

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 guanyldihydrazone 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 $C_{22}H_{19}N_5O_2$: 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 guanyldihydrazone 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 IIIC¹ 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°, reported¹¹ 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 $C_8H_6N_6Br_2 \cdot 2H_2O$: 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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(11) Thiele and Marais, *loc. cit.*

Improved Synthesis of 4-Ethylpyridine

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The syntheses of 4-ethylpyridine¹⁻⁵ from pyri-

(1) J. F. Arens and J. P. Wibaut, *Rec. trav. chim.*, **61**, 59 (1942).

(2) R. L. Frank and P. V. Smith, *Org. Syntheses*, **27**, 38 (1947).

(3) T. Urbanski, Z. Biernacki, D. Gürne, L. Halski, M. Mioduszewska, B. Serafinowa, J. Urbanski and D. Zelazko, *Roczniki Chem.*, **27**, 161 (1953); *Chem. Abstr.*, **48**, 13688b (1954).

(4) T. Vitali and M. Sardella, *Chimica (Milan)*, **7**, 229 (1952); *Chem. Abstr.*, **47**, 6414z (1953).

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

(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 nitroguanyldihydrazone. 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.

dine, acetic anhydride, acetic acid, and zinc lead to low yields of 35–41% based on the pyridine charged. Because of the increased interest in 4-substituted pyridines, particularly derivatives of isonicotinic acid, an investigation was undertaken to develop an improved synthesis of 4-ethylpyridine.

Theoretically, one half of the charged pyridine is regenerated in the course of the reaction so the maximum yield of 4-ethylpyridine is only 50%.⁶ In the present modified procedure the regenerated pyridine, in the reaction mixture, was subjected to further treatment in this same reaction mixture, was subjected to further treatment in this same reaction mixture, to increase the overall yield to 75%. Without using the regenerated pyridine, crude yields were increased from previously reported 35.5–41% to 48–50%. By using the regenerated pyridine, in what is referred to as the cyclic process, crude yields up to 78% were obtained. Yields of over 80% were obtained, based upon recovered pyridine. Less expensive iron powder (Belmont 98%) was substituted for activated zinc.⁷ (It was found that regular zinc powder gave yields similar to those obtained employing activated zinc). Iron filings and impure iron powder resulted in lower yields compared to pure powder. It was also determined that the violent exothermic reactions that occurred during certain stages of the original procedure were more readily controlled by running the reaction at higher temperatures and adding the iron at about 80–100° C. instead of 35–40° C. Water was used to replace acetic acid at one stage of the reaction, and benzene was substituted for chloroform in the extraction of the product.

A study of the influence of the initial concentration of acetic acid was also made. The experimental results indicated that this is important, and in the cyclic process a large initial quantity of the acid has an adverse effect, probably because the unreacted acid competes with acetic anhydride by forming a salt with pyridine in the second phase of the process.

Where the maximum theoretical yield of 4-ethylpyridine is 50%, the process is referred to as phase and where the regenerated pyridine is further treated, without prior separation from the reaction mixture, the process is referred to as cyclic.

EXPERIMENTAL

Phase process (optimum conditions). To 200 g. of pyridine, in a flask equipped with a thermometer, a $\frac{1}{16}$ h.p. motor and a sealed stainless steel stirrer, was added 600 ml. of acetic

(6) H. S. Mosher, "The Chemistry of Pyridines, II" in Elderfield, *Heterocyclic Compounds*, Vol. I, p. 482, Wiley, New York, 1950.

(7) L. E. Tenenbaum and T. I. Fand, U. S. Patent 2,712,019 (1955).

anhydride. The temperature was raised to 80° C., and 165 g. of iron powder (Belmont Grade 98.5%) was added, in portions, over a 1-hr. period, maintaining the same temperature. Over a 0.5-hr. period 30 ml. of water was added and the temperature was not permitted to exceed 97° C. The mixture was cooled to 90° C. and 103 g. of iron powder was added, in portions, over a 0.5-hr. period, the temperature being maintained between 80–90° C. The temperature of the reaction mixture was raised to 136° C. over a 0.5-hr. period and reflux maintained for 1.5 hr. With provisions for cooling, 500 ml. of water was slowly and carefully added, not permitting the temperature to exceed 110° C. After the water was added, the pH of the mixture was adjusted to 9.5–10 with 50% caustic and then steam distilled. The oily layer of the steam distillate was separated and the lower aqueous phase was saturated with potassium carbonate and then extracted with three 175 ml. portions of benzene. The benzene extracts were combined with the oily layer, dried over anhydrous potassium carbonate, and fractionated at atmospheric pressure. The fraction, b.p. 145–167° C., n_D^{25} 1.500 was collected, 131.0 g. (49.5%). Redistillation of the product gave 120.3 g., b.p. 160–167° C., yield, 45.5%. By titration of the lower boiling fractions with standard alkali, 92 g. as pyridine was accounted for.

Cyclic process. From a series of 12 runs, the following procedure was found to give optimum yields. Employing the same apparatus, as previously described for the phase process, 100 g. of pyridine and 300 ml. of acetic anhydride were heated to 80° C. and 84 g. of iron powder was gradually added over a 0.5-hr. period. The temperature was maintained at 80° C. for 1.5 hr., 30 ml. of acetic acid was added followed by the gradual addition of 42 g. of iron powder over 0.5-hr. Then 150 ml. of acetic anhydride was added and the temperature raised to 137° C. and maintained there for 1 hr. An additional 100 ml. of acetic anhydride was then added, permitting the temperature to fall to 127° C. Over the next 0.5-hr., 50 g. of iron powder was gradually added and the temperature rose to 136° C. The very viscous reaction mixture was stirred vigorously for 0.5 hr. and 60 ml. of acetic acid were added, producing a more fluid reaction mixture. At 136° C., a fourth gradual addition of 25 g. of iron powder was made over a 0.5-hr. period, and reflux maintained for 0.5 to 1 hr. Water and 50% caustic were then carefully added, permitting the temperature to remain above 100° C., while applying cooling. The reaction mixture was then treated as previously described. The crude yield was 102 g. of product, b.p. 145–170° C., n_D^{25} 1.500 (78%). Four grams of product boiling above 170° C. were also obtained, n_D^{25} 1.499. Fractionation of the crude resulted in a product, b.p. 160–167° C., n_D^{25} 1.500, neutralization equivalent 109, yield 70.5% of theory.

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Derivatives of (1-Aminocyclohexyl)methanol

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Nitrocyclohexane undergoes base-catalyzed condensations with formaldehyde to give (1-nitro-

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