[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

1,5-DISUBSTITUTED TETRAZOLES FROM 1-ACETYL-2-*para*-SUBSTITUTED BENZOYL HYDRAZINES AND *p*-NITROBENZENEDIAZONIUM CHLORIDE*[1]

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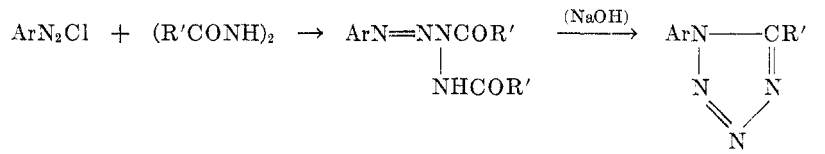
In 1910 Dimroth and de Montmollin (1) described the synthesis of a number of 1,5-disubstituted tetrazoles from the action of dilute sodium hydroxide on diazoaryl mono- and di-acyl hydrazines. The procedure involved the coupling of diazonium compounds with acid hydrazides or *sym*-diacyl hydrazines followed by cyclization of the resulting tetrazene (diazohydrazide).



Recently Wu and Herbst (2) reinvestigated the Dimroth procedure and, using *sym*-diacyl hydrazines, noted that the yield of tetrazole diminished as the size of the acyl group was increased. However, these authors were primarily interested in the preparative value of this reaction and made no attempt to elucidate the mechanism of tetrazole formation.

Unsymmetrical 1,2-diacyl hydrazines have never been submitted to the Dimroth method and it appeared that such a study would shed some light on the mechanism of this sequence of reactions. Accordingly, a number of 1-acetyl-2-*para*-substituted benzoyl hydrazines were treated with *p*-nitrobenzenediazonium chloride. Without attempting to isolate the intermediate tetrazenes, the mixture was treated with dilute sodium hydroxide to effect cyclization. The resulting tetrazoles (III, IV) were collected and separated by means of fractional crystallization.

The combined yield of tetrazoles (*cf.* Table I) exceeded 50% in every case save the first [X = $(CH_3)_2N$]. The reason for the low yield in the latter case is at present not clear. Significantly, the yield of 1-(4′-nitrophenyl)-5-methyltetrazole (III) in each case proved to be greater than that of the corresponding 1,5-diaryltetrazole (IV). Since the yield of III in three instances exceeded 50%, it would appear that the precursory tetrazenes (I, II) are not formed in equivalent amounts. The results of the present investigation indicate preferential coupling at the nitrogen atom adjacent to the benzoyl residue. Furthermore, the ratio of the yields of the two tetrazoles, III/IV, seems to increase as the electrophilic character of the *para*-substituent becomes more pronounced.

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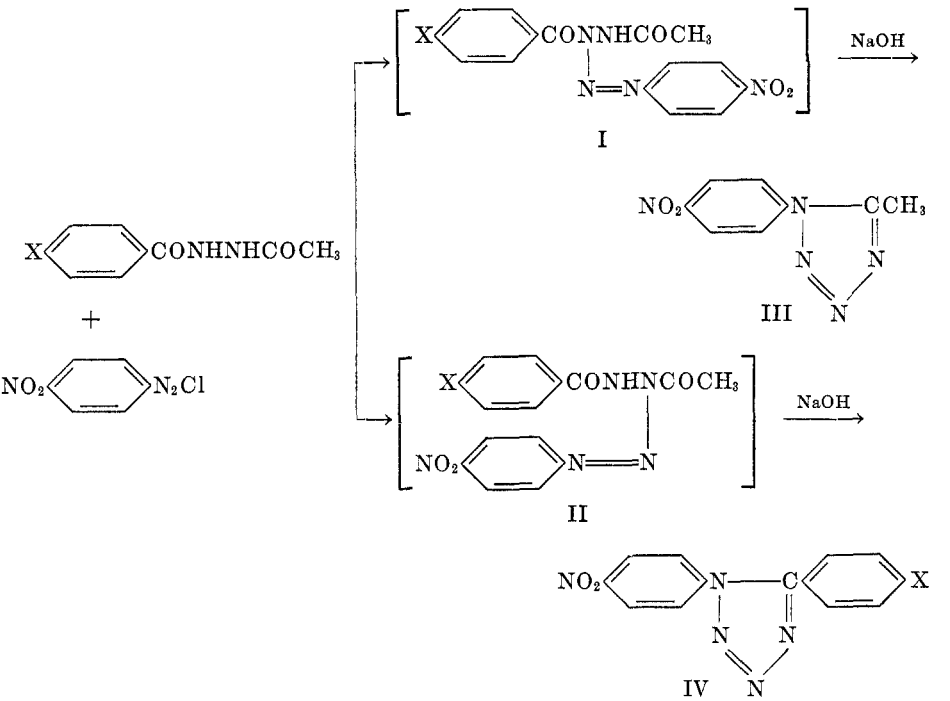
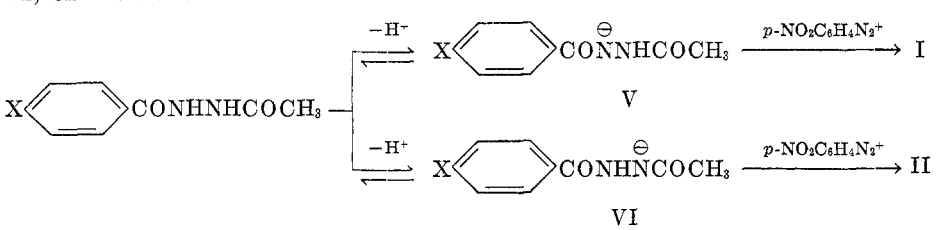


