2. The method developed in the preparation of these hydrocarbons is of such a nature that it should be applicable to the preparation of those corresponding methoxy and phenolic compounds believed likely to possess estrogenic activity, and experimental work in this direction is already under way.

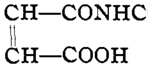
NEW YORK, N. Y. RECEIVED NOVEMBER 7, 1940

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, THE OHIO STATE UNIVERSITY]

The Action of Halogens on α,β-Unsaturated Ureides

BY CHESTER J. CAVALLITO AND CLAYTON S. SMITH

Unsaturated ureides of the type R—CH=CH—CONH—CONH$_2$ might be expected to react with halogens to form addition products of the type RCHX—CHX—CONH—CONH$_2$. However while attempting to prepare dibromosuccinuric acid, HOOC–CHBr—CHBr–CONH–CONH–CONH$_2$ by treating maleuric acid,



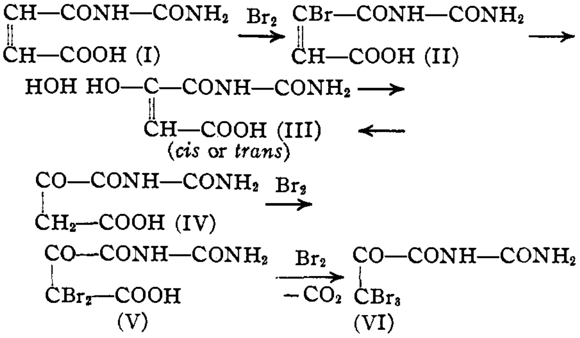
$\begin{matrix}\text{CH—CONHCONH}_2\\ \|\\ \text{CH—COOH}\end{matrix}$

, with bromine water, instead of the expected dibromo addition product, a white crystalline solid was obtained. This compound dissolved readily in alkalies and yielded almost immediately a white cloudy precipitate identified as bromoform. The production of bromoform by treatment of the bromination product of maleuric acid with alkali was an indication of the presence of a CBr$_3$—CO— instead of a —CHBr—CHBr— group in the molecule. A study was then conducted to determine the nature of the reaction of halogens, particularly bromine with maleuric acid, as well as the behavior of other unsaturated ureides with halogens.

Reaction of Bromine Water with Maleuric Acid.—The product obtained at room temperature was analyzed for C, H, N, and Br, and the empirical formula $C_4H_3O_3N_2Br_3$ obtained. The bromoform was obtained in practically quantitative yield by treatment with alkali. At about 5° the brominated product could be titrated as a monobasic acid. A mono-silver salt could also be obtained. This acidic character was attributed to a —CO—NH—CO— rather than to a carboxyl group since attempts to esterify the compound were unsuccessful. Alkaline hydrolysis of the tribromo derivative also yielded oxalic acid quantitatively, and some urea. Milder alkaline hydrolysis produced oxaluric acid, which could be easily broken down into oxalic acid and urea. This established the presence of a —CO—CO—NH—CO—NH$_2$ group in the molecule as well as CBr$_3$—CO—; thus, the compound was shown to be CBr$_3$—CO—CONH—CONH$_2$, tribromopyruvyl urea, previously prepared by Emil Fischer.[1]

The synthesis of tribromopyruvyl urea from maleuric acid must have involved several intermediate steps. In an effort to isolate the intermediates, maleuric acid was treated with bromine water at 0–10°. A yellow compound was obtained which from analysis appeared to be a monobromo substitution product of maleuric acid. The same monobromide was obtained by treating maleuric acid with bromine in carbon tetrachloride.

The monobromide did not liberate iodine from a potassium iodide solution, indicating that bromine was not attached to nitrogen. Heating with water to about 60–70° caused decomposition with the formation of carbon dioxide, Br$^-$, and some ammonia. If the monobromide were dissolved in cold alkali, and the solution acidified, a white compound was obtained which no longer contained bromine, but was not maleuric acid. Treatment of either the monobromide or its debromination product with bromine water at room temperature led to the formation of tribromopyruvyl urea. The analytical results and the chemical properties of the intermediate compounds indicated that the reaction of bromine water with maleuric acid proceeded as follows



