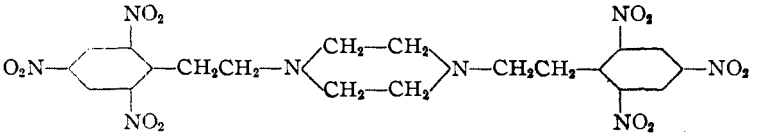
ethylamine, di-*n*-butylamine, dicyclohexylamine and piperazine.

The latter combined with two moles each of formaldehyde and TNT to give bis-(2,4,6-trinitrophenylethyl)-N_1N'-piperazine.



In general the reaction is applicable to secondary amines that readily form an N-methylol derivative with formaldehyde. Diphenylamine and similar very weakly basic amines which do not readily form N-methylol derivatives with formaldehyde fail to react. The formaldehyde used is preferably in the form of an aqueous 30–37% solution, but may also be used in the form of paraformaldehyde.

Experimental

2,4,6-Trinitrophenylethyl-N-morpholine.—The preparation of this compound is given as a typical example of the general procedure used for the preparation of these compounds.

To a stirred solution of 11.5 g. (0.05 mole) of 2,4,6-trinitrotoluene and 25 g. of dioxane cooled to 5°, there was gradually added 4.5 g. (0.05 mole) of morpholine, 1 g. of 2% sodium hydroxide solution, and 4.5 g. (0.05 mole) of 37% aqueous formaldehyde, the additions being made in the order given. The temperature of the reaction mixture was maintained between 5 and 10° while the various reagents were added and for a period of one hour thereafter. The mixture was warmed at 40–50° for one hour, then cooled to 10° and mixed with 100 g. of cold water containing 0.5 g. of concentrated hydrochloric acid. Stirring was continued and the mixture cooled until the product crystallized out. It was filtered, washed and dried in the air. The material thus obtained amounted to 15.5 g. (95% of theory) and melted at 125°. After recrystallization from a 1:1 mixture of benzene and ethanol, it formed tan-colored needles melting at 135°.

The picrate of the above compound melts at 161°. It was prepared by mixing equivalent quantities of the compound and picric acid in hot alcoholic solution. This procedure was typical of that used for the preparation of all picrates described.

In those cases in which the product obtained was an oil or was difficult to crystallize, the reaction product was taken up in ether, dried over anhydrous calcium chloride and the hydrochloride of the amine precipitated by passing dry hydrogen chloride into the solution. The salt was purified by recrystallization to obtain the pure hydrochloride of the tertiary amine.

In most cases, the theoretical yield of the crude reaction product was approached with little or no loss by decomposition or by-products. Dioxane was used as solvent in all the preparations.

Tables I, II and III include the compounds prepared, physical properties and analyses.

Acknowledgment.—The authors wish to express their appreciation to Mr. Clyde W. Nash of the Rohm and Haas Analytical Laboratories, Bristol, Pa., for the microanalyses reported here.

Summary

2,4,6-Trinitrotoluene (TNT) undergoes the Mannich reaction with formaldehyde and N-methylol-forming secondary amines to give 2,4,6-trinitrophenylethyl-N-*t*-amines. The following secondary amines were used: dimethylamine, diethylamine, dibutylamine, dicyclohexylamine, dibenzylamine, diethanolamine, N-methylaniline, morpholine, piperidine and piperazine. Piperazine condensed with two moles each of formaldehyde and TNT.

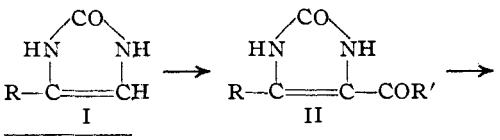
PHILADELPHIA, PA. RECEIVED JULY 26, 1946

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

Studies in the Imidazolone Series. The Synthesis of a Lower and a Higher Homolog of Desthiobiotin and of Related Substances[1]

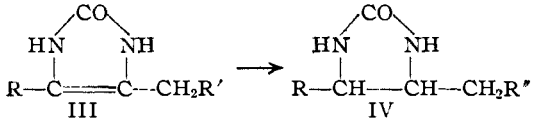
BY ROBERT DUSCHINSKY AND L. ALLEN DOLAN

In a previous paper,[1a] it was shown that Friedel–Crafts acylations of 4-methyl-2-imidazolone (I, R = CH_3), followed by hydrogenation of the obtained ketones (II), lead to imidazolidone compounds, the keto group being first reduced to methylene (III and IV).



(1) Presented before a session of the Division of Organic Chemistry, 109th Meeting of the American Chemical Society, Atlantic City, New Jersey, April 10, 1946.

(1a) Duschinsky and Dolan, THIS JOURNAL, 67, 2069 (1945).



In the present paper it is reported that 2-imidazolone (I, R = H) and 4-ethyl-2-imidazolone (I, R = C_2H_5) react in a similar manner.

