[CONTRIBUTION FROM THE R. B. WETHERILL LABORATORY OF CHEMISTRY, PURDUE UNIVERSITY]

Synthesis and Spectra of a Matched Series of 1,5-Disubstituted Tetrazoles

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The 1-methyl-5-(*o*-chlorophenyl)-, -5-(*m*-chlorophenyl)-, and -5-(*p*-chlorophenyl)tetrazoles as well as 1-(*o*-chlorophenyl)-, 1-(*m*-chlorophenyl)-, and 1-(*p*-chlorophenyl)-5-methyltetrazoles have been synthesized from the corresponding benzamides and acetanilides, respectively. Ultraviolet spectra of the tetrazoles are compared with those of the parent amides. Evidence is presented to support the first order interaction of the tetrazole ring with an aromatic substituent in the 5- position and the second order interaction of the tetrazole ring with an aromatic substituent in the 1-position. Infrared bands at 9.12–9.20μ and 10.05–10.25μ are assigned to the tetrazole ring system.

There have been several reports of the ultraviolet absorption spectra of tetrazoles which have a bare or substituted benzene ring attached to the 1-nitrogen or 5-carbon of the tetrazole ring. Garbrecht and Herbst[4] reported that 5-phenyltetrazole displays a λ_{max} 2400 Å with a log ϵ_{max} 4.16 and that 1-phenyl-5-methyltetrazole has a λ_{max} 2200Å with a log ϵ_{max} 3.85.[5,6] They state that a phenyl group in the 5 position gives rise to an absorption in the range of 2320–2400 Å, and that a phenyl in the 1-position appears to be without effect on the basic absorption characteristics of the tetrazole ring. Murphy and Picard[7] reported the spectra of 1-(3-nitrophenyl)-5-aminotetrazole, λ_{max} 2250 Å, log ϵ_{max} 4.07, and 1-(3-methylphenyl)-5-aminotetrazole, λ_{max} 2280 Å, log ϵ_{max} 4.15. The initial report of ultraviolet spectra characteristics of tetrazoles was by Elpern and Nachod[8]; they concluded that the tetrazole ring had little or no absorption itself in the usual ultraviolet region. They compared 1-cyclohexyltetrazole, no absorption above 2050 Å, with 1-phenyltetrazole, absorption from 2200 to 2500 Å. They also report the absorption of 1-methyl-5-phenyltetrazole, λ_{max} 2320 Å and log ϵ_{max} 4.02. This is in contrast to a report by Benson[9] that 1-(3′,4′-dimethylphenyl)-5-methyltetrazole showed a λ_{max} 2310 Å with a log ϵ_{max} 3.85. On the basis of these reports it appeared possible to prove the interaction or lack of interaction of the tetrazole ring with an aromatic substituent either at the 1- or 5- position of the tetrazole ring by the choice of proper systems.

This paper reports the synthesis of two series of 1,5-disubstituted tetrazoles wherein the interaction of an *ortho*, *meta*, and *para* chlorophenyl with the tetrazole ring could be shown when the aromatic substituent was first in the 1- position on the tetrazole ring, and second, when the aromatic substituent was in the 5- position, the carbon, of the tetrazole ring. The balancing substituent, usually without effect on the ultraviolet spectra, was chosen as the methyl group. The known *o*-chloro-, *m*-chloro, and *p*-chloroanilines were converted to the corresponding acetyl derivatives; the known *o*-chloro-, *m*-chloro-, and *p*-chlorobenzoic acids were converted to their corresponding *N*-methyl amides by way of the acid chlorides (Table I). Both sets of amides were studied in the ultraviolet and infrared regions. The amides were converted to the corresponding 1,5-disubstituted tetrazoles by way of the imino chlorides (not isolated) and subsequent *in situ* treatment with a benzene solution of hydrazoic acid.[10–12] The tetrazoles were carefully purified both by recrystallization and removal of the contaminating amides by hydrolysis of the latter in boiling 10% sulfuric acid (Table II). The pure

