analog of atebrin; 3,3'-diamino-4,4'-difluoroarsenobenzene, 3-amino-4-fluorophenylarsonic acid and 3-acetylamino-4-fluorophenylarsonic acid as analogs of the trypanocidal 3-amino-4-hydroxy-compounds; *p*-amino-*p'*-fluorodiphenylsulfone, *p*-chloro-*p'*-fluorodiphenylsulfone, *p*-fluoro-*p'*-hydroxydiphenylsulfone and *p,p'*-difluorodiphenylsulfone as analogs of diphenylsulfones of current interest; 2-acetoxymercuri-5-fluorophenol and two isomeric *s*-amyl-5-fluorophenols as analogs of the germicidal resorcinol derivatives; 3,3-bis-(4-fluorophenyl)-phthalide as an analog of phenolphthalein; and *p*-fluoro- derivatives of N^4-succinylsulfanilanilide and 4-succinimido-benzenesulfonanilide.]

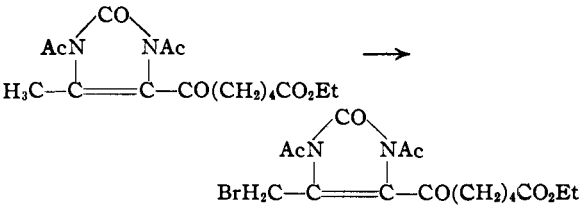
LAWRENCE, KANSAS RECEIVED AUGUST 23, 1947

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

Synthesis of Imidazolones Structurally Related to Biotin by Means of N-Bromosuccinimide[1]

BY ROBERT DUSCHINSKY AND L. ALLEN DOLAN

The preparation of 1,3-diacetyl-4-bromomethyl-5-(δ-carbethoxyvaleryl)-2-imidazolone as illustrated



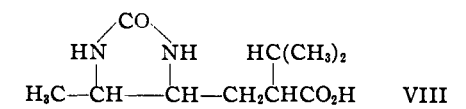
by application of Ziegler's[2] bromination method and the replacement of the bromine by oxygen-containing groups were essential steps in a recently reported synthesis of O-heterobiotin.[3]

The present paper demonstrates the versatility of the bromination and replacement reactions in the synthesis of a number of imidazolone derivatives. Some of them are structurally related to biotin since they possess its C,N skeleton and carry in the α-position of the side chains heteroatom-containing groups. The bromo compounds and substitution products are listed in Table I. Starting materials are the corresponding bromine-free compounds.

With the exception of 4-methyl-5-carbethoxy-2-imidazolone, which directly reacted with bromine to give I, diacylated imidazolones were used for the bromination by Ziegler's method.[4] The bromination was achieved by refluxing a carbon tetrachloride solution of such an imidazolone with one or, for the preparation of the dibromo compound IV, with two moles N-bromosuccinimide until the latter was completely converted into succinimide. The bromo compounds obtained in good yields are crystalline, not lachrymatory solids, which are sometimes inclined to undergo decomposition with release of hydrobromic and acetic acid. It is, therefore, advantageous to proceed at once with the desired replacement reaction. Depending on the reagent and reaction conditions, the replacement of the bromine may be accompanied by total or partial loss of the acetyl groups. Formation of mixtures of unacetylated, mono- and diacetylated products explains some of the low yields encountered in the substitution reactions.

Proof of the introduction of bromine into the methyl group has been established for the keto ester VI.[3] The same is true for compound I, because it was found to be identical with the product obtained from ethyl δ-ethoxy-β-ketobutyrate via 4-ethoxymethyl-5-carbethoxy-2-imidazolone (IA).[5]

The structure of III was established by conversion into an acetyl-free substitution and hydrogenation product. Thus, application of a method described for the preparation of 5-allyl-5-isopropylbarbituric acid[6] gave the barbiturate IIIA in fair yield. Due to its "de-aromatization" by acetyl groups,[3] the compound could be hydrogenated with palladium charcoal catalyst at room temperature, whereby only one of the two possible diastereomers, undoubtedly the *cis* form, was obtained in excellent yield.[7] It was readily deacetylated by cold sodium hydroxide. The obtained 4-methyl-5-(5'-isopropyl-5'-barbituryl-methyl)-2-imidazolidone was microbiologically inactive. Attempts to cleave the barbiturylimidazolone and imidazolidone for the purpose of obtaining the desthiobiotin isomer VIII correspond-



VIII

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

(2) Ziegler, Späth, Schaaf, Schumann and Winkelmann, *Ann.*, **551**, 80 (1942).

(3) Duschinsky and Dolan, "Jubilee Vol. Emil Barell," Basle, 146 (1946).

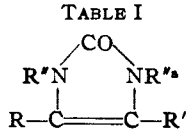
(4) 1,3-Diacetyl-4,5-dimethyl-2-imidazolone reacted also with bromine to give the dibromo derivative IV, but the yield was very low.

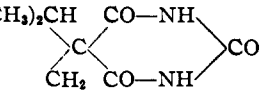
(5) Duschinsky and Dolan, THIS JOURNAL, **68**, 2350 (1946).

(6) Hoffmann-La Roche and Co., German Patent 526,854 (1930); *C. A.*, **25**, 4893 (1931).

(7) The barbiturate IIIA and its hydrogenation product were found devoid of hypnotic properties by Dr. G. Lehmann of the Pharmacological Laboratories of Hoffmann-La Roche Inc.

