

mixture was shaken until the odor of benzoyl chloride had disappeared. The mixture was cooled and acidified to Congo paper with hydrobromic acid. On standing a sticky solid separated and was collected on a filter.

This crude product was recrystallized from dilute alcohol and the crystals thus obtained were washed repeatedly with petroleum ether to remove the benzoic acid. The final yield was 6.5 g. (80% of the theoretical amount) of a product which melted at 143–145°.

Anal. Subs., 3.610 mg.: 0.189 cc. of N₂ at 25° and 743 mm. Calcd. for C₁₂H₁₅O₃NS: H, 5.61. Found: N, 5.53.

Some of the *d*- α -phenylethylamine salt was prepared in ethyl acetate but it was not found useful for resolution.

Summary

Synthetic γ -methylthiol- α -amino-*n*-butyric acid has been resolved and the levo isomer has been found to be identical with the naturally occurring amino acid, methionine.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

THE HALOFORM REACTION. III. TRIHALOACETYL DERIVATIVES OF MESITYLENE, DURENE AND ISODURENE

BY ARZY R. GRAY, JOSEPH T. WALKER AND REYNOLD C. FUSON

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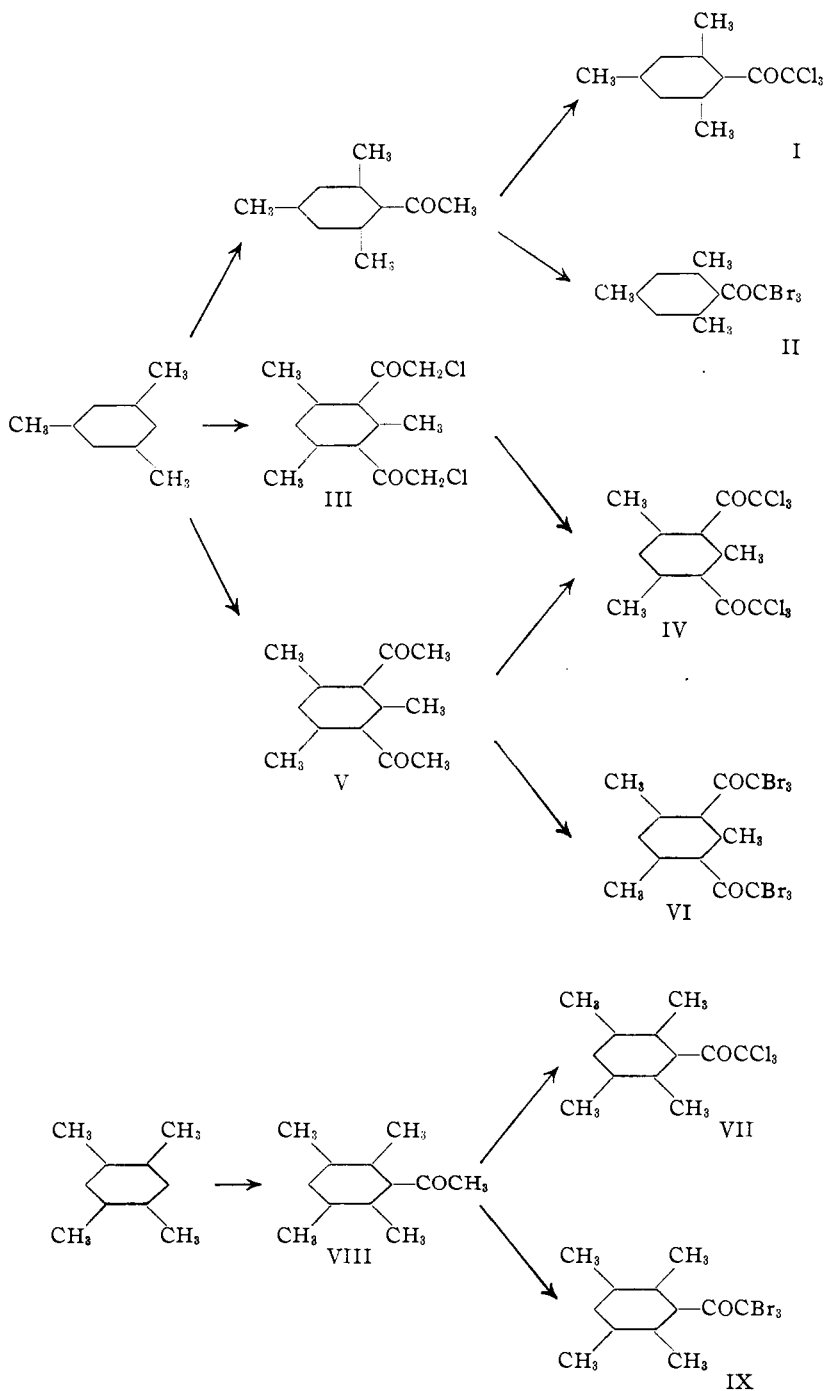
When it was discovered that solutions of the hypohalites converted certain di-ortho-substituted acetophenones into the corresponding trihalomethyl ketones,¹ the generality of the reaction was tested by trying it with a number of similar ketones. The present report includes the results obtained with the monoacetyl and diacetyl derivatives of mesitylene, durene and isodurene.