$$\begin{matrix}\text{CH—CONH—CONH}_2\\ \|\\ \text{CH—COOH (I)}\end{matrix}\xrightarrow{Br_2}\begin{matrix}\text{CBr—CONH—CONH}_2\\ \|\\ \text{CH—COOH (II)}\end{matrix}\longrightarrow$$

$$\text{HOH}\ \begin{matrix}\text{HO—C—CONH—CONH}_2\\ \|\\ \text{CH—COOH (III)}\\ (\textit{cis}\text{ or }\textit{trans})\end{matrix}\begin{matrix}\longrightarrow\\ \\ \longleftarrow\end{matrix}$$

$$\begin{matrix}\text{CO—CONH—CONH}_2\\ |\\ \text{CH}_2\text{—COOH (IV)}\end{matrix}\xrightarrow{Br_2}$$

$$\begin{matrix}\text{CO—CONH—CONH}_2\\ |\\ \text{CBr}_2\text{—COOH}\\ \text{(V)}\end{matrix}\xrightarrow[-CO_2]{Br_2}\begin{matrix}\text{CO—CONH—CONH}_2\\ |\\ \text{CBr}_3\\ \text{(VI)}\end{matrix}$$

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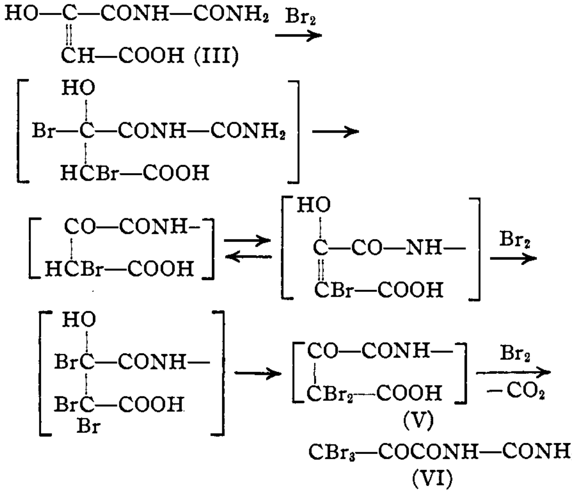
(1) Emil Fischer, *Ann.*, **239**, 185 (1887).

The debromination product of (II) might exist either as the keto or enol structure, (III) or (IV). Structure (III) was derived from a *cis* configuration, and unless an inversion took place during the hydrolysis, (III) should be the *cis* form. The debromination product readily reduced neutral potassium permanganate, thus favoring structure (III) rather than (IV). That the enol form would be more stable may be drawn as an analogy to the preferential existence of oxalacetic acid as the enol *cis* and *trans* isomers rather than the keto form.

It would appear more logical in the face of present theories of halogen replacement of α-hydrogen atoms in carbonyl compounds to postulate the bromination of enol structure (III) rather than (IV).



The theory that bromine reacts with the enolic form of compounds containing the carbonyl group was first proposed by Lapworth[2] and later work confirms this view.[3]

Experimental Part

Preparations

Maleuric Acid.—This compound was prepared according to the method of Dunlap and Phelps.[4] In order to prevent decomposition the reaction was carried out at 80° instead of 105°.

Maleamic Acid.—The method of Anschütz[5] was used in the preparation of this compound.

trans-**Crotonyl Urea.**—Fifty grams (47 cc.) of *trans*-crotonyl chloride was added to 29 g. of urea in about 100 cc. of carbon tetrachloride and refluxed for about ten minutes. The carbon tetrachloride layer was decanted, the residue washed with carbon tetrachloride, and the product recrystallized from hot water. *Anal.* Calcd.: C, 45.85; H, 6.25; Found: C, 46.0; H, 6.12.

trans-**Cinnamyl Urea.**—Seventy-five grams of *trans*-cinnamic acid (m. p. 133°) was heated in a flask with 70 g. of thionyl chloride until the evolution of hydrogen chloride and sulfur dioxide ceased, and the excess of thionyl chloride had been driven off. After cooling, 30.4 g. of urea was added and the mixture warmed until the reaction proceeded vigorously with evolution of hydrogen chloride. When hydrogen chloride fumes were no longer liberated, the product was cooled and washed well with ether, then with warm water, followed by methanol.

Anal. Calcd.: C, 63.2; H, 5.32. Found: C, 63.2; H, 5.15.