The 1-acetyl-2-*para*-substituted benzoyl hydrazines are weak acids which readily dissolve in cold dilute alkali. The coupling reaction was observed to occur rapidly in media ranging from weakly acidic to weakly basic. Furthermore, in the case of 1-acetyl-2-benzoyl hydrazine, it was impossible to detect the presence of any unreacted diazonium compound with β-naphthol almost immediately (one minute) after the reactants were mixed.

On the basis of these observations, it would seem that the mechanism of tetrazene formation involves an attack by the 1,2-diacyl hydrazine anion (V, VI) on the diazonium cation.



Since coupling appears to be a very rapid reaction, the yield of the two tetrazenes (I, II) should be determined by the quantity of V and VI present in the equilibrium mixture.

It is evident from Table I that the increase in the ratio of the yields of the two tetrazoles parallels the increase in the dissociation constants of the *para*-sub-

TABLE I

RATIO OF YIELDS OF TETRAZOLES OBTAINED FROM 1-ACETYL-2-*para*-SUBSTITUTED BENZOYL HYDRAZINES

X-C$_6$H$_4$-CONHNHCOCH$_3$ X =	K_a^b X-C$_6$H$_4$-COOH	YIELD OF I, %[a]	YIELD OF II, %[a]	YIELD I, % / YIELD II, %
$(CH_3)_2N$	9.4×10^{-6}	11	7	1.6
CH_3O	3.38×10^{-5}	42	11	3.8
CH_3	4.24×10^{-5}	40	10	4.0
H	6.30×10^{-5}	63	16	3.9
Cl	1.04×10^{-4}	54	7	7.7
Br	1.07×10^{-4}	60	7	8.6
NO_2	3.76×10^{-4}	49	5	9.8

[a] The yields are over-all yields of tetrazole based on the diacyl hydrazine, and represent the average of several determinations.

[b] Data taken from Reference 3.

stituted benzoic acids. Therefore, it seems reasonable to assume, as a first approximation, that V is stabilized by virtue of its proximity to the benzoyl residue and that this stabilization effect should be expected to facilitate the indicated dissociation as the electrophilic character of the *para*-substituent becomes more pronounced. This hypothesis is then essentially the same as that offered to explain the differences in the dissociation constants of the *para*-substituted benzoic acids (3).

The hypothesis advanced above appears to hold for the limited series we have chosen. However we have also found that the reaction between 1-acetyl-2-phenylacetyl hydrazine and *p*-nitrobenzenediazonium chloride led to the isolation of a preponderance of 1-(4′-nitrophenyl)-5-benzyltetrazole. Thus, the strict parallel to dissociation constants of the parent acids (K_a, phenylacetic acid 4.8×10^{-5}) does not appear to hold beyond the benzoic acids.

