N^1,N^4-Dipyrazinoylsulfanilamide.—To 1.1 g. (0.004 mole) N^4-pyrazinoylsulfanilamide and 1.0 g. (0.007 mole) of pyrazinoyl chloride was added 12 cc. of dry pyridine. The mixture was refluxed gently for one hour, cooled, and diluted with 100 cc. of ice water. The product was precipitated by strongly acidifying with concentrated hydrochloric acid and the precipitate filtered and washed several times with water. The product was then dissolved in 400 cc. of 95% alcohol and decolorized with activated charcoal. The volume of alcohol was reduced until precipitation occurred. The yield was 0.5 g. (33%).

An alternate procedure for purification consists of dissolving the impure product in sodium hydroxide (*p*H 8), decolorizing with activated charcoal and precipitating with hydrochloric acid.

N^4-Acetyl-N^1-pyrazinoylsulfanilamide.—To 1.5 g. (0.007 mole) of N^4-acetylsulfanilamide and 1.0 g. (0.007 mole) of pyrazinoyl chloride was added 12 cc. of dry pyridine. The mixture was refluxed gently for one hour, cooled, and diluted with 100 cc. of ice water. Precipitation was induced by strongly acidifying with concentrated hydrochloric acid. The precipitate was collected on a filter and washed several times with water. The crude product was decolorized (activated charcoal) and recrystallized from 50% alcohol and dried, yield 0.4 g. (20%).

N^1-Pyrazinoylsulfanilamide.—Two cc. of 10% sodium hydroxide was added to 0.3 g. of N^4-acetyl-N^1-pyrazinoylsulfanilamide. The mixture was heated gently for ten minutes, cooled, and strongly acidified with hydrochloric acid to precipitate the crude product. The precipitate was collected, washed with ice water, recrystallized from 50% alcohol, and dried; yield approximately 30%.

Acknowledgment.—The authors are indebted to the Research Laboratory of Mead Johnson and Company, Evansville, Indiana, for their generous supply of the pyrazinoic acid used in this study.

Summary

1. The name pyrazinoic acid is proposed for pyrazine monocarboxylic acid.

2. Five new pyrazinoyl derivatives of sulfanilamide have been prepared and described. The compounds were obtained by treating (impure) pyrazinoyl chloride with the appropriate sulfanilamide derivative.

3. There is reason to expect that some of the compounds may be of pharmacologic interest.

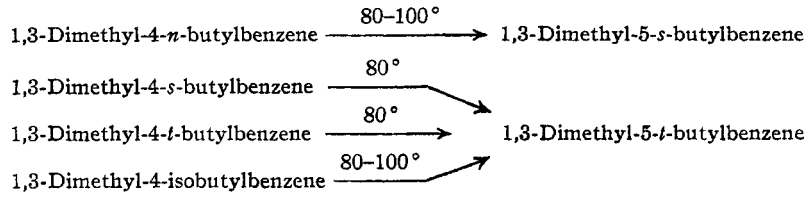
SAN FRANCISCO, CALIFORNIA RECEIVED JULY 24, 1940

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, UNIVERSITY OF MISSOURI]

The Action of Anhydrous Ferric Chloride on Alkylbenzenes[1]

BY DOROTHY NIGHTINGALE, RICHARD G. TAYLOR AND H. WAYNE SMELSER

The principal changes which take place when the 1,3-dimethyl-4-butylbenzenes are warmed with ferric chloride parallel for the most part those reactions which take place when these hydrocarbons react with aluminum chloride.[1a] A higher temperature is required, however, especially in the case of the 4-*n*-butyl and 4-isobutyl hydrocarbons. While pure 1,3-dimethyl-5-*t*-butylbenzene was not isolated from the reaction products of this latter hydrocarbon, the trialkyl fraction contains the 5-*t*-butyl hydrocarbon. The rearrangement reactions may be summarized as follows



The 1,3-dimethyl-4-propyl- and 4-ethylbenzenes do not form appreciable amounts of 1,3,5-hydrocarbon even on heating with ferric chloride at 150° for six hours. With aluminum chloride, the yields of 1,3,5-hydrocarbon under comparable conditions were approximately 45%.[2]

These results illustrate not only the effect of temperature but also of the structure of the radical in the 4 position on the ease with which the radical migrates. The secondary and tertiary butyl radicals migrate more readily than the primary radicals.