Curiously enough, compounds having different properties are described in the literature as 2-imidazolone. In 1892 Marckwald reported the synthesis of imidazolone from amino acetal (V) *via* ureido acetal (VI), and described it as a substance

$H_2NCH_2CH(OC_2H_5)_2$ (V) ⟶

$H_2NCONHCH_2CH(OC_2H_5)_2$ (VI) ⟶ I (R = H)

TABLE I

FRIEDEL-CRAFTS REACTIONS (I → II)

I, R is	H	H	H	CH_3	CH_3	CH_3	C_2H_5
g.	4.2	1.68	7.03	19.6	19.6	19.6	1.62
Moles $AlCl_3$	2	3	2	2	2	3	3
R'COCl, R' is	$(CH_2)_4CH_3$	$(CH_2)_4CO_2Et$	Ph	$(CH_2)_2CH_3$	$(CH_2)_4CH_3$	$(CH_2)_4CO_2Me$	$(CH_2)_4CO_2Et$
g.	6.75	3.84	11.8	21.3	26.9	35.7	2.77
Time, hours	3½	4½	4½	2½	4	5	4
Obtained II, R'	$(CH_2)_4CH_3$	$(CH_2)_4CO_2H$[a]	Ph[b]	$(CH_2)_2CH_3$	$(CH_2)_4CH_3$	$(CH_2)_4CO_2Me$[c]	$(CH_2)_2CO_2Et$
Yield, per cent.	41	25	58	.....	58	58	34
Melting point, °C.	255–258	229–230	313–316	234–235	227–228	175–176	108–109
Cryst. from solvent	50% ethanol	water	50% ethanol	30% ethanol	50% ethanol	water	10% ethanol
Cryst. from parts of	20	25	40	25	8	25	16
Formula	$C_9H_{14}O_2N_2$	$C_9H_{12}O_4N_2$	$C_{10}H_8O_2N_2$	$C_8H_{12}O_2N_2$	$C_{10}H_{16}O_2N_2$	$C_{11}H_{16}O_4N_2$	$C_{13}H_{20}O_4N_2$
Anal. % C Calcd.	59.32	50.94	63.82	57.12	61.20	54.99	58.19
Anal. % C Found	59.22	50.86	63.91	56.99	60.96	55.02	58.55
Anal. % H Calcd.	7.74	5.70	4.29	7.19	8.22	6.71	7.52
Anal. % H Found	7.40	5.58	3.95	7.26	8.18	6.47	7.18
Anal. % N Calcd.		13.20					10.44
Anal. % N Found		13.24					10.47

[a] The keto ester obtained as primary reaction product was converted into the corresponding keto acid by heating at 60° for forty-five minutes with 15 volumes 0.5 *N* sodium hydroxide, followed by reacidification with hydrochloric acid. [b] The *diacetyl derivative* was prepared by twice refluxing 3.76 g. ketone (II, R = Ph) with 50 cc. acetic anhydride and evaporating to a sirup and crystallizing from 150 cc. of ethanol; m. p. 137–139°, yield, 4.57 g.(84%). *Anal.* Calcd. for $C_{14}H_{12}O_4N_2$: C, 61.76; H, 4.44; N, 10.29. Found: C, 62.09; H, 4.33; N, 10.38. [c] Was subsequently converted into the free acid melting at 210–212°.[1]

TABLE II

HYDROGENATIONS (II → IV)

II, R, R' is	H, $(CH_2)_4CH_3$	H, Ph	H, $(CH_2)_4CO_2H$	CH_3, $(CH_2)_2CH_3$	CH_3, $(CH_2)_4CH_3$	CH_3, $(CH_2)_4CO_2H$	C_2H_5, $(CH_2)_4CO_2Et$
g.	0.36	3.76	0.21	5.16	1.96	2.26	0.54
PtO_2, g.	0.1	1.88	0.1	1.3	0.5	0.55	0.2
H_2 uptake in min. 2 moles	25	160	10	100	50	65	15
H_2 uptake in min. 3 moles	80	250[c]	35	>800	>500	>600	150
IV, R, R'' =	H, $(CH_2)_4CH_3$	H, C_6H_{11}[d]	H, $(CH_2)_4CO_2H$	CH_3, $(CH_2)_2CH_3$	CH_3, $(CH_2)_4CH_3$	CH_3, $(CH_2)_4CO_2H$	C_2H_5, $(CH_2)_4CO_2H$[e]
Yield in per cent.	41	ca. 50	73	91	89	85	86
Melting point, °C.	113–114[b]	158–159	144–145	135–136	124–125	162–163	173–174
Crystallized from	Water	15% ethanol	30 p. water	Water	Water	10 p. water	60 p. water
Sublimed °C./mm.[a]	140/0.2	140/0.1		130/0.1			
Formula	$C_9H_{18}ON_2$	$C_{10}H_{18}ON_2$	$C_9H_{16}O_3N_2$	$C_8H_{16}ON_2$	$C_{10}H_{20}ON_2$	See ref. 1a	$C_{11}H_{20}O_3N_2$
Anal. % C Calcd.	63.49	65.90	53.98	61.50	65.17		57.87
Anal. % C Found	63.65	65.72, 65.48	54.05	61.45	65.44		57.76
Anal. % H Calcd.	10.66	9.95	8.06	10.32	10.94		8.83
Anal. % H Found	10.21	9.57, 9.80	7.81	10.23	10.71		8.68
Anal. % N Calcd.			13.99		15.20		12.27
Anal. % N Found			13.72		15.05		12.18
MIR *S. cerev.*	$>10^6$	$>10^6$	6×10^5	1.3×10^6	$>1.3 \times 10^6$	growth	$>3.3 \times 10^6$
MIR *L. casei*	$>10^6$	$>10^6$	1.2×10^6	1×10^6	$>1.3 \times 10^6$	1.7×10^4	1.1×10^6