TABLE I

N-SUBSTITUTED AMIDES

R_1CONHR_2

Substituent			M.P	
R_1	R_2	Yield, %	Found	Reported
o-ClC_6H_4	CH_3	72	119–120	121.5[a]
m-ClC_6H_4	CH_3	72	71–73	75.0[a]
p-ClC_6H_4	CH_3	65	158–159	161[a]
CH_3	*o*-ClC_6H_4	64	87–88	86.7[b]
CH_3	*m*-ClC_6H_4	41	77–78	76.6[b]
CH_3	*p*-ClC_6H_4	79	178–179	178.4[b]

[a] P. J. Montagne, *Rec. trav. chim.*, **19**, 46 (1900). [b] N. V. Sidgwick and H. E. Rubie, *J. Chem. Soc.*, **119**, 1013 (1921).

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(4) W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1275 (1953).

(5) Ultraviolet wave lengths are reported in Angstroms (Å) because the differences in λ_{max} between compounds and between series are more clearly shown by this representation. The significance of the last figure is admittedly doubtful.

(6) G. W. Wheland "Resonance in Organic Chemistry," J. Wiley & Sons, Inc., New York, 1955, p. 245.

(7) D. B. Murphy and J. P. Picard, *J. Org. Chem.*, **19**, 1908 (1954).

(8) B. Elpern and F. C. Nachod, *J. Am. Chem. Soc.*, **72**, 3379 (1950).

(9) F. Benson, L. W. Hartzel, and W. L. Savill, *J. Am. Chem. Soc.*, **73**, 4457 (1951).

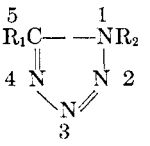
(10) J. von Braun and W. Rudolph, *Ber.*, **74**, 264 (1941).

(11) E. K. Harvill, R. M. Herbst, E. C. Schreiner, and C. W. Roberts, *J. Org. Chem.*, **15**, 662 (1950).

(12) R. M. Herbst, C. W. Roberts, H. T. F. Givens and E. K. Harvill, *J. Org. Chem.*, **17**, 262 (1952).

TABLE II

1,5-DISUBSTITUTED TETRAZOLES



Substituents		Yield,		Percentage Composition					
				Carbon		Hydrogen		Nitrogen	
R_1	R_2	%	M.P.	Calcd.	Found	Calcd.	Found	Calcd.	Found
o-ClC_6H_4	CH_3	27	69–70	49.36	49.71	3.63	3.57	28.79	28.51
m-ClC_6H_4	CH_3	79	86–88	49.36	49.29	3.63	3.65	28.79	28.98
p-ClC_6H_4	CH_3	31	119–120	49.36	49.70	3.63	3.84	28.79	28.60
CH_3	*o*-ClC_6H_4	55	80.5–82	49.36	49.55	3.63	3.95	28.79	28.76
CH_3	*m*-ClC_6H_4	73	98.5–99	49.36	49.61	3.63	3.90	28.79	28.65
CH_3	*p*-ClC_6H_4	72	86–88	49.36	49.61	3.63	3.75	28.79	28.86

TABLE III

ULTRAVIOLET ABSORPTION *B* BANDS OF *N*-SUBSTITUTED AMIDES AND DERIVED 1,5-DISUBSTITUTED TETRAZOLES

Substituents		Amides[a]		Tetrazoles[a]	
C or 5	N or 1	λ_{max} Å	log ϵ_{max}	λ_{max} Å	log ϵ_{max}
o-ClC_6H_4	CH_3	2300	3.95	2250	3.96
m-ClC_6H_4	CH_3	2320	3.99	2350	4.03
p-ClC_6H_4	CH_3	2360	4.11	2410	4.20
CH_3	*o*-ClC_6H_4	2400[b]	4.02	2220	4.01
CH_3	*m*-ClC_6H_4	2450[c]	4.19	2260	4.11
CH_3	*p*-ClC_6H_4	2490[d]	4.25	2290	4.07

[a] In 95% ethanol. [b] Reference 18 reports λ_{max} 2400 Å, log ϵ_{max} 4.02 for o-chloroacetanilide. [c] Reference 18 reports λ_{max} 2450 D, log ϵ_{max} 4.18 for *m*-chloroacetanilide. [d] Reference 18 reports λ_{max} 2490 Å, log ϵ_{max} 4.25 for *p*-chloroacetanilide.

tetrazoles from each series were studied in the ultraviolet and infrared regions (Tables III and IV).

