

3. A few chemical characteristics of these two hormones are also given.  
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[CONTRIBUTION FROM THE QUEEN'S COLLEGE, OXFORD]

## THE CONDENSATION OF BUTYL CHLORAL HYDRATE WITH ARYL HYDRAZINES

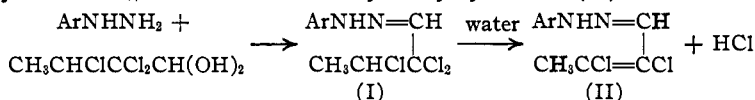
BY FREDERICK DANIEL CHATTAWAY AND HARRY IRVING

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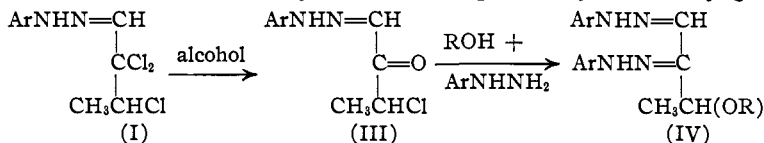
When butyl chloral hydrate is condensed with any aryl hydrazine, the hydrazone (I) first formed very readily undergoes a further reaction, the nature of which depends upon the solvent in which the change occurs.

In aqueous solution the initial hydrazone (I) loses hydrogen chloride and yields an  $\alpha,\beta$ -dichlorocrotonaldehyde-arylhydrazone (II).<sup>1</sup>

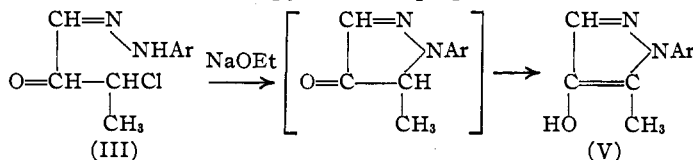


When, however, the condensation takes place in alcohol, the two  $\alpha$ -chlorine atoms of the initial hydrazone (I) are replaced by an atom of oxygen and a  $\beta$ -chloro- $\alpha$ -ketobutaldehyde-arylhydrazone (III) is formed.<sup>1</sup>

These ketonic hydrazones (III) are very interesting substances for, when heated with a substituted arylhydrazine and any alcohol, many of them yield sparingly soluble *osazones* (IV) in which not only is the  $\alpha$ -ketonic oxygen atom replaced by a hydrazine residue but also the remaining  $\beta$ -chlorine atom of the aldehyde chain is replaced by an alkoxy group.<sup>1</sup>



Again, when heated with an alcoholic solution of sodium ethoxide, these ketonic hydrazones (III) lose a molecule of hydrogen chloride, and ring closure takes place with the formation of the corresponding 4-hydroxy-1-aryl-5-methylpyrazoles (V).<sup>2</sup> This reaction affords a general means of synthesis for these hitherto unknown 4-hydroxypyrazoles which are isomeric with the well-known 3- and 5-pyrazolones prepared from acetoacetic ester.



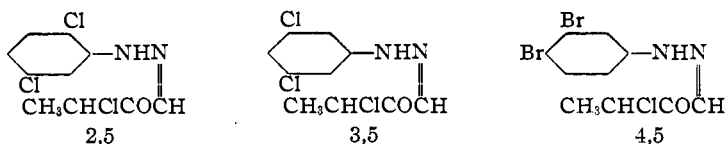
<sup>1</sup> Chattaway and Irving, *J. Chem. Soc.*, 87 (1930).

<sup>2</sup> Chattaway and Irving, *ibid.*, 786 (1931).

These reactions between butyl chloral hydrate and different arylhydrazines proceed with varying degrees of ease. With phenylhydrazine itself, and the three tolylhydrazines, the reaction, unless carefully controlled, may become very violent, when tarry products are formed from which nothing crystalline or definite can be isolated.<sup>3</sup> The introduction of halogens into the nucleus greatly moderates the violence of the initial reactions,<sup>3</sup> which proceed very smoothly when a 2,4-dihalogen substituted arylhydrazine is employed.<sup>1</sup>

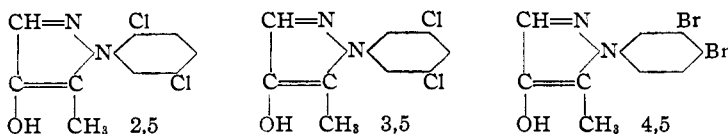
It was of interest, therefore, to investigate the effect upon the character of the reaction and the nature of the products of the presence of two halogen atoms in other positions, and of the presence of three halogen atoms in the 2,4,6-positions of the phenylhydrazine residue.