[a] Bath temperature. [b] *Cf.* Rodionov and Zvorykina, *Bull. acad. Sci. U. S. S. R. Class. sci. chim.*, 216 (1943); *C. A* **38**, 1474 (1944). [c] Total uptake: 5.7 moles in 500 minutes. [d] Cyclohexyl. [e] Crude reduction product was dissolved in 2 cc. of ethanol and 6.5 cc. of *N* sodium hydroxide and after allowing to stand 30 thirty minutes, acidified with 6.5 cc. of *N* hydrochloric acid.

not melting at the boiling point of sulfuric acid.[2] Later Fenton and Wilks[3] prepared from dihydroxymaleic acid a substance melting at 245°, which they found to be not identical with Marckwald's preparation, and therefore called iso-imidazolone. Finally Hilbert[4] obtained imidazolone by heating 2-imidazolone-4-carboxylic acid *in vacuo* to 230°, and found it identical with Fenton and Wilks' preparation. What Marckwald had obtained was not clear.

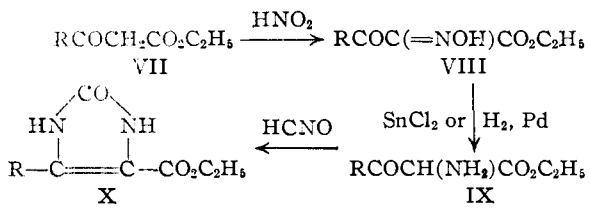
In the present investigation both Marckwald's and Hilbert's methods were followed. In the first case a mixture was obtained which was separated by sublimation *in vacuo* into a volatile and a non-volatile substance, which were both found to have the elementary composition of imidazolone. The volatile one melted at about 250° (dec.) and was found to be identical with the imidazolone prepared according to Hilbert, while the non-volatile one melted at about 310° (dec.). Upon hydrogenation only the former gave 2-imidazolidone, while the latter gave an undefined product.

It is believed that the high-melting substance is a dimer or a polymer, formed when ureido acetaldehyde, obtained by acid hydrolysis of the acetal, undergoes intermolecular condensation instead of cyclization. The formation of the high-melting

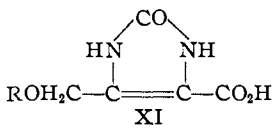
(2) Marckwald, *Ber.*, **25**, 2357 (1892).
(3) Fenton and Wilks, *J. Chem. Soc.*, **95**, 1329 (1909).
(4) Hilbert, THIS JOURNAL, **54**, 3414 (1932).

substance was minimized by hydrolyzing the acetal in great dilution and at room temperature.

It was previously reported that 4-methyl-5-carbethoxy-2-imidazolone (X, R = CH_3) gave, upon alkali hydrolysis, by spontaneous decarboxylation 4-methyl-2-imidazolone instead of the free acid.[1a] The influence of various substituents R in X on the decarboxylation reaction is now recorded. The unsubstituted 5-carboxy-2-imidazolone (R = H) proved to be stable toward alkali. Other esters were prepared as shown below (VII → VIII → IX → X). It was found that on alkali



hydrolysis the ethyl homolog (X, R = C_2H_5) undergoes decarboxylation spontaneously like the methyl homolog, but neither the ethoxymethyl ester[5] (X, R = $CH_2OC_2H_5$) nor the hydroxymethyl ester (X, R = CH_2OH), which was prepared *via* the bromomethyl ester[5] (X, R = CH_2Br), were decarboxylated. Both the ethoxymethyl and the hydroxymethyl esters were saponified to give stable acids (XI, R = C_2H_5 and H, respectively). The latter, despite being a γ-



hydroxy acid did not lactonize. Platinum-catalyzed hydrogenation of the ethoxymethyl ester (X, R = $CH_2OC_2H_5$) caused hydrogenolysis of the ethoxy group, yielding 4-methyl-5-carbethoxy-2-imidazolone (X, R = CH_3) which was not reduced further. The phenyl ester (X, R = C_6H_5) underwent decarboxylation to give 4-phenyl-2-imidazolone (I, R = C_6H_5), when saponified.

Friedel–Crafts condensations of imidazolone, 4-methyl-imidazolone, and 4-ethyl-imidazolone (I, R = H, CH_3, C_2H_5) with various acyl chlorides are reviewed in Table I, and hydrogenations in presence of platinum catalyst of the resulting ketones in Table II. The intermediates III were not isolated in these experiments, but when 5-benzoyl-imidazolone (II, R = H, R′ = C_6H_5) was hydrogenated in presence of palladium–charcoal, 5-benzyl-2-imidazolone (III, R = H, R′ = C_6H_5) resulted. From the hydrogenation rates for 2 moles uptake, corresponding to the reduction of the keto group, and 3 moles, corresponding to total reduction (6 moles for phenyl compounds), it is evident that the ring double bond in 5-acyl-2-imidazolones is hydrogenated relatively faster than in the corresponding 4-alkyl-5-acyl-2-imidazolones. Thus a side reaction can take place with such 5-acyl-imidazolones, the imidazolone nucleus being reduced prior to the conversion of the keto group into methylene. Repeated hydrogenations of 4-benzoyl-2-imidazolone yielded indeed a by-product which due to its low solubility in water and alcohol could be separated from 4-hexahydrobenzyl-2-imidazolidone and will be described later.

