1,2,4-TRIAZINOINDOLES

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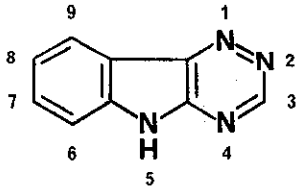
This article surveys the synthesis and chemistry of 1,2,4-triazinoindoles. Spectral data for several substituted 1,2,4-triazinoindoles are reported.

CONTENTS

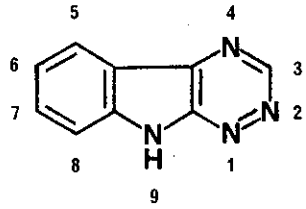
A. INTRODUCTION

The first synthesis of the 1,2,4-triazinoindole ring system was reported in 1927.[1] Although 1,2,4-triazinoindoles were considered of potential medicinal interest,[2,3] they were not intensively investigated until the late 1960's. The renewed interest in this ring system was spurred by the discovery of antiviral activity in a number of 3-substituted derivatives.

The triazine ring may be fused to the indole ring in two possible ways to afford either a 5,6-b or 6,5-b ring junction.



5H-1,2,4-Triazino[5,6-b]indole



9H-1,2,4-Triazino[6,5-b]indole

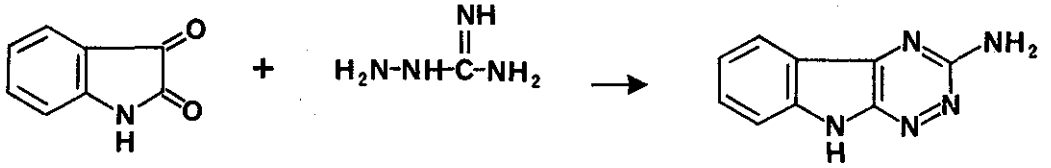
Although the cited names are in accordance with Chemical Abstracts nomenclature, a number of other names for these rings and their derivatives pervade the literature. They have been variously referred to as 5,6-isatotriazines, indotriazines, and 1,3,4-triazacarbazole. The prefix "as" (assymmetric) has also been used interchangeably with the numbers 1,2,4 to designate the position of the nitrogen atoms in the triazine ring. In this survey, the Chemical Ab-

stracts nomenclature will be used.

B. SYNTHESIS

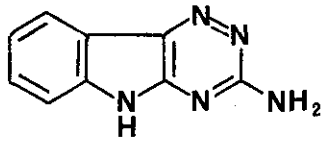
B.1 Synthesis of 1,2,4-Triazino[5,6-b]indoles

The first synthesis of triazinoindoles was reported by De[1] who treated aminoguanidine (1) with isatin to afford what was thought to be 3-amino-9H-1,2,4-triazino[6,5-b]indole (3). This reaction was later repeated by De and



2 1 3

Dutta[4] with substituted isatins to afford nitro and halogenated derivatives. Rajagopalan[2,3] also condensed aminoguanidine and isatin in boiling glacial acetic acid solution to afford what was reported to be 3-amino-1,2,4-indolotriazine (4). It was not until 1948 that King and Wright[5] established the correct structure for the isatin-aminoguanidine condensation product. King and Wright[5] also expressed doubt about the structure of the compounds, which were



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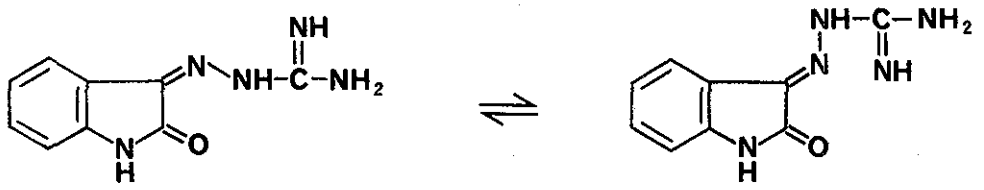
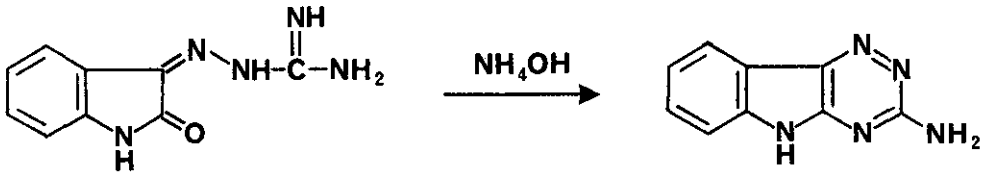
synthesized and tested by Rajagopalan.[2,3] According to King and Wright, Rajagopalan had, in fact, only obtained the initial condensation product, isatin-β-guanylhydrazone (5), which can exist in syn and anti forms.



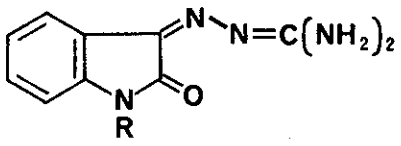
5 syn 5 anti

To accomplish the ring closure to the desired triazinoindole, King and Wright boiled the syn-β-guanylhydrazone with dilute ammonium hydroxide solution.



5 4

The aminoguanidine-isatin method was later used by Rossi and Trave[6] in the synthesis of fluorescent pigments (Cf. Section D). More recently, Tomchin and Ioffe[7] isolated the intermediate isatin-β-(syn and anti) hydrazones and proved that they existed in tautomeric forms (6) and (6a). The expected imino forms (7) and (7a) were not detected.



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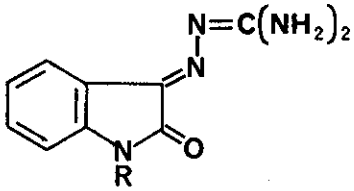
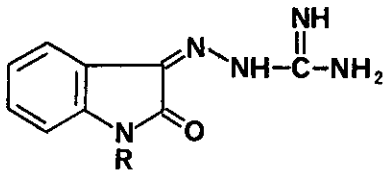


6a



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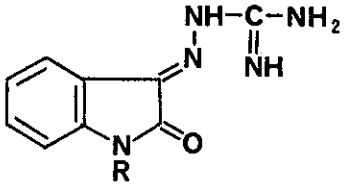
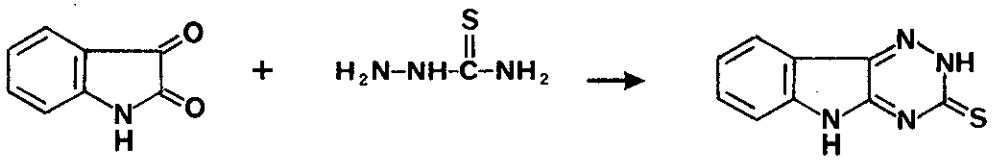