TABLE I



Bromo cpd. (R = CH_2Br) No.	R′	R″	Reactant	Substitution product isolated No.	R	R′	R″
I	CO_2Et	H	NaOEt	IA	CH_2OEt	CO_2Et	H
	CO_2Et	H	Ag acetate	IB	CH_2OAc	CO_2Et	H
II	H	Ac	Ethyl calcio malonate	IIA	$CH_2CH(CO_2H)_2$	H	H
	H	Ac	Dibenzylamine	IIB	$CH_2N(CH_2C_6H_5)_2$	H	Ac[b]
III	CH_3	Ac	Na isopropylbarbiturate	IIIA	$(CH_3)_2CH$ 	H	Ac
IV	CH_2Br	Ac	Na acetate	IVA	CH_2OAc	CH_2OAc	Ac
V	$CO(CH_2)_4CO_2Me$	Ac[c]	Ag benzoate	VA	$CH_2O_2CC_6H_5$	$CO(CH_2)_4CO_2Me$	Ac
	$CO(CH_2)_4CO_2Me$	Ac	Thiourea	VB	CH_2SCNH_2 ‖ $NH_2^+Br^-$	$CO(CH_2)_4CO_2Me$	Ac
	$CO(CH_2)_4CO_2Me$	Ac	Dibenzylamine	VC	$CH_2N(CH_2C_6H_5)_2$	$CO(CH_2)_4CO_2Me$	H
VI	$CO(CH_2)_4CO_2Et$	Ac	Dibenzylamine[d]	VIA	$CH_2N(CH_2C_6H_5)_2$	$CO(CH_2)_4CO_2Et$	Ac[b]
	$CO(CH_2)_4CO_2Et$	Ac	Dibenzylamine[e]	VIB	$CH_2N(CH_2C_6H_5)_2$	$CO(CH_2)_4CO_2Et$	H
	$CO(CH_2)_4CO_2Et$	Ac	Na_2SO_3	VIC	CH_2SO_3Na	$CO(CH_2)_4CO_2Et$	H
VII	COC_6H_5	Ac	Dibenzylamine	VIIA	$CH_2N(CH_2C_6H_5)_2$	COC_6H_5	Ac[b]
	COC_6H_5	Ac	$AgNO_2$	VIIB	CH_2NO_2	COC_6H_5	Ac

[a] The diacyl compounds are written as N,N-derivatives, although the possibility of N,O-acylation cannot be excluded. [b] One acetyl group only. [c] The dipropionyl derivative was also prepared. [d] Four moles at room temperature. [e] Five and one-half moles, refluxed in benzene.

ing in structure to Kögl's "α-biotin"[8] were abandoned when the accomplished synthesis of such desthiobiotin isomers by Brown and Ferger[9] became known to us.

Structures II, V and VII are assigned by analogy without direct proof. For the dibromo compound IV a symmetrical structure is assumed.

Treatment of the diacetyl bromo compounds with dibenzylamine, depending on the temperature and the excess of amine present, causes more or less stepwise removal of one acetyl group, replacement of the bromine and finally removal of the second acetyl group. 4-Dibenzylaminomethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone (VC), obtained from V in 70% yield, gave an oxime (84% yield) which upon palladium–charcoal catalyzed hydrogenation in presence of hydrochloric acid afforded 4-aminomethyl-5-(α-amino-ε-carbomethoxyamyl)-2-imidazolone dihydrochloride (IX) in 46% yield.

IX

The same sequence of reactions was performed with the ethyl ester VI.

Sulfur-containing substituents were introduced by treating bromoesters V and VI with thiourea and sodium sulfite, respectively. The isothiouronium bromide VB and the sodium sulfonate VIC resulted in fair to good yields.

(8) Kögl and Borg, *Z. physiol. Chem.*, **231**, 65 (1944).

(9) Brown and Ferger, THIS JOURNAL, **68**, 1507 (1946). We are indebted to Dr. Vincent du Vigneaud for communicating to us the contents of this paper prior to its publication.

It was previously reported that the keto group located in the α-position of *unacetylated* imidazolones undergoes easily hydrogenolysis and is converted into methylene.[5,10] In an analogous manner the keto esters VC and VIC lost the keto groups upon catalytic hydrogenation under mild conditions. Compound VC was also debenzylated. The ring double bond as well as the α-amino and α-sulfo groups remained intact, however. 4-Aminomethyl-5-(ε-carbomethoxyamyl)-2-imidazolone hydrochloride and the sodium salt of 4-sulfomethyl-5-(ε-carbethoxyamyl)-2-imidazolone were isolated in good yields.

1,3-Diacetyl-4-methyl-5-(ε-carbethoxyamyl)-2-imidazolone[10] and 1,3-diacetyl-4,5-dipropyl-2-imidazolone reacted with two moles of bromosuccinimide whereby an amount of succinimide was recovered which indicated bromination in the α-methylene groups. However, no crystalline dibromo derivatives could be isolated.

Experimental[11]

4-Bromomethyl-5-carbethoxy-2-imidazolone (I).—To a stirred boiling suspension of 51 g. of 4-methyl-5-carbethoxy-2-imidazolone[5] in one liter of carbon tetrachloride 48 g. of bromine was added within one hour. Boiling and stirring were continued for five more hours. After cooling the bromo ester was filtered and washed with carbon tetrachloride; yield 73.5 g. (98.5%). The substance decomposed *in vacuo* at *ca.* 220°. No depression was observed in admixtures with material obtained by a previously described method.[5]

(10) Duschinsky and Dolan, *ibid.*, **67**, 2079 (1945).