5-Carboxyamyl-2-imidazolidone (IV, R = H, R″ = $(CH_2)_4CO_2H$), a lower homolog of desthiobiotin, was previously synthesized by Dittmer and du Vigneaud[6] using a different method. Melting point and microbiological properties[7] were found in close agreement with these authors. 4-Ethyl-5-carboxyamyl-2-imidazolidone (IV, R = C_2H_5, R″ = $(CH_2)_4CO_2H$) represents the hitherto undescribed ethyl homolog of desthiobiotin. *cis*-Configuration of the hydrogen atoms attached to carbons 4 and 5 is assumed, since a strictly analogous hydrogenation had led to the *cis* form of desthiobiotin.[1a]

None of the newly prepared imidazolidone derivatives revealed any biotin activity (*i.e.*, less than 0.0001%) when assayed with *Saccharomyces cerevisiae*, strain 139, or *Lactobacillus casei*.

The molar inhibition ratios, reviewed in Table II, demonstrate that as an antibiotin for *Lactobacillus casei* the ethyl homolog is one-tenth as potent as "nor-desthiobiotin" (IV, R = H, R″ = $(CH_2)_4COOH$), and one hundredth as potent as desthiobiotin.

Experimental[8]

Ureidoacetal[2] (V).—To a mixture of 35 g. of aminoacetal[9] and 55 g. of crushed ice was added 52.6 cc. (1 mole) of 5 *N* hydrochloric acid previously cooled to −40° and immediately afterward a solution of 32 g. potassium cyanate (1.5 moles) in 70 cc. water. The reaction mixture was refluxed for ninety minutes, concentrated *in vacuo* to *ca.* 75 cc., and cooled. The separated colorless crystals were filtered off and washed with ice-cold water; yield was 33.6 g. (73%), ureidoacetal melting at 104–107°. Sublimation at 110–120° (bath) and 0.5 mm. raised the melting point to 107–108°, but for the next step the crude product was used. Chloroform extraction of the mother liquor gave a second, less pure, crop of 3.7 g.

2-Imidazolone (I, R = H). (A) **Marckwald's method.**[2] —A mixture of 6.28 g. of ureidoacetal, 5 cc. of 0.1 *N* sulfuric acid and 1 cc. of water was heated one hour at 55°, then 1 cc. of *N* sulfuric acid was added and heating continued on a water-bath for two hours. Upon cooling a slightly brownish crystalline material separated which was washed free of sulfate with water; yield was 1.91 g. This yielded upon heating at 0.4 mm. and 200–220° bath temperature 1.2 g. of sublimate melting at 250–251° (*in vacuo*), and a residue of 0.4 g. decomposing at 308–310° (*in vacuo*). The sublimate gave a strong purple ferric chloride reaction and was identified as 2-imidazolone by mixed

(5) An alternative and preferable synthesis of these esters is reported in a forthcoming paper.

(6) Dittmer and du Vigneaud, *Science*, **100**, 129 (1944).

(7) The microbiological assays were carried out in the Nutrition Laboratories of Hoffmann-La Roche, Inc., by methods which have been described [*cf.* Rubin, Flower, Rosen and Drekter, *Arch. Biochem.*, **8**, 79 (1945)].

(8) Melting points were determined with an uncalibrated set of Anschütz thermometers. For the reported microanalyses we are indebted to Dr. Al Steyermark and his staff.

(9) "Organic Syntheses," **24**, 3 (1944).

melting point with a sample prepared according to Hilbert's method.

Anal. Calcd. for $C_3H_4ON_2$: C, 42.85; H, 4.80; N, 33.32. Found: C, 42.56; H, 4.82; N, 33.09.

The non-volatile fraction was dissolved in 40 cc. of boiling water, from which it separated only upon concentration to a small volume. It was again dissolved in 30 cc. of aqueous alcohol and separated by evaporation to 10 cc. The still yellowish, not distinctly crystalline, material, decomposing at about 307–310°, gave a ferric chloride reaction.

Anal. Calcd. for $C_3H_4ON_2$: C, 42.85; H, 4.80; N, 33.32. Found: C, 43.13; H, 5.03; N, 33.75.

In another batch 120 g. of ureidoacetal and 2 l. of 0.078 *N* sulfuric acid were allowed to stand at room temperature for seventy-two hours. The sulfuric acid was eliminated by addition of 400 cc. of 0.39 *N* barium hydroxide solution. Evaporation to 400 cc. and cooling gave 30.5 g. of imidazolone (m. p. 245–248°). The mother liquor deposited on longer standing 1.45 mg. of material melting at 297–300°. Further concentration and cooling yielded a second crop of 15.9 g. imidazolone (m. p. 243–245°); total yield was 80%. The crude of imidazolone was used directly for Friedel–Crafts reactions.

(B) Hilbert's Method.[4]—5-Carboxy-2-imidazolone, prepared according to Hilbert by reaction of fuming sulfuric acid on tartaric acid and urea, was decarboxylated by heating 1-g. portions mixed with 3 g. of copper powder in a vacuum of 0.3 mm. The bath temperature was raised gradually from 230 to 300°. The yields averaged around 50%. The imidazolone was purified by resublimation, and melted then at 251.5–252°.

