

- (4) R. Brandes, "Ueber das Delphinin," *Schweigger's J. f. Chem. u. Phys.*, 25, 369-78 (1819).
- (5) J. P. Couerbe, "De la delphine," *Ann. Chim. Phys.*, (2) 52, 359-68 (1833). Also in *Ann. der Chem.*, 9, 101-8 (1834).
- (6) H. Dieterle, "Datura alba Nees," *Arch. Pharm.*, 264, 140-64 (1926).
- (7) J. Erdmann, "Ueber Delphinin," *Arch. Pharm.*, 117, 43-6 (1864).
- (8) M. O. Henry, "Sur la delphine et la solanine," *J. Pharm.*, 18, 661-6 (1832).
- (9) C. Kara-Stojanow, "Ueber die Alkaloide des *D. staphisagria*," *Pharm. Zeitsch. f. Russland*, 29, 628-30, 641-8, 657-64, 673-8, 689-92, 705-8, 721-6 (1890). This article is abstracted in *J. Chem. Soc. (Br.)*, 60, 842-3 (1891).
- (10) J. Katz, "Ueber die Alkaloide des *D. staphisagria*," *Pharm. Ztg.*, 735-6 (1900).
- (11) O. Keller, "Untersuchungen über die Gruppe der Helleboreen," *Arch. Pharm.*, 263, 274-93 (1925).
- (12) J. L. Lassaigne and H. Feneulle, "Analyse de la staphisaigre," *Ann. Chim. Phys.*, 12, 358-71 (1819).
- (13) L. N. Markwood, "The Isolation and Properties of the Alkaloids and Oil of Larkspur Seed (*Delphinium consolida*)," THIS JOURNAL, 13, 696-702 (1924).
- (14) Marquis, "Ueber die Alkaloide des *D. staphisagria*," *Arch. exptl. Path. und Pharmakol.* 7, 55-80 (1877). Also in *Pharm. Zeitsch. f. Russland*, 16, 449-59, 481-92, 513-22 (1877). Abstracted in *Jahresbericht*, 894-897 (1877).
- (15) J. Serck, "Beitrag zur Kenntniss des Delphinins," Dissertation, Dorpat (1874.)
- (16) B. Studer, "Ueber die Alkaloide der *Staphisagria*," *Schweiz. Wochenschrift f. Pharm.* 10, 132-4 (1872). Abstracted in *Jahresbericht über die Fortschritte der Pharmacognosie*, 7, 148 50 (1872).
- (17) Thomas Walz, "Delphinin," *Arch. Pharm.*, 260, 9-26 (1922).

CHLORINATION OF ANTIPYRINE. I. CHLOROANTIPYRINE.*

BY W. O. EMERY.

While the apparent ease with which antipyrine responds to the action of chlorinating agents has been noted by several investigators, its behavior in this respect has not apparently been accorded the importance it merits. Schweisinger¹ observed the formation of a white precipitate on treating antipyrine with an aqueous solution of calcium hypochlorite. Gay and Fortune,² on the other hand, found that this reagent is without effect on antipyrine in the cold, but does yield on boiling a yellow solution. Berenger³ reported that chlorine water, as also sodium hypochlorite solution, loses in contact with antipyrine its characteristic odor, yielding with the former a white precipitate. Michaelis and co-workers (Röhmer and Pasternack resp.)⁴ prepared by the action of phosphoroychloride on antipyrine the dichloro substitution product, $C_{11}H_{12}N_2Cl_2$, from which alkali readily regenerates the mother substance. In a study of the behavior of iodo- and bromoantipyrine toward potassium iodide and hydrochloric acid, Bougault⁵ mentioned a chloroantipyrine corresponding apparently with the composition, $C_{11}H_{11}N_2ClO$,

* Contribution from Special Collaborative Investigations, Bureau of Chemistry, U. S. Dept. of Agriculture.

¹ *J. Pharm. Chim.* (V), 11, 31 (1885).

² *Ibid.*, (V), 17, 596 (1888).

³ *Ibid.*, (V), 18, 393 (1903).

⁴ *Ber.*, 31, 3194 (1898); 32, 2398 (1899).

⁵ *J. Pharm. Chim.* (VII), 20, 248 (1919).

which he obtained, according to Leulier,¹ by the action of alkaline hypochlorites on antipyrine. Leulier made a somewhat specialized study of this reaction, employing as chlorinating agent a "liqueur de Labarraque" alkaline to litmus and with an active chlorine strength varying from 20 to 34 Gm. per liter. His yields of chloroantipyrine were, however, far from satisfactory, and the product, moreover, of only moderate purity. Even after recrystallization it retained a yellowish cast, and gave the same color tests as the mother substance (red with ferric chloride, green with sodium nitrite and acetic acid), facts explaining in all probability the relatively low chlorine content reported (about 1% under the theoretical), and, as will be subsequently shown, a melting temperature some five degrees below that of the chemically pure substance.