(11) Melting points were determined with an uncalibrated set of Anschütz thermometers. For the microanalyses we are indebted to Dr. Al Steyermark and his staff, for the microbiological assays to Dr. S. H. Rubin and his staff.

4-Ethoxymethyl-5-carbethoxy-2-imidazolone (IA).—To a solution of 11.1 g. of the foregoing bromo ester in 220 cc. of ethanol (obtained by short boiling and subsequent cooling) 43.2 cc. of *N* sodium ethoxide solution was added until the mixture was slightly alkaline to methyl orange. Evaporation *in vacuo* and crystallization of the residue from 5 cc. of water yielded 6.2 g. (65%) of needles, melting at 178–180° and showing no depression in admixtures with material obtained previously.[5]

4-Acetoxymethyl-5-carbethoxy-2-imidazolone (IB).—To a solution of 4.98 g. of bromo ester I in 90 cc. of hot acetic acid 3.34 g. of silver acetate was added with stirring. After ten minutes the silver bromide was filtered and the solution evaporated *in vacuo*. The residue was crystallized from 10 cc. of ether; yield 2.75 g. (60%). The substance was recrystallized by dissolving in 100 cc. of boiling ethyl acetate and adding 100 cc. of petroleum ether; m. p. 154–155°.

Anal. Calcd. for $C_9H_{12}O_5N_2$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.51; H, 5.36; N, 12.33.

1,3-Diacetyl-4-bromomethyl-2-imidazolone (II).—A solution of 9.1 g. of 1,3-diacetyl-4-methyl-2-imidazolone[10] in 30 cc. of carbon tetrachloride was refluxed with 8.55 g. of bromosuccinimide for twenty minutes until the potassium iodide reaction was negative and the succinimide was visible as a layer covering the top of the liquid. After cooling, the imide was filtered off, the filtrate evaporated *in vacuo* and the residue crystallized from ether; yield, 9.14 g. (70%). It crystallized in needles, melting at 80–81°, which were inclined to turn pink. For the analysis a sample was sublimed at 0.3 mm. and 90° (bath).

Anal. Calcd. for $C_8H_9O_3N_2Br$: C, 36.80; H, 3.47; N, 10.73. Found: C, 36.52; H, 3.34; N, 10.40.

4-(β,β-Dicarboxyethyl)-2-imidazolone (IIA).—The carbon tetrachloride solution obtained in the above described manner by reaction of 3.64 g. of 1,3-diacetyl-4-methyl-2-imidazolone and 3.54 g. of bromosuccinimide and filtering the succinimide was added slowly to 20 cc. of a 1.1 *N* calcio diethyl malonate[12] solution in carbon tetrachloride. The mixture was refluxed with stirring for four and one-half hours, then washed in a separatory funnel with water until the washings were bromine-free. The carbon tetrachloride layer was dried over sodium sulfate and evaporated to a yellow oil. After removing excess malonic ester by heating *in vacuo* in a bath at 140°, a solution of 8 g. of sodium hydroxide in 55 cc. of water was mixed with the residue and let stand overnight. Some tar was filtered off, the solution was concentrated on a water-bath to 20 cc., neutralized with hydrochloric acid and evaporated to dryness. The residue was extracted three times with 25 cc. of boiling dioxane. The dioxane extract was evaporated to dryness and extracted three times with 10 cc. of ether. The ether insoluble residue was crystallized from 6 cc. of water; yield 610 mg. (15%) as needles which after recrystallization from 10 cc. of water melted in an evacuated capillary tube at 253–255°.

Anal. Calcd. for $C_7H_8O_2N$: C, 42.00; H, 4.03; N, 14.00. Found: C, 41.80; H, 3.89; N, 13.76.

Acetyl-4-dibenzylaminomethyl-2-imidazolone (IIB).—A solution of 1.64 g. of II in 25 cc. of benzene was mixed with a solution of 6.3 g. (5 moles) of dibenzylamine in 25 cc. of benzene. The mixture was refluxed with stirring for three hours. The crystallized dibenzylamine hydrobromide (1.62 g.) was sucked off, the filtrate evaporated and finally dried *in vacuo* at 100°. The resulting honey-like mass was twice extracted with 50 cc. of petroleum ether whereupon it became almost solid. Crystallization from 10 cc. of methanol and recrystallization from ethanol gave 190 mg. (9%) of needles melting at 174–176°. The analysis indicated the presence of some diacetyl compound.

Anal. Calcd. for $C_{20}H_{21}O_2N_3$: C, 71.62; H, 6.31; N, 12.53; CH_3CO, 12.83. Found: C, 71.47; H, 6.17; N, 11.77; CH_3CO, 14.30.

(12) Prepared by modifying a method described by Lund, *Ber.*, **67**, 935 (1934).

1,3-Diacetyl-4-bromomethyl-5-methyl-2-imidazolone (III).—A solution of 19.6 g. of 1,3-diacetyl-4,5-dimethyl-2-imidazolone[13] in 200 cc. of carbon tetrachloride was refluxed for fifteen minutes with 17.5 g. (1 mole) of bromosuccinimide and worked up as described above. Crystallization from 30 cc. of ether yielded 22.3 g. (81.5%) of colorless needles melting at 84–89°.

Anal. Calcd. for $C_9H_{11}O_3N_2Br$: C, 39.29; H, 4.03. Found: C, 39.41; H, 4.45.