Derivatives of Mesitylene.—In addition to the trichloroacetylmesitylene (I) and tribromoacetylmesitylene (II) previously reported,² there have now been prepared the analogous di-(trichloroacetyl)-mesitylene (IV) and di-(tribromoacetyl)-mesitylene (VI). These were obtained by treating diacetylmesitylene (V) with solutions of sodium hypochlorite and sodium hypobromite, respectively. Both compounds are colorless solids which crystallize well. The hexachloro compound melts at 95–95.3° and the hexabromo compound at 160–161.5°. Di-(trichloroacetyl)-mesitylene was also prepared from di-(chloroacetyl)-mesitylene (III) by treatment with a solution of sodium hypochlorite.

Derivatives of Durene.—Acetyldurene (VIII) when treated with a solution of sodium hypobromite was slowly but completely converted into

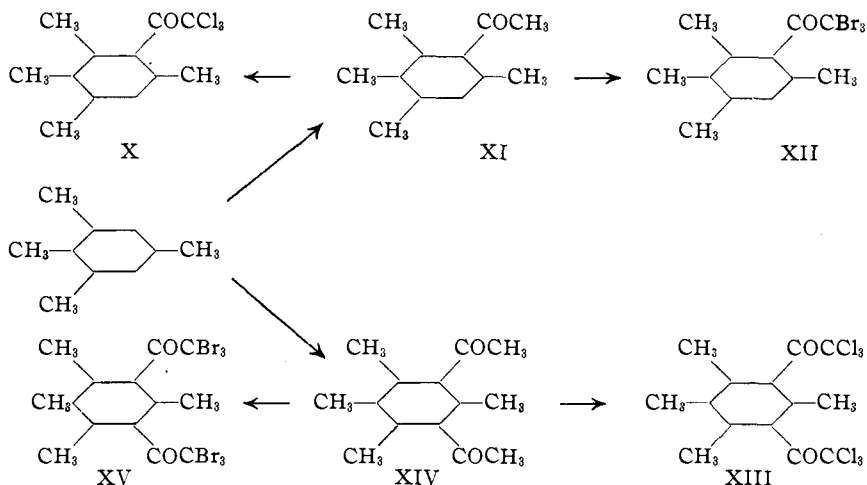
¹ Fuson and Walker, *THIS JOURNAL*, **52**, 3269 (1930).

² Ref. 1, p. 3273.



tribromoacetyldurene (IX), a colorless crystalline solid melting at 102–102.5°. With a solution of sodium hypochlorite the corresponding trichloro derivative, trichloroacetyldurene (VII), was obtained.

