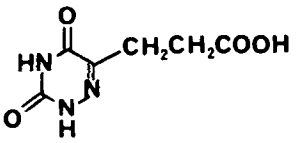
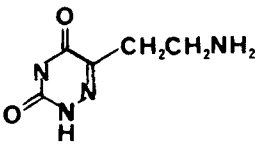


20

On the other hand, the presence of a remote functional group need not necessarily modify the nature of the ring system itself.[48] The esterification of the triazinepropionic acid 20 with methanol was followed by conversion to the acid hydrazide, under standard conditions. Treatment of the hydrazide with sodium nitrite, Curtius rearrangement and ethanolysis of the formed acyl azide, saponification and decarboxylation led to formation of the substituted ethylamine 21. Confirmation of the structure was available by S-methylation of 2-thio-5-acetylaminoethyl-6-azauracil, followed by hydrolysis.



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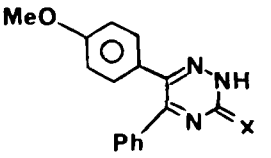
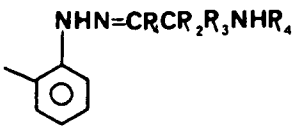


22

The reaction of 5,7-dichloro-1-methylbenzodiazepin-2-one with 4-morpholine glyoxylic acid hydrazide gave the annelated triazinedione, conveniently alkylated via its thallous salt.[49] Low temperature NMR studies revealed that the triazinedione compounds were relatively rigid but demonstrated a greater degree of puckering than the corresponding triazolones.

Ibrahim and coworkers have recently made use of the cyclocondensation reactions of benzoins with semicarbazide and itsderivatives.[50] Thus compounds 22 were prepared by the condensation of 4-methoxybenzoin, 4-methoxybenzil or 4-methoxybenzoin semicarbazone and semicarbazide hydrochloride. The cyclocondensation of 4-methoxybenzil with thiosemicarbazide gave the analogous triazinethione, which could be readily converted to the triazinone upon treatment with acetic anhydride. The reduction of either carbonyl compound (22, X = O or S) with iodine in buffered aqueous solution gave bis(6-(4-methoxyphenyl)-5-phenyl-1,2,4-triazin-3-yl)disulfide. 3,3'-Diiodobenzil was a further substrate for these transformations.



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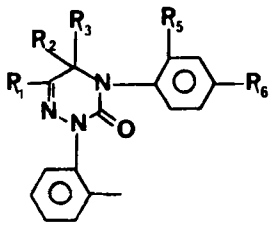
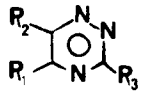


24

syn-α-Aminohydrazones 23 cyclized in the presence of formaldehyde and phosgene to give moderate to high yields of the triazines 24.[51] The hydrazones were themselves derived from the corresponding ketones and 2-tolylhydrazine.

Test data have been tabulated for the hypotonic, analgesic anti-inflammatory and central nervous activity of a wide variety of substituted 1,2,4-triazines 25.[52] In a typical preparative reaction, phenylglyoxal reacted with the hydroiodide salt of hydrazide 26 in ethyl alcohol to give 75% of the triazine. In a related pharmaceutical preparation,[53] aryl-substituted triazines 27 and 28, which exhibit significant analgesic activity, were prepared by cyclocondensation. The reaction of 4-methoxybenzoin with thiosemicarbazide in acetic acid gave 28 (Z = S, R_3 = H, n = 1, R_1 = R_2 = 4-MeO). The product was in turn treated with hydrogen peroxide in sodium hydroxide solution to yield 28 (Z = O, R_3 = H, n = 1, R_1 = R_2 = 4-MeO), which was then methylated to produce the methyl ether.

The methylcyclopropyl ring has been incorporated in the structure of some novel triazines useful as herbicides, compounds 29 and 30.[54,55] In the



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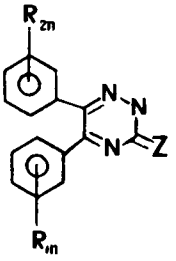

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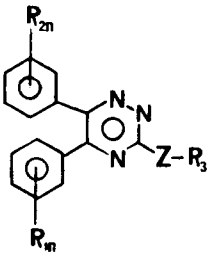

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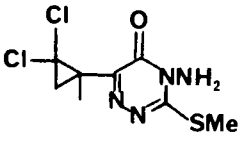
preparation of 29, (2,2-dichloro-1-methylcyclopropyl)glyoxylic acid was treated with 3-thiocarbazide, followed by S-methylation with methyl iodide.



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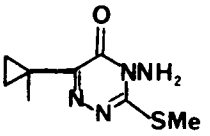
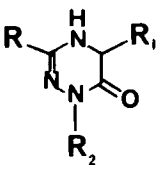


30

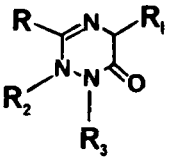
Successful use has been made of masked carboxyl equivalents in the preparation of a number of dihydro-1,2,4-triazines.[56] The reactions of the imino esters 31 with hydrazine or symmetrical dimethylhydrazine gave the appropriate dihydrotriazinones 32 and 33, respectively. On the other hand, when methylhydrazine was employed in the cyclocondensation, 2-methyl-2,5-dihydro-1,2,4-triazine-6(1H)-ones were obtained, along with some of

31



32, R = H

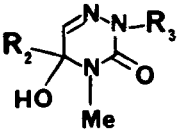
the 1-methyl-4,5-dihydro component. The 2,5-dihydro compounds 34 were shown to exist as zwitterions in polar aprotic solvents.



33, $R_2 = R_3 = CH_3$
34, $R_2 = CH_3$; R=H

In a study of the modes of reactivity of triazine precursors, the behavior of some semicarbazones has been explored in respect to the cyclizing agent. The study included monosemicarbazones 35 cyclizing under both acid and basic conditions. Thus upon treatment with aqueous sodium hydroxide, 35 (R = H, R_1 = Me) gave the addition products 36 (R_3 = H), although only degradation products were noted when 35 (R = Me, R_1 = H, Me) was subjected to the same conditions. Nonetheless, 35 (R = Me, R_1 = H, Me) gave the addition product 36 (R_3 = Me) and 37 as well when the cyclizing reagent was aqueous hydrochloric acid. Bromination reactions of some of the compounds in this series were also discussed.[57] Related cyclization procedures for semicarbazones of of 2-thienylglyoxal derivatives using bromine in acetic acid and hydrogen bromide in acetic acid have been reported.[58]

35



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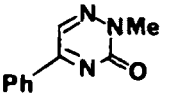
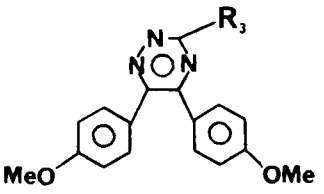


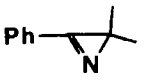
37

3-Substituted-5,6-diaryl-1,2,4-triazines have found use as topical anti-inflammatory agents.[59,60] In a characteristic preparation of these materials, anisil was treated with semicarbazide hydrochloride to give the cyclized product 38. Subsequent chlorination in good yield was effected with phosphorus oxychloride to give 39. Methylation with methyl triphenylphosphonium bromide occurred to produce 40, also useful as an anti-inflammatory compound.



38, R_3 = OH
39, R_3 = Cl
40, R_3 = CH_3

In a new variation of the cyclocondensation procedure, Eremeev, Elkinson and Liepins have used 2,2-dimethyl-3-phenylazirine 41 as a unique three-atom building block for 1,2,4-triazine synthesis.[61] Thus the reaction of the azirine with hydrazine was followed by treatment with acetaldehyde or 4-chlorobenzaldehyde to give the substituted tetrahydro-triazines 42. Isocyanates play a key role in the cyclocondensative prep-



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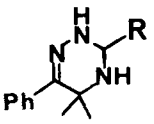
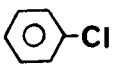
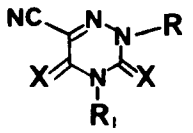


R= CH_3, 

42

aration of substituted 2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitiriles and some derivatives, as recently described by Winternitz.[62] The triazinecarbonitrile 43 (R = Ph, R_1 = Me, X = NH) reacted with phenylisocyanate to give the related urea derivative, which was cyclized with ethanolic ammonia to 44 (X_2 = NH), itself hydrolyzed to 44 (X_2 = O).