Ultraviolet spectra. For the purpose of discussion, the ultraviolet spectra of the amides and corresponding tetrazoles are separated into the compounds belonging to each class of substituted tetrazoles. Thus, the results for the chloroacetanilides and their 1-chlorophenyl-5-methyltetrazoles will be considered apart from the *N*-methylchlorobenzamides and the 1-methyl-5-chlorophenyltetrazoles.

1-Chlorophenyl-5-methyltetrazoles. Perhaps the most informative area of the ultraviolet spectrum for consideration of the interaction of an aromatic substituent with either an unshared pair of electrons or an unsaturated system is that classified by Moser and Konlenberg[13] as the B band of benzene and substituted benzenes. This is also called the "first primary band" and is usually centered about the 2300 Å. region.[14–16] The parent chloroanilines show spectra peaks in the B band region at 2380 Å (log ϵ_{max} 3.98) for the *o*-chloroaniline, 2400 Å (log ϵ_{max} 3.87) for the *m*-chloroaniline, and 2440 Å (log ϵ_{max} 3.95) for the *p*-chloroaniline.[17] The derived acetanilides show peaks in the B band region at 2400 Å (log ϵ_{max} 4.02) for the *o*-chloroacetanilide, 2450 Å (log ϵ_{max} 4.19) for the *m*-chloroacetanilide, and 2490 Å (log ϵ_{max} 4.25) for the *p*-chloroacetanilide.[18] A comparison of these data indicates that the acetylation of the amino group introduces an electron withdrawing moiety, decreasing the availability of the unshared electron pair on the nitrogen for interaction with the pi electrons of the benzene ring during a N→V transition,[19] but increasing the ease of the transition to the first excited state with the resonance form derivable from the spreading out of a negative charge on the acetamino moiety. This is evidenced by the slight, but real, bathochromic and hyperchromic shifts. When the anilides are converted to the corresponding 1-chlorophenyl-5-methyltetrazoles (see Table III) large hypsochromic effects with only moderate hypochromic effects are observed. This is to be compared with the fundamental absorption of the parent aromatic structures; if chlorobenzene, λ_{max} 2095 Å (log ϵ_{max} 3.87)[16] is compared with *o*-chlorodimethylaniline, λ_{max} 2550 Å (log ϵ_{max} 3.88)[20] it can be seen that the interaction of the tetrazole ring through the 1-nitrogen with the aromatic system is less than might be expected. It may also be noted, however, that there is not an absence of interaction. That there is some interaction either by the tetrazole ring itself or by the unshared pair of electrons on the 1-nitrogen is evidenced by the higher wave

(13) C. M. Moser and A. I. Kohlenberg, *J. Chem. Soc.*, 804 (1951).
(14) L. Daub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **69**, 2714 (1947).
(15) W. F. Forbes and W. A. Mueller, *Can. J. Chem.*, **33**, 1145 (1955).
(16) W. F. Forbes and A. S. Ralph, *Can. J. Chem.*, **34**, 1447 (1956).
(17) P. Grammaticakis, *Bull. soc. chim. France*, 534 (1951).
(18) H. Ungnade, *J. Am. Chem. Soc.*, **76**, 5133 (1954).
(19) Ref. 6, pp. 278–282.
(20) H. B. Klevens and J. R. Platt, *J. Am. Chem. Soc.*, **71**, 1714 (1949).

length of B band absorption in these tetrazoles or substituted chlorobenzenes than is found in dichlorobenzene itself.[21] It should also be noted that the tetrazole ring is effectively hypsochromic when compared to the dimethylamino group, it being postulated that the long unshared pair on nitrogen, in both series, should be nearly equivalently available for resonance interaction with the aromatic system. The apparent unavailability of these electrons for resonance interaction does not, however, appear to have the same effect on the intensity of the B band absorption at these lower wave lengths.