It has been found that in alcoholic solution 2,5-dichloro-, 3,5-dichloro- and 4,5-dibromophenylhydrazine hydrochlorides condense quietly and normally with butyl chloral hydrate and yield the corresponding  $\beta$ -chloro- $\alpha$ -ketobutaldehyde-arylhydrazones.



$\beta$ -Chloro- $\alpha$ -ketobutaldehyde-2,5-dichlorophenylhydrazone condenses with 2,5-dichlorophenylhydrazine hydrochloride when heated in methyl or ethyl alcoholic solution and  $\alpha$ -keto- $\beta$ -methoxy or ethoxy-butaldehyde-2,5-dichlorophenylosazone (Formula as IV) is formed. When butyl chloral hydrate and 2,5-dichlorophenylhydrazine condense in methyl alcohol, the ketonic hydrazone and the methoxy-osazone are formed together and must be separated by fractional crystallization.

When treated with an alcoholic solution of sodium ethoxide these ketonic hydrazones yield the corresponding 4-hydroxy-1-(2',5'-dichloro-, or 3',5'-dichloro-, or 4',5'-dibromophenyl)-5-methylpyrazoles



which closely resemble in properties the previously described members of the series.<sup>2</sup>

Since the introduction of two halogen atoms into the nucleus in any position so greatly lessens the violence of the reaction which takes place between butyl chloral hydrate and unsubstituted, or methyl substituted,

<sup>3</sup> Chattaway and Irving, *J. Chem. Soc.*, 751 (1931).

phenylhydrazine, it might be anticipated that the introduction of a third halogen atom would further modify the reaction and this is found to be the case.

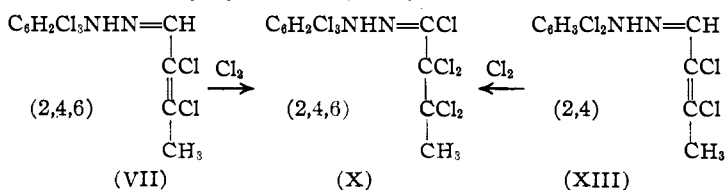
When butyl chloral hydrate and 2,4,6-trichlorophenylhydrazine hydrochloride interact in water, the unstable butyl chloral 2,4,6-trichlorophenylhydrazone (VI) first formed loses hydrogen chloride with the formation of  $\alpha,\beta$ -dichlorocrotonaldehyde-2,4,6-trichlorophenylhydrazone (VII) alone.

When, however, the interaction takes place in alcohol, this decomposition of the initial hydrazone (VI) proceeds only to a slight extent and only a small quantity of the unsaturated hydrazone (VII) separates. In the remainder of the butyl chloral 2,4,6-trichlorophenylhydrazone (VI) the two  $\alpha$ -chlorine atoms are hydrolyzed and replaced by an atom of oxygen with the formation of the pale yellow  $\beta$ -chloro- $\alpha$ -ketobutaldehyde-2,4,6-trichlorophenylhydrazone (VIII) which forms the bulk of the reaction product and remains dissolved in the mother liquors, whence it can only be separated and obtained free from the unsaturated hydrazone (VII) with the greatest difficulty.

When the unstable hydrazone (VI) formed by the interaction of butyl chloral hydrate and 2,4,6-trichlorophenylhydrazine hydrochloride in water is rapidly isolated by chloroform extraction, dried and warmed with acetic anhydride, acetylation occurs together with the hydrolysis of the two  $\alpha$ -chlorine atoms and *N*-acetyl- $\beta$ -chloro- $\alpha$ -ketobutaldehyde-2,4,6-trichlorophenylhydrazone (XI) is formed. This *N*-acetylhydrazone is also produced by the action of acetic anhydride upon  $\beta$ -chloro- $\alpha$ -ketobutaldehyde-2,4,6-trichlorophenylhydrazone (VIII) itself.