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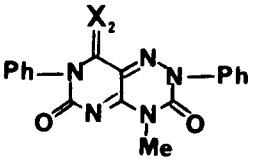
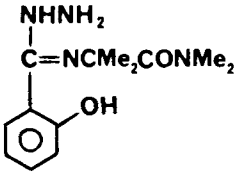


44

The literature has had much activity on the synthesis of triazinobenzodiazephines. These compounds have been the subject of intensive research into their properties as tranquilizers, sedatives, muscle relaxants, antiphlogistics and anticonvulsants.[63-70] Particular attention has focussed on materials substituted with halogens or other electron-withdrawing groups. The treatment of 7-chloro-2-hydrazino-5-phenyl-3H-1,4-benzodiazepine with the dimethyl acetal of pyruvaldehyde produced the related hydrazone, which was in turn cyclized with sulfuric acid to give the materials of interest.[71] It was recorded that at doses of 0.1-1 mg/kg, the triazines had significant effect.

When treated with phenacyl bromides, the isothiosemicarbazones of aliphatic carbonyl compounds gave complicated mixtures, from which it was possible to isolate in low yields 3,5-disubstituted 1,2,4-triazines. The course of the reaction was highly dependent on conditions.[72] In a similar vein, it has been noted[73] that 2-keto-isothiocyanates condense with various hydrazines to give aminoimidazolidinethiones or triazines, according to the method for carrying out the reaction. Treatment of 3-dimethylamino-2,2-dimethyl-2H-azirine with salicylaldehyde in acetonitrile at 25° gave 45 in 78% yield, cyclization of which took place smoothly in methanol to give 46. Nonetheless, replacement of methanol with dimethyl sulfoxide as cyclization solvent led to the formation of a mixture of 46 and 47.[74]

The recent upturn in interest in the aminoaryl-1,2,4-triazines has been stimulated by their utility in the synthesis of further novel



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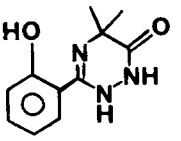

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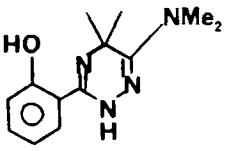
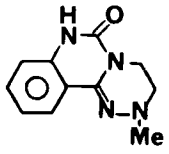


47

heterocyclics as well as by their own innate pharmacological properties. Thus heating 2-o-aminophenyl-1,4,5,6-tetrahydro-1-methyl-1,2,4-triazine at 200° or at 100° with polyphosphoric acid gave 48 or 49 respectively,[75] while a substantial number of triazinoquinazolines 50 were prepared by the acylation of the precursor aminoaryl compounds with acid chlorides, followed by cyclodehydration at 200°. The triazinoquinazolines have been investigated for their analgesic, antihistiminic and antidepressant characteristics.[76] Extensive background work has been done on the synthesis of the aminoaryl-1,2,4-triazines, revealing their analgesic properties and their ability to inhibit collagen-induced blood platelet aggregation, as noted in particular for compound 51.[77]

The familiar usefulness of the thiosemicarbazones, amidrazones and



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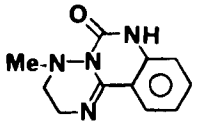

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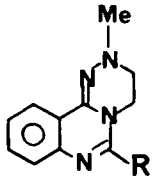

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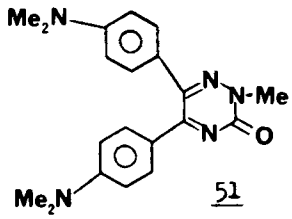
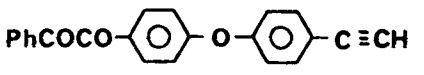


51

semicarbazones of benzil and diacetyl[78] in as-triazine preparation has recently been expanded and extended.[79] Treatment of benzil 52 with the 2-pyridyl derivative 53 in methanol at room temperature gave compounds 54 and 55 in 61% and 39% yields respectively.



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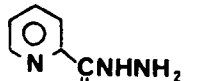

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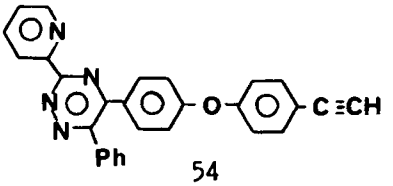

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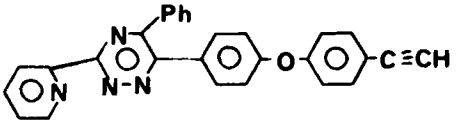
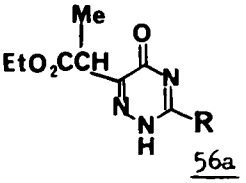
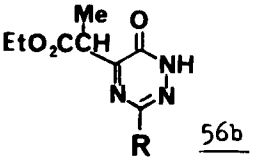


55

Among the cyclocondensative methods of lasting significance has been the reaction of keto-acids and their congeners with appropriately substituted hydrazines. The reaction of diethyl 2-methyl-3-oxosuccinate with a wide variety of benzamidrazones, for example, interestingly led to two isomeric as-triazines 56a and 56b.[80] Compounds 55 were conveniently aromatized, whereas those in series 56 were stable to aromatization conditions. In an attempt to develop new muscle relaxants and bronchodilators, Hartley and Oxford reported the reaction of keto-ester 57 with



56a

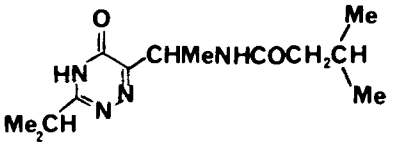


56b

isobutyramidrazone. The product 58 further cyclized in polyphosphoric acid to yield the corresponding imidazotriazine 59.[81] Similar approaches to the assembly of the heterocyclic have led to the discovery of a dramatic dependency of ring size on pH,[82] with pH 4 favoring the six-membered ring, as well as a number of specific preparative details pertinent to optimum

formation of the triazine.[83-87]

57



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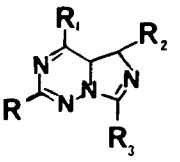
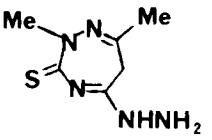


59

The cyclocondensation reactions of α-halocarbonyl compounds have provided a useful route to a variety of unusual systems. The triazepine 60 was treated with phenacyl bromide in ethanol at 20° for several hours



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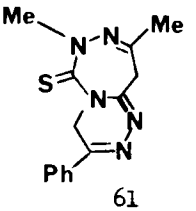
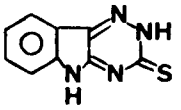


61

and gave rise to the triazinotriazepine derivative 61.[88] Liquid crystalline 3,6-diphenyl-1,2,4-triazines were prepared in fair to good yield by condensing para-substituted derivatives of benzoic acid hydrazide with appropriate phenacyl halides.[89] The melting characteristics of these materials were discussed. Recognition of the potential of N-aminoheterocyclics as synthons in general problems in organic synthesis[90-94] has been lately fostered by their increased availability; Neunhoffer and Degen have developed an important method, for example, for the preparation of 4-amino-1,2,4-triazines from suitable α-halo ketones.[95] Among the numerous substituted triazines and extended triazine ring systems prepared by the condensation reactions of α-halo ketones[96-101] are the elegant members of the triazinoindole family. Triazinoindolethione 62 was condensed with α-halo ketones and the products directly cyclized with polyphosphoric acid to give the thiazolotriazinoindoles 63. On the other

hand, the angular isomers 64 were obtained from the reaction of 2-hydrazino-4-arylthiazoles with isatin, followed by acid cyclization. Related methods produced indoles 65 and 66.[102] Compound 63 (R = H) was discovered to be effective in control of Aspergillus fumigatus.