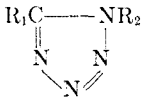
1-Methyl-5-chlorophenyltetrazoles. In the case of the three 1-methyl-5-chlorophenyltetrazoles there appears to be a greater interaction of either the tetrazole ring itself or the pi electrons of the –C=N– portion of the tetrazole ring with the aromatic substituent in the 5-position. Chlorobenzene with a λ_{max} 2095 Å (log ϵ_{max} 3.87) has its B band shifted to higher wave lengths by a number of *para*-substituents. Daub and Vandenbelt[14] report *p*-chlorobenzonitrile (λ_{max} 2375 Å; log ϵ_{max} 4.28) and *p*-chlorobenzoic acid (λ_{max} 2410 Å; log ϵ_{max} 4.21); both of these compounds have groups which possess electronic structures capable of entering into resonance interaction with the benzene ring, and hence, they produce bathochromic as well as hyperchromic effects. The interaction of the carbonyl bond pi electrons in the excited state obtains even when the *N*-methyl amide is formed (λ_{max} 2360 Å log ϵ_{max} 4.11) from the acid, although there is a slight hypsochromic effect.[22] On going from the *N*-methyl-*p*-chlorobenzamide to the corresponding 1-methyl-5-*p*-chlorophenyltetrazole there is a definite bathochromic effect of some 50 Å and a hyperchromic effect of some 3.47 log units. This contrasts with the hypsochromic effect of some 200 Å and a hypochromic shift of some 3.79 log units when the spectrum of the *p*-chloroacetanilide is compared with that of the corresponding 1-*p*-chlorophenyl-5-methyltetrazole.

The evidence presented appears to indicate that the tetrazole ring may interact with an aromatic moiety when the tetrazole ring is substituted by the aromatic moiety in the 5-position. The interaction when the aromatic moiety is in the 1-position appears to be less than the former case and in the compounds studied a second order effect. These conclusions support the results described by Garbrecht and Herbst.[4]

Infrared spectra. Infrared spectra were obtained on both series of amides and the derived tetrazoles. Lieber and co-workers report an extensive series of spectra of tetrazoles.[23] Tetrazole itself was assigned an absorption associated with the ring modes at 9.44 μ; 5-bromotetrazole, 9.36μ; 5-hydrazinotetrazole, 9.43μ and 10.09μ; and 5-aminotetrazole, 9.40μ and 10.04μ. Comparison of the spectra of the amides and tetrazoles of this report are in Table IV. The bands which are absent in the amides but which show up in the tetrazoles are indicated.

TABLE IV

INFRARED ABSORPTION PEAKS ASSIGNED TO THE 1,5-DISUBSTITUTED TETRAZOLES. PEAKS NOT PRESENT IN PARENT AMIDES



Substituents		Absorption Maxima In Microns[a] Nujol Mull			
R_1	R_2				
o-ClC_6H_4	CH_3	*8.35*	9.19	10.27	...
m-ClC_6H_4	CH_3	*8.35*	9.14	10.13	...
p-ClC_6H_4	CH_3	*8.33*	9.15	10.25	...
CH_3	*o*-ClC_6H_4	..	9.17	10.08	13.97
CH_3	*m*-ClC_6H_4	..	9.13	10.15	*13.98*
CH_3	*p*-ClC_6H_4	..	9.14	10.17	*14.05*

[a] The bands in *italics* are those which appear unique to the tetrazoles but which are not unassignable to other structures which were masked in the amides.