Succinuric Acid.—This compound was obtained by the method of Dunlap.[6] *Anal.* Calcd.: C, 37.5; H, 4.99. Found: C, 37.5; H, 5.12.

Reactions of the Halides.—The halogen in the monobromo and monoiodo maleuric acids was found to be quite unstable, and could be removed from the carbon atom on warming with water to above 60°. During the hydrolysis, carbon dioxide and some ammonia also were formed. The halogen was removed as Br^- from the monobromide and as iodine from the monoiodide.

The monohalides upon hydrolysis with cold alkali yielded the hydroxy derivative which might exist as *cis* or *trans* forms or rearrange to a keto structure. The hydroxy derivative also lost carbon dioxide when boiled with water, or if it were heated in dilute hydrochloric acid for about fifteen minutes, and then cooled, a white crystalline solid was obtained which sublimed below but melted at 300°. The same compound was obtained (in 75% yield) by boiling the monobromomaleuric acid with dilute hydrochloric acid. This high melting substance gave a red color with ferric chloride solution, reduced neutral permanganate, and formed an insoluble silver salt. Analysis indicated an empirical formula $C_3H_3O_3N$. The properties might fit those of a compound such as tartronimide (not described in literature). Further work will have to be done with these compounds.

Although the monobromide of maleuric acid is decomposed by alkalies around 25°, at about 5° it may be titrated as a monobasic acid (neutral equivalent: calcd., 237; found, 233). This is also true of tribromo- and triiodopyruvyl ureas. At about 25°, these trihalopyruvyl ureas may be titrated as dibasic acids. Tribromopyruvic acid was prepared (bromination of lactic acid) and upon titration with alkali, this compound acted as a dibasic acid (formation of oxalic acid) with the liberation of bromoform even at 0°. The ureide appeared to be definitely more stable toward hydrolysis than the free trihalo pyruvic acid.

The oxalic acid formed as a result of the alkaline hydrolysis of tribromo- and triiodo-pyruvyl urea was precipitated as the calcium salt and weighed. The analysis indicated a quantitative formation of oxalic acid by the alkaline hydrolysis. If the N-chlorotribromopyruvyl urea were made alkaline, then neutralized and the liberated oxalate determined, it was found that far less than the theoretical quantity of oxalate had formed. The Cl^+ had apparently oxidized part of the oxalate.

Tribromopyruvyl urea could be regenerated easily from

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[2] Lapworth, *J. Chem. Soc.*, **85**, 30 (1904).

[3] H. B. Watson, *Chem. Rev.*, **7**, 173 (1930).

[4] Dunlap and Phelps, *Am. Chem. J.*, **19**, 492 (1897).

[5] R. Anschütz, *Ann.*, **259**, 137 (1890).

[6] Dunlap, *Am. Chem. J.*, **18**, 332 (1896).

TABLE I

Compound prepd.	Starting material	Time of react., hr.	Yield, %	M. p. (dec.) °C., cor.	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found
β-Bromomaleuric acid[b]	Maleuric acid	2[c]	90–95	147	11.8	11.6	33.7	33.7
Tribromopyruvyl urea	Maleuric acid[i]	6[d]	27[i]	260[j]	7.63[g]	7.7	65.35	65.25
Dibromosuccinic acid[h]	Maleic acid Maleamic acid[h]	6[e]		230–280[k]			58.0	57.8
α,β-Dibromobutyryl urea[l]	*trans*-Crotonyl urea[m]	2	85[l]	150	9.6	9.72	55.4	55.5
α,β-Dibromophenyl propionyl urea	*trans*-Cinnamyl urea	2	95	180	8.0	7.8	45.7	45.6
N-Chlorotribromopyruvyl urea[n]	Tri-bromopyruvyl urea		90	210			Br 59.7 Cl 8.82	59.5 8.67
β-Iodomaleuric acid[o]	Maleuric acid	4[a]	75	150–155	9.86	10.1	44.75	44.88
Triiodopyruvyl urea[p]	Maleuric acid	24	12[p]	220	5.51	5.35	75.0	74.8
Dibromosuccinamic acid				170	5.09	4.9	58.2	58.1
β-Hydroxymaleuric acid			30	230–270	16.1[q]	15.95[q]		

