quantity of nitroaminoguanidine and its final titer was *ca.* 30% too low. The 3-hydroxy-4-methoxy analogue prove impossible to analyze as after an eight-day period, the chloroform layer acquired a permanent red color which completely obscured the visual endpoint sought. The titrimetric endpoints obtained with both the acetone and benzaldehyde nitroguanylhydrazones were also some 40 and 20% too low respectively.[5] These low values suggested that perhaps nitroaminoguanidine had lost some of its hydrazine function under the given analysis conditions. A trial confirmed that this was possible. Thus, when a number of *ca.* 0.1 g. samples of nitroaminoguanidine, dissolved in 20 ml. of water and 30 ml. of concentrated hydrochloric acid were heated on a steam bath for varying periods of time (5–30 minutes), and then, after quenching the reaction by immersion of the reaction solutions in ice, titrated with iodate as before, a loss of hydrazine function with a rate constant of roughly 2×10^{-3} sec.$^{-1}$ was observed. Under conditions more closely related, temperature-wise, to the hydrazone hydrolyses but involving much greater time intervals (20–90 days) than the previous blank trials, nitroaminoguanidine was again discovered to undergo partial loss of hydrazine function. While this hydrazine dissipation may not be the sole cause of the anomalous iodate values, in any event it can demonstrably be accepted as a factor therein particularly with those hydrazones which prove slowest to hydrolyze.

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Polynitrogen Systems from the Hydrazinocarbonic Acids. Part IX.[1] The Synthesis and Bromination of Some 5-Tetrazolyl- and Related -hydrazones

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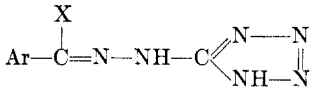
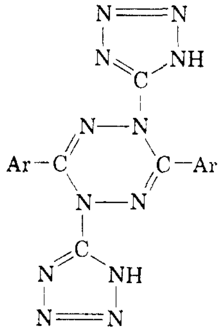
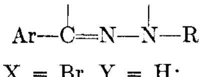
We have developed the utility of 5-hydrazinotetrazole as a means of characterizing carbonyl compounds somewhat more fully than the scattered literature data[3] thereon previously achieved. Some preliminary observations have also been made on the possibility of ω-bromination of the 5-tetrazolylhydrazones (I). The reactions encountered with the benzylidene derivative (IA) typify the complexities involved. When IA was brominated under the standard conditions utilized, namely, using equimolar quantities of bromine and hydrazone in glacial acetic acid solution (or suspension) at room temperature, it formed apparently the crude ω-bromo derivative (IB). This when crystallized from anhydrous chloroform was obtained pure. When it was boiled in glacial acetic acid, it dehalogenated and reverted to the parent hydrazone (IA). When refluxed in 50% aqueous ethanol for a few minutes IB was oxidized and the hydrogen-abstracted derivative so isolated may possibly be the tetrazine (IIA).[4] When IA was treated with an excess of bromine, again in glacial acetic acid medium, considerable hydrolysis of the hydrazone accompanied the ω-bromination effected. Finally, when IA was allowed to react in an excess of bromine without any additional solvent ring—as well as ω—bromination occurred, yielding most probably IC. The 3-nitrobenzylidene analogue of IA, *viz.*,



I, A, Ar = C_6H_5, X = H;
B, Ar = C_6H_5, X = Br;
C, Ar = 4(?)Br—C_6H_4, X = Br;
D, Ar = 3—NO_2—C_6H_4, X = H

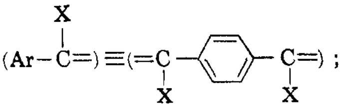


II, A, Ar = C_6H_5;
B, Ar = 3—NO_2—C_6H_4



$\mathrm{Ar{-}\overset{X}{C}{=}N{-}\overset{Y}{N}{-}R}$

III, A, X = Br, Y = H;
B*, R = C(=NH)—NH—NO_2;

C*, 

D, X = H, Y = C(=O)—C_6H_5, R = C(=NH)—NH—C(=O)—C_6H_5;
E, X = NH_2, Y and R as in D;
For substances starred (*), X = Y = H

$(Ar{-}CH{=}N{-}NH{-})_2C{=}N{-}R$
IV, A, R = H;
B, R = (—N=CH—Ar).

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(1) Part VIII, F. L. Scott, W. N. Morrish, and J. Reilly, *J. Org. Chem.*, **22**, 690 (1957).