Amination of alkylthiotriazines have resulted in the symthesis of the 6-aza analogues of trimethoprim.[103] A thorough study has been made of the behavior of the alkylthio derivatives towards amines.[104]



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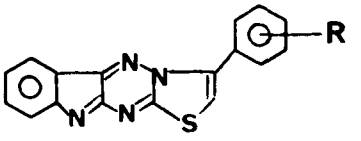

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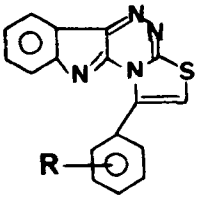

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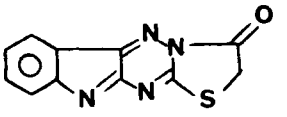

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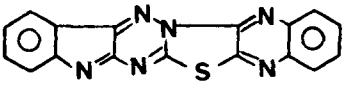
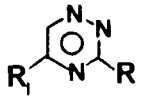


66

Isocyanates and isothiocyanates have not received much attention in the cyclocondensation scheme. The intriguing studies which have been done point up the need for further work in this neglected area. Daunis and Follet used isothiocyanates to introduce triazolyl substituents into compounds already bearing a preformed as-triazine ring,[105] whereas Sirrenberg, Eve and Schmidt developed useful triazine herbicides from isocyanates.[106]

Substantial effort has been devoted to an unravelling of the cycloaddition reactions of 1,2,4-triazines. These mechanistic studies have provided new means for elaboration of the triazine framework.[107,108] Thus treatment of triazines 67 with dimethyl acetylenedicarboxylate provided pyrrolo[2, 1-f][1,2,4]triazines 68. The absence of solvent played a crucial role in product determination, allowing for the formation of pyridino[2, 1-f][1,2,4]triazines 69 and [1,3]oxazino[2, 3-f][1,2,4] triazines 70.[109]



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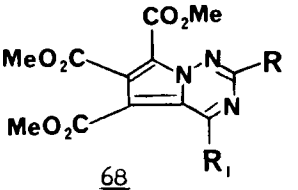

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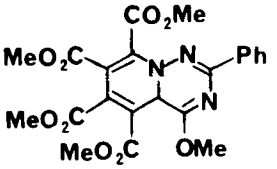

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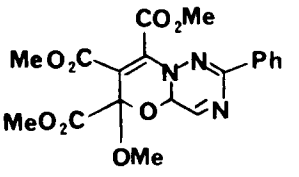

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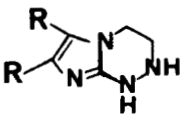
Exceptional versatility is inherent in the ring closure reactions to as-triazines of variously substituted hydrazines, in which the particular technique may take advantage of a one-step intramolecular cyclization between appropriately placed functional groups or of a two-stage reaction done in one vessel.[110-117] Seven categories of as-triazinobenzodiazepines were prepared by Moffet and coworkers either by condensing substituted hydrazines with 2-thiobenzodiazepines or by closing the triazino ring of suitably substituted hydrazones from 2-hydrazinobenzodiazepines.[118] Imidazotriazines 71 and 72 have been prepared by cyclization of the corresponding dihalides 73 and 74 in the presence of hydrazine hydrate at

160-190°.[119,120]

4. Reductive Cyclization

In a highly productive preparative procedure hinging on reductive cyclization, as-triazino[5,6-c]quinoline and its derivatives result.



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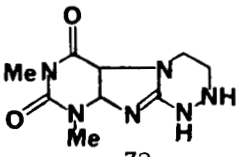

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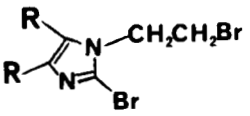

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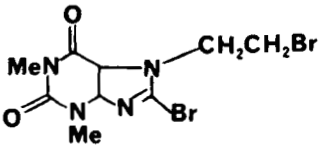

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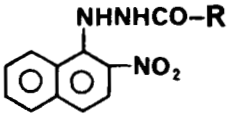
Acylhydrazinoquinolines 75 were hydrogenated conveniently to give the dihydroderivative 76. When 76 was carefully oxidized using potassium hexacyanoferrate, aromatization occurred; the unsaturated compounds were prepared as part of an investigation into their anti-inflammatory and bacteriocidal properties.[121-123]



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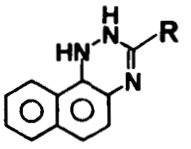
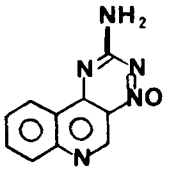


76

In related work, the same team of experimentalists cyclized quinoline 77 with base to prepare the N-oxide 78. Hydrogenation of the latter led smoothly to 2-amino-as-triazino[6,5-c]quinoline in good yield.[124] Photolytic reduction of Metamitron 79 takes place with loss of herbicidal activity, and a similar process has been observed in the case of Metribusin.[125]

77



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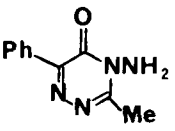
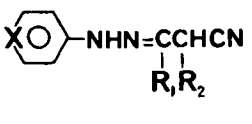


79

Several direct synthetic routes to reduced 1,2,4-triazines have been investigated which utilize nitriles as convenient starting materials. In one procedure, ketones were treated with sodium cyanide and thiosemicarbazide under acidic conditions to afford the cyanothiosemicarbazones; use of concentrated hydrochloric acid then produced immediate cyclization. Alternatively, the nitriles were first converted to the related carboxythiosemicarbazones and then cyclized by refluxing in diphenyl ether.[126] Hydrazono nitriles 80 underwent base-catalyzed cyclocondensation in ethanol to give either pyrazolobenzotriazines 81 (X = CH, yields ca. 60%) or pyrazolopyridotriazines 82 (X = N, yields about 70%). Reduction of the oxides occurred readily with sodium dithionite.[127] Cyclocondensation of succinonitrile with hydrazine 83 yielded triazine 84



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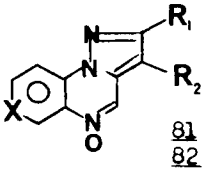
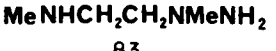


81
82

in good material balance, and by a similar process the method was extended to the preparation of the difunctionalized ethane and butane, 85a and 85b respectively. The obvious synthetic potential of the latter compounds has not yet been fully developed.[128] In several cases, nitriles have proved especially useful in the genesis of extended ring systems from preformed triazines[129] or monocyclic compounds with a high degree of substitution.[130]

Aldehydes and ketones and their derivatives have been useful starting



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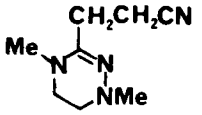

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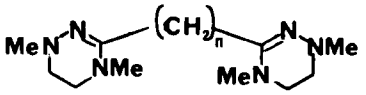
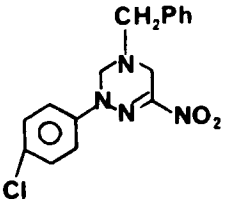
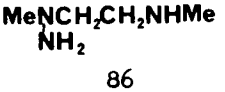


85a, n=2
85b, n=4

materials in triazine preparation. Thus the reaction of the 4-chlorophenylhydrazone of nitroformaldehyde with benzylamine and formaldehyde in refluxing ethanol for 25 hours gave the nitrotriazine in high yield. At shorter reaction times the intermediate hemiaminal could be isolated.[131] Aminal formation proceeded without complication in the case of the reactions of a variety of ketones and aldehydes with the hydrazine 86, giving the as-triazines in yields of about 65%.[132] Isatin is known to form the β-thiosemicarbazone upon treatment with thiosemicarbazide, and the effects of methyl substituents on subsequent base-catalyzed ring closure to the triazines 87 have been recently studied. Energies of activation for the cyclization have been provided.[133] Among the numerous heterocyclic products formed from the reaction of aromatic aldehyde azines with potassium tert-butoxide in refluxing toluene were 3,5,6-triaryl-1,2,4-triazines, 2,5-dihydro- and 1,4,5,6-tetrahydro-1,2,4-triazines.[134] The 4-thiazolidinone derivatives of certain aldehydes have been reported to react with reagent hydrazine to give the six-membered