Some time ago the writer had occasion, in connection with a study of the progressive halogenation of antipyrine, to observe the marked difference in behavior of chlorine toward antipyrine in solvents like water, methanol, acetic acid and chloroform. The results obtained in these operations varied to such an extent, and were so unusual when viewed from the manner in which iodine and bromine in particular react with antipyrine, that further study seemed justified. While there is every reason to believe that the reaction is inaugurated in accordance with the equations:



it has not been possible in any of the experiments so far undertaken with free chlorine to intercept or isolate monochloroantipyrine, the substance primarily sought and comparable with iodo- and bromoantipyrine. In every instance where this compound might reasonably be expected, only higher chlorinated products appeared containing two, three or more atoms of chlorine to the molecule, according to the particular solvent employed during chlorination. These results would seem to show that chloroantipyrine, if and when formed as above indicated, has an equal or greater affinity for chlorine than the mother substance, and is therefore immediately after formation converted into higher chlorinated derivatives. Shortly after this the writer's attention was directed to Bougault's reference to this product by Leulier's work on chloroantipyrine, and it was accordingly deemed expedient to repeat the latter's experiments in part with a view to betterment of his procedure and preparation of chloroantipyrine in chemically pure condition, preliminary to a careful study of its properties, more especially of its behavior toward chlorine. While the chlorinating agent employed by Leulier was a "liqueur de Labarraque," alkaline to litmus and with an active chlorine content varying from 20 to 34 Gm. per liter, that used by the writer was an alkaline aqueous solution containing approximately 20% sodium hypochlorite.

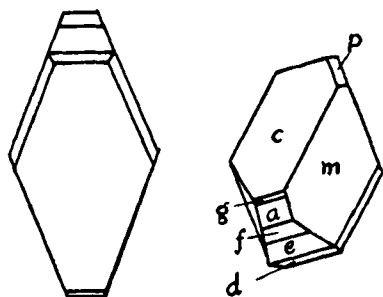
EXPERIMENTAL.

Sodium Hypochlorite.—To prepare this reagent for use in chlorinating antipyrine, a 40% solution of sodium hydroxide in water is first chilled to the temperature of melting ice, then treated with chlorine to a point just under complete conversion to sodium chloride and sodium hypochlorite, so that the solution will

¹ *J. Pharm. Chim.* (VII), 29, 447 (1924).

after filtration (by suction on a small porous plate) from precipitated sodium chloride still be distinctly alkaline to litmus and contain about 20% sodium hypochlorite. Should the treatment with chlorine have been excessive, the desired alkalinity may be restored through addition of a few drops of concentrated caustic soda.

Chloroantipyrine.—To a solution of 5 Gm. of antipyrine in 25 cc. of water chilled to about 5° add 20 cc. of the above reagent likewise chilled to the same temperature. Stir vigorously with a thermometer or glass rod, allowing the temperature to rise slowly until at about 10° a straw-yellow precipitate begins to separate, and increases rapidly in volume with rise in temperature to about 16°. Dilute with 25 to 30 cc. of cold water, stirring the while, and when no further increase in amount of precipitate is perceptible, filter rapidly on a small suction plate and wash several times with cold water. Yield, about 4.5 Gm. dry product, which viewed under the microscope is seen to consist of diamond-shaped leaflets. These melted at 127–8°. To purify, treat the crystals in 2.5 Gm. portions with about 200 cc. of boiling water, and after almost complete solution pass the liquid through a wet-folded filter in order to eliminate a small amount of difficultly soluble tarry material, then set aside to cool, whereupon the filtrate slowly deposits faint yellow leaflets melting about 127–8° (Leulier 123–4°). A second similar treatment with



Crystal graph of Chloroantipyrin.

boiling water yields pale straw-colored leaflets melting about 128–9°. A final recrystallization from dilute methyl alcohol (following previous contact with purified animal charcoal) should give snow-white crystals melting at 129°. On allowing an alcoholic solution of the compound thus purified to slowly evaporate, transparent measurable crystals are obtained. Larger and more beautiful ones result from the spontaneous evaporation of a dilute solution of the product in a mixture of methyl and isopropyl alcohols.

Chloroantipyrine is a colorless, odorless solid permanent in the air, melting at 129° and crystallizing from water mostly as snow-white laminated aggregates, from alcohol in single and multiple plates or pyramidal forms of the monoclinic system. The product subjected to crystallographic examination¹ consisted of clear, brilliant pyramidal crystals about 7 to 8 mm. long, 4 to 5 mm. broad and of varying thickness. They were unusually distorted due to the over-development of the back domes and the pyramid, while the elongation of the prisms along the *c* axis frequently lead to coffin-shaped crystals. The latter were measured on the two-circle reflecting Goldschmidt goniometer, being oriented on the prism zone. The reflections as a rule were excellent, the front dome *g* and the back dome *f*, however, yielded poor reflections. The measurements recorded are the average reflections from ten crystals.