7a

A second, more general method for the synthesis of 1,2,4-triazinoindoles, first reported in the patent literature in 1965[8], involved the condensation of isatin with thiosemicarbazide (9) to afford 5H-[1,2,4]triazino[5,6-b]indole-3(2H)thione (10) in high yield. The isolation of the isatin-β-thiosemi-



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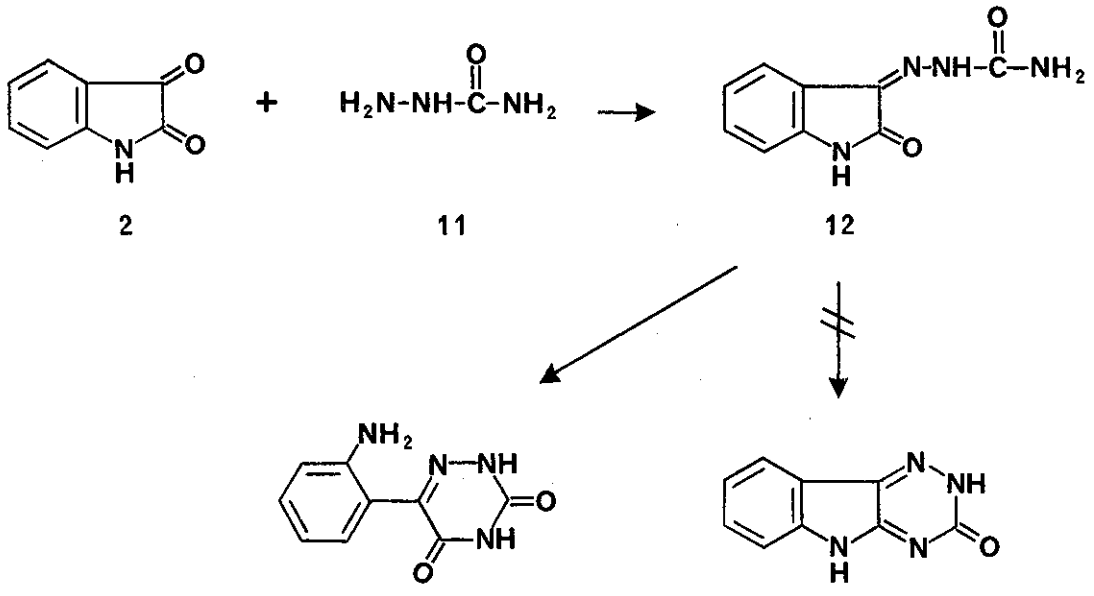
carbazone intermediate and the conditions for its cyclization were studied by Tomchin and Ioffe.[9] These workers concluded that ring closure occurs only in alkaline medium. This finding is consistent with the results of King and Wright[5] who were only able to cyclize isatin-β-guanylhydrazones in boiling ammonium hydroxide solution. This observation casts further doubt on the re-

sults obtained by Rajagopalan since this author used acetic acid as the cyclization agent.

The reaction of isatin with semicarbazide (11) afforded the expected oxygen analog, isatin-3-semicarbazone (12). This compound, however, did not cyclize to a 1,2,4-triazinoindole.

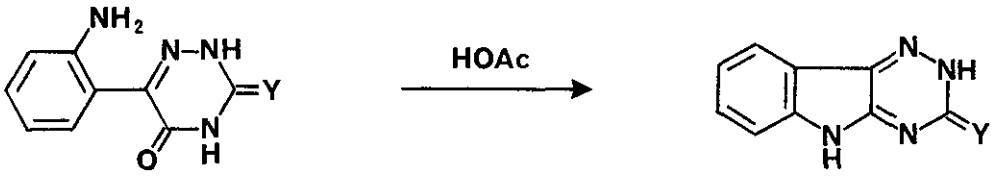


2 11 12

13a

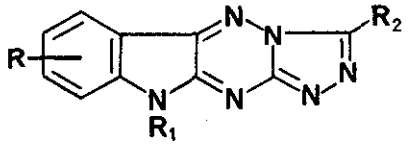
A compound identified as 6-(2-aminophenyl)-1,2,4-triazine-3,5(2H,4H)-dione (13a) was isolated instead.[10] Doleschall and Lempert[11], however, found that (13a) could be induced to undergo ring closure under a variety of conditions. They further established that 6-(2-aminophenyl)-3-thio-1,2,4-triazine-3,5(2H,4H)-dione (13b) could be cyclized in an acid medium. These authors synthesized several 1,2,4-triazinoindoles by this method using boiling acetic

acid or hydrochloric acid. Alternately, they found that ring closure could be effected in boiling dimethylformamide. Tomchin and Ioffe[12] later confirmed these findings by cyclizing 13a or the corresponding 3-thione (13b), respectively in acetic acid.



13a Y=O
13b Y=S

Less general synthetic methods have been used to prepare specific 1,2,4-triazino [5,6-b] indoles. Compounds with the general formula 14 were synthesized via the condensation of isatin with a 3,4-diamino-1,2,4-triazole.[13] Similarly, 1-amino-1,2-dihydro-1,3,4-triazacarbazole-2-thione (15) was prepared by treating isatin with 3-thiocarbazide.[14]



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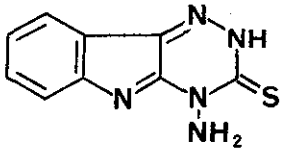

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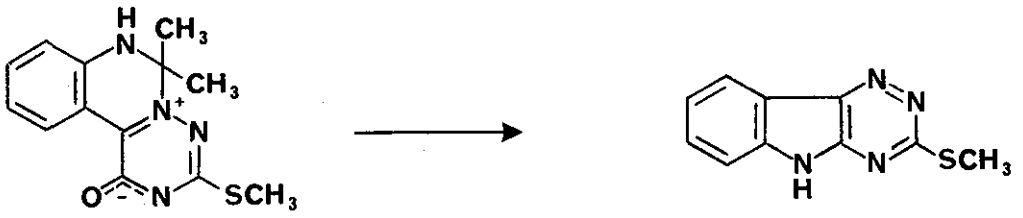
Finally, Doleschall and Lempert[15,16] found that thermolysis of compound 16 in boiling anhydrous DMF afforded the thiomethyl triazinoindole (17). Compound 16 presumably decomposes to acetone and 6-(2-aminophenyl)-3-thiomethyl-1,2,4-triazine-5-one which then cyclizes spontaneously under the conditions of

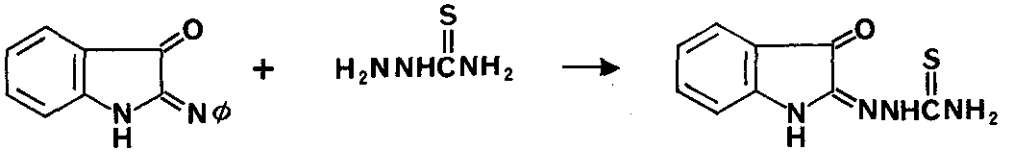
the reaction.