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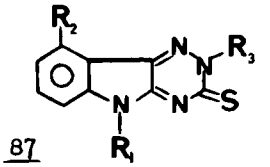
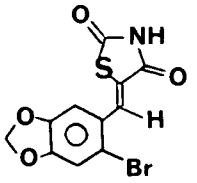


87

ring: in this way, 88 produced 89.[135] Aldehyde condensation has provided significant pathways to quinazolo- and imidazo-triazines from parent compounds in which one of the heterocyclic rings was present in diamino-substituted form.[136-137]



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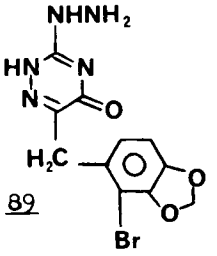

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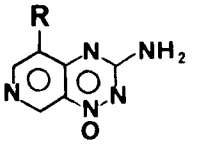
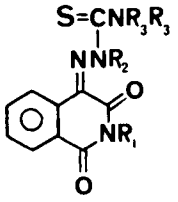


90

An excellent preparation of pyrido-as-triazine 90 resulted from the base-catalyzed cyclocondensation of guanidine with 4-methoxy-3-nitro-pyridine.[138] A series of isoquinotriazines was prepared by treatment of phthalonimides with aminoguanidine; the intermediate compounds 91 could be isolated and characterized before cyclization in base to give 92. The sulfur-containing analogues were similarly prepared from the thiosemicarbazides.[139] A Japanese patent refers to the antibacterial and protozoacidal activities of furfurylidene derivatives such as 93 formulated



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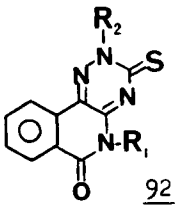

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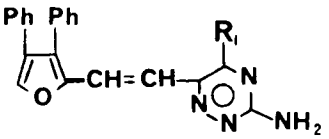


93

by heating the related aminoguanidine derivatives 94 in dimethylformamide at 130° for about 2 hours.[140]

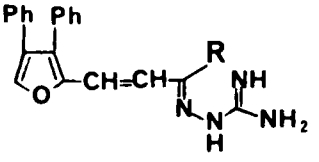
In the manganese dioxide oxidation of 4-phenyl-1,2-diaminoimidazole in refluxing benzene for 7 hours, 5-phenyl-3-amino-1,2,4-triazine was obtained as the chief heterocyclic product, along with 4-phenyl-1,2,3-

triazole. Changes in solvent and conditions permitted variation in the relative proportions of these two components formed.[141] The dehydrogenation reactions of as-triazinediones have been studied using such reagents as sodium nitrite, sodium perchlorate, ferric chloride and p-benzoquinone.[142,143]

Goldin and Baturina have investigated the cyclocondensation reactions of appropriately substituted ω-aminohydrazines with a number of carboxylic acids and their derivatives, including the anhydrides, esters, amides and hydrazides, with the acid chlorides conspicuously absent.[144] Triazolotriazines 95 were prepared as antiviral and antimetabolic agents by refluxing 5-hydrazino-6-arylthio-as-triazin-3(2H)-ones with formic acid.[145] Among the numerous methods for the preparation of 6-azauracils (vide infra) has been reported the base-catalyzed cyclization of glyoxylic acid semicarbazone in hot ethylene glycol.[146]

5. Diazonium Coupling

Coupling of diazonium salts has provided fruitful entries into a number of triazine systems. Thus Slouka and coworkers found that coupling of diazotized primary aromatic amines with amides or imides, followed by saponification, gave triazines 96, themselves further subject to thermal cyclization to the triazinoquinazolines 97.[147] On the other hand, aryldiazonium salts reacted with ethyl 3-indolylcarbamate to give the 2-aryl-2,3-dihydro-9H-1,2,4-triazino[6,5-b]indol-3-ones 98.[148] Diazotization of N-substituted 3-aminophthalimides gave hydrazones 100 in nearly



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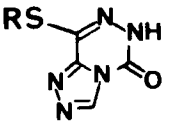

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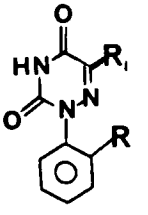

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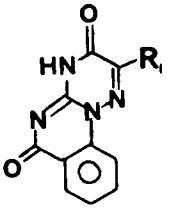
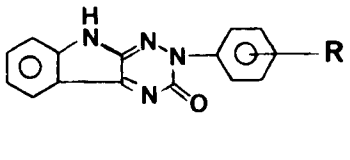


97

quantitative yields. Cyclization of the hydrazones by heating produced the series of azauracils 101.[149]



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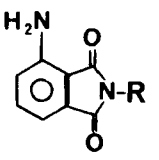

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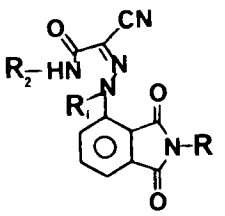

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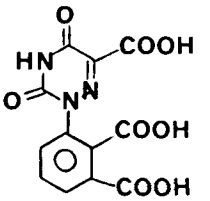
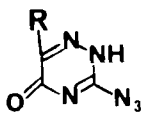


101

The 3-azido-2,5-dihydro-5-oxo-1,2,4-triazines 102 were prepared from the corresponding 3-hydrazino precursors by treatment with nitrous acid. Spontaneous cyclization of the azides led to the formation of tetrazolo-triazines 103, as shown by carbon-13 NMR spectroscopy.[150] Ege, Gilbert and Franz have investigated the cyclization of ynamines 104 using diazoazoles 105 in addition reactions leading to azolo[5,1-c][1,2,4] triazines 106.[151]



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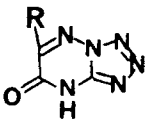

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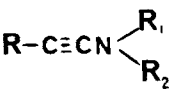

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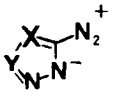

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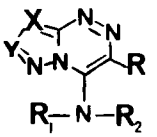

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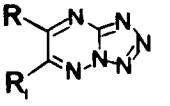
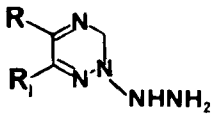


107

A combination of general synthetic methods has been most successful in the preparation of bicyclic triazines, particularly those which bear a nitrogen at the ring junction; and the domain of possible structural variations among these compounds has increased vastly. In many cases, the construction of these bicyclic materials begins with a preformed, appro-

priately substituted monocyclic as-triazine. Approaches to the design of the azolotriazines have been especially imaginative. In one method, due advantage was taken of the spontaneous cyclization of 1-azido compounds in the formation of tetrazolo[1,5-b][1,2,4]triazines 107. Treatment of 108 with nitrous acid allowed direct isolation of the fused 5,6-ring heterocycles.[152] Alkylation of 3-amino-5,6-diphenyl-1,2,4-triazine with bromoethanol gave substitution at nitrogen-2, and cyclization with thionyl chloride produced the imidazole.[153] Simply heating 3-amino-1,2,4-triazine in concentrated hydrochloric acid at 100° for 24 hours was shown to lead to imidazo[1,2-b][1,2,4]triazine.[154] In the presence of a base,



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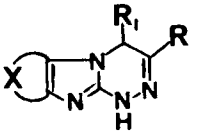

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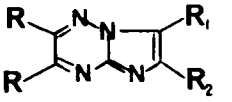
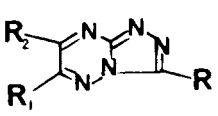


110

α-haloketones condense with 2-hydrazinoimidazoles, yielding the related dihydroimidazo[2,1-c][1,2,4]triazines 109.[155] Complementing the latter study has been the experimental work indicating that imidazolotriazines 110 are obtained in moderate to excellent yields by heating the progenitor aminotriazines with α-bromoketones at temperatures above 60°. The intermediate imines may optionally be isolated.[156] A thorough investigation of the reactions of ethyl acetoacetate with 3,4-diamino-5-oxo-4,5-dihydro-1,2,4-triazine has revealed factors governing the formation of the panoply of triazine products formed.[157] Triazolotriazines have been of keen interest from the theoretical standpoint because they constitute a novel class of heteroaromatic 10-Π electron systems. Representatives 111-114 of this unique category of bridgehead nitrogen systems were prepared by Daunis,[158] either from 3-amino- or 3-hydrazino-as-triazines or, alternatively, from 5-chloro, 3,4-diamino- or 3-hydrazino-s-triazoles.[159] Although the major