Derivatives of Isodurene.—Acetylisodurene (XI) was found to yield tribromoacetylisodurene (XII) and trichloroacetylisodurene (X) when treated with solutions of sodium hypobromite and sodium hypochlorite, respectively. In a similar fashion di-(trichloroacetyl)-isodurene (XIII) and di-(tribromoacetyl)-isodurene (XV) were prepared from diacetylisodurene (XIV). The yields in these reactions were nearly quantitative.



An examination of the yields obtained in these hypohalite halogenations (see table) shows that in most cases the trihaloacetyl derivatives are quite stable to cold alkali. Here as in cases previously reported¹ it is evident that the hindrance exerts a retardation of the haloform reaction of such nature as to permit the isolation of the trihalomethyl ketones formed as intermediates. The cleavage of these by strong alkali was attempted in three instances but without success. The tribromoacetyldurene (IX), trichloroacetyldurene (VII) and trichloroacetylisodurene (X) when treated under varying conditions with hot concentrated alkali failed in every case to yield the corresponding acid.

Experimental Part

Preparation of the Ketones.—All of the ketones used were prepared by the Friedel and Crafts method as modified by Adams and Noller³ for the preparation of methyl aryl ketones. When one mole of acetic anhydride was used for every mole of the hydrocarbon, the acetyl derivative was formed. In order to prepare the diacetyl derivatives it was necessary only to double the amount of acetic anhydride used. The yields were variable but in general quite satisfactory.

³ Adams and Noller, *THIS JOURNAL*, **46**, 1889 (1924).

Method of Halogenation

Chlorination.—In all cases the chlorinations were carried out with a sodium hypochlorite solution made up in the following manner. Chlorine gas was bubbled into one-half of an ice-cold solution of 15 g. of sodium hydroxide dissolved in 150 cc. of water until the solution was just acid. Then the other half of the solution was added. The ketone (one to two grams) was placed together with this solution in a tightly stoppered flask and put on a shaker where it was shaken until the reaction was complete.

Bromination.—The brominations were carried out in the same manner as that just described for the chlorinations. The sodium hypobromite solutions were prepared by adding 15 g. of bromine to an ice-cold solution of 15 g. of sodium hydroxide dissolved in 150 cc. of water.

In the accompanying table are listed all of the ketones used and the trihaloacetyl derivatives which were prepared from them. The table gives for each new compound the melting point (corrected), the solvent used in its recrystallization, the analytical figures for a halogen analysis, the yield and finally the time allowed for the reaction to go to completion.

TABLE I
PREPARATIVE DATA

Ketone	Halogen derivative	M. p., °C. (solvent)	Analysis for Br or Cl		Yield	Time of reaction, days
			Calcd.	Found		
Diacetyl- mesitylene	Hexachloro (IV) ^a	95–95.3 (alcohol)	51.8	51.6	45	7
	Hexabromo (VI)	160–161.5 (glacial acetic)	70.8	70.8	62	3
Acetyl- isodurene	Trichloro (X)	B. p. 158.5–159.5 (7 mm.)	38.1	37.9	50	0.5
	Tribromo (XII)	83.8–84.3 (dil. alc.)	58.1	58.1	98	4
Diacetyl- isodurene	Hexachloro (XIII)	134.8–135.2 (dil. acetone)	50.1	49.7	97.3	3
	Hexabromo (XV)	180.5 (decomp.) (dil. acetone)	69.3	69.2	82.5	3
Acetyl- isodurene	Trichloro (VII)	107.0–107.5 (dil. acetone)	38.1	38.0	98	2.5
	Tribromo (IX)	102–102.5 (dil. alc.)	58.1	57.9	95	5.5

^a This compound was made also from di-(chloroacetyl)-mesitylene.

