Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.94; H, 6.22; N, 5.41.

B. Elimination of CH_3OH from VI and VII.—A solution of 0.1 g of VI in 10 ml of methanol and an analogous solution of VII were each treated with 0.2 g of Na_2CO_3 and allowed to stand at room temperature. After 2 hr, analysis by thin layer chromatography (silica gel G, 2:1 acetone–benzene) indicated 50% conversion of VI into XXVII and less than 5% of the corresponding conversion of VII. Sodium ethoxide (0.1 g) was added to the mixtures and the reactions were completed by refluxing the solution of VI for 10 min and that of VII for 3.5 hr. The mixtures were concentrated under a stream of nitrogen, diluted with cold water, neutralized, and extracted with chloroform. The extracts were dried and evaporated to give crystalline residues which were recrystallized from acetonitrile. Both products were found to possess identical melting points, ultraviolet, infrared, and pmr spectra with the compound XXVII prepared by the above described mercuric acetate dehydrogenation of IV.

Study of the Solvent and pH Dependence of the Reaction of 6,7-Dimethoxy-3,4-dihydroisoquinoline with 2-Acetylcyclohexanone.—Mixtures of 0.96 g of 6,7-dimethoxy-3,4-dihydroisoquinoline and 0.7 g of 2-acetylcyclohexanone were dissolved in 10 ml each of (a) water, (b) dimethyl sulfoxide, (c) ethanol, (d) benzene, (e) 2% NaOH, (f) 1 *N* HCl, and (g) 1 *N* acetic acid, and the batches were heated to 78–82° (a variation of batch d was provided with a Dean–Stark trap for possible azeotropic water entrainment). Samples taken from the vigorously stirred reaction mixtures after 2, 4, and 24 hr were analyzed by thin layer chromatography using silica gel G and benzene–acetone (1:1) mixture. The progress of the reactions was estimated by a visual comparison of the intensities of the product spot (R_f 0.49).

Acknowledgment.—We wish to thank Professor E. L. Eliel for his helpful discussions. The authors are indebted to Mr. C. Puchalski and Mr. A. Caro for technical assistance in the phase of this work concerned with structure proof and reaction mechanism. We wish to express our gratitude to Mr. A. Lewis and his associates, Mrs. U. Zeek, Mr. R. Puchalski, and Mr. R. DeSimone, for analytical and spectral data. We thank Dr. A. W. Ruddy and his associates, Messrs. F. McMillan, R. Novack, and O. Kukla, for large-scale preparation of intermediates.

3-Aryl-1,2-dihydroquinoxalines

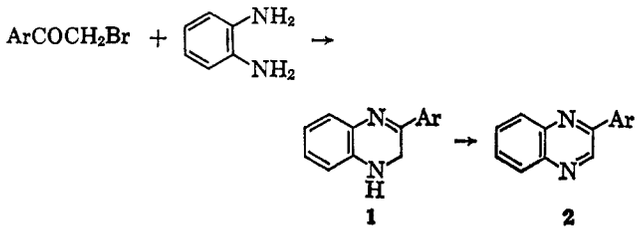
J. FIGUERAS

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

Received April 9, 1965

Under sufficiently mild conditions, 2-haloacetophenones react with *o*-phenylenediamine to give 3-aryl-1,2-dihydroquinoxalines in good yield. The structure of these compounds is established by acetylation, oxidation to quinoxalines, and physical methods.

Hinsberg[1,2] reported that 2-bromoacetophenone gave directly 2-arylquinoxalines (**2**) in reaction with *o*-phenylenediamine or *m*-toluylenediamine in boiling alcohol. He suggested that the dihydroquinoxaline

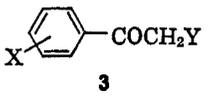


1 **2**

(**1**) was an intermediate product readily oxidized by air to the corresponding quinoxaline (**2**). Buu-Hoï and Khoi[3] reported quantitative yields of 2-arylquinoxalines (**2**) directly from the reaction of 2-bromo-3′-nitroacetophenone and 2-bromo-4′-nitroacetophenone with *o*-phenylenediamine in the presence of sodium acetate under conditions of gentle warming. In an attempt to repeat Buu-Hoï's procedure, it has been found that the dihydroquinoxalines (**1**) may be obtained in good yield if reaction is allowed to occur at room temperature, preferably under a nitrogen atmosphere. Compounds of this type have been previously prepared by partial reduction of 2,3-diphenylquinoxaline or by condensation of benzoin with *o*-phenylenediamine.[4]