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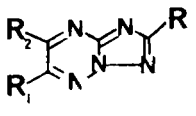

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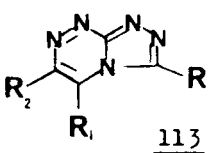

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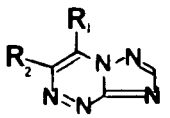

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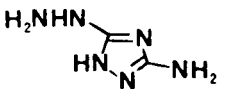

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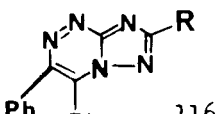


116, R=NH_2
117, R=H

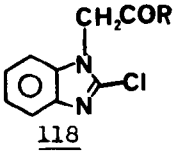
products formed upon reaction of 3-(ß-chloroethyl)amino-1,2,4-triazines with ethylenimine were the corresponding 3-ethylenimino compounds, some imidazo[1,2-b][1,2,4]triazines and their dihydro derivatives were also noted.[160] One creative approach to the triazolotriazines involved treatment of 3-amino-5-hydrazino-1,2,4-triazole 115 with benzil. Deamination of the resulting 116 took place with amyl nitrite and gave the reduced form 117, remarkable for its propensity to form covalent solvates.[161] A variety of chlorobenzimidazoles 118 underwent reaction with both aliphatic and aromatic hydrazines in hot dimethylformamide to give 1,4-dihydro derivatives 119 of 1,2,4-triazino[3,4-a]benzimidazole.[162]

Nitrogen-bridged pyridotriazine derivatives 121 resulted from the condensation reactions of acrylates with 1-aminopyridinium iodides 120 in aqueous potassium carbonate. The aziridines or azirines were suggested as possible intermediates.[163] 1-Dimethylamino-3-phenacylphthalazinium chloride 122 formed an ylid upon treatment with base; the ylid underwent cyclization with hydrazine to give the triazinophthalazine 123.[164] A number of triazinoquinazolines 124, some of which increased hexabarbital sleep time, were prepared by heating a pre-formed aminophenyltriazine with the appropriate pyridine carboxaldehyde for a few hours in ethanol.[165]

6. Diels-Alder Reactions

Comparatively few references occur in the literature to methods for triazine elaboration pendant on the Diels-Alder reaction, and this poten-

tially very productive area remains less fully explored. As part of a larger program of research aimed at elucidating the characteristics of



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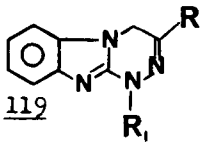

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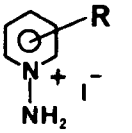

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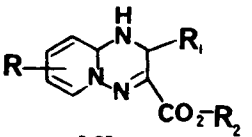

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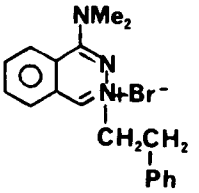

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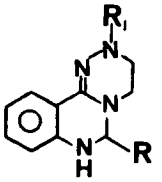

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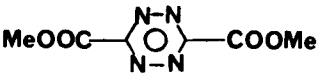
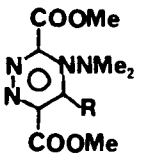


125

inverse Diels-Alder additions, Seitz and Overheu discovered that aldehyde dimethylhydrazones reacted with dicarbomethoxytetrazine 125 to produce the triazines 126. Surprisingly, the related ketone hydrazones reacted under similar conditions to give pyridazines 127. The authors concluded that the latter reaction occurred from the enamine form.[166] Several triazines also resulted from the reaction of 125 with variously substituted cyanamides in an allied study.[167] Spiroheptatriene 128 reacted with



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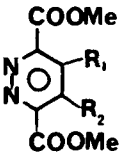

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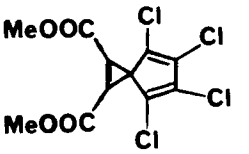
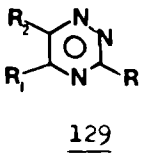


128

trisubstituted triazines 129 to produce the novel cyclopentapyridotriazines 130, the structure determination being made by x-ray analysis.[168] Com-

peting cycloaddition processes have been studied in the reactions of 1,2,4-triazines with ynamines. Thus triazines 131 reacted with 132 to give exclusive formation of the 2,5-addition products, namely the pyrimidines 133; in cases for which 2,5-addition was precluded by substitution of phenyl at the 5-position, 3,6-addition led to the pyridine 134 in 85% yield.[169]



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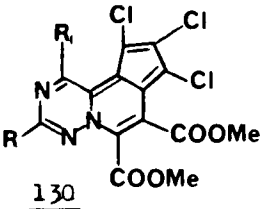

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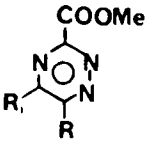

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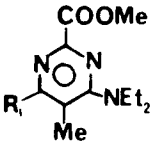

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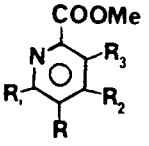
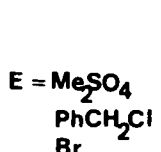


134

7. Aromatic Substitution

Both electrophilic and nucleophilic aromatic substitution have broadened the scope of structural variations possible in the synthesis of useful triazines. In a recent study, Robba, Maume and Lancelot found some interesting comparisons among various electrophiles as they reacted with systems 136 and 137.[170] Thus bromine and nitric acid produced mixtures of polysubstituted derivatives, with the reaction occurring in the benzene ring. On treatment with dimethyl sulfate or benzyl chloride, however, clean substitution took place at the lactam nitrogen. Friedel-Crafts alkylation reactions of triazinediones and triazinedithiones have been examined. Under Friedel-Crafts conditions, treatment of 138 with benzene gave 139.[171] In a related study, it was found that thiophenotriazines resulted from exposure of 3-styryltriazinones to phosphorus pentasulfide.[172] 3,5-bis (Methylthio)triazines 140 underwent methanolysis with sodium methoxide in methanol to varying extents, depending on the temperature of



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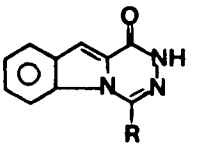

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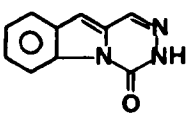

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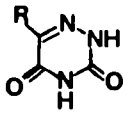
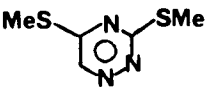


138, R=PhCHCH
139, R=Ph_2CHCH_2



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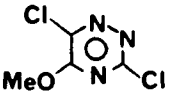
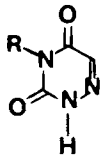


142

the reaction. At room temperature, the 5-methylthio group was selectively cleaved, whereas at reflux both groups were replaced.[173]

8. Halogenation

Several procedures have been provided for the halogenation of the as-triazine ring at the reactive 3-position.[174-176] The most commonly employed reagents have been phosphorus pentachloride and phosphorus oxychloride. Chlorination at this position provides a direct link to an abundance of aminated compounds derived from nucleophilic substitution[177-180] by ammonia or primary and secondary amines. Piskala, Gut and Sorm have made a thorough inquiry into the reactions of halogenated triazines with nucleophiles and have compared the reactivities of halogen atoms at different sites. 3,5,6-Trichloro-1,2,4-triazine 141 reacted with one equivalent of sodium methoxide in methanol to give 142, resulting from 5-substitution. With two equivalents of the alkoxide, a mixture was obtained, comprised of 3- and 6-substitution. Finally, with an excess, all three chlorines were replaced.[181] Selective methylation of N2 in compounds 143 was facilitated by use of a mixture of hexamethyldisilazane and trimethylsilyl chloride to prepare the intermediate bis-O-trimethylsilyl derivatives. Treatment of the latter with methyl iodide led without