The cyclization reaction is frequently accompanied by the formation of azides, amides, and amines as a result of a competing reaction in which the intermediate tetrazene is cleaved into several fragments under the same conditions which promote cyclization. While the present study was limited to the use of *p*-nitrobenzediazonium chloride, we have observed that other diazonium compounds, *e.g. p*-toluenediazonium chloride, afford a much lower yield of tetrazole and a larger proportion of tarry products arising, presumably, from linear cleavage.

Despite the apparent complexity of the sequence of reactions involved in tetrazole formation, it is possible to advance a mechanism which will account for all the products of the side reaction as well as cyclization. For these purposes it is convenient to consider a tetrazene (VII) derived from 1-acetyl-2-(4′-toluoyl) hydrazine. As the first step it is suggested that the *p*-toluoyl residue is removed with the simultaneous formation of a resonance stabilized anion (IX) whose contributors are a, b, c, d, e. The additional resonance forms (IX a, b) made possible by the nitro substituent in VII would be expected to further stabilize the anion and consequently reduce the tendency toward cleavage (X, XI,

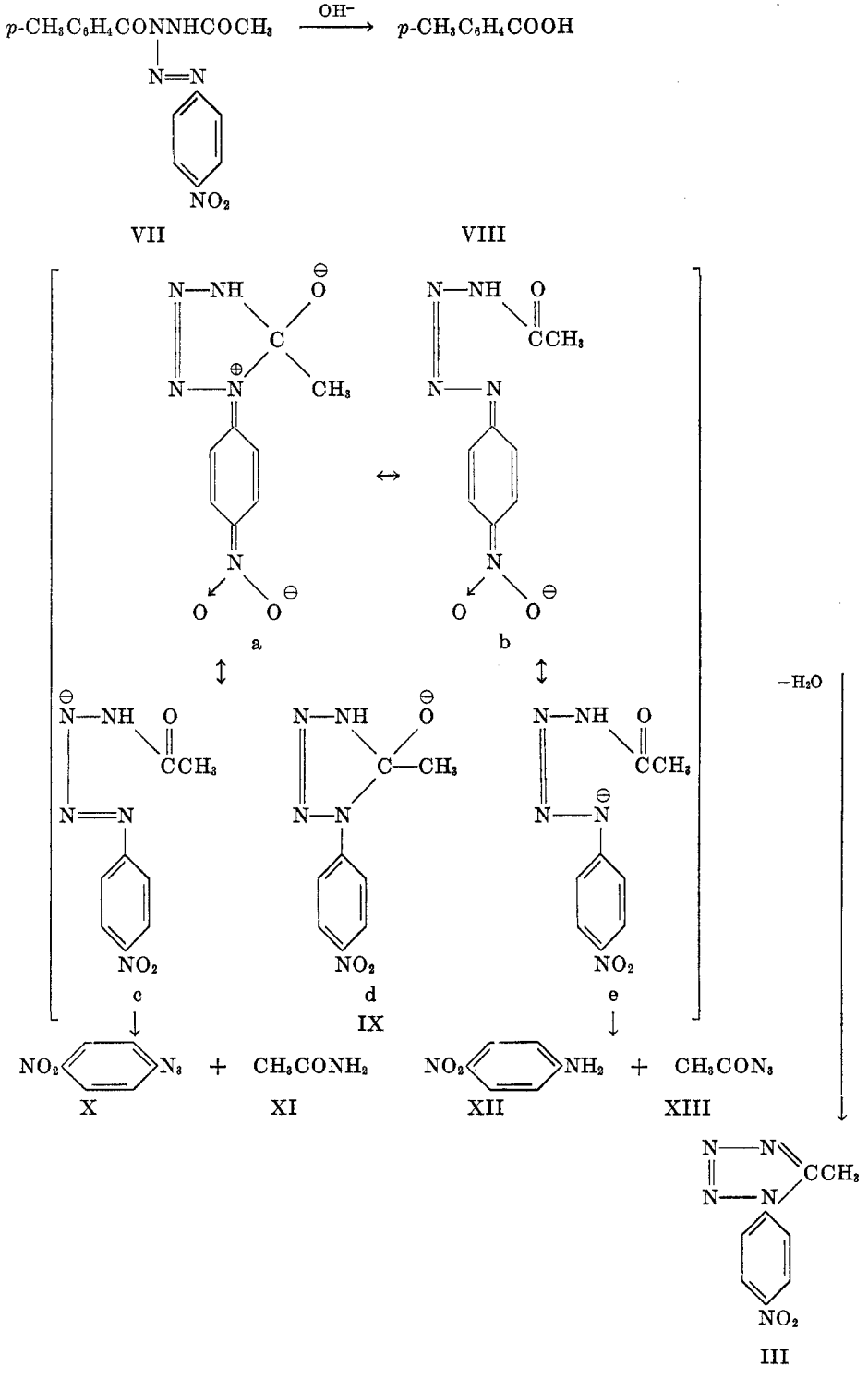

p-CH3C6H4CONNHCOCH3
OH-
p-CH3C6H4COOH
VII
VIII
a
b
c
d
e
IX
X
XI
XII
XIII
III
-H2O

TABLE II

para-SUBSTITUTED BENZHYDRAZIDES AND ACETYL DERIVATIVES

X-C$_6$H$_4$-CONHNH$_2$ X =	M.P., °C.		ACETYL DERIVATIVES							
	Lit.	Obs.	M.p., °C.	Formula	C		H		N	
					Calc'd	Found	Calc'd	Found	Calc'd	Found
$(CH_3)_2N$	170–171[a]	169–170	204	$C_{11}H_{15}N_3O_2$	59.71	59.60	6.83	6.73	18.99	19.13
CH_3O	136[a]	136[b]	150–151	$C_{10}H_{12}N_2O_3$	57.68	57.87	5.81	5.99	13.46	13.66
CH_3	117[c]	116–117	186–187	$C_{10}H_{12}N_2O_2$	62.48	62.40	6.29	6.52	14.58	14.58
H	112.5[d]	112	169–170	[h]	—	—	—	—	—	—
Cl	163[e]	162–163	209–211	$C_9H_9ClN_2O_2$	50.83	51.16	4.26	4.44	13.18	13.70
Br	164[f]	162–164	225	$C_9H_9BrN_2O_2$	42.04	41.80	3.53	3.62	10.90	10.82