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(3) *Vide* (a) J. Thiele and H. Ingle, *Ann.*, **287**, 233 (1895); (b) J. Thiele and J. T. Marais, *Ann.*, **273**, 144 (1893); (c) J. Thiele, *Ann.*, **303**, 66 (1898); (d) K. A. Hofmann, H. Hock, and H. Kirmreuther, *Ann.*, **380**, 131 (1911); (e) F. L. Scott, D. G. O'Donovan, and J. Reilly, *J. Appl. Chem.*, **2**, 368 (1952).

(4) Compare: F. D. Chattaway and A. J. Walker, *J. Chem. Soc.*, **127**, 975, 1687 (1925); F. D. Chattaway and A. B. Adamson, *J. Chem. Soc.*, 157, 843 (1930); F. D. Chattaway and G. D. Parkes, *J. Chem. Soc.*, 113 (1926); F. D. Chattaway, T. Deighton, and A. Adair, *J. Chem. Soc.*, 1925 (1931); F. D. Chattaway and A. B. Adamson, *J. Chem. Soc.*, 2787, 2792 (1931); F. D. Chattaway and H. Irving, *J. Chem. Soc.*, 90 (1935).

ID, also appeared to result in some of the appropriate tetrazine (IIB), under suitable reaction conditions. The complexities in the other tetrazolylhydrazone brominations have not been clarified as yet.

We have also examined as a cognate study the reactions of some representative acylhydrazones with bromine. These reactions which were again intended to provide access to the synthetically useful[4] ω-bromo derivatives (IIIA), were generally unsuccessful. Thus under the standard conditions described above the specific substituted aldehydic derivatives of diamonoguanidine (IVA),[5] triaminoguanidine (IVB), and nitroaminoguanidine (IIIB) employed were recovered unchanged. However, when one example of this last group, *viz.* IIIC, was allowed to react under forcing conditions some, though anomalous, reaction was detected. With an acylated guanylhydrazone, the dibenzoyl derivative (IIID), ω-bromination, detected *via* its aminolysis product the hydrazidine (IIIE), apparently did occur. However, with simpler monoaminoguanyl derivatives the bromination reactions involved were again complex. Finally when these hydrazone brominations were attempted at the reflux temperature of the (glacial acetic acid) solvent extensive decomposition of the hydrazone was observed.

EXPERIMENTAL[6]

5-Tetrazolylhydrazones. 5-Hydrazinotetrazole dihydrochloride was prepared by essentially the method of Thiele and Marais (*loc. cit.*). The following illustrates the general technique[cf. 3a] used in the preparation of its aldehydic derivatives. To 5.0 g. of 5-hydrazinotetrazole dihydrochloride, dissolved in 125 ml. of warm water containing 10 ml. of ethanol, was added 8.5 g. of sodium acetate trihydrate and, immediately following this, 2.9 ml. of cinnamaldehyde were run in, drop-wise, with constant agitation of the solution. An opalescent liquor resulted which on vigorous shaking deposited a thick mass of yellow-orange, colored material. The mixture was refluxed for a further 10 min. to ensure completion of reaction and then was allowed to cool. The yellow solid thus obtained weighed 4.84 g. (82% yield), m.p. 199–200°. The filtrate, on ether extraction, yielded a further quantity (0.08 g.) of the hydrazone. After 2 recrystallizations from 70% aqueous ethanol, and one from absolute ethanol, the cinnamaldehyde 5-tetrazolylhydrazone was obtained as golden yellow microcrystals, m.p. 207°.

Anal. Calcd. for $C_{10}H_{10}N_6$: C, 56.1; H, 4.7; N, 39.3. Found: C, 56.0; H, 4.5; N, 39.5.

The remaining derivatives prepared are summarized in Table I.

Hydrazone bromination attempts. The acylhydrazones whose reactions will be described first were themselves prepared by standard methods from the literature.

(*a*) *With aminoguanidine derivatives.* (1) A solution of 0.47 ml. of bromine in 28 ml. of glacial acetic acid was added, dropwise, to a well-stirred slurry of 2.0 g. of di-2-nitrobenzylidene diaminoguanidine in 100 ml. of the same solvent. On filtering, washing, drying, and recrystallizing the residual solid, it proved to be unchanged hydrazone (82% yield).