2-Imidazolidone.—A solution of 252 mg. of imidazolone, prepared from ureidoacetal, in 10 cc. of acetic acid was hydrogenated in presence of 100 mg. of pre-reduced platinum oxide catalyst. After two and one-half hours, the uptake stopped at 80 cc. (calcd. 75 cc.). The filtered solution showed no ferric chloride reaction, and left on evaporation a colorless oil which deposited crystals upon treatment with ether and alcohol. After sublimation at 0.9 mm. and 130–140° (bath) the substance melted at 131–132°, as reported by Fischer and Koch.[10]

Anal. Calcd. for $C_3H_6ON_2$: C, 41.85; H, 7.02. Found: C, 42.08; H, 6.96.

A similar reduction of the non-volatile imidazolone by-product resulted in an uptake of only 65 cc. of hydrogen; no imidazolidone could be isolated.

Ethyl α-Oximinopropionylacetate (VIII, R = C_2H_5).—To a solution of 16.8 g. of ethyl propionylacetate, prepared according to Breslow, Baumgarten and Hauser,[11] in 27 cc. of acetic acid, was added dropwise with stirring and within one hour a solution of 7.36 g. sodium nitrite in 18 cc. water, the temperature being kept by cooling at 5 to 7°. Then 60 cc. of water was added and stirring was continued, while the temperature was allowed to rise to 24° within two hours. After eliminating the excess of nitrous acid by addition of urea, the mixture was extracted twice with 50 cc. of ether. The ether extract was washed three times with 15 cc. of sodium bicarbonate solution, the third washing being alkaline. After drying the ethereal solution over sodium sulfate, the solvent was evaporated, leaving 13.53 g. (67%) of a light yellow oil; $n^{26}D$ 1.439. The product was not pure, as shown by the analysis.

Anal. Calcd. for $C_7H_{11}O_4N$: C, 48.55; H, 6.40; N, 8.09. Found: C, 50.07; H, 6.81; N, 6.16, 5.77.

4-Ethyl-5-carbethoxy-2-imidazolone (X, R = C_2H_5).—A mixture of 3.05 g. of the foregoing oximino compound, 13.5 cc. of ethanol, 1.76 cc. of 10 *N* hydrochloric acid and 35 cc. of water was hydrogenated for forty minutes in the presence of 0.6 g. of a 3.3% palladium–charcoal catalyst at about 1600 pounds pressure and at a temperature of *ca.* 30°. After filtering from the catalyst, 1.76 cc. of 5 *N* hydrochloric acid and a solution of 2.14 g. of potassium cyanate in 8 cc. of water were added. The mixture was concentrated in an evaporating dish on a water-bath until the volume was 20 cc. Upon cooling 1.94 g. (60%) of ester crystallized which melted at 171–173°. Recrystallization from water and sublimation at 0.6 mm. and 200° (bath) raised the melting point to 182–184°.

Anal. Calcd. for $C_8H_{12}O_3N_2$: C, 52.16; H. 6.57; N, 15.21. Found: C, 52.57; H, 6.24; N, 15.50.

4-Ethyl-2-imidazolone (I, R = C_2H_5).—To a solution of 3.94 g. of the foregoing crude ethyl ester in 214 cc. of boiling water was added a solution of 9 g. of barium hydroxide octohydrate in 50 cc. of boiling water. After heating the mixture for four and one-half hours at 85° the deposited barium carbonate (4.3 g.) was filtered off. After elimination of the remaining barium ions by addition of 11.2 cc. of *N* sulfuric acid, the solution was concentrated to dryness. The residue treated with 20 cc. boiling water yielded on cooling 1.45 g. needles melting at 192–194°, and evaporation of the mother liquor gave a second crop of 0.37 g. (total 76%). The compound gives an intense purple ferric chloride reaction; it can be sublimed at 0.7 mm. and 170–175° (bath).

Anal. Calcd. for $C_5H_8ON_2$: C, 53.55; H, 7.19. Found: C, 53.26; H, 6.87.

Kolshorn[12] obtained ethylimidazolone from aminomethyl ethyl ketone, but reported a melting point of 166–167°.

Ethyl γ-Ethoxy-acetoacetate (VII, R = $CH_2OC_2H_5$).—According to Wahl and Doll,[13] 924 g. of ethyl ethoxyacetate reacted by gradual addition of 483 g. of sodium and 1848 g. of ethyl acetate (3 moles) for eight hours at 85–90°. Unreacted sodium was destroyed by addition of ethanol, then the mixture poured on 3 kg. of ice and 1800 cc. of concentrated hydrochloric acid. The ester was extracted with 4 liters of ether, the ether washed with sodium carbonate solution, dried over sodium sulfate and distilled. Using a 1-meter Fenske column, fractions were taken between 106 and 125° at 17 mm. pressure, and their ethoxyl content determined. Twice refractionated material (*ca.* 30 g.), boiling between 108 and 113°, $n^{25}D$ 1.425–1.427, and showing an ethoxyl content of 46–49% (calcd. 51.7%), was used for the following step.

Ethyl α-Oximino-β-oxo-γ-ethoxybutyrate (VIII, R = $CH_2OC_2H_5$).—To a solution of 25.8 g. of the foregoing ester in 45 cc. of acetic acid was added within one hour a solution of 10.7 g. of sodium nitrite in 15 cc. of water, the temperature being kept at 5–7°. After allowing the mixture to stand for one hour at room temperature it was diluted with 250 cc. of water and twice extracted with 100 cc. of ether. The ether extract, dried over sodium sulfate, was evaporated and the residue dried at 40° *in vacuo* over sodium hydroxide. The obtained crystalline material weighed 23.6 g. (79%) and melted at 58–64°. Recrystallization of 20.2 g., by dissolving in 6.5 cc. of ether and cooling to −40° gave 15.9 g. of colorless needles melting at 78–80°.