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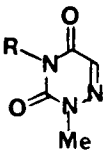

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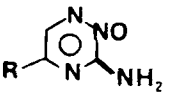


145

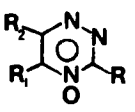
complication to 144 in high yield.[182]

In the preparation of a number of coccidiostatic triazines, which all bore close structural relationships to one another, Mylari found a simple procedure for the decarboxylation of 3-triazinecarboxylic acids.[183] From time to time, mild methods are required for the conventional functional group conversion of triazinecarboxylic esters to the parent carboxylate salts, a subject area which has been recently investigated.[184] Special protocols have been developed for the preparation of as-triazines bearing unusual substituents at the 3-position, including 3-aminocarbonylarenesulfonamido groups[185] and 3-perfluoroalkyl residues.[186]

9. Oxidation

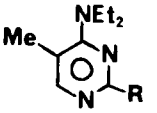
Methods for the preparation of 1,2,4-triazine oxides have included the use of mild oxidizing agents.[187] Thus Paudler and coworkers found that addition of m-chloroperbenzoic acid to substituted 3-amino-1,2,4-triazines in acetonitrile led cleanly to 3-amino-1,2,4-triazine 2-oxides 145, whereas oxidation of 3-methoxy-1,2,4-triazines gave reaction at N-1.[188] A special procedure was developed for the synthesis of the parent, 1,2,4-triazine 2-oxide itself, as well. The authors concluded that 3-amino-3-imino tautomerism must be possible in order for N-2 oxidation to take place. Subsequently bromination reactions of the 2-oxides have been studied.[189] Triazine 4-oxides 146 resulted upon cyclization of 147 or upon treatment of 148 with 149.[190]

1,2,4-Triazine 2-oxides substituted at the 6-position by an appropriate heteroatom undergo an addition-elimination sequence with alcohols to yield the 6-alkoxy compounds, although the 1-oxides are inert under similar conditions.[191] Triazine 4-oxides reacted with dienophiles such as 150 in a [4+2] cycloaddition process to give moderate yields (ca. 40%) of the pyrimidines 151.[192]



146

147 EtOCR:NN:CR_1R_2:NOH
148 H_2NN:CR_1R_2:NOH
149 EtOCR:NH·HCl
150 Et_2NC:CMe

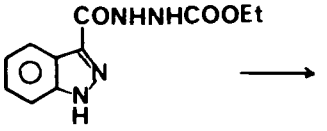


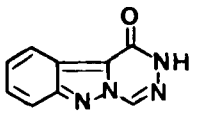
151

Many of the important methods useful in the general preparation of 1,2,4-triazines can also be very productively applied to the synthesis of the triazinones and triazinediones, chief among these being the cyclocondensation technique.[193-214] Thus Robba, Lancelot, Maume and Rabaron prepared 152 by the cyclization reaction shown below, using a diacylhydrazine precursor.[215] In the quest for potential antineoplastic agents, substituted 3,5-dioxo- and 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazinones were synthesized.[216] Treatment of the unsaturated α-ketoacids 153 with semicarbazide or thiosemicarbazide led to efficient formation of addition products 154, which readily cyclized to yield the desired products of the investigation 155. Lovelette has recently noted a convenient synthesis of 3-amino-6-hydrazino-5(2H)[1,2,4]triazinone 156. Upon refluxing in neat acid of heating with orthoester in dimethylformamide, ring closure occurs across N-1 of the triazine moiety, leading to the

formation of 3-alkyl or 3-aryl-8(5H)-5-triazolo[3,4f][1,2,4]triazinone 157.[217]

Alkylation of triazinethiones has played a significant role in the search for coccidiostatic agents[218] and herbicides.[219] Methylation of triazinoquinazoliumolates 158 with methyl iodide in nitromethane gave a high yield of the N-2 methylated methiodide 159, which produced the pseudobase 160 upon mere treatment with bicarbonate solution.[220] 3-(Methylthio)triazinone 161 was conveniently formed by S-methylation of the related 3-mercapto compound using methyl bromide in water at pH 12.0.[221]

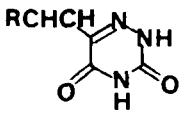




152

153 RCH:CHCO$_2$H

154 RCH:CHC(CO$_2$H):NNHCONH$_2$



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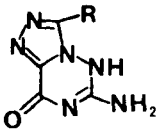

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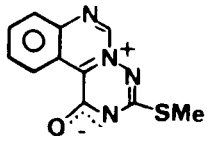
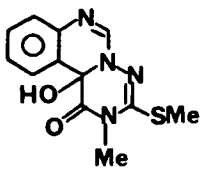


158

Although specific application has been made of the cyclization of α-halocarbonyl derivatives to build up the triazinone framework,[222] much of the synthetic activity involving the α-halo compounds has been directed at side chain elongation[223] or the fusion of new rings[224,225] onto a preformed triazinone or triazinethione. Similarly, the diazotization techniques discussed above have constituted useful reactions in the preparation of triazinediones.[226,227] In a novel oxidation procedure, potassium permanganate oxidation of 162 led to carboxyphenyltriazinones 163.[228] The dehydrogenation of the carboxylic acid hydrazide 164 took

place with mercuric ion-EDTA and gave 165. The formation of the latter


159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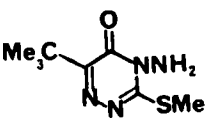
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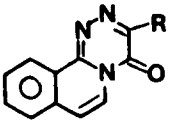
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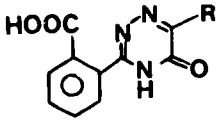
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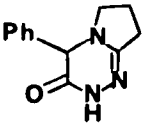
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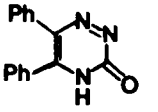
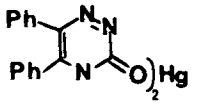

166

product was sensitive to the ring size in the starting hydrazide.[229] Mercuric acetate oxidation of 166 gave a very high yield of bis(5,6-diphenyl-1,2,4-triazin-3-one)mercury 167. Careful treatment of 166 with lead tetraacetate in triethylamine-methylene chloride, on the other hand, led cleanly to 4H-5,6-diphenyl-1,2,4-triazin-3-one.[230] Several articles have appeared on the modification of triazinone carboxylate groups.[231-233] As part of their wider program in the development of effective new herbicides, Draber, Dickore, Timmler, Eve and Schmidt have prepared N-(1,2,4-triazin-5-on-4-yl)glycine derivatives. Aminotriazinones 168a were stirred with glyoxylic acid and ethanol for 12 hours at ambient temperature to give compounds 168b in high yields.[234-235]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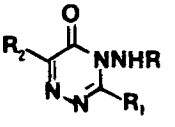
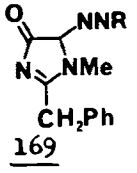
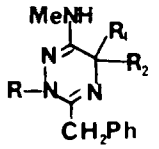

168a, R=H
168b, R=CH(OR$_3$)COR$_4$

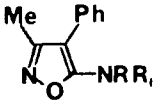

169

Preparations of triazinones have been effected from other heterocyclic systems. Thus acid catalyzed cleavage of imidazolinones 169 gave triazinones 170. Interestingly, Grignard reaction of the latter gave the dihydrotriazines 171.[236] Adembri and coworkers have found that

isoxazoles 172 undergo rearrangement under photolytic conditions to give pyrazolones, pyrazolinones and tetrahydrotriazinones.[237] Imidazolones, dihydrooxadiazinones and tetrahydrotriazinones resulted from the reaction of α-amino acid esters with tert-butylisocyanide when the mixture contained palladium (II) ion. The crucial intermediates, diaminocarbene-palladium (II) complexes, were characterized in this study.[238]



170, R, R_2 = O
171, R_1 = OH, R_2 = Ph



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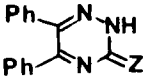

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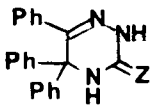
Under Friedel-Crafts conditions, triazinones and triazinethiones 173 (Z = O,S) reacted with benzene to produce the triphenyl compounds 174.[239] Appropriately substituted 4-aminotriazin-5-ones are readily reduced to the corresponding triazine by sodium borohydride in methanol.[240] An interesting rearrangement has recently been noted, in which hexahydro-1,2,4-triazine-3,5-dione serves as a useful precursor of the hydantoins 175.