The trialkyl fraction from the 4-*t*-butyl hydrocarbon after heating with ferric chloride for three hours at 65–70° was mainly unchanged hydrocarbon. At 80° for one and one-half hours, the yield of 1,3,5-hydrocarbon was 68%. Similar results were obtained with the 4-*s*-butyl hydrocarbon.

Some 1,3,5-hydrocarbon was formed from the 4-*n*-butyl hydrocarbon when the time and temperature of the reaction were increased. The trinitro derivative of 1,3-dimethyl-5-*s*-butylbenzene was not isolated from the nitra-

(1) Original manuscript received October 16, 1939.

(1a) Nightingale and Smith, THIS JOURNAL, **61**, 101 (1939).

(2) Nightingale and Carton, *ibid.*, **62**, 280 (1940).

tion product of the trialkyl fraction, but some of the diacetamino derivative was obtained.

The trialkyl fraction from the 4-isobutyl hydrocarbon would not solidify at −70°, but nitration of this product yielded some trinitro-1,3-dimethyl-5-*t*-butylbenzene.

A comparison of the amounts of the various fractions from the butyl hydrocarbons when treated with ferric chloride and with aluminum chloride shows a larger trialkyl fraction, larger amounts of high boiling product, and a much smaller amount of material unaccounted for when ferric chloride is used.

The fractions boiling above the trialkyl fraction contain halogen, but no one product was isolated from them. Since ferric chloride is a chlorinating agent as well as a condensing agent for alkylations, these fractions are probably a mixture of highly alkylated benzenes and any halogen compounds which may be formed.

These data substantiate the observations by Ipatieff and Pines[3] that a tertiary butyl group splits off from the benzene ring more readily than a secondary butyl group, and that the butyl group is more readily cleaved than an isopropyl group. They report no data for primary radicals larger than ethyl. To confirm this relationship further, the butyl hydrocarbons were heated with decahydronaphthalene in the presence of aluminum chloride according to the directions of Ipatieff and Pines.[3] No butanes were obtained from the *n*-butyl and isobutyl hydrocarbons at temperatures up to 75° whereas the yields of butane from the *t*-butyl and *s*-butyl hydrocarbons were 41 and 24%, respectively, at 60°.

The failure of ferric chloride to promote the migration of alkyl groups as effectively as does aluminum chloride may be due in part to chlorination rather than rearrangement of those hydrocarbons such as 1,3-dimethyl-4-*n*-propylbenzene in which the radical is more firmly held in the 4 position. During this process the ferric chloride is reduced to the inactive ferrous chloride. In an atmosphere of nitrogen, freshly prepared anhydrous ferrous chloride did not react with either 1,3-dimethyl-4-*t*-butyl- or 4-isopropylbenzene under the conditions for the reactions with ferric chloride or aluminum chloride. Rearrangement must therefore take place before all the ferric chloride is reduced.

Cyclopropane and *m*-xylene react in the presence of ferric chloride to form 1,3-dimethyl-4-*n*-propylbenzene in 19% yield as compared with a 44% yield with aluminum chloride as the catalyst under the same experimental conditions.[2] No propylbenzene was formed from benzene and *n*-propyl formate with ferric chloride in place of aluminum chloride, using Bowden's[4] experimental conditions for the reaction. *n*-Butyl formate also failed to react with benzene under these conditions. Benzene and *t*-butyl chloride with ferric chloride as the catalyst gave a good yield of *t*-butylbenzene.

The diacetamino and dibenzamino derivatives of the trialkylbenzenes have been more satisfactory than the trinitro derivatives for purposes of identification. Yields of these derivatives are good and mixtures of isomers show satisfactory melting point depressions. Some of the hydrocarbons such as 1,3-dimethyl-4-isobutyl- and 4-*n*-butylbenzene either have not formed a solid trinitro derivative at all or in poor yield.[1] It may be, however, that the individual di-derivatives of these trialkylbenzenes are mixtures due to the possible initial formation of two dinitro compounds, but melting points are reproducible provided the nitrations are carried out carefully at *low* temperatures.

Acknowledgments.—The authors wish to thank E. I. du Pont de Nemours and Company for the gift of *m*-xylene and the University Research Council for a grant for the purchase of other chemicals for this investigation.

Experimental

The hydrocarbons were all prepared by procedures described in previous publications.[1,2] The anhydrous ferric chloride was "Reagent" quality of the General Chemical Company.

The rearrangement products were identified by means of their trinitro or diacetamino derivatives and by their freezing points.