Anal. Calcd. for $C_8H_{13}O_5N_2$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.07; H, 6.44; N, 7.18, 7.11.

4-Ethoxymethyl-5-carbethoxy-2-imidazolone (X, R = $CH_2OC_2H_5$).—To a solution of 24 g. of stannous chloride dihydrate in 40 cc. of concentrated hydrochloric acid, kept under continuous stirring at 15°, was added within twenty minutes 10.2 g. of the foregoing oximinoester. After addition of 0.5 g. mossy tin and one hour of additional stirring, the mixture was diluted with 125 cc. water and treated with hydrogen sulfide. The filtrate from the sulfide was cooled to 0° and partly neutralized by addition of 185 cc. of 2 *N* sodium hydroxide. To the still acid solution, containing the amino ester IX, was added a solution of 4.5 g. of potassium cyanate in 15 cc. of water and enough sodium hydroxide to adjust the *p*H to 2. Standing overnight raised the *p*H to 6.5. Evaporation *in vacuo* to a volume of 50 cc. gave the first crop of crystals, and concentration to dry-

(10) Fischer and Koch, *Ann.*, **232**, 227 (1886).

(11) Breslow, Baumgarten and Hauser, THIS JOURNAL, **66**, 1286 (1944).

(12) Kolshorn, *Ber.*, **37**, 2477 (1904).

(13) Wahl and Doll, *Bull. soc. chim.*, [4] **13**, 468 (1913).

ness, followed by extraction with boiling ethanol and crystallization of the extract from water, a second crop. Total yield was 5.35 g. (50%). The product was recrystallized from 3 volumes of water, and for the analysis sublimed at 170–180° (bath) and 1 mm., m. p. 179–180°.

Anal. Calcd. for $C_9H_{14}O_4N_2$: C, 50.46; H, 6.59; N, 13.08; C_2H_5O, 42.07. Found: C, 50.59; H, 6.57; N, 13.13; C_2H_5O, 42.20.

Monoacetyl Derivative.—One gram of the foregoing ester was refluxed for one-half hour with 10 cc. of acetic anhydride and the resulting solution evaporated to dryness The partly crystalline residue was taken up and washed with *ca.* 30 cc. of ether. The yield was 100 mg. melting at 148–149° and subliming at 170° (bath) and 0.5 mm.

Anal. Calcd. for $C_{11}H_{16}O_5N_2$: C, 51.55; H, 6.29; N, 10.95; C_2H_5O, 35.16. Found: C, 51.73; H, 6.05; N, 10.55; C_2H_5O, 35.41.

Diacetyl Derivative.—When 50 volumes of acetic anhydride was used and refluxing and evaporating repeated, no crystalline material, but a colorless oil boiling at 100° (bath) and 0.6 mm. resulted.

Anal. Calcd. for $C_{13}H_{18}O_6N_2$: C, 52.34; H, 6.08; C_2H_5O, 30.21. Found: C, 51.96; H, 6.03; C_2H_5O, 29.45.

Hydrogenolysis of Ester X (R = $CH_2OC_2H_5$).—A solution of 430 mg. ethoxy ester in 7 cc. acetic acid was hydrogenated with 100 mg. pre-reduced platinum oxide catalyst at room temperature and atmospheric pressure. After three hours the uptake stopped, with exactly one mole hydrogen absorbed. Evaporation of the filtered solution gave 340 mg. (100%) crystalline 4-methyl-5-carbethoxy-2-imidazolone (X, R = CH_3), melting at 222°, and identified by mixed melting point with a sample prepared from VIII (R = CH_3).[1a]

4-Ethoxymethyl-5-carboxy-2-imidazolone (XI, R = C_2H_5).—A mixture of 2.14 g. of ester X (R = $CH_2OC_2H_5$), 20 cc. of water and 10 cc. of *N* sodium hydroxide was heated at 50° for twenty-three hours. Addition of 10 cc. of *N* hydrochloric acid to the clear solution gave 1.51 g. (81%) of needles, which were recrystallized from 60 volumes of 50% ethanol. The product decomposes above 270°.

Anal. Calcd. for $C_7H_{10}O_4N_2$: C, 45.16; H, 5.41; C_2H_5O, 24.19; neut. equiv., 186.1. Found: C, 45.07; H, 5.39; C_2H_5O, 24.04; neut. equiv., 193.5.

The **acid chloride** was obtained by refluxing for ten minutes 1.33 g. of the foregoing acid with 70 cc. of dioxane and 7 cc. of thionyl chloride, evaporating the filtered solution and crystallizing the residue from 7 cc. of benzene. The yield was 1.02 g. (70%). It was recrystallized from 10 volumes of benzene and melted at 131–132°.

Anal. Calcd. for $C_7H_9O_3N_2Cl$: Cl, 17.33. Found Cl, 17.01.