NO_2	210[g]	210	237	$C_9H_9N_3O_4$	48.43	48.59	4.06	4.19	18.83	19.04

[a] Staudinger and Endle, *Ber.*, **50,** 1045 (1917). [b] Curtius and Welsbach, *J. prakt. Chem.*, [2] **81,** 548 (1910). [c] Stolle and Stevens, *J. prakt. Chem.*, [2] **69,** 369 (1904). [d] Curtius, *J. prakt. Chem.*, [2] **50,** 278 (1894). [e] Kahl., *Z. Ver. Rubenzuck, Ind.*, 1091 (1904) [*Chem. Zentr.*, **II,** 1493 (1904)]. [f] Curtius and Portner, *J. prakt. Chem.*, [2] **58,** 199 (1898). [g] Curtius and Trachmann, *J. prakt. Chem.* [2] **51,** 168 (1895). [h] See Reference [d], m.p. 170°.

and XII, XIII). By the same reasoning the additional stabilization accorded IX would favor tetrazole formation.

In connection with the first step, the formation of IX we are able to report the isolation of *p*-toluic acid (VIII) in a quantity which is slightly greater than the amount of tetrazole (III) detected. This observation appears to be in accord with the hypothesis advanced above, namely, that the *p*-toluoyl group is removed prior to cyclization rather than after or at the same time as tetrazole formation. The small difference in yields of tetrazole and *p*-toluic acid also indicates that linear cleavage occurs only to slight extent during the course of this cyclization.

It is obvious that the same mechanism might equally well be applied to the isomeric tetrazene in which the removal of an acetyl group would represent the first step toward both cleavage and cyclization. Additional work is now in progress to ascertain the merit of the series of hypotheses advanced above.

EXPERIMENTAL[2]

Mono- and di-acyl hydrazines. The *para*-substituted benzhydrazides were prepared from the corresponding benzoic methyl or ethyl esters according to the general procedure described by Smith (4). Treatment of the *para*-substituted benzhydrazides with excess acetic anhydride provided the 1,2-diacyl hydrazines in good yield. The description of the preparation of 1-acetyl-2-(4′-nitrobenzoyl) hydrazine illustrates the general procedure employed for the synthesis of the compounds listed in Table II.