1,3-Diacetyl-4-methyl-5-(5′-isopropyl-5′-barbituryl-methyl)-2-imidazolone (IIIA).—A solution of 21.96 g. of the foregoing freshly prepared bromo compound in 80 cc. of dioxane was added gradually to a cooled solution of 13.89 g. of 5-isopropyl-barbituric acid in 81 cc. of *N* sodium hydroxide which held 0.2 g. of copper–bronze powder in suspension. After shaking the mixture consisting of two layers for fourteen hours it was evaporated to a heavy oil which was dissolved in 70 cc. of methanol. Gradual addition of 70 cc. of water yielded crystals which were washed with 90 cc. of 50% methanol until they were bromine free; yield 13.93 g., m. p. 164–172°. Extraction with 100 cc. of dry ether left undissolved 10.89 g. material melting at 183–186° (37.4%). The product can be recrystallized from aqueous 40% ethanol. It melts then at 189–191°.

Anal. Calcd. for $C_{16}H_{20}O_6N_4$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.61; H, 5.37; N, 15.51.

1,3-Diacetyl-4-methyl-5-(5′-isopropyl-5′-barbituryl-methyl)-2-imidazolidone.—The foregoing ether-washed imidazolone (IIIA) (2.44 g.) was hydrogenated for three hours with 750 mg. of 10% palladium-charcoal catalyst in 25 cc. of acetic acid at room temperature and atmospheric pressure until 1 mole hydrogen was taken up and the reaction stopped. The filtered solution was evaporated and the well-dried residue became crystalline upon addition of 20 cc. of ether; yield 1.97 g. (83%), melting at 237–241°, and after recrystallization from 30 volumes of 50% ethanol at 243–244°.

Anal. Calcd. for $C_{16}H_{22}O_6N_2$: C, 52.45; H, 6.05. Found: C, 52.61; H, 6.39.

4-Methyl-5-(5′-isopropyl-5′-barbiturylmethyl)-2-imidazolidone.—The above diacetyl compound (760 mg.) was dissolved in 7.2 cc. of *N* sodium hydroxide. After five hours the solution was neutralized with 7.2 cc. of *N* hydrochloric acid. The separated crystals were filtered and washed with water; yield 490 mg. (84%), melting at 261–263°, and after recrystallization from water at 269–271° (*in vacuo*). The compound revealed neither biotin nor antibiotin activity for *Saccharomyces cerevisiae* No. 139 and *Lactobacillus casei*.

Anal. Calcd. for $C_{12}H_{18}O_4N_2$: C, 51.05; H, 6.43; N, 19.85. Found: C, 51.17; H, 6.50; N, 19.70.

1,3-Diacetyl-4,5-bis-(bromomethyl)-2-imidazolone (IV).—A solution of 3.92 g. of 1,3-diacetyl-4,5-dimethyl-2-imidazolone in 40 cc. of carbon tetrachloride was refluxed for thirty minutes under stirring with 7.08 g. (2 moles) of bromosuccinimide. The solution filtered from the succinimide was concentrated to a sirup which became crystalline upon addition of 10 cc. of dry ether. The crystals were washed with ether; yield 3.51 g. (49.6%), m. p. 108–110°. The product can be recrystallized from ether containing 4% dioxane.

Anal. Calcd. for $C_9H_{10}O_3N_2Br_2$: C, 30.53; H, 2.85; N, 7.91. Found: C, 30.97; H, 3.07; N, 7.97.

1,3-Diacetyl-4,5-bis-(acetoxymethyl)-2-imidazolone (IVA).—A mixture of 380 mg. of IV, 10 cc. of dry acetone and 1 g. of anhydrous potassium acetate was shaken for forty-eight hours. Addition of ether to the filtered solution produced 135 mg. (43%) of crystals melting at *ca.* 133°, which after sublimation at 0.4 mm. and 160° (bath) melted at 143–145°.

Anal. Calcd. for $C_{13}H_{16}O_7N_2$: C, 50.00; H, 5.16; N, 8.97. Found: C, 49.95; H, 5.18; N, 8.98.

(13) Biltz, *ibid.*, **40**, 4801 (1907).

1,3-Diacetyl-4-methyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone.—A mixture of 37.9 g. of 4-methyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone[5] and 165 cc. of acetic anhydride was refluxed for twenty minutes. The resulting solution was concentrated to a small volume first at atmospheric pressure, then *in vacuo*. The residue was taken up with 165 cc. of acetic anhydride. The refluxing and evaporating were repeated. The final residue was dried for one hour at 100° *in vacuo* and crystallized by addition of 40 cc. of methanol and cooling in an acetone–Dry Ice-bath; yield 44.2 g. (87%), melting at 68–69°, and after recrystallization from methanol at 69–70°.

Anal. Calcd. for $C_{15}H_{20}O_6N_2$: C, 55.55; H, 6.22. Found: C, 55.59; H, 6.16.

The **dipropionyl derivative** was obtained as described above in a yield of 84% by substituting propionic anhydride for acetic anhydride. It melted at 65–66°.

Anal. Calcd. for $C_{17}H_{24}O_6N_2$: C, 57.94; H, 6.86. Found: C, 57.74; H, 6.76.

1,3-Diacetyl-4-bromomethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone (V).—A solution of 16.2 g. of 1,3-diacetyl-4-methyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone in 95 cc. of carbon tetrachloride was refluxed for one hour with 8.55 g. of bromosuccinimide. The solution filtered from the succinimide (4.44 g.) was evaporated and the residue crystallized from 50 cc. of cold ether; yield 18.5 g. (92%) colorless needles melting at 58–60°, and after recrystallization from 4 volumes of methanol at 59–61°.