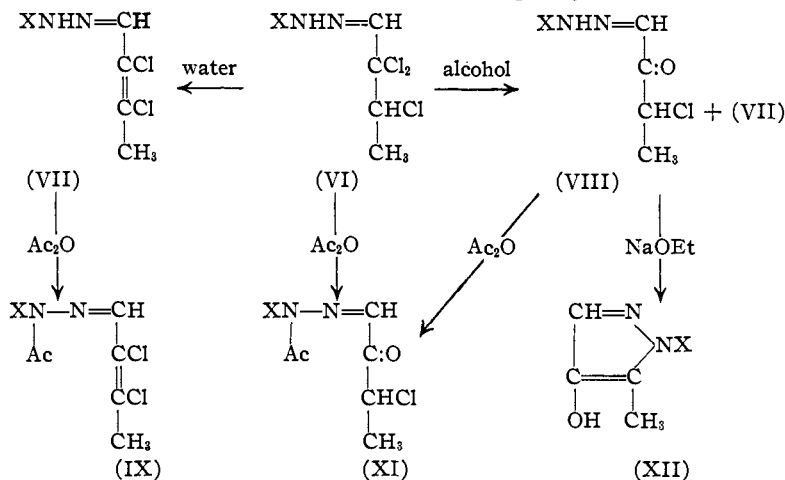
When  $\beta$ -chloro- $\alpha$ -ketobutaldehyde-2,4,6-trichlorophenylhydrazone (VIII) is warmed with an alcoholic solution of sodium ethoxide, loss of hydrogen chloride and ring closure take place with the formation of 4-hydroxy-1-(2',4',6'-trichlorophenyl)-5-methylpyrazole (XII) which forms a sodium salt, a well characterized colorless hydrochloride, and a 4-benzoate.

$\alpha,\beta$ -Dichlorocrotonaldehyde-2,4,6-trichlorophenylhydrazone (VII) yields a colorless monoacetyl derivative (IX) and when strongly reduced forms 2,4,6-trichloroaniline. On chlorination two atoms of chlorine are added at the double bond while a third substitutes the methine hydrogen atom yielding  $\omega,\alpha,\alpha,\beta,\beta$ -pentachlorobutaldehyde-2,4,6-trichlorophenylhydrazone (X) identical with the product of chlorination of  $\alpha,\beta$ -dichlorocrotonaldehyde-2,4-dichlorophenylhydrazone (XIII).<sup>1</sup>



A completely parallel series of reactions takes place when butyl chloral hydrate and 2,4,6-tribromophenylhydrazine hydrochloride interact in water, or in alcohol.

Thus, where X = 2,4,6-trichloro-, or tribromophenyl-



### Experimental Part

The Action of 2,5-Dichlorophenylhydrazine Hydrochloride upon Butyl Chloral Hydrate in Ethyl Alcohol: Formation of  $\beta$ -Chloro- $\alpha$ -ketobutaldehyde-2,5-dichlorophenylhydrazone (VI).—Ten grams of 2,4-dichlorophenylhydrazine hydrochloride (1 mol), 9 g. of butyl chloral hydrate (1 mol), and 75 cc. of ethyl alcohol were gently warmed together. As the reactants dissolved a bright red color developed and, when the boiling point of the alcohol was reached, a vigorous reaction set in, hydrogen chloride was freely evolved, and the alcohol continued to boil for some time without further heating. The bright red color gradually disappeared and the solution became pale yellow.

Half the alcohol was then distilled off and the concentrated solution left to cool, when  $\beta$ -chloro- $\alpha$ -ketobutaldehyde-2,5-dichlorophenylhydrazone separated as a mass of yellow crystals. It was collected, washed with a little cold ligroin and recrystallized from boiling alcohol, in which it was moderately soluble, and from which it separated in very slender flattened prisms of a pale lemon color, m. p. 142–143°.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_9\text{ON}_2\text{Cl}_3$ : Cl, 38.0. Found: Cl, 37.75.

The condensation of butyl chloral hydrate with 3,5-dichloro-, and with 4,5-dibromophenylhydrazine hydrochloride in ethyl alcohol proceeded similarly and yielded the following compounds.

$\beta$ -Chloro- $\alpha$ -ketobutaldehyde-3,5-dichlorophenylhydrazone separated as compact prisms of a dull golden color, from a boiling 50% mixture of alcohol and pyridine, m. p. 118.5–120° (decomp.). It is very sparingly soluble in boiling alcohol.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_9\text{ON}_2\text{Cl}_3$ : Cl, 38.0. Found: Cl, 37.75.