EXPERIMENTAL[24]

Acetanilides. The *o*-chloro-, *m*-chloro-, and *p*-chloroacetanilides were prepared in a standard fashion from the chloroanilines and acetic anhydride.[11]

N-Methylbenzamides. The *N*-methyl-*o*-chloro-, *N*-methyl-*m*-chloro-, and *N*-methyl-*p*-chlorobenzamides were prepared from the corresponding acid chlorides, distilled under reduced pressure,[25] and methylamine. The known acetanilides and benzamides are in Table I.

1,5-Disubstituted tetrazoles. Both series of tetrazoles were made from the corresponding N-substituted amides by the procedure originally described by von Braun and Rudolph[10] and further investigated by Herbst.[11,12] A typical procedure, applicable to either type of amide, is presented for the sake of clarity.

Preparation of 1-methyl-5-(p-chlorophenyl)tetrazole. *N*-Methyl-*p*-chlorobenzamide (35.6 g.; 0.21 mole) was covered with 650 ml. of anhydrous benzene in a 3 necked, round bottomed flask equipped with a stirrer, dry addition port, and condenser with a drying tube and connected to an open T tube to a water aspirator. Phosphorus pentachloride (44.1 g.; 0.212 mole) was added portion-wise with rapid stirring through the dry port. The resulting mixture was stirred for

(21) G. N. Lewis and M. Kasha, *J. Am. Chem. Soc.*, **67**, 992 (1945).

(22) It should be noted that H. Ley and H. Specker, *Ber.*, **7b**, 192 (1939) report other derivatives of benzoic acid which also appear to have a slight hypsochromic effect: benzoic acid (λ_{max} 2280 Å, log ϵ_{max} 4.0),[13] benzamide (λ_{max} 2250 Å, log ϵ_{max} 3.78), *N,N*-dimethylbenzamide (λ_{max} 2300 Å, log ϵ_{max} 3.75) (shoulder), and ethyl benzoate (λ_{max} 2300 Å, log ϵ_{max} 4.20).

(23) E. Lieber, D. R., Levering, and L. J. Patterson, *Anal. Chem.*, **23**, 1594 (1951).

(24) Melting points (capillary) corrected. Analysis by Dr. C. S. Yeh and Mrs. S. L. Margerum of this Department. Ultraviolet spectra were obtained with a Cary recording spectrophotometer by Mr. Robert Curry. Infrared spectra by Dr. J. Amy.

(25) P. F. Frankland, S. R. Carter and E. B. Adams, *J. Chem. Soc.*, **101**, 2470 (1915).

1 hr. at room temperature and then for 15 min. at 40°. The mixture was nearly clear at this time. A slight vacuum was applied to remove hydrogen chloride and the resulting solution of the imino chloride was cooled to 15°. A solution of hydrazoic acid (330 ml.; 5.5% or 0.424 mole) was added dropwise from a funnel replacing the dry port. A slight vacuum was maintained on the system to prevent escape of hydrazoic acid to the hood and room. The mixture was stirred at 25° for 2 hr. and under reflux (no vacuum) for 3 hr. The benzene was removed by distillation (under reduced pressure) and the residue treated with 100 ml. of water and sufficient sodium hydroxide to make alkaline (*p*H 8.5). The resulting solid was filtered by suction and washed with water. There was obtained 27.9 g. of crude product, m.p. 113.6–118.6°; on three recrystallizations from benzene the melting point was still not sharp. It was suspected that there was unreacted amide present (in these compounds mixed melting points rarely show depression), and the total crude material was boiled under reflux in 400 ml. of 10% sulfuric acid. This gave a product free of amide, m.p. 118.8–120.3°, from benzene.

In the preparations of the other new tetrazoles similar purifications were followed. The data for these compounds are in Table II.