4-Bromomethyl-5-carbethoxy-2-imidazolone (X, R = CH_2Br).—A solution of 855 mg. of ethoxy ester (X, R = $CH_2OC_2H_5$) in 8 cc. of 48% hydrobromic acid was heated five minutes at 80°. Cooling, followed by addition of 10 cc. of water, yielded 830 mg. (83%) of crystals, which after recrystallization from 70 volumes of dioxane melted at 218–220° (*in vacuo*, dec.).

Anal. Calcd. for $C_7H_9O_3N_2Br$: C, 33.75; H, 3.64; Br, 32.09; C_2H_5O, 18.09. Found: C, 33.86; H, 3.63; Br, 32.44; C_2H_5O, 18.05.

4-Hydroxymethyl-5-carbethoxy-2-imidazolone (X, R = CH_2OH).—When 250 mg. of the foregoing bromo ester was dissolved in 3 cc. boiling water and the obtained solution cooled, 105 mg. (56%) of bromine-free crystals separated, which were purified by sublimation *in vacuo* at 210–220° (bath); m. p. 216–218°.

Anal. Calcd. for $C_7H_{10}O_4N_2$: C, 45.16; H, 5.41; C_2H_5O, 24.20. Found: C, 45.34; H, 5.33; C_2H_5O, 24.75.

4-Hydroxymethyl-5-carboxy-2-imidazolone (XI, R = H).—A solution of 93 mg. of the foregoing ester was dissolved in 5 cc. of 0.1 *N* sodium hydroxide and heated for twenty-four hours at 50°. Upon acidification with 0.5 cc. of *N* hydrochloric acid and concentration to about 2 cc., 55 mg. of an acid separated, which could be recrystallized from 4 cc. of boiling water. The product decomposes above 200°.

Anal. Calcd. for $C_5H_6O_4N_2$: C, 37.98; H, 3.83; neut. equiv., 158.1. Found: C, 37.55; H, 3.88; neut. equiv., 162.1.

4-Phenyl-5-carbethoxy-2-imidazolone (X, R = C_6H_5).—To a prehydrogenated suspension of 1 g. of 2.5% palladium–charcoal in 10 cc. of *N* hydrochloric acid and 10 cc. of ethanol was added 2.31 g. of ethyl α-oximino-γ-benzoylacetate (VIII, R = C_6H_5), prepared according to Wolff and Hall[14] from ethyl benzoylacetate and nitrous acid. The mixture was hydrogenated at room temperature and atmospheric pressure until after one hundred and seventy minutes, 490 cc. (2 moles) was absorbed. The filtered solution, containing the amino ester (IX, R = C_6H_5), was boiled with 1.21 g. of potassium cyanate and 1 cc. of 5 *N* hydrochloric acid for ten minutes. An oily precipitate separated which became crystalline upon addition of 5 cc. of acetone. Filtering and washing with acetone yielded 700 mg. (30%) needles melting at 215–217°. The product can be recrystallized from aqueous alcohol and sublimed at 170–180° (bath) and 0.1 mm.

Anal. Calcd. for $C_{12}H_{12}O_3N_2$: C, 62.06; H, 5.21. Found: C, 61.80; H, 5.38.

4-Phenyl-2-imidazolone (I, R = C_6H_5).—Hot solutions of 1.3 g. of barium hydroxide octahydrate in 8 cc. of water and 730 mg. of the foregoing ester in 10 cc. of ethanol and 20 cc. of water were mixed. A bulky precipitate resulted. After heating at 80° for sixteen hours it had disappeared, being replaced by a dense deposit containing some long needles. It was filtered, washed with hot water and treated with 10 cc. of 50% glacial acetic acid, whereby the barium carbonate was dissolved and the phenylimidazolone left undissolved. The original mother liquor deposited on cooling and acidifying with acetic acid another 100 mg. (total 41%) identical material. It was recrystallized from 12 volumes of glacial acetic acid. The melting point was 330–333° (*in vacuo* dec.) and was not depressed in admixtures with a sample of phenylimidazolone prepared according to Rupe[15] from α-aminoacetophenone and potassium cyanate.

Anal. Calcd. for $C_9H_8ON_2$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.10; H, 4.74; N, 17.73.

The **Friedel–Crafts reactions** reviewed in Table I were run in 5 to 10 volumes of nitrobenzene based on the quantity of imidazolone at 60–65° and worked up by pouring on ice and washing of the reaction product with water and ether as previously reported.[1a]

The **hydrogenations** reviewed in Table II were run at room temperature and atmospheric pressure in glacial acetic acid with pre-reduced platinum oxide catalyst.

5-Benzyl-2-imidazolone (III, R = H, R′ = C_6H_5).—A suspension of 375 mg. of II (R = H, R′ = C_6H_5) and 140 mg. of 10% palladium–charcoal in 20 cc. of acetic acid was hydrogenated at atmospheric pressure and room temperature, until the benzoyl compound had gone into solution. After six hours the uptake had stopped with 2 moles hydrogen absorbed. The filtered solution gave upon evaporation and treatment of the residue with 10 cc. of 50% ethanol, 90 mg. (26%) crystals, which were purified by recrystallization from 6 cc. of 50% ethanol and sublimation at 180–190° (bath) and 0.6 mm.; m. p. 241–243°. The alcoholic solution of the substance gives with ferric chloride a deep purple coloration.

Anal. Calcd. for $C_{10}H_{10}ON_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.79; H, 5.25; N, 15.93.