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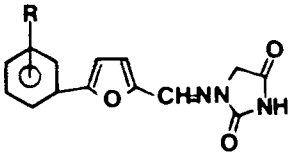

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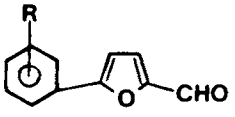

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Thus aldehyde 176 (R = p-NO_2) was refluxed with the dione in acetic acid to give the imino adduct in 76% yield.[241] The ability of the triazinedione to "stand-in" for the 5-membered N-amino heterocyclic in synthesis is a valuable characteristic of the compound and represents significant synthetic potential.

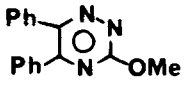
10. Reduction

The preparation of reduced triazines, including both dihydro and tetrahydro compounds, has taken several courses, some of the most pro-

ductive of which involve direct reduction techniques.[242] Reduction of the triazines 177 with a slight excess of sodium borohydride in a mixture of methanol and tetrahydrofuran gave the products 178 in good yields. The dihydrotriazines were readily alkylated with methyl iodide and suffered cyclization with dimethyl acetylenedicarboxylate.[243] Cyclocondensation methods have been used with success.[244,245] Dychenko, Pupko and Pel'kis have prepared substituted 2,3,4,5-tetrahydro-1,2,4-triazines from nitroformaldehyde 4-substituted arylhydrazones.[246] The hydrazones were treated with aldehydes and amines to give a variety of heterocycles 180. Modifications of the triazines in reduced form have embraced alkylation,[247] halogenation[248] and transformation to aldehydes.[249] In the latter example, the triazole 181 was treated with a carboxylic acid or reactive carboxylate derivative to produce the triazoloquinazolium compound 182. Reduction with sodium borohydride and subsequent hydrolysis gave the aldehyde in about 50% yield.

11. Azauracils

Particular impetus has been lent to the furthering of useful tech-



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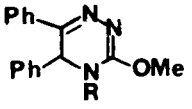

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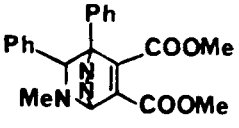

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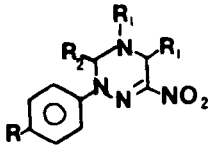

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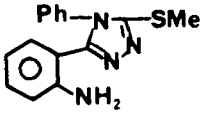

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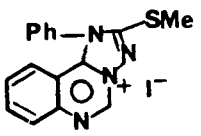

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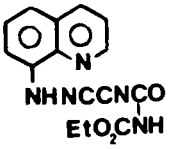

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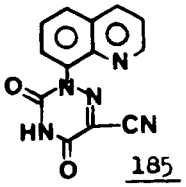

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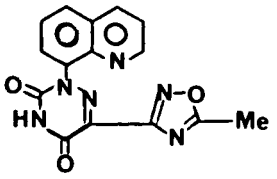
niques for the preparation of azauracils by the realization of the pharmacological applications which these compounds have give rise to. Especially imaginative and productive approaches have been taken by Slouka and coworkers.[250] In a recent example, 8-aminoquinoline was diazotized and coupled with 183 to give 184. Cyclization produced the nitrile 185, which in turn reacted with hydroxylamine and acetic anhydride to produce 186.[251] The yields for each of the individual steps were greater than 90%. Yoneda, Nitta and coworkers have developed a new synthesis of 1-aryl-6-azauracils as well. With an excess of urea at 200° for several hours, 6-amino-5-(arylazo)uracils 187 gave 188,



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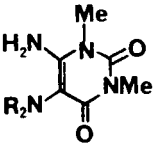

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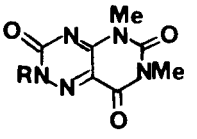

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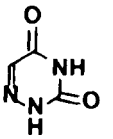

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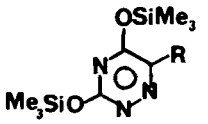
alkaline hydrolysis and decarboxylation of which led to the desired 2-aryl-1,2,4-triazine-3,5(2H,4H)-diones.[252] The general problem of the synthesis of 6-azauracil has been the subject of a new computer simulation program.[253] In an investigation of the isomerization, alkylation and cyclization of glyoxylic acid semicarbazone derivatives, Hrebabecky and Beranek found that the Z-isomer 189 cyclized with sodium methoxide to yield 6-azauracil 190.[254] The x-ray crystallographic structure has been determined for the 2:1 adduct of 6-aza-2-thiothymine and triethylamine.[255] Reactions promoted by Friedel-Crafts catalysts, especially by stannic chloride, have been the subjects of a number of investigations,[256-259] some of which have led to the preparation of carcinostatic agents. Thus the reaction of trimethylsilyl compounds 191 with lactol ethers 192 in methylene chloride in the presence of stannic

chloride gave the N1-(2'-furanidyl)- and N1-(2'-pyranidyl)uracils 193 in yields up to 85%.[260] Further synthetic uses of trimethylsilylated uracils have been made.[261,262]



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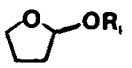

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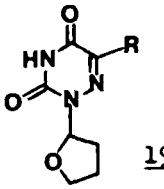

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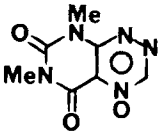
Significant advances have been noted in the preparation of azapyrimidines and mercaptopyrimidine derivatives.[263-265] The latter compounds can react with methylhydrazine by direct substitution of the thio group.[266]

Photochemical reactions have been employed in the preparation of azauracils. A study of the ultraviolet spectra of these compounds has shown sensitivity of the maxima to substitution at the 5-position.[267] 6-Azauracil and its derivatives experience photochemical cycloaddition to enol acetates to yield labile azetidines; the latter readily decompose in water, and bromine oxidation of the 5-substituted-5,6-dihydro-6-azauracils thereby produced leads in a direct fashion to the desired 5-substituted azauracils. Application of this process to 6-azauridine compounds gives good yields of the functionalized nucleosides.[268-270] 6-Azauracil undergoes mild reduction with zinc powder in dilute acetic acid to produce the 5,6-dihydro material.[271] An extensive review of the hydrogenated compounds has appeared.[272]

The cyclocondensation method has been used in the preparation of a spectrum of both simple and elaborated azauracils.[273-277] Among the new syntheses is that of fervenuline 4-oxide 194, prepared in 72% yield by treatment of 1,3-dimethyl-6-hydrazino-5-nitrosouracil with a mixture of dimethylformamide with phosphorus oxychloride.[278] The "reverse"

process, that is, cleavage of fervenuline and its derivatives with amines to produce ureidotriazines, has been examined.[279]



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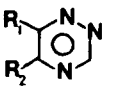

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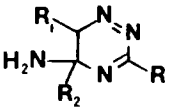

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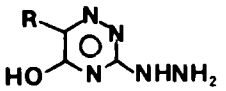
12. Physical Organic Methods