Rearrangements with Ferric Chloride.—The ferric chloride was added directly to the hydrocarbon. The mixture warmed up spontaneously to about 40° in most cases. Hydrogen chloride was evolved rapidly. The flask was heated in a water-bath until the evolution of hydrogen chloride slackened. The material was poured on ice, extracted with ether, washed free of iron salts, dried and vacuum distilled through a column packed with single turn glass helices. The wash water contained ferrous salts. The high boiling fractions contained halogen.

1,3-Dimethyl-4-*t*-butylbenzene.—The hydrocarbon (30 g.) was warmed with ferric chloride (7.6 g.) at 80° for one and one-half hours. Distillation at 17 mm. yielded the

(3) Ipatieff and Pines, THIS JOURNAL, **59**, 56 (1937).

(4) Bowden, *ibid.*, **60**, 645 (1938).

following fractions: (I) 1 g. 35–91°; (II) 20 g. 91–92°; (III) 4 g. 93–97°; 3 g. residue. The freezing point of II was −21 to −22°. The diacetamino derivative melted at 310° and did not depress the melting point of diacetamino 1,3-dimethyl-5-*t*-butylbenzene.

1,3-Dimethyl-4-*s*-butylbenzene.—The hydrocarbon (31 g.) was warmed with ferric chloride (7.8 g.) for one and one-half hours at 80°. The reaction products were fractionated at 17 mm.: (I) 3 g. 35–91°; (II) 17 g. 91–92°; (III) 5 g. 93–97°; (IV) 4 g. above 97°.

The freezing point of II was −21° and the freezing point of a mixture of this fraction and the trialkyl fraction from the 4-*t*-butyl hydrocarbon was also −21°. The diacetamino derivative melted at 310° and did not depress the melting point of diacetamino-1,3-dimethyl-5-*t*-butylbenzene. These data identified this product as 1,3-dimethyl-4-*t*-butylbenzene.

1,3-Dimethyl-4-*n*-butylbenzene.—The hydrocarbon (27 g.) was warmed with ferric chloride (6.8 g.) at 80–100° for two and one-fourth hours. The reaction at 80° was not as vigorous as with the preceding hydrocarbons and the temperature was raised to 100° toward the end of the period. The reaction products were fractionated at 17 mm.: (I) 1 g. 35–91°; (II) 11 g. 91–94°; (III) 7 g. 94–105°; (IV) 5 g. above 105°.

Fraction II became slightly viscous at −70° but would not solidify. A few crystals separated from the oily nitration product but they were not trinitro-1,3-dimethyl-5-*s*-butylbenzene. The small amount of crude diacetamino derivative melted at 270°. Repeated extraction of the product with ether raised the melting point to 278° and the melting point of this material and diacetamino-1,3-dimethyl-5-*s*-butylbenzene was 278–280°.

1,3-Dimethyl-4-isobutylbenzene.—The hydrocarbon (21 g.) was warmed with ferric chloride (5.4 g.) for two and one-fourth hours at 80–100°. The reaction product yielded the following fractions at 22 mm.: (I) 1 g. 35–91°; (II) 11 g. 9–94°; (III) 2 g. 94–105°; (IV) 6 g. above 105°.

Fraction II would not solidify at −70°. After standing some time, crystals of trinitro-1,3-dimethyl-5-*t*-butylbenzene, m. p. 113°, separated from the oily nitration product of this fraction. This fraction therefore contains 1,3-dimethyl-5-*t*-butylbenzene. The melting point of the diacetamino derivative could not be raised above 260°.

The 1,3-Dimethyl-4-propylbenzenes.—The 1,3-dimethyl-4-*n*-propylbenzene (32 g.) and 8 g. of ferric chloride were heated for six hours at 150°. The products of the reaction were fractionated at 8 mm.: (I) 2 g. 40–70°; (II) 12 g. 72°; (III) 7 g. 100°; 5 g. residue.

The diacetamino derivative of II melted at 284° and did not depress the melting point of the diacetamino derivative of 1,3-dimethyl-4-*n*-propylbenzene.

At lower reaction temperatures there was less high boiling material and less residue.

Similar results were obtained with **1,3-dimethyl-4-isopropylbenzene** and **1,3-dimethyl-4-ethylbenzene.** The only products isolated were the unchanged 1,3,4-hydrocarbons.