$\beta$ -Chloro- $\alpha$ -ketobutaldehyde-4,5-dibromophenylhydrazone separates from boiling 75% alcohol + 25% pyridine mixture in fine golden yellow prisms, m. p. 195–196° (decomp.). It is very sparingly soluble in boiling alcohol.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_9\text{ON}_2\text{ClBr}_2$ : Br, 43.4; Cl, 9.6. Found: Br, 43.6; Cl, 9.7.

The Interaction of 2,5-Dichlorophenylhydrazine Hydrochloride with  $\beta$ -Chloro- $\alpha$ -ketobutaldehyde-2,5-dichlorophenylhydrazone in Methyl Alcohol: Formation of  $\alpha$ -Keto- $\beta$ -methoxybutaldehyde-2,5-dichlorophenylosazone. (Formula as IV.)—Two grams of the hydrazone (1 mol) and 1.5 g. of 2,5-dichlorophenylhydrazine hydrochloride (1 mol) in 20 cc. of methyl alcohol were boiled for about five minutes and then cooled. The *osazone* (2 g.) which separated even at the boiling point of the alcohol (in which it is very sparingly soluble) was crystallized from boiling pyridine, in which it is readily soluble, and from which it separates in fine bright yellow compact prisms, m. p. 220° (decomp.).

*Anal.* Calcd. for  $C_{17}H_{16}ON_4Cl_4$ : Cl, 32.65. Found: Cl, 32.9.

The corresponding ethoxy-osazone, similarly prepared in ethyl alcoholic solution, crystallized from boiling alcohol-pyridine mixtures in fine bright yellow, highly refractive prisms with domed ends, m. p. 190° (with slight decomp.).

*Anal.* Calcd. for  $C_{18}H_{18}ON_4Cl_4$ : Cl, 31.65. Found: Cl, 31.6.

The Interaction of Butyl Chloral Hydrate and 2,5-Dichlorophenylhydrazine Hydrochloride in Methyl Alcohol.—When a powdered mixture of 10 g. of 2,5-dichlorophenylhydrazine hydrochloride (1 mol) and 9 g. of butyl chloral hydrate (1 mol) suspended in 25 cc. of methyl alcohol was treated in the way described for the reaction in ethyl alcohol (page 266), the same phenomena were observed as in that case; when cold, however, the reaction mixture had almost solidified to a pulp of crystals. These were separated and extracted with 50 cc. of boiling ethyl alcohol, a quantity (A) remaining undissolved. The solution, on cooling, deposited yellow needle-like crystals which after repeated crystallization from alcohol melted at 142–143°, alone or mixed with  $\beta$ -chloro- $\alpha$ -ketobutaldehyde-2,5-dichlorophenylhydrazone.

*Anal.* Calcd.: Cl, 38.0. Found: Cl, 37.95.

The material (A), after being extracted twice more with 50 cc. of boiling ethyl alcohol, left a yellow crystalline residue sparingly soluble in most of the common organic solvents; this separated from boiling pyridine, in which it was moderately easily soluble, in bright yellow, compact prisms, m. p. 220° (decomp.), identical with the methoxy-osazone described above.

*Anal.* Calcd.: Cl, 32.7. Found: Cl, 32.95.

4-Hydroxy-1-(2',5'-dichlorophenyl)-5-methylpyrazole (V). (Ar = 2,5-Dichlorophenyl.)—Five grams of  $\beta$ -chloro- $\alpha$ -ketobutaldehyde-2,5-dichlorophenylhydrazone (1 mol) was added to a solution of 3 g. of sodium (2 mols + excess) in 100 cc. of ethyl alcohol. The deep orange solution produced was kept at room temperature for two hours, during which time sodium chloride separated, and was then very slowly heated to the boiling point of the alcohol and poured into 1000 cc. of boiling water. The rather turbid brown solution obtained was boiled with animal charcoal, filtered hot, concentrated to 250 cc., cooled and neutralized with hydrochloric acid; 4-hydroxy-1-(2',5'-dichlorophenyl)-5-methylpyrazole then separated as a sand-colored precipitate. This was dissolved in 100 cc. of hot 10% caustic potash solution, boiled with animal charcoal, and reprecipitated from the cooled filtrate by neutralization with hydrochloric acid. After repetition of this process it was crystallized from boiling acetone-light petroleum, from which it separated as colorless leaflets, m. p. 162–163°.

*Anal.* Calcd. for  $C_{10}H_8ON_2Cl_2$ : Cl, 29.2. Found: Cl, 29.1.