TABLE I

NEW 5-TETRAZOLYLHYDRAZONES

Carbonyl Compound	Product Formula	Physical Appearance	M.p., °C.	Yield, %	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found[e]
4-Chlorobenzaldehyde	$C_8H_7N_6Cl$	Short, colorless needles	233	98	43.1	43.1	3.1	3.4	37.8	37.8[a]
3,4-Dimethoxy benzaldehyde	$C_{10}H_{12}N_6O_2$	Fibrous needles	217	97	48.4	47.8	4.8	4.6	33.9	34.4[b]
2,3-Dimethoxy benzaldehyde	$C_{10}H_{12}N_6O_2$	Soft, amorphous powder	212	98	48.4	48.3	4.8	4.7	33.9	34.4[c]
4-Isopropyl benzaldehyde	$C_{11}H_{14}N_6$	White plates	227	92	57.4	57.6	6.1	6.3	36.5	36.2
2-Hydroxy benzaldehyde	$C_8H_{10}N_6O_2$[d]	Ivory granules	212	98	43.2	43.6	4.5	4.7	37.8	38.2
2-Nitro benzaldehyde	$C_8H_7N_7O_2$	Fine yellow granules	245[e]	96	41.2	41.1	3.0	2.6	42.1	42.0
3-Nitro benzaldehyde	$C_8H_7N_7O_2$	White[f] microcrystals	250	99	41.2	41.5	3.0	3.3	42.1	42.3
3-Hydroxy-4-methoxy benzaldehyde	$C_9H_{12}N_6O_3$[d]	Yellow microcrystalline powder	212	100	42.9	42.4	4.8	4.8	33.3	33.7

[a] Calcd.: Cl, 16.0. Found: Cl, 15.7. [b] Calcd.: OCH_3, 25.0. Found: OCH_3, 25.1. [c] Calcd.: OCH_3, 25.0. Found: OCH_3, 24.8. [d] The physical data recorded are for the monohydrate. [e] Starts to decompose at 200°, darkens and begins to sublime at 225°. [f] Purified in the absence of light, this substance is white. It rapidly turns yellow with light exposure.

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(5) The symbol subsequent to each hydrazide represents the substituted aldehydic hydrazone of the specific hydrazide.

(6) All melting points are uncorrected. All microanalyses are by Drs. Wieler and Strauss, Oxford, England.

Evaporation of the acetic acid filtrate to dryness, *in vacuo*, at 30° afforded a further 15% yield of unchanged hydrazone. Two other analogous substances, dibenzylidene and di-3-nitrobenzylidene diaminoguanidines, when tested similarly also afforded merely unreacted hydrazone. When these brominations were attempted at 100° over 1–3 hr. periods, extensive decomposition of the hydrazones resulted.

(2) The corresponding reaction[7a] with tribenzylidene triaminoguanidine nitrate yielded initially an orange powder, m.p. 190° (yield 6.6 g. from 5 g. of hydrazone). When this powder was crystallized from either aqueous ethanol or acetic acid, it dehalogenated, the major product recovered being the original hydrazone. When a suspension of the orange powder in ethanol was treated with an excess of concentrated ammonia solution, a yellow solid, m.p. 198°, was obtained which proved to be merely the starting hydrazone free base.

Anal. Calcd. for $C_{22}H_{20}N_6$: C, 71.7; H, 5.4; N, 22.8. Found: C, 71.6; H, 5.0; N, 23.0.

When 1.0 g. of this orange powder was suspended in ethanol and treated with 0.56 ml. of phenylhydrazine, the light yellow transparent crystals which separated (0.6 g.), after further crystallization from ethanol, melted at 248° and corresponded to tribenzylidene triaminoguanidine hydrobromide.

Anal Calcd. for $C_{22}H_{21}N_6Br$: C, 58.8; H, 4.5; N, 18.7. Found: C, 59.4; H, 5.0; N, 18.6.

These two reactions demonstrate (a) that no ring halogenation occurred during the original bromination attempt, and (b) that the product isolated did not display the normal replacement reactions of ω-bromo halides.[4] Whether its physical properties and chemical reactions are due merely to loosely-bound, or even occluded, bromine, is not yet settled.

(3) Benzylidene guanylhydrazone was first benzoylated[7b] by the standard Schotten-Baumann technique.[8] The product, obtained in 90% yield, after recrystallization from aqueous ethanol melted at 164°.

Anal. Calcd. for $C_{22}H_{18}N_4O_2$: C, 71 4; H, 4.9; N, 15.1. Found: C, 71.5; H, 4.9; N, 15.5.

It was ascribed the structure (IIID) on the basis of previous data in the literature.[9] On bromination under the standard conditions a crude ω-bromo derivative (*sic.*), yield 83%, m.p. 261–267°, was obtained. This, on treatment with an excess of concentrated ammonium hydroxide solution, afforded the hydrazidine (IIIE) in 73% yield. After crystallization from ethanol this had a m.p. of 230°.