A paramount concern toward the meaningful application of the 1,2,4-triazines to problems in agriculture and medicine has been the pursuit of detailed knowledge about their structure, stability and reactivity, largely through the methods of physical organic chemistry. The unambiguous structural assignment was made of the σ-adduct of ammonia and representative triazines 195 based on clear-cut data from proton and carbon-13 NMR spectroscopy; the compound was shown to be 196.[280] The problem of ring-chain tautomerization in 3-hydroxythiazolo[3,2-b]-*as*-triazin-7-ones was worked through to a determination of the activational free energy by using proton NMR.[281] Proton NMR data for typical triazinones were consistent with quinonoid structure in solution.[282] The conformational analyses of the perhydro-1,2,4-triazines have been thoroughly described.[283,284] Carbon-13 NMR[285-287] and nitrogen-14 NMR[288-290] have been increasingly used in structure determination. A French group has been in the forefront of studies aimed at fixing the mass spectrometric fragmentation patterns of 1,2,4-triazine derivatives.[291-292] Other experiments have been aimed at the mass spectra of the triazinones[293] and the triazine oxides.[294] Photophysical methods and product studies have strongly implicated carbenoid and nitrenoid intermediates in the photolytically-induced decompostion of triazines and their synthetic precursors.[295-298] Other problems which have proven susceptible to

solution by the methods of physical organic chemistry have included the effect of acid and other reagents on the key steps in the cyclocondensation procedure,[299-304] the effects of substitution in the 6-position and of the reagent on the orientation of 197,[305] and the details of the mechanism of bromination of 6-azauracil in aqueous acid.[306] Specific application of ultraviolet spectroscopy has permitted the detailed study of the tautomerism of triazolotriazines[307] and the electronic structures of cytosine, 5-azacytosine and 6-azacytosine.[308] X-ray crystallographic



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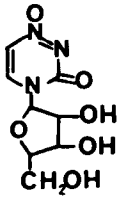

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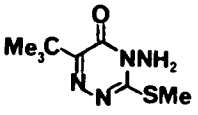

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results have revealed interesting features of the 1,2,4-triazine system. The canonical structure of 1,2,4-triazine with an N1-N2 single bond more closely represents the ground state of the molecule than the one with an N1-N2 double bond.[309] A further study[310] proposes that the nonionic canonical structure hardly contributes to the resonance hybrid. The evaluation of ionization potentials and electron affinities calculated by a free-electron model shows them to be in better agreement with experimental data than similar results from SCF-LCAO-MO treatments.[311] The range of physical organic methods has also included the determination of ESCA spectra and molecular charge distribution,[312] polarographic measurements,[313] recording of magnetic CD spectra,[314] taking of heats of sublimation[315] and the resolution of the question of amino-imino tautomerism in some fused 1,2,4-triazin-5-ones by infrared spectroscopy.[316]

Owing to intense biomedical interest in their capacity as analogues of ribonucleosides, the aldosylated 1,2,4-triazines have figured highly in recent carbohydrate research. Because the synthetic chemistry of

these materials may in large part be understood on the basis of the previously discussed reactions of the triazine moiety itself, we present the new references to the preparative articles but refrain from detailed treatment of modifications of the sugar unit.[317-371] Physical measurements of the properties of these materials have lagged behind the runaway activity of their preparation, but representative attempts at a better understanding of their characteristics have included the accumulation of basicity, NMR and UV data,[372] fluorescence and CD spectra,[373] data on intermolecular interactions[374,375] and analysis of conformation.[376]

13. Applications

We have previously alluded to a number of the useful applications of 1,2,4-triazines as pharmaceutical ingredients, and no small amounts of research effort, in both the laboratory and the clinic, have been devoted to the elucidation of their functions as antibacterials,[377-379] antimalarials,[380] anti-inflammatory agents,[381-384] antiviral compounds,[385-398] antipsoriatics,[399-401] antihypertensives,[402] antiarthritics,[403] and coccidiostats.[404-408] Nonetheless, it is clear that their full potential remains far from realized. Indeed, in some cases, researchers are still striving to gain some of the most basic--but most complex--information about general morphological and systemic effects which administration of the compounds can have in experimental animals.[409-416] It is clear, however, that evidence is accumulating to the effect that these materials have an important role to play in developing cancer chemotherapy. Uricytin 198, for example, in some recent experiments, cured all test mice with L1210-XIII leukemia. The fact that tumor-specific antibodies had been produced was indicated when it was observed that serum from the cured animals reacted strongly only with L1210-XIII cells. When innoculated with L1210-XIII cells, the cured animals showed no signs of tumor induction.[417-418] 5-Fluorouracil showed antitumor activity against human cancer colon carcinomas when tested in a new model for *in vivo* evaluation

of effectiveness in mice which allowed for quantitation of both antitumor results and host toxicity.[419] Fluorouracil, among other antineoplastic drugs screened, prolonged survival more than two weeks in a study of the effect of donor pretreatment on rat cardiac allografts.[420] A correlation has been sought between the cytostatic activity of triazines and their average quasi-valence number.[421] Changes in amino acid metabolism caused by 6-azauridine triacetate and their relationship to cancer chemotherapy have been investigated.[422] The effects of triazine derivatives on several biochemical pathways have been the subject of increasing interest in the formulation of new drugs.[423-434] A recent study probes the acceptor activity of uracil nucleosides in the dinucleoside monophosphate synthesis catalyzed by pancreatic ribonuclease: in the reaction of cyclic UMP with the hydroxyl groups of uracil compounds, the pyrimidine ring system contributes to the binding of the acceptor to the enzyme.[435] The work is representative of a wide body of the literature concerned with the effect of acceptor modification on syntheses enzymically catalyzed[436-439] and the larger questions of enzyme binding,[440-453] immunosuppression,[454] RNA synthesis,[455] and radioprotection.[456] Physical methods,[457-467] in particular ESR techniques,[468,469] have found useful application in the determination of the biochemical phenomena. Triazines have been recently used as determinors of biochemical systems in their capacity as embryotoxins,[470] inhibitors of DNA synthesis,[471] mutagens,[472] and in many other roles as well.[473-486] Triazine-protein conjugates have been prepared, although not a great deal has been worked out concerning their biological activity.[487-491]

The proven effectiveness of various 1,2,4-triazines, particularly those with nitrogen- or sulfur-containing side chains, in large scale agricultural operations has led to many studies to find the best methods for their applications to croplands and their behavior after initial

spreading and prolonged exposure to soil conditions. Aside from the possibly damaging effects to the desirable plants, use of repeated doses of the triazine herbicides is not without detrimental economic fallout. Thus it has been a concern that such materials as 199 hydrolyze rapidly in aqueous solution, confounding good determinations of their release rates. Recently, attempts have been made at the development of polymeric controlled activity herbicide systems containing pendant 199. The rates of release can be varied by changing the cross-linking dimensions of the polymers, and mobility in soil of the herbicide may be reduced with an accompanying increase in residual phytotoxicity.[492-494] Other studies have had as their foci the detection and fate of triazine herbicides in particular varieties of soil and different environmental conditions.[495-507] The evaluation of the herbicides has necessarily been made within the context of the cultivation of specific crops, and one finds applications formulated for potatoes,[508-511] tomatoes,[512-522] soybeans,[523-530] sugar beets,[531-538] tarragon,[539] bulbs,[540] broadbeans and other legumes,[541-542] wheat,[543-550] alfalfa,[551,552] asparagus,[553] rice[554] and oats.[555] On the other hand, emphasis in related work has been placed on targetting specific weeds for elimination.[556-564] In this connection plant physiologists have been chiefly concerned with obtaining data on the complex effects of triazine herbicides on nitrite accumulation,[565] phytotoxicity,[566] photosynthetic reactions[567] and metabolic drifts during flowering.[568] Several papers have appeared on technical improvements in preparation and application methods for the herbicide mixtures.[569-573] The concerted search for new and specific herbicides has given rise to several noncondensed aromatic triazinones, largely synthesized by the cyclocondensation method,[574-581] and attendant experiments have attempted to probe the particular results of these in plan biochemical processes.[582-592] Tolerances have been established under the Food, Drug and Cosmetic Acts for

triazine herbicide residues in various crops,[593-597] and several articles have been put forth concerning their toxicology and environmental impact.[598-608] A number of interesting techniques have been applied to their detection and determination, including electrochemical,[609,610] conductometric[611] and crystallographic[612-616] methods. Although the area of greatest commercial development has been agrochemical, other significant industrial attention has been paid to the use of as-triazines as synthetic high polymers,[617-620] chemical coatings,[621] photographic fogging agents,[622-630] dyes[631] and intermediates in plastics manufacture.[632-652] Thus the iron content of wines may be obtained colorimetrically by use of 3-(2-pyridyl)-5,6-diphenyl-1,2,4-triazine.[653]

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