[a] Reaction temp. 5–10°. [b] When 20% bromine was used and carbon tetrachloride was the solvent instead of water a purer product was obtained. Two days were required for this reaction. [c] Temp. of reaction 0–10°. [d] Temp. of reaction, 25°, at start, soon rose to 35°. [e] Temp. of reaction 35°. [f] Prepared from β-bromomaleuric acid (5 g.) in 25 cc. of water to which 10% NaOH had been added until solution of the acid was complete. Hydroxymaleuric acid was then precipitated by addition of dilute HCl. [g] Further analyses: H, calcd. 0.82; found 0.76; C, calcd. 13.08; found 12.8. [h] By use of bromine water. Also gave a small amount of material which gave the bromoform reaction. [i] 30% yield from β-bromomaleuric acid and 50% from β-hydroxymaleuric acid.[f] Also 24% yield from β-iodomaleuric acid and excess bromine water after stirring for 24 hours. [j] Recrystallized from hot water. [k] When heated the product decomposed yielding hydrogen bromide and bromomaleic acid, m. p. 140°. [l] A red compound formed at first and then lost bromine to give the dibromide. [m] Reaction the same at 0–5° or in carbon tetrachloride. [n] Product appeared as long crystalline rods on chilling. Alkali treatment yielded bromoform and hypochlorite. [o] Yellow product. [p] Golden-yellow crystals in 18% yield from monobromomaleuric acid and 20% from mono-iodomaleuric acid, all with iodine bromide. [q] Neut. equiv., calcd. 174, found 170.

its N-chloro derivative by warming with water. The position of the chlorine atom was assumed to be on the imide rather than amide nitrogen of the ureide, due to the greater reactivity of the hydrogen atom attached to the former group.

The tribromopyruvyl urea also formed a crystalline (hexagonal plates) insoluble mono silver derivative when a methanol solution of the ureide was treated with an aqueous silver nitrate solution. The silver atom was believed to be on the imide hydrogen (*Anal.* Calcd. for $C_4H_2O_3N_2Br_3Ag$: Ag, 22.8. Found: Ag, 22.5). Treatment of the silver derivative with alkali yielded bromoform almost immediately.

Triiodopyruvyl urea was quite stable toward acid hydrolysis. The compound could be boiled in water without decomposition. Small amounts of alkali or organic amines produced hydrolysis.

Heating the tribromopyruvyl urea with dry aniline led to the formation of oxaluranilide and bromoform.

Although dilute alkalies and tribromopyruvyl urea yielded bromoform and oxaluric acid, occasionally with stronger alkali, some of the relatively insoluble trisodium cyanurate was formed. The cyanuric acid had probably formed from HOCN derived from the urea residue.

Succinuric acid failed to react with bromine water between 0 and 30°. Maleuric acid gave only oxidative degradation products with chlorine water. Iodine failed to react with maleuric acid.

In Table I, unless stated otherwise in the footnotes, the halogen element was used as a reagent, the temperature of reaction was that of the room and the solvent or suspension medium was water. All of the reaction mixtures were stirred during the time of reaction.

Possible Biological Applications

The ease with which tribromopyruvyl urea hydrolyzed to yield bromoform under conditions of mild alkalinity led to a consideration of the possible hypnotic properties of the ureide. The ingestion of tribromopyruvyl urea might lead to the gradual formation of small amounts of bromoform in the alkaline intestinal tract without producing toxic symptoms at the same time. The pharmacologic effect would be to produce mild sedation over a long period of time. Preliminary tests on rats seem to indicate that this is the case.

Bacteriological tests indicate that the N-chlorotribromopyruvyl urea has bactericidal properties resembling those of other chlorine liberating compounds. The bactericidal properties are especially evidenced under mildly alkaline conditions.

Summary

Maleuric acid reacted with bromine water at about 0–10° to form a β-bromomaleuric acid. This compound was rather easily hydrolyzed at room temperature to yield β-hydroxymaleuric acid.

Treatment of maleuric acid, monobromomaleuric acid, or hydroxymaleuric acid with bromine water at about 30–35° led to the formation of tribromopyruvyl urea.

Maleic acid, maleamic acid, *trans*-crotonyl urea, and *trans*-cinnamyl urea reacted with bromine water to form dibromo addition products. Succinuric acid did not react with bromine.