1-(2',5'-Dichlorophenyl)-5-methylpyrazolyl-4-benzoate separated as a white solid when 1.3 g. of benzoyl chloride (1 mol + excess) was added to a vigorously shaken solution of 0.5 g. of the 4-hydroxypyrazole in 10 cc. of 10% aqueous potassium hydroxide. It is easily soluble in boiling alcohol from which it separates in colorless flattened prisms, m. p. 133–134°.

*Anal.* Calcd. for  $C_{17}H_{12}O_2N_2Cl_2$ : Cl, 20.4. Found: Cl, 20.7.

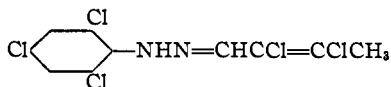
The action of sodium ethoxide upon alcoholic solutions of  $\beta$ -chloro- $\alpha$ -ketobutaldehyde-3,5-dichloro- (and 3,4-dibromo-)phenylhydrazone yielded the corresponding 4-hydroxypyrazoles which were isolated and purified as described above (page 267).

**4-Hydroxy-1-(3',5'-dichlorophenyl)-5-methylpyrazole** crystallizes from boiling chloroform, in which it is moderately soluble, in colorless prisms, m. p. 180–181°.

*Anal.* Calcd. for  $C_{10}H_8ON_2Cl_2$ : Cl, 29.2. Found: Cl, 29.0.

**4-Hydroxy-1-(3',4'-dibromophenyl)-5-methylpyrazole** separates from acetone–light petroleum, in colorless slender prisms, m. p. 132–133°.

*Anal.* Calcd. for  $C_{10}H_8ON_2Br_2$ : Br, 48.2. Found: Br, 47.8.



**The Interaction of 2,4,6-Trichlorophenylhydrazine Hydrochloride with Butyl Chloral Hydrate in Water: Formation of  $\alpha,\beta$ -Dichlorocrotonaldehyde-2,4,6-trichlorophenylhydrazone (VII).**—A solution of 18 g. of 2,4,6-trichlorophenylhydrazine hydrochloride (1 mol) in 800 cc. of water at 60° was added to a solution of 14 g. of butyl chloral hydrate (1 mol) in 600 cc. of water also at 60°. The mixture immediately became turbid, owing to the separation of yellow oily droplets, which turned first pink and then red, finally coalescing to form a viscous crimson mass. When cold, the supernatant liquid was decanted and the red viscous material was extracted with chloroform, in which it was readily soluble. The chloroform solution, after drying over calcium chloride, was kept at the ordinary temperature in an open dish for six days until the evolution of hydrogen chloride, which had been continuous from the first, had apparently ceased.

The chloroform had then evaporated, leaving a brown semicrystalline mass. The crystals were separated, washed free from viscous material with light petroleum, and recrystallized repeatedly from boiling alcohol (animal charcoal).

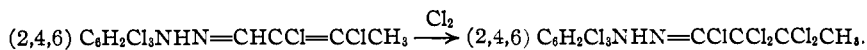
$\alpha,\beta$ -Dichlorocrotonaldehyde-2,4,6-trichlorophenylhydrazone crystallizes from boiling alcohol or acetic acid, in which it is only moderately soluble, in slender colorless prisms with a faint steel-blue reflex, m. p. 156–157°.

*Anal.* Calcd. for  $C_{10}H_7N_2Cl_5$ : C, 36.1; H, 2.1; N, 8.4; Cl, 53.3. Found: C, 36.4; H, 2.1; N, 8.4; Cl, 53.3.

**Reduction of  $\alpha,\beta$ -Dichlorocrotonaldehyde-2,4,6-trichlorophenylhydrazone.**—Three grams of the hydrazone was dissolved in 20 cc. of glacial acetic acid and boiled with excess of zinc dust and 10 cc. of concentrated hydrochloric acid (one hour). *2,4,6-Trichloroaniline* which separated from the clear reaction mixture on dilution with water crystallized from dilute aqueous acetic acid, in slender prisms, m. p. 77°.

*Anal.* Calcd.: Cl, 54.2. Found: Cl, 54.0.

The acetyl derivative melted at 203°, alone or mixed with an authentic specimen.