A solution of 97.5 g. of ethyl *p*-nitrobenzoate (0.5 mole) was added dropwise over a period of 30 minutes to 40 g. (0.8 mole) of 100% hydrazine hydrate heated on a steam-bath. The mixture was then refluxed for four hours, cooled, and the yellow solid collected. The dry filter cake was washed first with ethanol, then ether; m.p. 210° (*cf.* Table II), yield 73 g. (80%).

[2] All melting points are corrected. Analyses by Micro-Tech Laboratories, Skokie, Illinois.

p-Nitrobenzhydrazide (24 g., 0.133 mole) was suspended in 25 cc. of acetic anhydride (0.266 mole) giving rise to a slightly exothermic reaction. The reaction mixture was then cooled to room temperature and the product was collected. The slightly yellow solid was washed with ethanol, ether, and finally recrystallized from dioxane, m.p. 237° (*cf.* Table II), yield 27 g. (91%).

The preparation of 1-acetyl-2-phenylacetyl hydrazine will also be described, as the melting point and analysis could not conveniently be incorporated in Table II.

Phenylacethydrazide (4) (10 g., 0.06 mole) was suspended in 11.3 cc. of acetic anhydride and after the initial exothermic reaction had subsided the reaction mixture was cooled to room temperature, and the product was collected and recrystallized from water, m.p. 173–174°; yield 27 g. (100%).

Anal. Calc'd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58.

Found: C, 62.64; H, 6.50; N, 14.91.

1,5-Disubstituted tetrazoles. The application of the Dimroth procedure to the reaction between a 1-acetyl-2-*para*-substituted benzoyl hydrazine required in every case, following cyclization, the separation of a 1,5-diaryltetrazole from 1-(4′-nitrophenyl)-5-methyltetrazole. For purposes of identification an authentic sample (1, 2) of the latter was prepared from diacetyl hydrazine and *p*-nitrobenzenediazonium chloride. Mixture melting points between the authentic sample and the corresponding product isolated in each case failed to exhibit any depression.

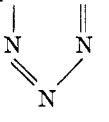
In no case was any attempt made to isolate the intermediate tetrazene. Therefore the yields of tetrazoles indicated below are over-all yields, based on the quantity of diacyl hydrazine employed.

The coupling reaction between *p*-nitrobenzenediazonium chloride and 1-acetyl-2-(4′-bromobenzoyl)hydrazine, the cyclization and the separation of the two tetrazoles are described as a typical example. The physical constants and analytical data of the tetrazoles prepared in this study are summarized in Table III. It is to be noted that an arbitrary number has been assigned to each tetrazole in order to avoid undue repetition.

To a mixture of 2.3 g. of *p*-nitroaniline (0.017 mole) in 8 cc. of 6 *N* hydrochloric acid, kept at 0°, was added a solution of 1.3 g. of sodium nitrite (0.017 mole) in 5 cc. of water.

TABLE III

1,5-DISUBSTITUTED TETRAZOLES *p*-$NO_2C_6H_4N$——CR



CODE	R	M.P., °C.	FORMULA	C		H		N	
				Calc'd	Found	Calc'd	Found	Calc'd	Found
T-1 (Ref. 1)	CH_3	129–130	—	—	—	—	—	—	—
T-2	*p*-$(CH_3)_2NC_6H_4$	220–221	$C_{15}H_{14}N_6O_2$	58.06	58.20	4.55	4.58	27.09	26.88
T-3	*p*-$CH_3OC_6H_4$	180	$C_{14}H_{11}N_5O_3$	56.56	56.70	3.73	3.92	23.56	23.75
T-4	*p*-$CH_3C_6H_4$	161–162	$C_{14}H_{11}N_5O_2$	59.78	59.91	3.94	3.69	24.90	24.76
T-5 (Ref. 1)	C_6H_5	148–149	—	—	—	—	—	—	—
T-6	*p*-ClC_6H_4	188–189	$C_{13}H_8ClN_5O_2$	51.75	51.59	2.67	2.63	23.22	23.61
T-7	*p*-BrC_6H_4	199	$C_{13}H_8BrN_5O_2$	45.10	45.20	2.33	2.28	20.23	20.13
T-8	*p*-$NO_2C_6H_4$	262	—	—	—	—	—	—	—
T-9	$C_6H_5CH_2$	115–116	$C_{14}H_{11}N_5O_2$	59.78	59.78	3.94	4.10	24.90	25.03