Anal. Calcd. for $C_{22}H_{19}N_5O_2$: C, 68.6; H, 4.9; N, 18.2. Found: C, 68.1; H, 4.7; N, 18.9.

The brominations of simpler guanylhydrazones has proven complex and is still under investigation.

(4) Bromination attempted under the above conditions at room temperature left benzylidene, furfurylidene, and 2,4-dinitrobenzylidene nitroaminoguanidines unaffected.[1,10] Under reflux conditions the hydrazones decomposed. When IIIC[1] was analogously refluxed for 8 hr. in acetic acid with 1 equivalent of bromine, a cream powder (in addition to unreacted, essentially insoluble hydrazone) was isolated. This crystallized from acetic acid as an ivory colored amorphous powder, m.p. > 360°. Its structure is still unknown.

Anal. Calcd. for $C_{11}H_{11}N_6Br_2O_2$: C, 32.2; H, 2.6; N, 20.0; Br, 38.2. Found: C, 32.3; H, 2.8; N, 19.2; Br, 38.1.

(*b*) *With benzylidene 5-hydrazinotetrazole* (*IA*). When IA, m.p. 235°, reported[11] m.p. 235°, was allowed to react under the general conditions of bromination at room temperature as detailed above it afforded IB in 72% yield. This crystallized from anhydrous chloroform as a white, amorphous powder, m.p. 176°.

Anal. Calcd. for $C_8H_7N_6Br$: C, 36.0; H, 2.6; N, 31.5; Br, 30.0. Found: C, 36.1; H, 2.9; N, 32.0; Br, 29.4.

When recrystallized from glacial acetic acid IB reverted to IA. In 50% aqueous ethanol, IB underwent further change and the new product was isolated as colorless, glistening blades, m.p. 188° (dec.).

Anal. Calcd. for $(C_8H_6N_6)_x$: C, 51.6; H, 3.2; N, 45.2. Found: C, 51.1; H, 3.2; N, 44.7.

By analogy with the observations of Chattaway *et al.*,[4] this product has been assigned, provisionally, the dihydro tetrazine structure (IIA). When reacted with excess bromine without further solvent IA formed apparently IC,[cf. 4] which crystallized from glacial acetic acid as fine white needles, softening at 187° and melting at 190°.

Anal. Calcd. for $C_8H_6N_6Br_2.2H_2O$: C, 25.1; H, 2.6; N, 22.0; Br, 41.9. Found: C, 25.5; H, 2.8; N, 21.5; Br, 41.2.

When the 3-nitrophenyl analogue of IA, *viz.*, ID was allowed to react similarly, with bromine in acetic acid at room temperature but with a 3 day reaction period, the initial product then being crystallized from aqueous ethanol, it afforded, together with 70% unreacted hydrazone, the 3-nitrophenyl substituted tetrazine (IIB), in 20% yield. This crystallized as white needles, m p. 194°.

Anal. Calcd for $(C_8H_5N_7O_2)_x$: C, 41.6; H, 2.2; N, 42.4. Found: C, 41.8; H, 2.1; N, 42.0.

It should be reiterated that the presently adopted tetrazine formulations for IIA and IIB are merely based (a) on good microanalytical confirmation of the proposed structures and (b) by analogy with the behavior of related phenylhydrazones.[4] Additional structural evidence is being sought.

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[7] We are indebted for assistance with these reactions to (a) Dr. M. F. Cashman, M.S. and (b) Miss M. McGrath, M.S.

[8] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., page 98, John Wiley and Sons, Inc., New York, N. Y., 1956.

[9] Compare W. G. Finnegan, R. A. Henry, and G. B. L. Smith, *J. Am. Chem. Soc.*, **74**, 2981 (1952).

[10] This was not the case with the formaldehyde nitroguanylhydrazone. When, *e.g.*, a solution of 3 ml. of bromine in 30 ml. of acetic acid was added to the solid hydrazone at room temperature, a violent, explosive reaction occurred. Even at greater dilution, and at −4 to −10°, again very vigorous interaction with copious evolution of hydrogen bromide, was detected. Decomposition, and not ω-bromination, was the sole result encountered.

[11] Thiele and Marais, *loc. cit.*

Improved Synthesis of 4-Ethylpyridine

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The syntheses of 4-ethylpyridine[1–5] from pyri-

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[5] J. P. Wibaut and J. F. Arens, *Rec. trav. chim.*, **60**, 119 (1941).