**Action of Chlorine upon  $\alpha,\beta$ -Dichlorocrotonaldehyde-2,4,6-trichlorophenylhydrazone.**—A rapid stream of chlorine was passed into a suspension of 3 g. of the hydrazone in 10 cc. of glacial acetic acid. The temperature rose somewhat, hydrogen chloride was freely evolved, and a bright red color developed which gradually faded to a very faint yellow. When no further change appeared to be taking place (five minutes), the solution was set aside for twenty-four hours, during which time  $\alpha,\alpha,\beta,\beta,\omega$ -pentachloro-butanaldehyde-2,4,6-trichlorophenylhydrazone separated. This crystallized from boiling

acetic acid, in slender colorless prisms (phototropic), m. p. 84–85°, identical with the authentic specimen prepared by the chlorination of  $\alpha,\beta$ -dichlorocrotonaldehyde-2,4-dichlorophenylhydrazone.<sup>4</sup>

When boiled with acetic anhydride containing a drop of concentrated sulfuric acid for several minutes, the octachlorohydrazone yielded  $\alpha,\alpha,\beta,\beta,\omega$ -pentachlorobutaldehyde-*N*-acetyl-2,4,6-trichlorophenylhydrazone, m. p. 108–109° (acetic acid), alone or mixed with an authentic specimen.

**The Action of Acetic Anhydride upon  $\alpha,\beta$ -Dichlorocrotonaldehyde-2,4,6-trichlorophenylhydrazone.**—This hydrazone is unchanged by boiling acetic anhydride. When, however, it is boiled with acetic anhydride containing a drop of concentrated sulfuric acid, acetylation proceeds smoothly and on cautious addition of water  $\alpha,\beta$ -dichlorocrotonaldehyde-*N*-acetyl-2,4,6-trichlorophenylhydrazone separates as a colorless solid. It separates from boiling alcohol, in which it is readily soluble, in fine colorless compact rhombic prisms, m. p. 91–92° (decomp.).

*Anal.* Calcd. for  $C_{12}H_9ON_2Cl_6$ : C, 38.5; H, 2.5; N, 7.5; Cl, 47.3. Found: C, 39.0; H, 2.5; N, 7.4; Cl, 47.1.

**The Interaction of Butyl Chloral Hydrate with 2,4,6-Trichlorophenylhydrazone Hydrochloride in Ethyl Alcohol.**—Eighteen grams of 2,4,6-trichlorophenylhydrazone hydrochloride (1 mol) and 14 g. of butyl chloral hydrate (1 mol) were warmed with 150 cc. of ethyl alcohol. As the reactants dissolved a bright red color developed but on heating to 50–60° for a short time the color faded to orange and finally a clear pale yellow solution was obtained. After standing for twenty-four hours at the ordinary temperature 0.75 g. of  $\alpha,\beta$ -dichlorocrotonaldehyde-2,4,6-trichlorophenylhydrazone (VII) (m. p. 156–157° from alcohol) separated, identical with the compound previously obtained (page 268) when the reaction was carried out in water.

The mother liquors, concentrated to 50 cc. by distillation of the alcohol under reduced pressure (50 mm.), were poured into water (1000 cc.) and extracted with benzene. The benzene extracts, dried over sodium sulfate, were allowed to evaporate spontaneously when a viscid mass of  $\beta$ -chloro- $\alpha$ -ketobutaldehyde-2,4,6-trichlorophenylhydrazone (VIII) remained which solidified when repeatedly triturated with ligroin and seeded with a crystal obtained from a previous preparation. The crude solid (13–14 g.) so obtained was collected, washed with light petroleum to remove adhering viscous material, and recrystallized to constant chlorine analysis from a boiling mixture of benzene and light petroleum (animal charcoal).

$\beta$ -Chloro- $\alpha$ -ketobutaldehyde-2,4,6-trichlorophenylhydrazone is very soluble in cold alcohol, chloroform, acetone and acetic acid, moderately soluble in cold benzene, and very sparingly soluble in 40–60° petroleum ether, or water. It separates from a boiling mixture of benzene and light petroleum in compact yellow monoclinic prisms with domed ends, m. p. 107–109°.

*Anal.* Calcd. for  $C_{11}H_8ON_2Cl_4$ : C, 38.2; H, 2.55; N, 8.9; Cl, 45.2. Found: C, 38.1; H, 2.5; N, 9.15; Cl, 45.6.

When vigorously reduced with tin and boiling hydrochloric acid this hydrazone yielded 2,4,6-trichloroaniline, which was identified by its acetyl derivative, m. p. 203°.