The diazonium salt solution was then added in small portions with stirring to a solution of 3.86 g. of 1-acetyl-2-(4′-bromobenzoyl) hydrazine (0.015 mole) in 30 cc. of 1 *N* sodium hydroxide kept at 0°. Without isolation of the intermediate tetrazene which separated as a voluminous yellow precipitate at approximately *p*H 6–8 (pHydrion paper), 100 cc. of 5 *N* sodium hydroxide was added with stirring. A clear solution resulted from which the tetrazoles separated slowly at room temperature on standing for 12–18 hours. The solids were collected, washed with water, and sucked dry.

Separation of 1-(4′-nitrophenyl)-5-(4′-bromophenyl)tetrazole (T-7) from 1-(4′-nitrophenyl)-5-methyltetrazole (T-1). The dry solid was next suspended in 30 cc. of cold, concentrated hydrochloric acid and a small amount of brown, insoluble material was removed by filtration. This residue was next dissolved in 40 cc. of hot absolute ethanol, the solution treated with Norit, and, on cooling, the 1,5-diaryltetrazole (T-7) separated in the form of small, off-white plates, m.p. 199°, yield 0.38 g. (7%) (see Table III for analysis). The acid filtrate was diluted to a volume of 400 cc. and the solution was cooled in a refrigerator for several hours which caused the deposition of a yellow solid amounting to 1.9 g., m.p. 120–129°. A single recrystallization from absolute alcohol gave 1.85 g. (60% yield) of T-1, m.p. 128–129°.

In addition to the example described above, the difference in solubility in cold, concentrated hydrochloric acid provided a rather facile separation of T-1 from the following 1-(4′-nitrophenyl)-5-aryltetrazoles: 4′-chlorophenyl- (T-6), 4′-anisyl- (T-3), and 4′-dimethylaminophenyl- (T-2). In the latter case (T-2), an especially clean separation was effected as a result of salt formation. Thus, dissolution in hydrochloric acid and dilution with water caused the precipitation of only T-1. Neutralization of the filtrate with dilute potassium hydroxide produced pure T-2.

Occasionally it was noted that a small amount of the 1,5-diaryltetrazole dissolved on treatment with hydrochloric acid and hence reappeared with the major constituent on dilution. In these cases, it was found possible to complete the separation by fractional crystallization from absolute ethanol.

The procedure outlined above was modified somewhat for some of the more difficult separations and these are discussed individually.

1,5-Di-(4′-nitrophenyl)tetrazole (T-8). The mixture of brown solids obtained following cyclization was suspended in 60 cc. of hot benzene and the insoluble material was removed by filtration. The filtrate was cooled to room temperature causing the deposition of a yellow solid (T-1), m.p. 126–129°.

Concentration of the filtrate to 10 cc. produced an additional crop of the same yellow solid, m.p. 126–129°, combined weight 2.2 g. The yellow material was suspended in 15 cc. of cold, concentrated hydrochloric acid and a brown insoluble residue was removed by filtration, 0.12 g., m.p. 250–258°. The combined insoluble residues were recrystallized from ethyl benzoate to give 0.3 g. (5% yield) of the T-8, m.p. 262° (5). The hydrochloric acid filtrate was diluted with water and the 1-(4′-nitrophenyl)-5-methyltetrazole isolated in the previously described manner, m.p. 129–130°, yield 2.0 g. (49%).

1-(4′-Nitrophenyl)-5-phenyltetrazole (T-5). The crude mixture of tetrazoles (2.8 g., m.p. 100–125°) was dissolved in 20 cc. of benzene and the solution decolorized with Norit. On cooling, a yellow solid (T-1) deposited, 1.64 g., m.p. 128–129°. The filtrate was evaporated to dryness and the residue was recrystallized from 40 cc. of absolute ethanol, to give 0.44 g. of the 1,5-diaryltetrazole (T-5) as a white, amorphous solid, m.p. 148–149°. The ethanol filtrate was evaporated to dryness and the residue was taken up in a small volume of benzene (5–7 cc.). On cooling, an additional 0.29 g. of T-1, m.p. 128–129°, was obtained to raise the total yield to 1.93 g. (63%).