Alkylations in the Presence of Ferric Chloride.—The alkylation of *m*-xylene with cyclopropane was carried out as previously described[2] with 120 g. of *m*-xylene, 15 g. of cyclopropane, and 9 g. of ferric chloride. The yield of **1,3-dimethyl-4-*n*-propylbenzene was 19%.**

A mixture of 105 g. of benzene and 12 g. of ferric chloride was cooled to 10° and 25 g. of *t*-butyl chloride added. No hydrogen chloride was evolved at this temperature, but when the temperature was raised to 26°, the reaction proceeded smoothly. The yield of ***t*-butylbenzene** was 80%. The wash water contained ferrous ion.

Derivatives.—The procedure for the preparation of the diacylamino derivatives of the trialkylbenzenes is essentially that of Ipatieff and Schmerling[5] with some necessary precautions. The nitrating mixture (5 to 8 cc.) of 2:1 sulfuric acid (d. 1.84) nitric acid (d. 1.42) in a test-tube was cooled to −8 to −18° and stirred mechanically while 1 cc. of the hydrocarbon was added dropwise. The mixture was stirred five to ten minutes after all the hydrocarbon was added, and then allowed to come to room temperature. The product was poured onto cracked ice, extracted with ether, and washed with 20% sodium carbonate solution and with water until the aqueous layer was colorless. The nitro compound was reduced and the diamine isolated as described by Ipatieff and Schmerling.[5] The ether extract of the aqueous solution was discarded. After evaporation of the ether extract of the alkaline solution (30% sodium hydroxide), 5 cc. of pure acetic anhydride was added to the diamine and the mixture allowed to stand until the acylation was complete (sometimes two days). Benzoylation of the diamine was carried out by the usual Schotten–Baumann procedure. The derivatives could be purified by crystallization from alcohol, but repeated extraction with ether was equally effective. The dibenzamino derivatives were less satisfactory than the diacetamino derivatives for purposes of identification. Mixtures of isomeric dibenzamino derivatives do not show as large melting point depressions as do the diacetamino derivatives.

A copper block was used for all melting point determinations. The higher melting isomers sublime somewhat with slight decomposition at the melting point.

TABLE I

DERIVATIVES[a]

	$RC_6H(CH_3)_2(NHCOCH_3)_2$		$RC_6H(CH_3)_2(NHCOC_6H_5)_2$	
R	M. p., °C.	Nitrogen, % calcd.: 10.14	M. p., °C.	Nitrogen, % calcd.: 7.00
4-*n*-Butyl	240	9.90	225	7.00
4-Isobutyl	255	10.15	210	6.97
4-*s*-Butyl	266	9.97	195	6.86
4-*t*-Butyl	294	9.96	310	7.13
5-*s*-Butyl	278	10.02	255	6.85
5-*t*-Butyl	310	9.88	285	7.14

[a] Semi-micro analyses by R. G. Taylor.

The 1,3-Dimethyl-4-butylbenzenes with Decalin.—The procedure used was that of Ipatieff and Pines.[3] The same amounts of reagents were used for all the reactions: 15 g. of hydrocarbon, 8 g. of aluminum chloride, and 25 g. of decahydronaphthalene. The reaction mixture was heated at 60° for one and one-half hours.

The yield of isobutane from the 4-*t*-butyl hydrocarbon was 4.2 cc., b. p. −10 to 0°, all but about 0.5 cc. distilling at −10°. From the 4-*s*-butyl hydrocarbon the yield of butane was 2.4 cc., b. p. −10 to 0°.

(5) Ipatieff and Schmerling, THIS JOURNAL, 60, 1476 (1938).

No butane was obtained from either the **4-*n*-butyl** or **4-isobutyl** hydrocarbon, even when the mixture was heated at 75° for an additional three hours.

1,3-Dimethyl-4-ethylbenzene and Aluminum Chloride.—The hydrocarbon (30 g.) and aluminum chloride (9 g.) were heated at 130° for six hours. The following fractions were obtained at 7 mm.: (I) 2 g. 40–54°; (II) 4 g. 54–60°; (III) 12 g. 60–73°; 7 g. residue.

The trinitro derivative of III melted at 126° and did not depress the melting point of trinitro-1,3-dimethyl-4-ethylbenzene m. p. 126°, recorded value 129°.[6] Some 1,3,-5 isomer may have been formed, however.

Summary

The 1,3-dimethyl-4-*s*- and 4-*t*-butylbenzenes undergo rearrangement to 1,3-dimethyl-5-*t*-butylbenzene when warmed with ferric chloride at 80°.