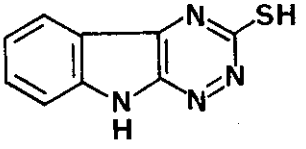
16 17

B.2 Synthesis of 1,2,4-triazino[6,5-b]indoles

The first synthesis of a 1,2,4-triazino[6,5-b]indole was reported by Tomchin, Ioffe, and Shirokii.[17] These workers reacted isatin-β-anil (18) with thiosemicarbazide and isolated isatin-β-thiosemicarbazone (19). The thiosemicarbazone could be cyclized to compound 20 by refluxing the reaction mixture with aqueous sodium hydroxide.

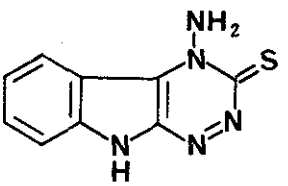


18 19



20

The 2- and 9-N-methyl derivatives were prepared using the appropriately substituted precursors. The oxygen analogs of (20) were synthesized by a similar procedure. The same authors also reported the reaction of isatin-β-anilide with excess 3-thiocarbazide to afford the corresponding 4-amino derivative (21).



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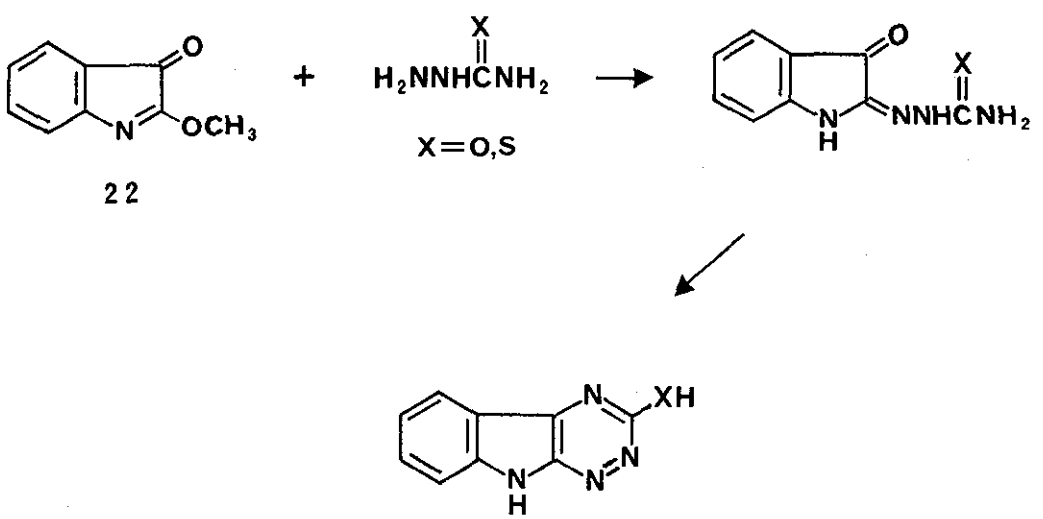
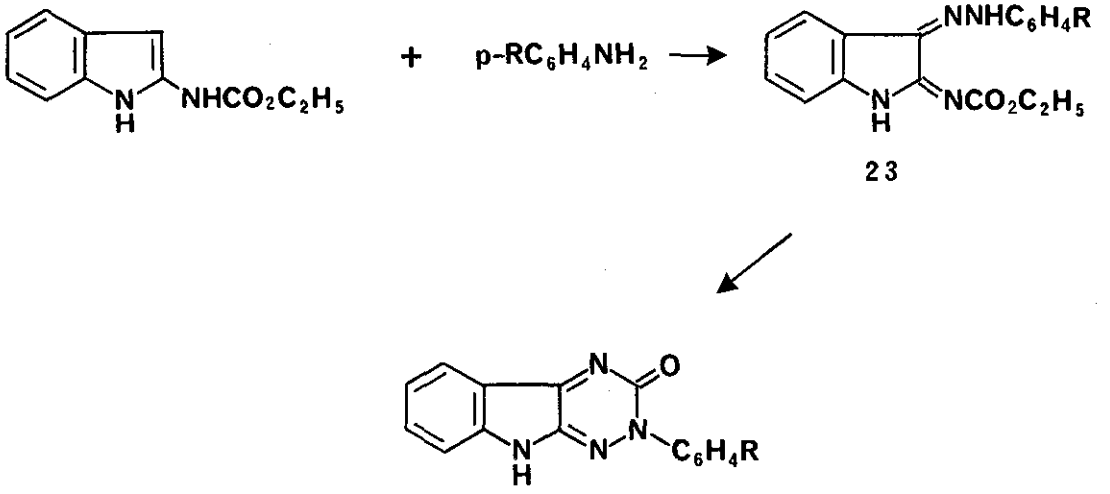
Dmitrukha and Pel'kis[18] prepared isatin-β-semicarbazone via the condensation of 22 with semicarbazide. Subsequent cyclization of the semicarbazone led to the corresponding triazinoindole. Similar results were obtained with thiosemicarbazide.[18]



22

More recently, Bell and Zalay[19] used the isatin-β-anilide-thiosemicarbazide method to prepare 1,2,4-triazino[6,5-b]indoles.

A new synthetic approach to this heterocycle was reported by Pec and Slouka[20] in 1975. The method involved the diazotization-coupling of a substituted aniline with 2-(ethoxycarbonylamino)indole to afford the hydrazone (23) which was subsequently cyclized to the desired ring system in boiling decalin.