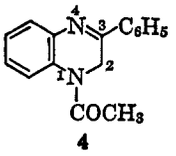
(1) O. Hinsberg, *Ann.*, **237**, 327 (1887).
(2) O. Hinsberg, *ibid.*, **292**, 245 (1896).
(3) N. P. Buu-Hoï and N. H. Khoi, *Bull. Soc. Chim. France*, **15**, 753 (1950).
(4) Y. T. Pratt, "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 485 ff.

Substituted α-haloacetophenones (**3**, X = H, 4-OCH_3, 4-Br, 4-NO_2, and Y = Br; X = 3-NO_2 and Y = Cl) were allowed to react with *o*-phenylenediamine to give dihydroquinoxalines corresponding to structure **1**. The assigned structure is supported by several pieces of evidence: the dihydroquinoxalines give monoacetyl derivatives with acetic anhydride (see Table I), indicating the presence of one reactive N–H group; they are readily oxidized by a variety of agents (see Experimental Section) to quinoxalines; they show an absorption band in the infrared region at 3300–3400 cm^{-1}, characteristic of the N–H group. The infrared absorption band disappeared after acetylation or oxidation of the dihydro compounds.



3

The nmr spectra of 3-phenyl-1,2-dihydroquinoxaline (**1**, Ar = C_6H_5) and its acetyl derivative (**4**) are in

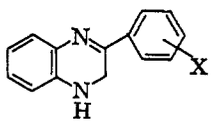


4

agreement with the assigned structures. In particular both spectra contain peaks characteristic of the methylene protons at C-2 (3-phenyl-1,2-dihydroquinoxaline, singlet at δ = 4.44 ppm; 1-acetyl-3-phenyl-1,2-dihydroquinoxaline, singlet at 4.82 ppm), verifying the assignment of the double bond in the

TABLE I

DIHYDROQUINOXALINES AND DERIVATIVES

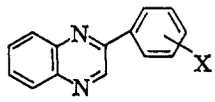


	Dihydroquinoxalines								Acetylated dihydroquinoxalines							
			Calcd, %			Found, %					Calcd, %			Found, %		
X	Yield, %	Mp, °C (crystn solvent)	C	H	N	C	H	N	Yield, %	Mp, °C (crystn solvent)	C	H	N	C	H	N
H	55	141–142[a] (ethanol)	80.6	5.8	13.5	80.4	5.8	13.4	65	103–104 (cyclohexane)	76.8	5.6	11.2	76.8	5.6	11.2
3-NO_2	83	112–114[b] (ethanol)	66.2	4.3	16.6	66.0	4.3	16.8	43[c]	194.5–195.5 (benzene)	65.0	4.4	14.2	65.0	4.7	14.3
4-NO_2	91	144–146[d]	66.2	4.3	16.6	66.0	4.1	16.5	51[e]	141–142 (carbon tetrachloride)	65.0	4.4	14.2	65.1	4.3	14.6
4-Br	81	121–122[f]	58.6	3.8	9.8	58.6	3.8	9.8	...[g]							
			27.9 (Br)			28.0 (Br)										
4-OCH_3	66	138–139[h] (methanol)	75.6	5.9	11.8	75.6	6.0	11.7	54	142.5–143 (acetonitrile)	72.9	5.7	10.0	72.6	5.5	10.2

[a] Yellow needles. [b] Bright orange, amorphous. The compound resolidified and remelted at 164–165°. [c] Prepared in pyridine. [d] Product was washed with methanol: brick red, amorphous. [e] Product was isolated by diluting the reaction mixture with 50:50 diethyl ether–petroleum ether. [f] Product was washed with methanol: bright yellow, amorphous. [g] Not prepared. [h] Lemon yellow plates.