The benzene filtrate was evaporated to dryness once again and the residue was recrystallized from absolute ethanol to give an additional 0.18 g. of the 1,5-diaryltetrazole, m.p. 148–149°, combined weight, 0.62 g. (16% yield). A mixture melting point with an authentic sample of T-5, obtained according to the procedure described by Dimroth (1), failed to show any depression (148–149°).

1-(4'-Nitrophenyl)-5-(4'-tolyl)tetrazole (T-4). The crude mixture of tetrazoles was suspended in 50 cc. of hot toluene and a small amount of insoluble material was removed by filtration. The filtrate was seeded with a crystal of 1-(4'-nitrophenyl)-5-methyltetrazole, cooled in an ice-bath and the yellow solid was collected, weight 1.03 g., m.p. 126–129°. An additional 0.14 g. of the same material, m.p. 125–129°, was obtained on concentrating the toluene filtrate. The combined solids (1.16 g.) were recrystallized from 15 cc. of absolute ethanol to give 1.12 g. (0.0055 mole, 40% yield) of pure T-1, m.p. 129–130°.

The toluene filtrate was evaporated to dryness and the residue was recrystallized twice from 95% ethanol to give 0.42 g. (10% yield) of the 1,5-diaryltetrazole (T-4) in the form of small white plates, m.p. 161–162° (see Table III for analysis).

An additional 0.06 g. of T-1, m.p. 129–130°, was obtained on concentrating the aqueous alcohol filtrate, total weight, 1.22 g. (40% yield).

The clear alkaline filtrate from which the mixture of tetrazoles was initially isolated was acidified with dilute hydrochloric acid upon which a white solid, m.p. 170–180°, separated immediately. Recrystallization from water gave 0.8 g. (0.006 mole) of material, m.p. 179–180°, which was identified as p-toluic acid by means of mixed melting points.

1-(4'-Nitrophenyl)-5-benzyltetrazole (T-9). The crude mixture of tetrazoles was suspended in 5 cc. of cold, concentrated hydrochloric acid and the insoluble residue was removed by filtration; total acid-insoluble material 1.46 g., m.p. 113–116°. One recrystallization from absolute ethanol gave 1.33 g. of a light yellow solid (T-9), m.p. 115–116°.

The acid filtrate was diluted with water and the precipitated material was collected, 0.5 g., m.p. 110–126°. Recrystallization first from 15 cc. of absolute ethanol and then from benzene gave 0.34 g. of T-1, m.p. 129–130°.

The alcohol and benzene filtrates were evaporated to dryness and the residue was suspended in 2 cc. of cold, concentrated hydrochloric acid. Repeating the technique described above, an additional 0.05 g. of T-1, m.p. 129–130°, and 0.05 g. of T-9, m.p. 115–116°, was isolated. Combined weight of T-1, 0.39 g. (19%). Combined weight of T-9, 1.38 g. (49%). (See Table III for analysis).

SUMMARY

The preparation of 1,5-disubstituted tetrazoles by the coupling of diazotized *p*-nitroaniline with 1-acetyl-2-*para*-substituted benzoyl hydrazines and cyclization of the tetrazenes formed as intermediates has been investigated. From the ratio of the two tetrazoles isolated, it appears that preferential coupling occurs at the nitrogen adjacent to the *para*-substituted benzoyl residue. This preferential coupling appears to be enhanced by the presence of electrophilic substituents in the *para* position. The hypothesis has been advanced that the benzoyl group stabilizes the anion resulting from dissociation of the diacyl hydrazine and thus promotes both dissociation and coupling.

CHICAGO 15, ILLINOIS

REFERENCES

(1) DIMROTH AND DE MONTMOLLIN, *Ber.*, **43**, 2904 (1910).
(2) WU AND HERBST, *J. Org. Chem.*, **17**, 1216 (1952).
(3) REMICK, *Electronic Interpretations of Organic Chemistry*, 2nd Edition, John Wiley and Sons, Inc., New York, New York, 1949, p. 64.
(4) SMITH, *Org. Reactions*, **3**, chapter 9 (1949).
(5) VON BRAUN AND RUDOLPH, *Ber.*, **74**, 2168 (1941).