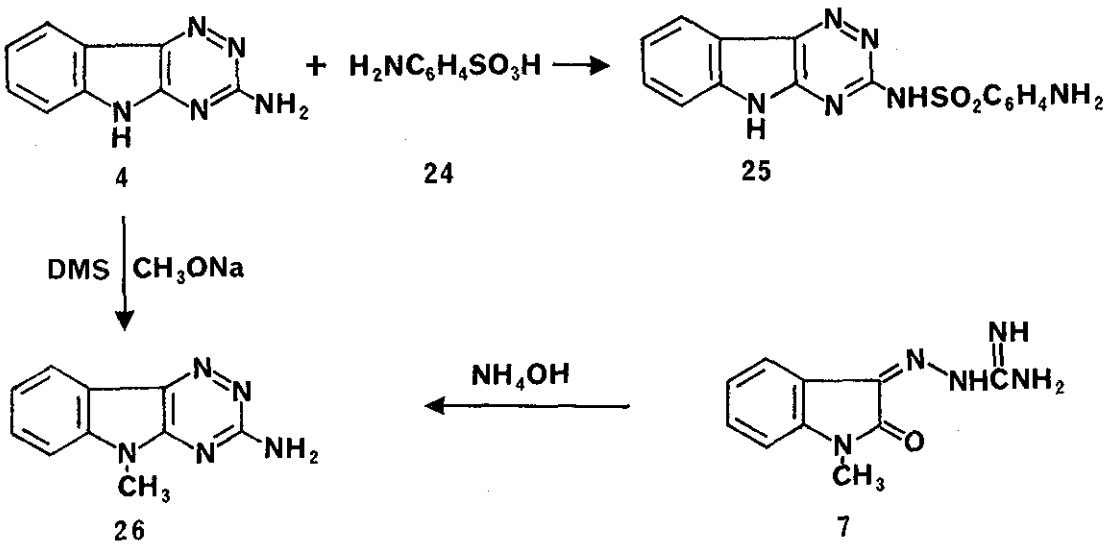
C. REACTIONS

C.1 Reactions of 1,2,4-Triazino[5,6-b]indoles

C.1.a Alkylation or Acylation at N, S or O

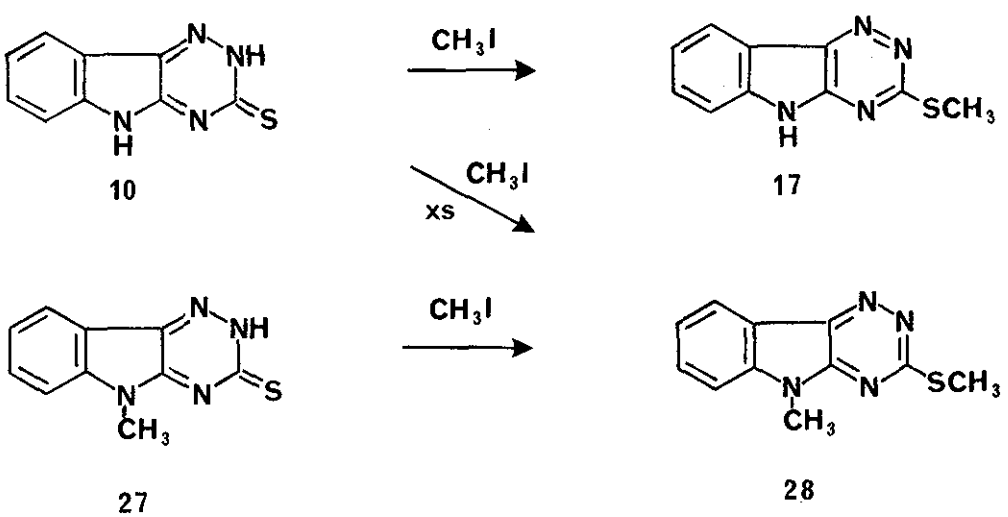
Rajagopalan[2,3] described the reaction of 4 with sulfanilic acid (24) to form 25 which he called 3-sulfanilamidoindotriazine. Since there is some doubt as to whether Rajagopalan was working with a triazinoindole or an intermediate isatin-β-guanylhydrazone, the structure of this product must also be in doubt. King and Wright[5] treated 4 with methyl sulfate in the presence of sodium methoxide and formed 26. This product was identical to the

product obtained by cyclizing N-methylisatin syn-β-guanylhydrazone (7).



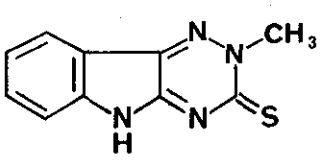
4 24 25 26 7

Tomchin and Ioffe[21] studied the alkylations of the 3-sulfur derivatives. The methylation of 10 using one mole of methyl iodide produced only one product 17, the 3-thiomethyl derivative. However, when excess methyl iodide was used, alkylation also occurred at the 5-nitrogen. Methylation of compound 27 (obtained by the cyclization of N-methylisatin-β-thiosemicarbazone) afforded the same product 28.



10 17 27 28

When 29 was heated with an excess of methyl iodide in alkaline media, the evolution of methanethiol was noted.[22] To explain this phenomenon, Ioffe and Tomchin assumed that methylation had proceeded as expected at the 3-thione group to afford 30 but that this compound was rapidly hydrolyzed to 31. The same authors treated 10 with chloroacetic acid and isolated only one product, 32, again supporting the preferential alkylation at sulfur.[23] The tendency of the 3-thiotriazinoindoles to alkylate first on the sulfur atom and then at the 5-nitrogen was verified by Gladych et al,[24] in reactions carried out in dimethylformamide with sodium hydride.



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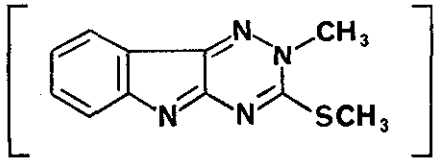

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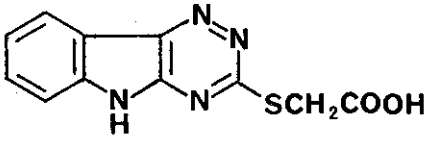
NaOH