Chlorine water reacted with tribromopyruvyl urea to form an N-chloro-tribromopyruvyl urea.

Iodine did not react with maleuric acid. Iodine bromide in water at 0–10° reacted with maleuric acid to form a monoiodo derivative, which on further treatment with iodine bromide at about 30° yielded triiodopyruvyl urea.

Bromination of the monoiodo derivative yielded tribromopyruvyl urea, while treatment of the monobromide with iodine bromide solution gave triiodopyruvyl urea.

Tribromopyruvyl urea upon alkaline hydrolysis yielded bromoform.

Preliminary experiments on rats showed that the administration of tribromopyruvyl urea by mouth produced a mild sedation. Bacteriological tests indicated that N-chloro-tribromopyruvyl urea had an antiseptic action.

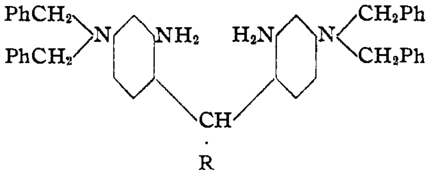
COLUMBUS, OHIO RECEIVED AUGUST 28, 1940

[CONTRIBUTION FROM THE ORGANIC CHEMICAL LABORATORY OF THE UNIVERSITY OF FLORIDA]

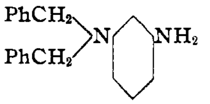
Reactions of Aldehydes with Amines. III. With N,N-Dibenzyl-N′-acetyl-*m*-phenylenediamine[1]

BY F. G. SINGLETON[2] AND C. B. POLLARD

In an attempt to prepare a series of 5-substituted-2,8-tetrabenzyldiamino-acridines, it became necessary to synthesize, as intermediates, compounds of formula (I), where R is hydrogen, alkyl, or aryl.

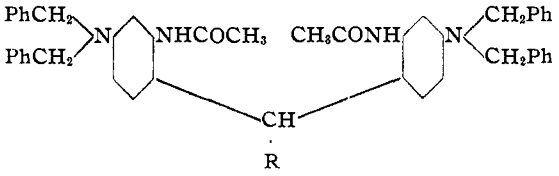


(I)



(II)

(III)



(IV)

A search of the literature revealed that analogous compounds are produced by condensing *m*-diamines such as *m*-phenylenediamine[3] and *m*-tolylenediamine[4] with aldehydes. From formaldehyde and *m*-tolylenediamine[5] is obtained a diphenylmethane derivative from which Acridine Yellow may be prepared by cyclization. When N,N-dialkyl-*m*-phenylenediamines are used, the condensation occurs para to the *substituted* amine group. Thus bis-(2-amino-4-dimethylamino)-diphenylmethane is obtained from N,N-dimethyl-*m*-phenylenediamine and formaldehyde.[6]

No difficulty was envisioned in condensing N,N-dibenzyl-*m*-phenylenediamine (II) with aldehydes to form series (I). The compound (II) was prepared by the method described in the second paper[7] of this series and treated with aldehydes under conditions usually used for this type of condensation. However, the aldehydes condensed with the amine hydrogens and produced Schiff bases instead of (I). Since these reactions failed to produce (I) because of the reactivity of the primary amine group, the acetyl derivative (III) of (II) was prepared and substituted for the free amine. Under these conditions compounds of structure (IV) were isolated. The benzoyl derivative of (II) acts in the same manner. Experiments now being carried out show that these compounds are readily cyclized to acridines.

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(1) This paper is abstracted from a portion of a dissertation submitted by F. G. Singleton to the Graduate Council of the University of Florida in partial fulfillment of the requirements for the degree of Doctor of Philosophy, August, 1940.

(2) Present address: Kansas State College, Manhattan, Kansas. Part of this work was done in the laboratory of Mme. Ramart-Lucas, professor at the Sorbonne, while Mr. Singleton was Research Fellow (1938–39) of the Société des Amis de l'Université de Paris.

(3) German Patent 45,294.

(4) German Patent 45,298.

(5) Ullmann and Maric, *Ber.*, **34**, 4307 (1901).

(6) German Patent 59,179.

(7) Singleton and Pollard, THIS JOURNAL, **63**, 240 (1941).