When boiled for several minutes with acetic anhydride containing a drop of concentrated sulfuric acid, this hydrazone yielded  $\beta$ -chloro- $\alpha$ -ketobutaldehyde-*N*-acetyl-2,4,6-trichlorophenylhydrazone (XI) which separated from boiling alcohol, in which it is readily soluble, in colorless rhombic plates, m. p. 136–137°.

*Anal.* Calcd. for  $C_{12}H_{10}O_2N_2Cl_4$ : C, 40.6; H, 2.8; N, 7.9; Cl, 39.8. Found: C, 40.9; H, 3.0; N, 8.5; Cl, 39.8.

<sup>4</sup> Chattaway and Irving, *J. Chem. Soc.*, 91 (1930).

The same compound was obtained by the action of acetic anhydride upon butyl chloral 2,4,6-trichlorophenylhydrazine itself. Ten grams of 2,4,6-trichlorophenylhydrazine hydrochloride (1 mol) in 600 cc. of water at 60° and 6 g. of butyl chloral hydrate (1 mol) in 500 cc. of water also at 60° were allowed to interact as described above (page 268). After five minutes the whole was cooled rapidly and the *butyl chloral 2,4,6-trichlorophenylhydrazine* which had separated as a viscous mass was extracted with chloroform and dried over calcium chloride. The chloroform was then removed rapidly by a current of hot air and 20 cc. of acetic anhydride was added to the residue, when a brisk exothermic reaction ensued, the red color faded to a pale yellow, and a crystalline mass of *β-chloro-α-ketobutaldehyde-N-acetyl-2,4,6-trichlorophenylhydrazine* separated, identical with the above.

*Anal.* Calcd.: Cl, 39.8. Found: Cl, 39.7.

**4-Hydroxy-1-(2',4',6'-trichlorophenyl)-5-methylpyrazole (XII)** was prepared by warming *β-chloro-α-ketobutaldehyde-2,4,6-trichlorophenylhydrazine* (5 g.) with a solution of 3 g. of sodium (excess) in 50 cc. of ethyl alcohol, and was isolated and purified in the same way as the 4-hydroxypyrazoles described above (page 267).

**4-Hydroxy-1-(2',4',6'-trichlorophenyl)-5-methylpyrazole** crystallizes from a boiling mixture of chloroform and petroleum ether (b. p. 60–80°) in well-developed colorless prisms, m. p. 152–153°.

*Anal.* Calcd. for  $C_{10}H_7ON_2Cl_3$ : Cl, 38.3. Found: Cl, 38.3.

It dissolves in boiling concentrated hydrochloric acid, in which it is somewhat sparingly soluble, and on cooling the *hydrochloride*,  $C_{10}H_7ON_2Cl_3 \cdot HCl$ , separates in fine colorless prisms with domed ends, m. p. 175° (decomp.). When dissolved in water, it is hydrolyzed quantitatively to the parent 4-hydroxypyrazole, m. p. 152°.

The sodium salt of 4-hydroxy-1-(2',4',6'-trichlorophenyl)-5-methylpyrazole  $C_{10}H_6N_2Cl_3(ONa)$  separates rapidly as a felt of colorless prisms on cooling a solution of the 4-hydroxypyrazole in warm 20% caustic soda solution.

**1-(2',4',6'-Trichlorophenyl)-5-methylpyrazolyl-4-benzoate**, prepared by the Schotten-Baumann reaction, crystallizes from boiling alcohol in colorless flattened prisms with domed ends, m. p. 113°.

*Anal.* Calcd. for  $C_{17}H_{11}O_2N_2Cl_3$ : Cl, 27.9. Found: Cl, 28.0.

The interaction of butyl chloral hydrate with 2,4,6-tribromophenylhydrazine hydrochloride in water, or in alcohol, yields an entirely analogous series of compounds.

**α,β-Dichlorocrotonaldehyde-2,4,6-tribromophenylhydrazine** crystallizes from boiling alcohol, in which it is rather sparingly soluble, in faintly colored needles, m. p. 157°.

*Anal.* Calcd. for  $C_{10}H_7N_2Br_3Cl_2$ : C, 25.75; H, 1.5; N, 6.0; Cl + Br, 66.75. Found: C, 26.1; H, 1.7; N, 6.3; Cl + Br, 66.9.