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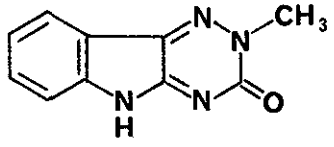
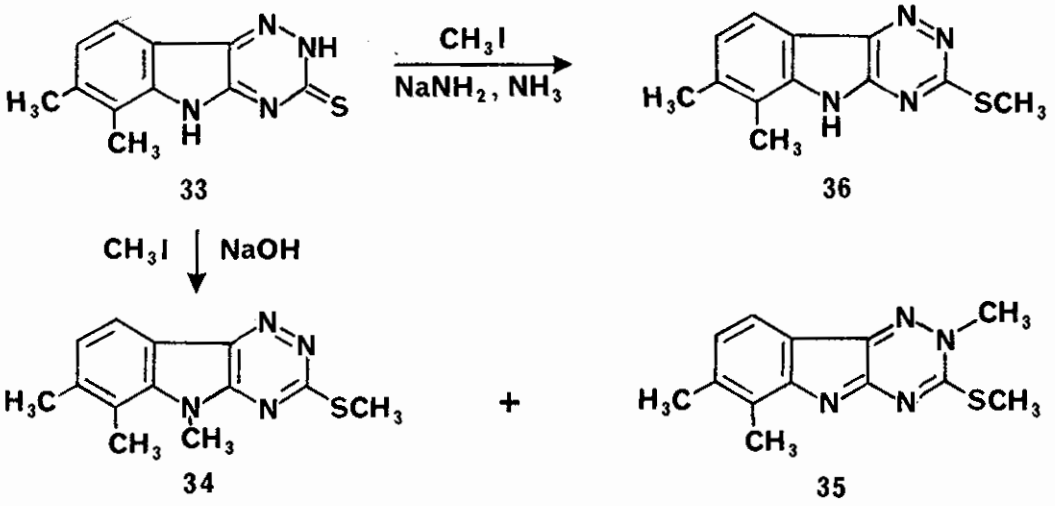


31

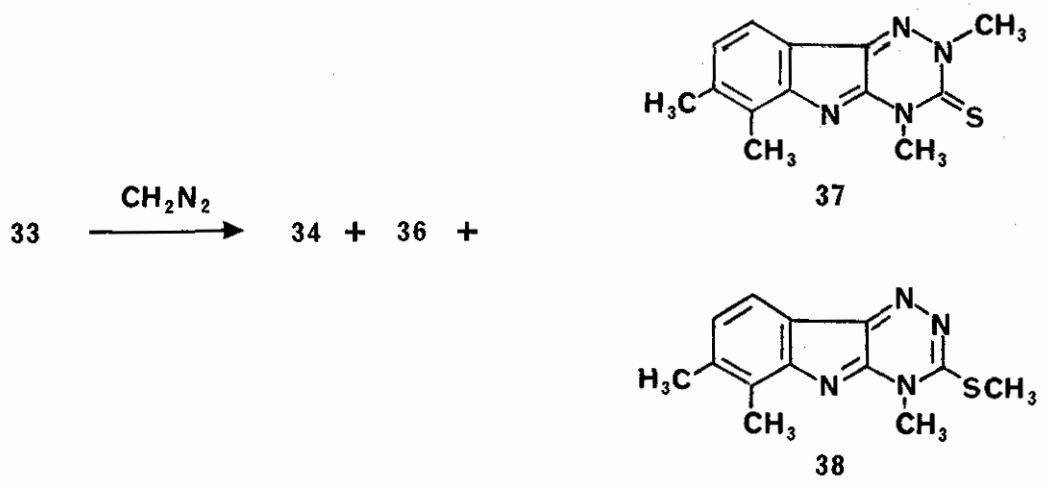
The alkylation of 6,7-dimethyl-5H-1,2,4-triazino[5,6-b]indole-3(2H)-thione (33) was studied extensively by Romanchick and Joullie.[25] Methylation of 33 with methyl iodide in either aqueous sodium hydroxide or sodium ethoxide solution led to the formation of two isomers, 34 and 35, while the action of methyl iodide in sodamide/liquid ammonia led to the formation of 36 in quantitative yield.



33 36

34 35

When 33 was reacted with diazomethane in ether/dioxane, four products, 34, 36, 37, and 38 were obtained in 26%, 23%, 22%, and 29% yields, respectively.



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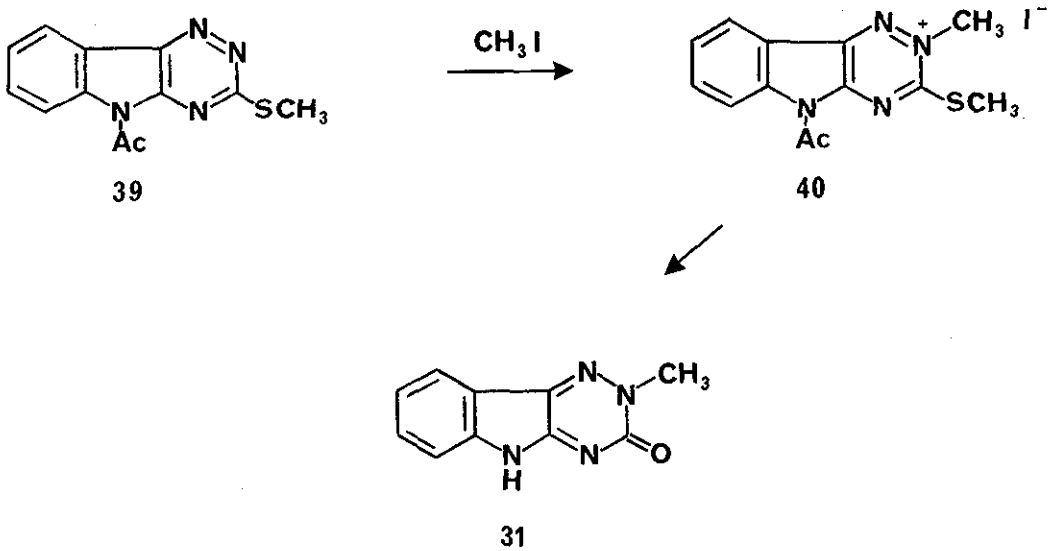
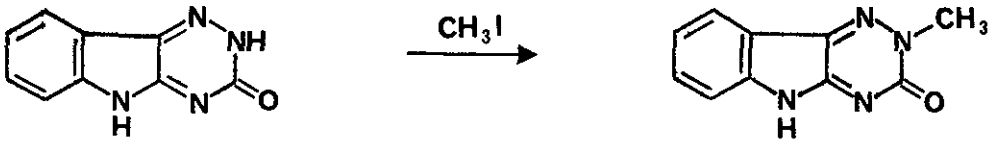
38

An interesting aspect of this work was the analysis of the alkylation results using the HSAB (hard-soft-acids-bases) Principle proposed by Pearson.[26] Under soft conditions the soft, highly polarizable sulfur alkylates first while under hard conditions nitrogen is the more favorable site for alkylation.