Summary

1. A discrepancy concerning 2-imidazolone reported in the literature was clarified.

2. The alkali hydrolysis of 5-carbethoxy-2-

(14) Wolff and Hall, *Ber.*, **36**, 3614 (1902).

(15) Rupe, *ibid.*, **28**, 251 (1895).

imidazolones (X) containing various substituents R in position 4 was studied. Depending on the nature of the substituent R, either the decarboxylated imidazolones (I, R = CH_3, C_2H_5, C_6H_5) or the corresponding acids (XI, R = C_2H_5, H) were obtained.

3. Friedel–Crafts acylations of 2-imidazolone, 4-methyl-2-imidazolone, and 4-ethyl-2-imidazolone were performed, and the obtained ketones (II) were hydrogenated to imidazolidone derivatives (IV). Thus a lower (IV, R = H) and a higher (IV, R = C_2H_5) homolog of desthiobiotin were synthesized.

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No-Bond Resonance. The Competitive Bromination of Toluene and *t*-Butylbenzene

BY ERNST BERLINER AND FRANCES J. BONDHUS

Electrophilic substitution of *p*-alkyltoluenes takes place predominantly in the position *ortho* to the methyl group.[1,2,3] Le Fèvre,[2] who summarized the existing experimental data, realized that the course of substitution reactions on *p*-alkyltoluenes did not proceed according to the accepted order of the inductive effect, and ascribed the reversed order to steric repulsion due to increasing size of the alkyl groups. Baker and Nathan, however, interpreted the reactions on the basis of the now well known no-bond resonance effect without resorting to steric hindrance.[4,5,6] While there is little doubt as to the validity of the interpretation and the general usefulness of the concepts of no-bond resonance (hyperconjugation), it still seemed of interest to investigate the case of the *p*-alkyltoluenes. For example, the fact that *p*-*t*-butyltoluene is nitrated exclusively in the position *ortho* to the methyl group cannot be interpreted as indicating that the *t*-butyl group is completely incapable of increasing the electron density on the benzene ring. A preponderance of electron releasing capacity of the methyl group over that of the *t*-butyl group may be sufficient to cause the reaction to proceed entirely in one direction. Also, in spite of the electronic effects, some steric effect of the bulky *t*-butyl group cannot be completely discounted. Finally, in view of the strong *para* directing character of the *t*-butyl group and the fact that *t*-butylbenzene is more easily substituted than benzene, there must be some electron release from this group, which may or may not be the ordinary inductive effect, but cannot be due to first order hyperconjugation.

With this in mind the relative rates of substitution of toluene and *t*-butylbenzene by bromine were determined. Nuclear bromination is an electrophilic substitution reaction, and therefore belongs to those reactions for which an increased no-bond resonance effect should be expected. The usual comparison of the reactivity of two compounds toward substitution is the parallel bromination of hydrocarbons and the evaluation of the individual rate constants. By this method the rates of bromination of different alkylbenzenes have recently been determined by de la Mare and Robertson,[7] who interpreted their results in the light of hyperconjugation. Instead of employing the parallel method a simultaneous competitive bromination of the two hydrocarbons was chosen in the present investigation, because such a study lends itself to an immediate interpretation of the data, irrespective of the exact mechanism of the reaction, the nature of the active substituting agent, or accidental variations in temperature and other reaction conditions.[8] No matter what the conditions are, in a competitive bromination the hydrocarbon that furnishes the greater electron density at the point of attack will be brominated to the greater extent.

Toluene and *t*-butylbenzene were brominated simultaneously in 92% acetic acid using iodine as a catalyst, and the resulting mixture was analyzed for the amounts of bromotoluene and bromo-*t*-butylbenzene formed.

Experimental

The procedure followed was similar to the one used by Ingold and collaborators[8a,b] in the competitive nitration of benzene and toluene, but in the present case all of the brominated products could not be obtained in a single fraction. Two series of artificial mixtures, containing the same constituents as were obtained during the actual bromination, were prepared and their refractive indices and densities determined. One mixture consisted of *t*-butylbenzene and bromotoluene, the other of bromotoluene and bromo-*t*-butylbenzene. In the recovery of the brominated products the more volatile solvents were distilled, and the remainder was separated into two fractions. The amounts of brominated hydrocarbons in the two fractions were determined by measurements of the densities and refractive indices. The amounts of the three possible position isomers obtained from each hydrocarbon were not determined, and only the total brominated product was

(1) Battegay and Haeffely, *Bull. Soc. Chim.*, **35**, 981 (1924).

(2) Le Fèvre, *J. Chem. Soc.*, 980 (1933); 1501 (1934).

(3) Brady and Day, *ibid.*, 114 (1934).

(4) Baker and Nathan, *ibid.*, 1844 (1935).

(5) Watson, "Modern Theories of Organic Chemistry," 2nd ed., Oxford University Press, 1941, pp. 96–98.

(6) For a recent summary see Deasy, *Chem. Rev.*, **36**, 145 (1945).

(7) de la Mare and Robertson, *J. Chem. Soc.*, 279 (1943).

(8) (a) Ingold and Shaw, *ibid.*, 2918 (1927); (b) Ingold, Lapworth, Rothstein and Ward, *ibid.*, 1959 (1931); (c) Ingold and Smith, *ibid.*, 905 (1938); (d) Bird and Ingold, *ibid.*, p. 919; (e) Benford and Ingold, *ibid.*, p. 929.