Anal. Calcd. for $C_{15}H_{19}O_6N_2Br$: C, 44.68; H, 4.75. Found: C, 44.74; H, 4.54.

1,3-Dipropionyl-4-bromomethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone.—It was obtained in an analogous manner with a yield of 53%, m. p. 59–61°.

Anal. Calcd. for $C_{17}H_{23}O_6N_2Br$: C, 47.34; H, 5.37. Found: C, 47.38; H, 5.40.

1,3-Diacetyl-4-benzoxymethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone (VA).—A solution of 4.03 g. of crude bromo ester V in 50 cc. of dioxane was shaken for two days with 5 g. of silver benzoate. The filtered bromine-free solution was evaporated. The residue was extracted with ether which left some silver-containing material undissolved. The ether extract was evaporated to an oil which became crystalline upon addition of methanol; yield 2.34 g. (53%). The material melting at *ca.* 90° was recrystallized by dissolving in 40 cc. of ether, adding methanol and evaporating the ether *in vacuo;* yield 1.8 g. of crystals melting at 90–93°.

Anal. Calcd. for $C_{22}H_{24}O_8N_2$: C, 59.45; H, 5.44; N, 6.30. Found: C, 59.70; H, 4.90; N, 6.12.

1,3-Diacetyl-4-guanylthiomethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone Hydrobromide (VB).—To a solution of 0.76 g. of thiourea in 50 cc. of anhydrous dioxane 4.03 g. of bromo ester V was added. The mixture was refluxed for ten minutes, then cooled, whereupon the hydrobromide crystallized in fine leaflets. It was filtered and washed with dioxane and ether; yield 3.23 g. (68%). The substance melted at 161–162° and after recrystallization from 12 volumes of dioxane at 164–165°.

Anal. Calcd. for $C_{16}H_{23}O_6N_4SBr$: C, 40.09; H, 4.84; N, 11.69; S, 6.69. Found: C, 40.13; H, 4.90; N, 11.62; S, 6.24.

Acetyl-4-bromomethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone.—When a carbon tetrachloride solution of diacetyl bromo ester V was treated for fifteen minutes at room temperature with one mole of dibenzylamine a substantial amount (*ca.* 20%) of monoacetyl bromo ester crystallized out. It was recrystallized from benzene, m. p. 129–130°.

Anal. Calcd. for $C_{13}H_{17}O_5N_2Br$: C, 43.22; H, 4.75; N, 7.76; Br, 22.13. Found: C, 43.53; H, 4.73; N, 7.85; Br, 22.15.

4-Dibenzylaminomethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone (VC).—Solutions of 44 g. of crude bromo ester V in 700 cc. of benzene and of 120 g. (5.6 moles) of dibenzylamine in 100 cc. of benzene were mixed and refluxed with stirring for six and one-half hours. After cooling the crystallized 28.5 g. (94%) of dibenzylamine hydrobromide was filtered off. The filtrate was evaporated to a yellowish sirup which was washed by four extractions with a total of 1.5 liters of petroleum ether. The petroleum ether insoluble oil became crystalline when mixed with 250 cc. of ether. The still pasty crystals were filtered off and recrystallized from 200 cc. of methanol; yield 33.2 g. (70%), m. p. 134–135°. After a second recrystallization the substance melted at 135–136°.

Anal. Calcd. for $C_{25}H_{29}O_4N_3$: C, 68.49; H, 6.71; N, 9.65. Found: C, 68.92; H, 6.51; N, 9.66.

The **free acid** was prepared from the foregoing ester by heating on a water-bath for one hour with a mixture of 10 volumes of *N* sodium hydroxide and 5 volumes of methanol and neutralizing with hydrochloric acid. It was recrystallized from aqueous ethanol, m. p. 207–208°.

Anal. Calcd. for $C_{24}H_{27}O_4N_3$: C, 68.39; H, 6.46. Found: C, 68.26; H, 6.17.

Acetyl-4-dibenzylaminomethyl-5-(δ-carbethoxyvaleryl)-2-imidazolone (VIA).—To a solution of 835 mg. of bromo ethyl ester VI in 20 cc. of benzene 790 mg. of dibenzylamine (2 moles) in 20 cc. of benzene was added dropwise with stirring. Dibenzylamine hydrobromide was filtered off after letting the mixture stand for twenty hours. Since only 300 mg. of hydrobromide (59%) was recovered another 790 mg. of dibenzylamine was added. An additional crop of dibenzylamine hydrobromide (total 90%) was filtered off after letting the mixture stand overnight. The filtrate was concentrated to a sirup which was mixed with ethanol to produce 430 mg. (45%) of crystals melting at 98–100°, and after recrystallization from 5 cc. of ethanol at 101–102°.

Anal. Calcd. for $C_{28}H_{33}O_5N_3$: C, 68.41; H, 6.77; CH_3CO, 8.76. Found: C, 68.31; H, 7.27; CH_3CO, 9.18.

4-Dibenzylaminomethyl-5-(δ-carbethoxyvaleryl)-2-imidazolone (VIB).—The bromo ethyl ester VI (8.34 g.) after reaction with 21.5 g. (5.5 moles) of dibenzylamine in the manner described for the methyl ester V gave 6.93 g. (74%) of dibenzylamino compound melting at 103–106°. Several recrystallizations from 95% ethanol raised the melting point to 107–109°. The product was acetyl free and contained one molecule water of crystallization.

Anal. Calcd. for $C_{26}H_{31}O_4N_3 \cdot H_2O$: C, 66.79; H, 6.68; N, 8.99. Found: C, 67.16, 67.23; H, 6.67, 6.85; N, 9.01.