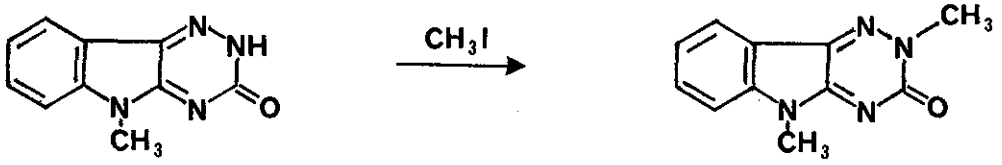
Doleschall and Lempert[27] found that triazinoindoles could form quaternary ammonium salts when refluxed with excess methyl iodide in nitromethane as illustrated by the formation of (40). Subsequent hydrolysis of 40 affords 31.



The alkylation of 3-oxygen analogs was studied by Tomchin and Ioffe.[22] Unlike the 3-thione derivatives, the 3-oxo compounds alkylate only at nitrogen in an alkaline medium. Thus, the methylation of 41 in sodium hydroxide gives 31 while 42 affords 43 under the same conditions.

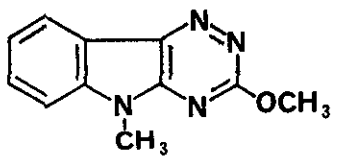


41 31



42 43

The methylation of the sodium salt of 42 in benzene affords only one product 43, while the silver salt yields a mixture of 43, 44 and 45 under the same conditions.



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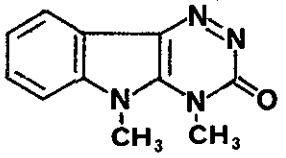

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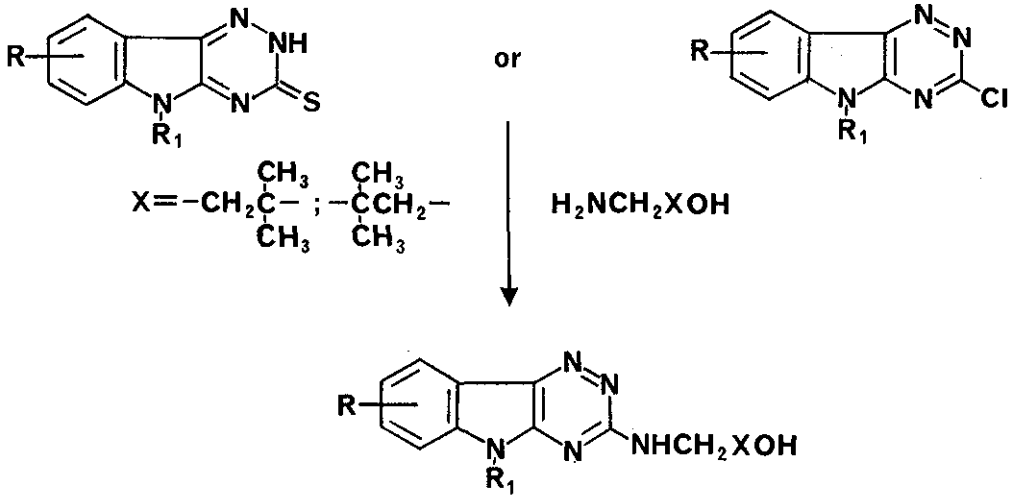
C.1.b. Displacement Reactions at the 3-Position

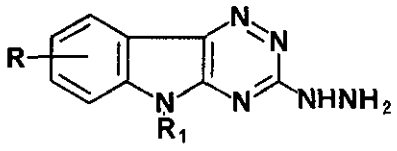
The displacement of substituents at the 3-position of the triazinoindole ring system has proven to be a valuable method of introducing

important side chains. In many cases, the pharmacological activity of a compound depends on the number of carbons in these side chains or the functional groups they possess. Therefore, displacement reactions at the 3-position are of great practical interest.

Amines and amine derivatives have been found to effect displacements at the 3-position under a variety of conditions. Aminoalcohols, for example, were used by chemists at Smith Kline and French to displace 3-thio, 3-thiomethyl or 3-chloro groups in syntheses of antiviral compounds.[28,29] They also used amino-alkylnitriles to synthesize the corresponding

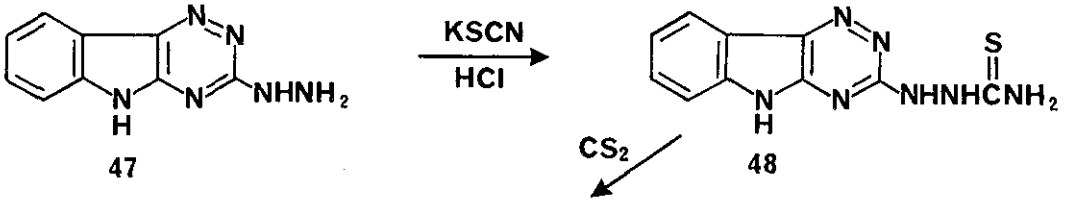


carboxylic acids.[30] A recent article by these authors describes the synthesis of sixty-four substituted 5H-[1,2,4]triazino[5,6,-b]indoles by this route. Displacement reactions by alkyl amines were also reported by chemists at Allen and Hanburys, Ltd.[31, 32, 33] The displacement of the 3-thio or 3-thiomethyl groups on triazinoindoles with hydrazine was reported by several workers.[33,34,35] The products 46 were tested for a broad spectrum of pharmacological activity.

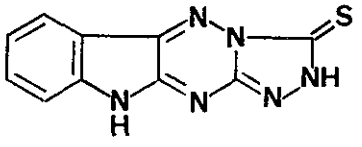


46

Tomchin, Ioffe and Zhukova[35] found that treatment of 47 with potassium thiocyanate and hydrochloric acid gave 48 which could be cyclized in carbon disulfide to 3-mercapto-s-triazolo[4'3':2,3]-as-triazino [5,6-b]indole (49).