Stability to Aqueous Alkalies

Tribromoacetylurene.—Three-tenths of a gram of tribromoacetylurene was heated overnight with 30 g. of a 40% sodium hydroxide solution at 95–100°. After a short time the floating tribromoacetylurene crystals became discolored. The crystals at the end of the run appeared to be considerably decomposed as evidenced by the dark brown color of the floating mass, but none of the material appeared to have dissolved. The solid was filtered, the filtrate acidified with hydrochloric acid and evaporated to dryness. This residue was extracted with ether and the ether evaporated to dryness. No solid material was obtained, indicating that no cleavage had occurred.

Trichloroacetylurene.—The trichloroacetylurene was found to escape from a boiling solution of 40% sodium hydroxide, so the experiment was carried out in a closed tube. A small quantity of the material in the form of fine colorless needles was put into 20 g. of a 40% solution of sodium hydroxide and the mixture was digested on a water-bath at 95–100°. After three hours no change could be noted.

Two-tenths of a gram of the material and 20 cc. of a solution of 40% sodium hydroxide were placed in a sealed Pyrex tube of slightly more than 20-cc. capacity and the tube was maintained at 120° for six hours. The only change observable in the trichloroacetylurene was that it had melted and become slightly discolored. It was filtered, washed, dried and weighed. No loss in weight was found. The solid which was easily crystallized from dilute acetone was shown to be the original trichloroacetylurene by the method of mixed melting points. The filtrate from the mixture was acidified with

hydrochloric acid, evaporated to dryness and extracted with hot alcohol. When the alcohol portion was evaporated to dryness, no residue was obtained.

Trichloroacetylisdurene.—One-half gram of trichloroacetylisdurene was maintained at 120° with 25 cc. of a solution of 40% sodium hydroxide in a sealed tube. Close observation showed only slow changes in the oil. At the end of thirteen hours considerable brown solid was found to have formed in the now discolored oil. At the end of twenty-six hours most of the oil had become dark brown or had changed over to the solid. The oil and solid mixture was filtered, washed with water and treated with acetone. Only a slight amount of light brown residue failed to dissolve. The acetone extract was evaporated to yield a small quantity of brown oil, presumably some of the starting material. The alkali filtrate was acidified with hydrochloric acid, evaporated to dryness and extracted with hot alcohol. This extract failed to yield any 2,3,4,6-tetramethylbenzoic acid, although a very small quantity of residue was obtained.

Summary

It has been shown that acetyl derivatives of mesitylene, durene and isodurene are converted into the corresponding trihaloacetyl compounds by treatment with solutions of sodium hypohalites. The following compounds have been prepared: di-(trichloroacetyl)-mesitylene (IV), di-(tribromoacetyl)-mesitylene (VI), tribromoacetyldurene (IX), trichloroacetyldurene (VII), tribromoacetylisdurene (XII), trichloroacetylisdurene (X), di-(trichloroacetyl)-isodurene (XIII) and di-(tribromoacetyl)-isodurene (XV). Long treatment of the trihaloacetyl derivatives of durene and isodurene with hot concentrated alkali failed to cleave these compounds into the corresponding acid derivatives.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ILLINOIS, AND THE LILLY RESEARCH LABORATORIES, ELI LILLY AND CO., INDIANAPOLIS, INDIANA]

THE ANTIPYRETIC ACTION OF PARA-ACETYLAMINOPHENYLURETHANS

BY RICHARD F. B. COX, C. R. ECKLER AND R. L. SHRINER

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The combination in a single molecule of antipyretic, analgesic and hypnotic action would give a very useful therapeutic compound. One of the groupings which is associated with antipyretic action is the acetylaminophenyl grouping, which is present in acetanilide and phenacetin. Hypnotic activity is exhibited by certain urethans such as hedonal¹ (the urethan of pentanol-2). Some urethans, especially phenylurethan, also possess antipyretic effects. Hence it was thought that the preparation of a series of compounds combining these two groups might lead to useful substances. The present investigation was carried out on compounds of the type $\text{CH}_3\text{CONHC}_6\text{H}_4\text{NHCOOR}$ (*p*).

¹ Dreser, *Wiener klin. Wochenschr.*, 1899, 1007.