Upon drying *in vacuo* at 100° the substance melted to a yellowish resin and became anhydrous.

Anal. Calcd. for $C_{26}H_{31}O_4N_3$: C, 69.46; H, 6.94. Found: C, 69.43; H, 7.01.

4-Dibenzylaminomethyl-5-(α-oximino-ε-carbomethoxyamyl)-2-imidazolone.—A solution of 8.7 g. of crude methyl ester (VA) in 14 cc. of pyridine was mixed with 2.8 g. (2 moles) of finely powdered hydroxylamine hydrochloride and heated with occasional shaking for thirty-eight hours at 39°. After initial dissolution crystallization started. The reaction mixture was diluted with 120 cc. of water, the crystals were filtered and washed chlorine free with water, then with methanol and ether; yield 7.55 g. (84%), m. p. 188–190°. For the analysis the oxime was recrystallized from 12 volumes methanol. It melted at 191–192°.

Anal. Calcd. for $C_{25}H_{30}O_4N_4$: C, 66.64; H, 6.71; N, 12.44. Found: C, 66.40; H, 6.80; N, 12.76.

4-Dibenzylaminomethyl-5-(α-oximino-ε-carbethoxyamyl)-2-imidazolone was obtained in 65% yield from the crude ethyl ester (VIB) in the above described manner. It was recrystallized from 100 volumes of ethanol and melted at 184–185°.

Anal. Calcd. for $C_{26}H_{32}O_4N_4$: C, 67.22; H, 6.94. Found: C, 67.14; H, 6.84.

4-Aminomethyl-5-(α-amino-ε-carbomethoxyamyl)-2-imidazolone Dihydrochloride (IX).—A mixture of 13.16 g. of crude 4-dibenzylaminomethyl-5-(α-oximino-ε-carbo-

methoxyamyl)-2-imidazolone, 135 cc. of methanol, 5 cc. of concentrated hydrochloric acid and 7 g. of prehydrogenated palladium oxide catalyst (Baker and Co.) was hydrogenated for one hour at room temperature and four hours at 50° at a pressure of 900–1000 lb. The filtered solution was evaporated *in vacuo* below 40° to a sirup, which was mixed with 35 cc. of methanol and 60 cc. of ether. On standing in the cold 4.38 g. (46%) of thin plates was obtained which melted and decomposed at 173–175°, and after dissolving in 20 volumes of hot methanol and adding 5 volumes of ether at 176–178°. The product gave an intense red ferric chloride reaction indicating the presence of the imidazolone double bond.

Anal. Calcd. for $C_{11}H_{20}O_3N_4 \cdot 2HCl$: C, 40.13; H, 6.74; N, 17.02; Amino N, 8.51. Found: C, 39.82; H, 6.53; N, 17.03; Amino N, 8.78, 8.31.

4-Aminomethyl-5-(α-amino-ε-carbethoxyamyl)-2-imidazolone dihydrochloride was obtained in 56% yield by an analogous hydrogenation in ethanol of 1.75 g. of corresponding oximino ethyl ester. The substance was recrystallized from 85% ethanol and ether. It melted at 164–166° and gave an intense ferric chloride reaction.

Anal. Calcd. for $C_{12}H_{22}O_3N_4 \cdot 2HCl$: C, 41.99; H, 7.05; N, 16.32; Amino N, 8.16. Found: C, 41.97; H, 6.90; N, 16.26; Amino N, 8.41.

4-Aminomethyl-5-(ε-carbomethoxyamyl)-2-imidazolone Hydrochloride.—A suspension of 970 mg. of keto ester (VC) and of 1 g. of prehydrogenated palladium oxide catalyst in 20 cc. of methanol and 0.2 cc. of concentrated hydrochloric acid was hydrogenated at room temperature and atmospheric pressure. Two moles of hydrogen was absorbed in twenty minutes, two additional moles in three hours. The filtered solution was evaporated to a small volume until crystals separated, the amount of which was increased by addition of acetone; yield 410 mg. (70%), m. p. 181–182°. Two recrystallizations from a little methanol raised the melting point to 186–188°. The substance gives an intense red ferric chloride reaction.

Anal. Calcd. for $C_{11}H_{19}O_3N_3 \cdot HCl$: C, 47.56; H, 7.26; N, 15.13; Amino N, 5.04. Found: C, 47.70; H, 7.11; N, 14.92; Amino N, 5.34.

Sodium Salt of 4-Sulfomethyl-5-(δ-carbethoxyvaleryl)-2-imidazolone (VIC).—A mixture of 1.53 g. of bromo ester VIA, 0.93 g. of sodium sulfite (2 moles) and 5 cc. of water was refluxed until after fifteen minutes a clear solution was obtained. Considerable sulfur dioxide evolution was observed. The resulting slightly acidic solution gave upon evaporation *in vacuo* a crystalline cake. In order to decompose any remaining sulfite the product was dissolved in 5 cc. of hot 10% acetic acid and the resulting solution evaporated. The final residue was dissolved in 2 cc. of hot water. Upon addition of 8 cc. of ethanol and cooling, fine needles separated which were washed bromine free by 80% ethanol; yield 0.59 g. (45%). The substance melted under decomposition in an evacuated capillary tube at about 272° and after recrystallization by dissolving in 2 cc. of 10% warm acetic acid and adding 10 cc. of ethanol, whereby 0.52 g. was recovered, at 280–282°.