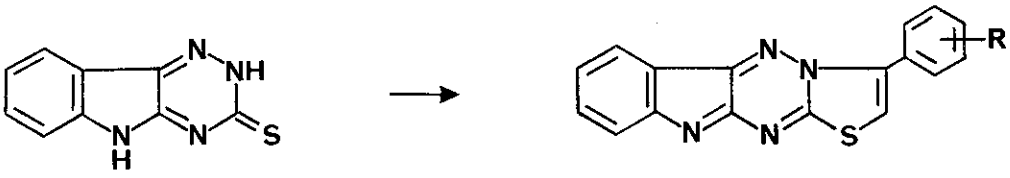


47 48



49

Dhaka et al[36] recently reported the synthesis of a number of mercapto derivatives. Triazinoindolethione (10) was condensed with α-haloketones and the resultant product then cyclized to give thiazolotriazinoindoles (50). Compound 10 was also treated with chloroacetic acid, and the product cyclodehydrated to give 51(X=O). A similar reaction with 1,2-dibromoethane afforded 52(X=H_2). When 10 was treated with 2,3-dichloroquinoxaline, compound 53, a quinoxalinotriazinoindole, was formed.



10

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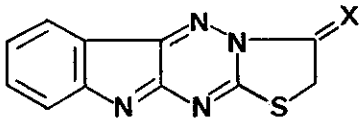
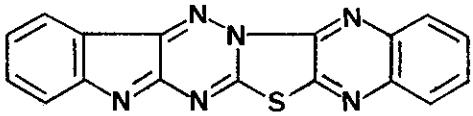


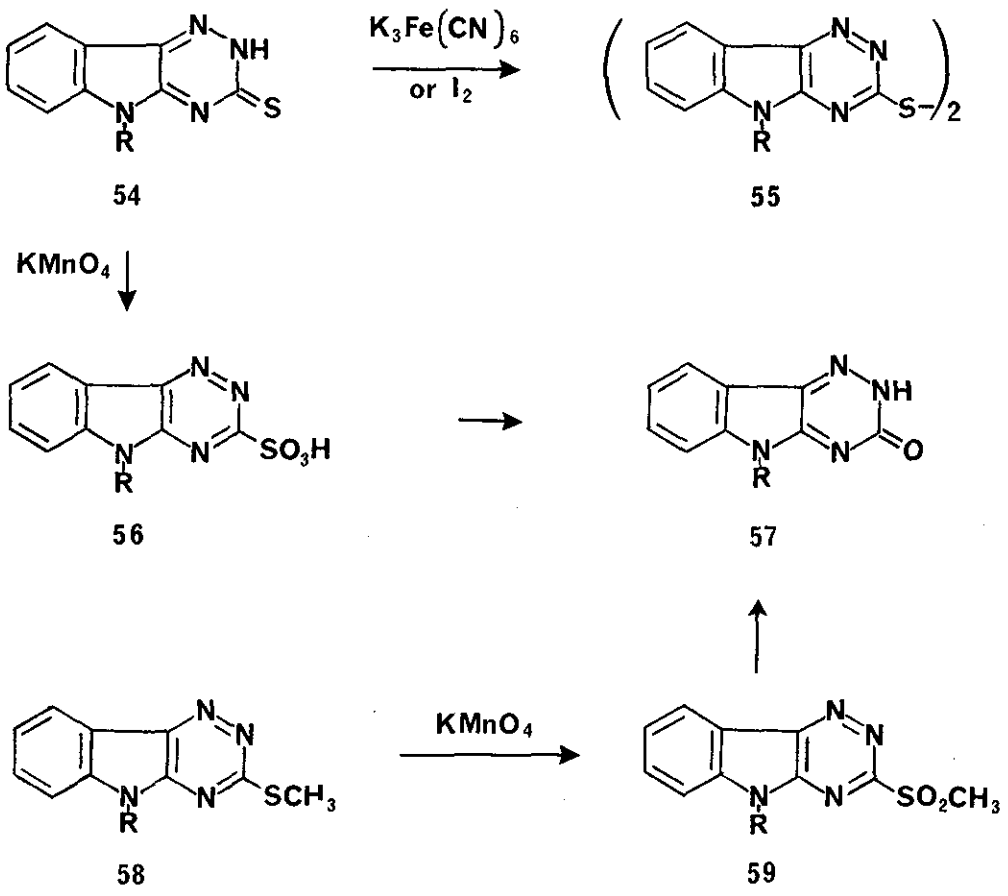
51 X=O
52 X=H_2



53

C.1.c Oxidation Reactions

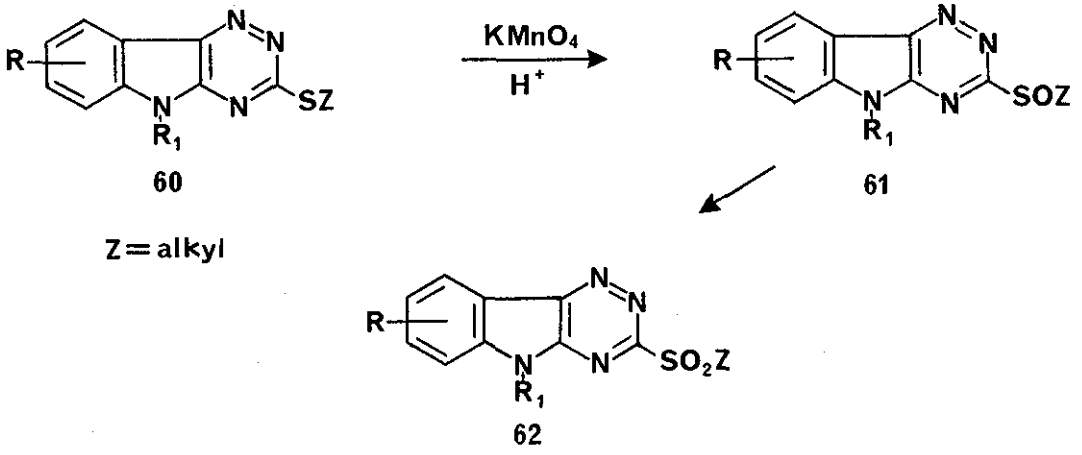
Tomchin and Ioffe[9] found that the 1,2,4-triazino[5,6-b]indole-thiones (54) could be oxidized with iodine or potassium ferricyanide to the corresponding disulfide (55). Further investigations by the same authors indicated that the reaction of 54 with basic potassium permanganate affords the oxygen analog (57), via the intermediate sulfonic acid (56). Similarly, the thiomethyl derivative (58), under the same conditions, yields 57 via the sulfone (59).



54 55 56 57 58 59

Investigators at Smith Kline and French[30] completed the conversion of 54 to 57 using either hydrogen peroxide or chloroacetic acid.

Oxidation of thioalkyl derivatives (60) with acidic potassium permanganate solution on the thio-alkyl derivatives (60) was reported by investigators at Allen and Hanburys, Ltd.[37] Under these conditions, both the sulfoxide (62) and the sulfone (61) could be isolated.