The optical examination,² checked by a monochromatic illuminator, showed the refractive indices to be: n_{α} 1.501 (± 0.002); n_{β} 1.680 (only approximate, since the substance is somewhat soluble in the immersion liquid); n_{γ} 1.733 (and

¹ Carried out by Mr. Raymond M. Hann of the Oil, Fat and Wax Laboratory, Bureau of Chemistry.

² Courtesy of Mr. G. L. Keenan of the Microchemical Laboratory, Bureau of Chemistry.

ANGLES OF CHLOROANTIPYRINE.

Monoclinic, prismatic. Symbols.				a:b:c = 2.8527:1:0.9732, $\beta = 63^\circ 15'$.				
No.	Let- ter.	Miller.	Goldschmidt.	Description.	Observed.		Calculated.	
					φ	ρ	φ	ρ
1	c	001	0	Prominent	90°	26° 45'	90°	26° 45'
2	a	100	$\infty 0$	Prominent	90°	90°	90°	90°
3	m	110	∞	Prominent	21° 26'	90°	21° 26'	90°
4	g	301	+30	Minute, rarely present	90°	58°	90°	58° 12'
5	d	201	$\bar{2}0$	Sometimes absent	90°	15°	90°	14° 35'
6	e	401	$\bar{4}0$	Largest back dome	90°	45° 56'	90°	45° 41'
7	f	501	$\bar{5}0$	Poorly developed	90°	57±	90°	54° 35'
8	p	111	$\bar{1}1$	Prominent	6° 56'	44° 26'

soluble). In parallel polarized light, nicols crossed: birefringence extremely strong. In convergent polarized light, crossed nicols: partial biaxial interference figures, usually showing one optic axis up.

Chloroantipyrine is as one might reasonably expect more resistant to the action of nascent hydrogen than the corresponding bromine and iodine derivatives. Thus, when treated in methanol-acetic acid solution with zinc dust, no reduction of chloroantipyrine takes place, while such treatment in the case of bromo- and iodoantipyrine effects only partial reduction of the former, but complete conversion of the latter to antipyrine. However, with hydrogen and platinum *via* Voorhees and Adams¹ all three derivatives are uniformly reduced to antipyrine.

Analysis. Calculated for $C_{11}H_{11}N_2ClO$: C, 59.31; H, 4.98; N, 12.59; Cl, 15.93. Found: C, 59.22; H, 5.02; N, 12.70; Cl (Carius), 15.84.

The *periodide*, $(C_{11}H_{11}N_2ClO)_2 \cdot HI \cdot I_2$, dark ruby-red prisms, and the *picrate*, $C_{11}H_{11}N_2ClO \cdot C_6H_3N_5O_1$, chrome-yellow acicular crystals melting 117–8°, were prepared by the usual methods.

SUMMARY.

A method has been perfected for the preparation of chloroantipyrine in chemically pure form.

WASHINGTON, D. C.

VOLUMETRIC DETERMINATION OF STRYCHNINE AND BRUCINE IN NUXVOMICA AND ST. IGNATIUS BEAN.

Volumetric determination of total alkaloids: Dissolve the alkaloids obtained and purified as directed in a former article (Y. B., 1921, 252) in an excess of hot N/10H₂SO₄ and titrate the H₂SO₄ consumed. *Destruction of brucine:* Add to the neutral liquid obtained in the preceding titration 2.5 cc. of 50 per cent H₂SO₄ for each Gm. of total alkaloids. Evaporate the solution to 15 cc., cool and add as many times 15 cc. of a mixture of equal parts of HNO₃ (sp. g. 1.42) and water as there are Gm. of total alkaloids. *Determination of strychnine:* At the end of 1 hour make the red liquid obtained in the preceding operation alkaline with NaOH. Shake out the strychnine with several portions of CHCl₃. Add a measured excess of N/10H₂SO₄ to the CHCl₃ shakings and heat on a water-bath until all of the CHCl₃ has been driven off. Titrate the excess of acid with N/10NaOH. If S cc. of acid was consumed, then $S \times 0.0334 =$ Gm. of strychnine. $N - S = B$ cc. $B \times 0.0394 =$ Gm. of brucine.—E. Dufilho (*Bull. Soc. Pharm. Bordeaux*, 65, 7 (1927). Through *Ph. J. and Ph.*, Sept. 17, 1927.

¹ *J. Am. Chem. Soc.*, 44, 1397.