Anal. Calcd. for $C_{12}H_{17}O_7N_2SNa$: S, 9.00; Na, 6.45; C_2H_5O, 12.65. Found: S, 8.91; Na, 6.57; C_2H_5O, 12.10.

Sodium Salt of 4-Sulfomethyl-5-(ε-carboxyamyl)-2-imidazolone.—The foregoing keto compound (320 mg.) was hydrogenated at room temperature and atmospheric pressure with 300 mg. of prehydrogenated platinum oxide catalyst (Baker and Co.) in 10 cc. of acetic acid. Although in twenty minutes the hydrogen uptake (2 moles) had practically stopped, shaking was continued for fifty minutes. The filtered solution was evaporated *in vacuo* and the obtained residue dissolved in 5 cc. of methanol. Addition of 10 cc. of ether and scratching produced crystallization in microscopic rhombs; yield 230 mg. (76%). The substance was recrystallized with little loss by dissolving in 5 cc. of hot 90% methanol and adding 12 cc. of ether. It melted and decomposed *in vacuo* at about 252° and gave an intense red ferric chloride reaction indicating the presence of the imidazolone double bond.

Anal. Calcd. for $C_{12}H_{19}O_6N_2SNa$: C, 42.10; H, 5.59; S, 9.36; Na, 6.72. Found: C, 42.59; H, 6.11; S, 9.11; Na, 6.80.

1,3-Diacetyl-4-bromomethyl-5-benzoyl-2-imidazolone (VII).—A solution of 2.86 g. of 1,3-diacetyl-4-methyl-5-benzoyl-2-imidazolone[10] in 25 cc. of carbon tetrachloride was refluxed for twenty-five minutes with 1.77 g. of bromosuccinimide. The filtrate from the recovered succinimide (94%) was evaporated to a sirup which became crystalline upon addition of 25 cc. of ether; yield 3.25 g. (89%), m. p. 131–132°. Recrystallization from 20 volumes of ethanol did not change the melting point.

Anal. Calcd. for $C_{15}H_{13}O_4N_2Br$: C, 49.33; H, 3.59. Found: C, 49.44; H, 3.64.

Acetyl-4-dibenzylaminomethyl-5-benzoyl-2-imidazolone (VIIA).—Solutions of 3.13 g. of VII in 40 cc. of benzene and 3.38 g. (2 moles) of dibenzylamine in 20 cc. of benzene were mixed and stirred for two hours, then allowed to stand overnight. The filtrate from the dibenzylamine hydrobromide was evaporated to a volume of *ca.* 10 cc. and mixed with 10 cc. of petroleum ether. The formed crystals were filtered and washed with methanol. The mother liquor gave a second crop on evaporation and addition of 20 cc. of methanol: total yield 1.58 g. (42%) melting at about 195°. Recrystallization from 10 volumes of ethanol raised the melting point to 204–205°, without causing much loss of material.

Anal. Calcd. for $C_{27}H_{25}O_3N_3$: C, 73.78; H, 5.73; N, 9.56; CH_3CO, 9.80. Found: C, 74.32; H, 5.59; N, 9.75; CH_3CO, 10.14.

1,3-Diacetyl-4-nitromethyl-5-benzoyl-2-imidazolone[14] **(VIIB).**—A solution of 1.5 g. of VII in 25 cc. of anhydrous dioxane was shaken for fifteen hours with 2 g. of dry silver nitrite. The solution was rendered bromine free by addition of 1 g. more of silver nitrite and stirring for one hour at 50°. A small amount of sodium chloride was added to the filtrate in order to eliminate silver ions. Evaporation to a sirup and addition of 20 cc. of 50% ethanol yielded 440 mg. (30%) of crystals melting at 137–138° and after recrystallization from 20 cc. of ethanol at 139–140°. The substance contains apparently one molecule of water of crystallization which is not eliminated by drying *in vacuo* at 60°.

Anal. Calcd. for $C_{15}H_{13}O_6N_3 \cdot H_2O$: C, 51.58; H, 4.33; N, 12.03. Found: C, 52.02; H, 4.09; N, 11.80.

1,3-Diacetyl-4,5-dipropyl-2-imidazolone.—4,5-Dipropyl-2-imidazolone[15] (16.8 g.) was acetylated by twice refluxing and evaporating with 90 cc. of acetic anhydride. It was crystallized from ethanol at −30°; yield 18.88 g. (74%), m. p. 57–59°.

Anal. Calcd. for $C_{13}H_{20}O_3N_2$: C, 61.88; H, 7.99. Found: C, 62.19; H, 7.81.

Acknowledgment.—The authors are indebted to Mrs. Donna Ressetar and Mr. Sigfried Muller for technical assistance in a portion of this work.

Summary

A number of 4- and 5-substituted 2-imidazolones were brominated in the α-position of the side chains by applying with one exception Ziegler's N-bromosuccinimide method to the diacyl derivatives. The bromo compounds were submitted to various replacement reactions (Table I).

Imidazolones were prepared which possess the C,N-skeleton of biotin and carry in the α-positions oxygen, nitrogen and sulfur-containing groups (VA, VB, VC, VIA, VIB, VIC, and IX).

Catalytic hydrogenation of the double bond in the diacetyl compound IIIA was possible under

(14) The alternative formulation as nitrous acid ester is less likely in view of the stability of the compound toward water and alcohol.

(15) Basse and Klinger, *Ber.*, **31**, 1221 (1898).

mild conditions. Catalytic hydrogenation of the unacetylated compounds VC and VIC caused reduction of the α-keto group to methylene whereas the double bond and the α-amino and α-sulfo group remained intact.