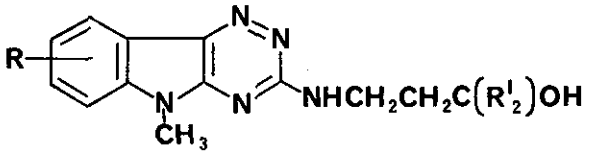


C.2 Reactions of 1,2,4-Triazino [6,5-b] indoles

The reactions of the 1,2,4-triazino[6,5-b]indoles were studied by Bell and Zalay,[19] Tomchin and Ioffe,[17,38,39] and Dmitrukha and Pel'kis[18] and, in all cases, were found to be similar to those of the [5,6-b] ring system.

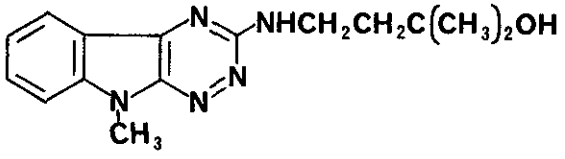
D. USES OF 1,2,4-TRIAZINOINDOLES

Recent studies of 1,2,4-triazinoindoles were promoted by their antiviral activity. Investigators at Smith Kline and French[28-30,40-47] and at Allen and Hanburys, Ltd.[13,24,31-33,37,40] have synthesized and tested hundreds of substituted 1,2,4-triazinoindoles in their search for antiviral agents. Their findings indicate that compounds with the general formula 63 have the greatest overall antiviral activity. Compound 63 (R=H,R'=Me) inhibited rhinovirus, herpes simplex, pseudorabies, vaccinia, Semliki Forest, picorna virus and various DNA viruses when tested in vitro.[42] This substance also showed promising results against a variety of mouse infections and rhinovirus respiratory infection in chimpanzees. It is currently being tested in man. The activity of this triazinoindole is apparently due to a specific inhibition of viral RNA synthesis.[46]



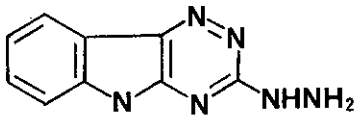
63

The broad range of antiviral activity exhibited by 1,2,4-triazino[5,6-b]-indoles prompted Bell and Zalay[19] to synthesize and evaluate the [6,5-b] analogs. These authors reported that compound 64 showed considerably more activity against Rhino 2 virus than the [5,6-b] analog.



64

Triazinoindoles had also been tested earlier as potential bacteriocides by Jeney and Zsolnai.[49] More recently, Tomchin et al[50] have tested these compounds for analgesic properties. Dhaka et al[36] found (50) to be an effective fungicide against Aspergillus Fumigatus, while chemists at Warner-Lambert discovered that triazinoindoles, particularly 3-hydrazino-5-substituted 1,2,4-triazino[5,6-b]indoles,(46) [34] had considerable promise as an antihypertensive.



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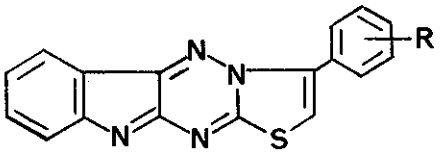

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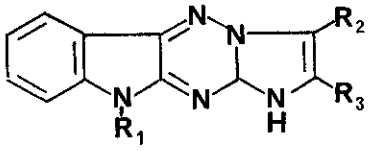
One non-pharmacological use of triazinoindoles was reported by Rossi and Trave[6] in 1958. They found compounds of the general formula 65 to be useful as fluorescent paint pigments.



65

E. SPECTRA

E.1 Ultraviolet Spectra

The data recorded from the ultraviolet spectra of various triazino-[5,6-b]indoles are presented in Table 1.[25] All samples were run in 95% ethanol with λ_{max} measured in nanometers (nm) and the extinction coefficients shown as log ε. All compounds possessing the C=S chromophore show strong bands in the region 290-308 nm. The ring absorptions vary with substitution and are more difficult to assign.

E.2 Infrared Spectra

The infrared data reported by Romanchick and Joullie[25] are representative of this class of compounds. The NH absorption was observed for various derivatives between 2900-3450 cm^{-1}. Double bond vibrations for C=N and C=C appear in the region 1590-1630 cm^{-1}. Other bands depend on the substitution of the various derivatives.

E.3 Nuclear Magnetic Resonance Spectra

Nuclear magnetic resonance data for 1,2,4-triazinoindoles are rather scarce in the literature. The spectra of a series of 6,7-dimethyl derivatives are shown in Table 2. This data was instrumental in the identification of methylated isomers.

TABLE 1

ULTRAVIOLET SPECTRA OF 1,2,4-TRIAZINOINDOLES

Compound	λ_{max} nm(log ε) taken in 95% EtOH
33	236(3.52), 260(3.48) and 306(4.22)
34	232(4.15), 272(4.43) and 354(3.89)
35	232(4.03), 278(4.56) and 336 (3.70)
36	230(4.17), 270(4.47) and 352(3.93)
37	248(3.83), 262(4.09), 290(4.49) and 382(3.92)
38	266(4.37) and 364(4.06)

TABLE 2

PROTON MAGNETIC RESONANCE SPECTRA OF 1,2,4-INDOLOTRIAZINES (δ, ppm)

Compound	Aromatic Methyl	SCH_3	NCH_3	Aromatic Protons	Solvent
33	2.1(6H,s)			7.00 and 7.13(1H,d)	CF_3COOH
34	2.40(3H,s) 2.54(3H,s)	2.69(3H,s)	3.89(3H,s)	7.04 and 7.17(1H,d) 7.93 and 8.06(1H,d)	$CDCl_3$
35	2.45(3H,s) 2.62(3H,s)	2.75(3H,s)	4.04(3H,s)	7.04 and 7.17(1H,d) 7.72 and 7.85(1H,d)	$CDCl_3$
36	2.33(6H,s)	2.67(3H,s)		7.25 and 7.38(1H,d) 7.85 and 7.98(1H,d)	CF_3COOH
37	2.30(6H,s)		4.10(3H,s) 4.22(3H,s)	7.25 and 7.38(1H,d) 7.73 and 7.86(1H,d)	CF_3COOH
38	2.45(3H,s) 2.53(3H,s)	2.84(3H,s)	3.98(3H,s)	7.09 and 7.22(1H,d) 7.92 and 8.05(1H,d)	$CDCl_3$

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