Some 1,3-dimethyl-5-*t*-butylbenzene is formed from the 4-isobutyl hydrocarbon, but a higher temperature is required. This is also true of the 4-*s*-butyl hydrocarbon.

Only unchanged 1,3,4-hydrocarbon was isolated from the two 1,3-dimethyl-4-propylbenzenes and 1,3-dimethyl-4-ethylbenzene, after warming them with ferric chloride at temperatures up to 150°.

(6) Smith and Kiess, THIS JOURNAL, **61**, 994 (1939).

COLUMBIA, MISSOURI RECEIVED OCTOBER 21, 1940

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

The Chlorination of Pyrimidine Thiocyanates[1]

BY TREAT B. JOHNSON[2] AND GYULA DE SÜTÖ-NAGY[3]

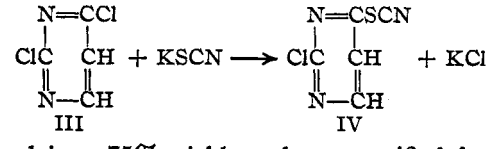
The remarkable chemotherapeutic success attained by sulfanilamide, sulfapyridine and sulfathiazole led the authors to attempt the synthesis of some sulfonamide derivatives in the pyrimidine series. That the synthesis of such constructions might open up a new route to a new type of useful therapeutical agents was postulated by one of the authors[4] (de S.-N.) already in 1938.

In a recent United States Patent issued under the title "Sulfonyl Halides"[5] is described a method for the commercial production of sulfonyl chlorides II by the action of aqueous chlorine on organic thiocyanates I.[6]

$$\underset{\text{I}}{\text{R—SCN}} + 3\text{Cl}_2 + 2\text{H}_2\text{O} \longrightarrow \text{CNCl} + 4\text{HCl} + \underset{\text{II}}{\text{R—SO}_2\text{Cl}}$$

This reaction has proved of wide application whether the organic nucleus R attached to the —SCN group in I, is substituted or unsubstituted, and whether it is alkyl, aryl, arylalkyl and alicyclic in nature. The mechanism of this reaction was discussed in a recent publication from this Laboratory.[7]

Attempts have now been made by the authors to apply this technique for the preparation of sulfonyl chlorides to a thiocyanate of the pyrimidine series. The pyrimidine chosen for preliminary investigation was 2-chloro-6-thiocyanopyrimidine IV, already described by Chi and Chen,[8] and which is prepared by interaction of 2,6-dichloropyrimidine[9] III with potassium thiocyanate. The thiocyanate IV was easily obtained in a 75% yield, and was purified for our work by crystallization from absolute alcohol and melted at 125–126°.



(1) Researches on Pyrimidines, CLXVI.

(2) This investigation was supported in part by a grant from the George Sheffield Research Fund of the Sheffield Scientific School of Yale University. This preliminary paper is presented at this time on account of the resignation of Dr. de Sütö-Nagy to accept the opportunity to undertake new work in the field of physiological chemistry. While the investigation is incomplete the authors desire to file a record at this time of their preliminary observations. The research will be continued by the senior author.

(3) Assistant Professor in the Institute of General Pathology, Royal Hungarian University of Budapest, Hungary, on sabbatical leave for 1939–1940.

(4) Experiments of C. Moncorps and O. Gunther (*Klin. Wochschr.*, 979 (1933), and those of G. de Sütö-Nagy (Kliebert: Congr. Hungarian Physiol. Soc. 1938, Ref.: *Orvosi Hetilap*, 1938, No. 38) suggest that certain pyrimidines of the cytosine type may actually stimulate the characteristic function of the reticuloendothelial system in the animal organism.

(5) "Sulfonyl Halides," by Treat B. Johnson (to Röhm and Haas Company), U. S. Patent No. 2,174,856 (September 26, 1939); *Chem. Abstr.*, **34**, 778 (1940). See also "Process of preparing sulfonyl halides and sulfonic acids from pseudothioureas," U. S. Patent No. 2,146,744 (February 14, 1939).

(6) T. B. Johnson and I. B. Douglass, THIS JOURNAL, **61**, 2548 (1939).

(7) T. B. Johnson, *Proc. Natl. Acad. Sci.*, **25**, 448 (1939).

(8) Yuoh-Fong Chi and Yun-Chwang Chen, *J. Chem. Eng.* (China), **5**, 35 (1938).

(9) S. Gabriel, *Ber.*, **38**, 1690 (1905); T. B. Johnson and G. Menge, *J. Biol. Chem.*, **2**, 114 (1906).