NUTLEY, NEW JERSEY RECEIVED JULY 2, 1947

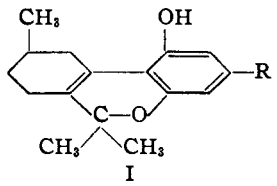
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE SCHOOL OF MEDICINE, UNIVERSITY OF UTAH]

Tetrahydrocannabinol Homologs. XVII.[1]

BY ROGER ADAMS, BEN F. AYCOCK, JR., AND S. LOEWE

Modification of the 3-alkyl substituent of the synthetic tetrahydrocannabinol molecule (I) has resulted in the production of compounds of varying marihuana activity. Such compounds containing a 1′-methylalkyl side-chain have been shown to possess greatly enhanced activity compared to their *n*-alkyl analogs, and the most potent compound previously synthesized, the homolog with a 1′-methylheptyl group, has an activity greater than that of natural tetrahydrocannabinol.[1] Two additional members of the series, the 1′-methyloctyl and the 1′-methylnonyl, have now been synthesized.

The effect of distance from the aromatic ring of a substituent methyl in the 3-alkyl group has been investigated by the synthesis and testing of compounds with the 2′-, 3′- and 4′-methylpentyl groups in the 3-position. In Table I are included for comparison the pharmacological activities of these compounds, the 1′-methyloctyl and 1′-methylnonyl homologs and certain closely related compounds.



I

Inspection of Table I leads to several interesting conclusions. The 1′-methyloctyl homolog (no. 5) has an activity double that of the next lower member (no. 4) and over four times that of natural tetrahydrocannabinol (no. 14); thus it becomes the most potent substance ever tested. As a result of the unusual duration of action of the next higher homolog (no. 6) it is impossible to say where the peak of activity in this series occurs. The 1′-methylnonyl compound is only slightly soluble in propylene glycol and therefore was injected as an emulsion. This fact may account for the prolonged action exhibited by this substance.

It is also apparent that substitution of the alkyl group in the position in the side-chain next to the ring has a much greater effect than in a more distant position, the activity falling from 3.7 in the 1′-methylpentyl to 1.14 in the 4′-methylpentyl. Furthermore, the order of activity of the various isomeric hexyl side chains studied shows that all

TABLE I

PHARMACOLOGICAL ACTIVITY OF TETRAHYDROCANNABINOL HOMOLOGS

	3-Substituent	No. of expts.	Potency
1	$-C_6H_{11}$-*n*	20	1.00 standard
2	$-C_6H_{13}$-*n*[2]	7	1.82 ± 0.18 (max. in *n*-series)
3	$-C_8H_{17}$-*n*[2]	7	0.66 ± 0.12
4	$-CH(CH_3)C_6H_{13}$[1]	10	16.4 ± 3.67
5	$-CH(CH_3)C_7H_{15}$	19	32.6 ± 3.02[3]
6	$-CH(CH_3)C_8H_{17}$	7	2.08 ± 1.49[3,4]
7	$-CH(CH_3)C_4H_9$[1]	8	3.17 ± 0.33
8	$-CH_2CH(CH_3)C_3H_7$	7	1.58 ± 0.41[3]
9	$-CH_2CH_2CH(CH_3)C_2H_5$	10	1.26 ± 0.18[3]
10	$-CH_2CH_2CH_2CH(CH_3)_2$	4	1.14 ± 0.10[3]
11	$-CH(C_2H_5)C_3H_7$[1]	11	1.67 ± 0.33
12	Natural tetrahydrocannabinol acetate (from charas)[5]	5	14.6 ± 1.05
13	Natural tetrahydrocannabinol by hydrolysis of 12[5]	15	7.8 ± 0.47
14	Tetrahydrocannabinol from cannabidiol[6]	20	7.3 ± 0.89

except the 1′-methylpentyl have a lower potency than the *n*-hexyl, the activities falling in the order: 1′-methylpentyl > *n*-hexyl > 1′-ethylbutyl > 2′-methylpentyl > 3′-methylpentyl > 4′-methylpentyl (isohexyl). It is significant that although the isohexyl homolog was reported to have negligible activity[7] by the Gayer test,[8] its potency, according to the dog ataxia test, is even greater than that of the standard.

The methods of preparation of these homologs are essentially those of Adams and Baker,[9] and

(1) For previous paper see Adams, Chen and Loewe, THIS JOURNAL, **67**, 1534 (1945).

(2) Adams, Loewe, Jelinek and Wolff, *ibid.*, **63**, 1971 (1941).

(3) The values for these compounds were calculated in the basis of standard error values. Miller and Tainter, *Proc. Soc. Exper. Biol. and Med.*, **57**, 261 (1944); Loewe, in press.

(4) Values for No. 6 are incommensurable, since this substance has at least five times the duration of action of its congeners in doses of equal intensity of peak effect.

(5) Wollner, Matchett, Levine and Loewe, THIS JOURNAL, **64**, 26 (1942).

(6) Adams, Loewe, Smith and McPhee, *ibid.*, **64**, 694 (1942).

(7) Russell, Todd, Wilkinson, MacDonald and Woolf, *J. Chem. Soc.*, 826 (1941).

(8) For a discussion of the Gayer test and the dog ataxia test used in these studies, see S. Loewe, *J. Pharm. Exper. Therap.*, **84**, 78 (1945), and "The Marihuana Problem in the City of New York," The Jacques Cattell Press, Lancaster, Pa., 1944, p. 175.

(9) Adams and Baker, THIS JOURNAL, **62**, 2405 (1940).