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Sterically Hindered Reactions of Grignard Reagents with Schiff Bases

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N-Benzylidene-*tert*-butylamine added methyllithium and allylmagnesium bromide, but not methylmagnesium iodide. Lithium aluminum hydride smoothly reduced *N*-benzylidene-*tert*-butylamine to *N*-*tert*-butylbenzylamine. With allylmagnesium bromide, *N*-benzylidene-*n*-octadecylamine formed *N*-*n*-octadecyl(α-allylbenzyl)amine. *N*-Benzylidenemethylamine reacted with *tert*-butylmagnesium chloride to give *N*-methyl(α-*tert*-butylbenzyl)amine and with *n*-octadecylmagnesium iodide to give *N*-methyl(α-octadecylbenzyl)amine.

Campbell *et al.*[1] treated a number of *N*-benzylidenealkylamines with various alkylmagnesium halides to synthesize *N*-alkyl(α-alkylbenzyl)amines:

$$C_6H_5—CH{:}N—R' + RMgX \longrightarrow C_6H_5—CH(R)—NHR'$$

They found that, when equimolar amounts of Grignard reagent and aldimines were used, satisfactory yields (60–75%) were obtained only with the most reactive Grignard reagents and the simplest Schiff bases. Thus with *N*-benzylidenemethylamine ethylmagnesium bromide gave a 75% yield of *N*-methyl(α-ethylbenzyl)amine, but with *N*-benzylideneethylamine only a 39% yield of *N*-ethyl(α-ethylbenzyl)amine was obtained.

The present work was undertaken to obtain some knowledge of: (1) the effect of bulky alkyl groups in the Schiff base on the reactivity of the C:N; and (2) the steric requirements of the alkyl Grignard reagent. *N*-Benzylidene-*tert*-butylamine was selected as a bulky *N*-alkyl Schiff base, and *tert*-butylmagnesium chloride as a Grignard of high steric requirement.

N-Benzylidene-*tert*-butylamine was prepared by Hurwitz[2] in a 63% yield. However, he recorded no physical constants. Methylmagnesium iodide would not add to this Schiff base even under forcing conditions. This indicates that the steric requirements of the *N*-*tert*-butyl group are appreciable. On the other hand methyllithium did add to give *tert*-butyl(α-methylbenzyl)amine. Organolithium compounds are known to be much more reactive than the corresponding Grignard reagents.[3]

The failure of methylmagnesium iodide to react with *N*-benzylidene-*tert*-butylamine prompted an attempt to add allylmagnesium bromide. Gilman and Eisch[4] found that this latter Grignard reagent added in a 1,2-manner to aromatic ketimines having high steric requirements. In line with Gilman's observation we found that allylmagnesium bromide gave good yields of *N*-*tert*-butyl(α-allylbenzyl)-amine. The reactivity of this Grignard reagent as compared to that of methylmagnesium iodide seems to confirm Gilman's view that the mechanism of this 1,2-addition to the azomethine linkage proceeds by a nucleophilic attack of the allyl anion on the positively polarized carbon atom adjacent to the nitrogen in the Schiff base. The reactivity of allylmagnesium bromide was also shown by its addition to the high molecular weight *N*-benzylidene-*n*-octadecylamine to form *N*-octadecyl(α-allylbenzyl)amine.

N-Benzylidenemethylamine was used to test the reactivity of *tert*-butylmagnesium chloride. During the progress of this work Thies and Schoenenberger[5] carried out the same reaction but were unable to isolate any product from addition. They obtained only starting material and the dimer of the Schiff base, *N*,*N*′-dimethyl-1,2-diphenylethylenediamine. In this work the 1,2-addition product,

(1) K. N. Campbell, C. H. Helbing, M. P. Florkowski, and B. K. Campbell, *J. Am. Chem. Soc.*, **70**, 3868 (1948).

(2) M. D. Hurwitz, U. S. Patent **2,582,128**, (Jan. 8, 1952); *Chem. Abstr.*, **46**, 8146 (1952).

(3) H. Gilman and R. H. Kirby, *J. Am. Chem. Soc.*, **55**, 1265 (1933).

(4) H. Gilman and J. Eisch, *J. Am. Chem. Soc.*, **79**, 2150 (1957).

(5) H. Thies and H. Schoenenberger, *Arch. Pharm.*, **289**, 408 (1956).