**α,β-Dichlorocrotonaldehyde-N-acetyl-2,4,6-tribromophenylhydrazine** separates from boiling alcohol, or acetic acid, in which it is readily soluble, in compact colorless rhombic plates, m. p. 113–114° (decomp.).

*Anal.* Calcd. for  $C_{12}H_9ON_2Cl_2Br_3$ : Cl, 14.0; Br, 47.2. Found: Cl, 14.0; Br, 47.4.

**β-Chloro-α-ketobutaldehyde-2,4,6-tribromophenylhydrazine** separates from a mixture of benzene and light petroleum in rosetts of pale yellow prisms, m. p. 122–123° (decomp.).

*Anal.* Calcd. for  $C_{10}H_8ON_2ClBr_3$ : Cl, 7.9; Br, 53.6. Found: Cl, 7.9; Br, 53.45.

**β-Chloro-α-ketobutaldehyde-N-acetyl-2,4,6-tribromophenylhydrazine** crystallizes from boiling alcohol (sparingly soluble) in colorless rhombic plates, m. p. 171–172°.

*Anal.* Calcd. for  $C_{12}H_{10}O_2N_2ClBr_3$ : C, 29.4; H, 2.1; N, 5.7; Cl, 7.25; Br, 49.0. Found: C, 29.4; H, 2.1; N, 5.7; Cl, 7.3; Br, 49.25.



4-Hydroxy-1-(2',4',6'-tribromophenyl)-5-methylpyrazole separates from a mixture of boiling chloroform and light petroleum (b. p. 60–80°) in short colorless prisms, m. p. 177.5–178°.

*Anal.* Calcd. for C<sub>10</sub>H<sub>7</sub>ON<sub>2</sub>Br<sub>3</sub>: Br, 58.4. Found: Br, 58.5.

1-(2',4',6'-Tribromophenyl)-5-methylpyrazolyl-4-benzoate separates from boiling alcohol in clusters of colorless rhombic prisms, m. p. 128–130°.

*Anal.* Calcd. for C<sub>17</sub>H<sub>11</sub>O<sub>2</sub>N<sub>2</sub>Br<sub>3</sub>: Br, 46.6. Found: Br, 46.5.

### Summary

1. The influence of halogens in the nucleus upon the character of the reaction and the nature of the products obtained when arylhydrazines condense with butyl chloral hydrate in various solvents, is described.

2. 2,5-Dichloro-, 3,5-dichloro- and 4,5-dibromophenylhydrazines condensed in alcohol yield the corresponding  $\beta$ -chloro- $\alpha$ -ketobutaldehyde-arylhydrazones.

3. 2,4,6-Trichloro (or bromo-)-phenylhydrazine condensed in water yields  $\alpha,\beta$ -dichlorocrotonaldehyde-2,4,6-trichloro(or bromo-)-phenylhydrazone, but, when condensed in alcohol, a mixture of this unsaturated hydrazone with  $\beta$ -chloro- $\alpha$ -ketobutaldehyde-2,4,6-trichloro (or bromo)-phenylhydrazone.

4. All the  $\beta$ -chloro- $\alpha$ -ketobutaldehyde-arylhydrazones yield the corresponding members of the new series of 4-hydroxy-1-aryl-5-methylpyrazoles when treated with an alcoholic solution of sodium ethoxide.

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[CONTRIBUTION FROM THE LABORATORIES OF GEORGE PINESS, M.D., LOS ANGELES]

### *dl*-BETA-PHENYLISOPROPYLAMINES

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In a previous paper<sup>1</sup> it was demonstrated with *dl*- $\beta$ -phenylisopropylamine that the introduction of a methyl group into the side chain of  $\beta$ -phenylethylamine furnishes a compound differing from the latter with regard to certain of its effects when administered as a drug compound. The *dl*- $\beta$ -phenylisopropylamine exerts a pressor effect for a longer period of time and is quite effective after oral administration. Because of the very considerable importance of developing drug compounds of this general type that are active after oral administration, it seemed important to study some derivatives of *dl*- $\beta$ -phenylisopropylamine having one or more hydroxyl groups introduced into the benzene ring.

The compounds of particular interest for this study, *dl*- $\beta$ -4-hydroxyphenylisopropylamine and *dl*- $\beta$ -3,4-dihydroxyphenylisopropylamine, have

<sup>1</sup> Piness, Miller and Alles, *J. Am. Med. Assn.*, **94**, 790 (1930).