TABLE II

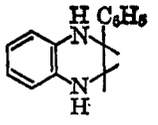
QUINOXALINES



X	Yield, %[a]	Oxidizing method	Mp, °C (crystn solvent)	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	71	C	76–77[b] (cyclohexane)	81.6	4.8	13.6	81.6	5.0	13.6
3-NO_2	37	A	186–187[c] (50:50 ethanol–ethyl acetate)	66.9	3.6	16.7	66.6	3.8	16.6
4-NO_2	55	A	187–188[d] (acetonitrile)	66.9	3.6	16.7	66.6	3.7	17.0
4-Br	75	A	136–137 (ethanol)	58.9	3.2 28.0 (Br)	9.8	59.0	3.3 27.8 (Br)	9.8
4-OCH_3	20	A	98–99	76.2	5.1	11.9	75.9	5.1	12.2
	75	B	(ethanol)						

[a] Based on dihydroquinoxaline. [b] Lit.[12] mp 78°. [c] Lit.[13] mp 196°. This material gave the corresponding amine, mp 165° (lit.[3] mp 165°), after reduction with stannous chloride, according to the procedure of Buu-Hoï and Khoi.[3] [d] Lit.[3] mp 190°.

hetero ring to the 3,4 position. The presence of the lone double bond in the hetero ring is confirmed by hydrogenation of 3-phenyl-1,2-dihydroquinoxaline, which consumed 1 mole of hydrogen to give a good yield of 2-phenyl-1,2,3,4-tetrahydroquinoxaline (**5**).



5

The nmr spectrum of the tetrahydro derivative is in excellent agreement with the assigned structure, **5**.

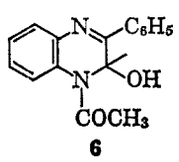
Mass spectral data do not give conclusive support to structure **1**; in general, the dihydroquinoxalines give strong peaks corresponding to the dehydrogenated compounds **2**, and much weaker peaks at two mass units more. Presumably the dihydroquinoxalines dehydrogenate readily at the heated inlet of the mass spectrometer. Derivatives of 3-phenyl-1,2-dihydroquinoxaline have the expected mass spectra, however. The acetyl derivative (**4**) gives an intense molecular ion peak at m/e 250; the tetrahydro compound (**5**) gives an intense molecular ion peak at m/e 210.

The dihydroquinoxalines are oxidized to the corresponding quinoxalines (Table II) with benzoquinone, ferric ion, or *m*-nitrobenzoic acid. Isolation of 2-phenylquinoxaline (**2**, Ar = phenyl) and its 4-methoxy derivative (**2**, Ar = 4-methoxyphenyl) from oxidation mixtures with benzoquinone is complicated by complex formation between the quinoxaline and the hydroquinone produced in the reaction. Such complexes were previously reported by Taylor and Hand.[5]

(5) E. C. Taylor and E. S. Hand, *J. Org. Chem.*, **27**, 3734 (1962).

Complex formation is avoided in these cases by using other oxidants. *m*-Nitrobenzoic acid was used as an oxidant for preparing 2-phenylquinoxaline from the dihydro compound; 3,3′-dicarboxyazoxybenzene was detected in the oxidation mixture. Ferric chloride as an oxidant gave a good yield of the quinoxaline corresponding to 3-(4-methoxyphenyl)-1,2-dihydroquinoxaline. Benzoquinone was a useful oxidant for dihydroquinoxalines in which electron-attracting substituents (nitro or bromo) were present in the pendant phenyl ring. In these cases, the complexes were sufficiently less stable that materials could be prepared which were free from hydroquinone after recrystallization.

As expected, the dihydroquinoxalines show markedly poor keeping properties, even in the solid state. The acetylated materials were somewhat more stable, although these also changed after several months. 1-Acetyl-3-phenyl-1,2-dihydroquinoxaline (**4**) gave the hydroxylated product (**6**) after several months' storage in the dark in a polyethylene-capped bottle, presumably as the result of autoxidation. Aerial oxidation products of other dihydroquinoxalines were not examined.



6

Experimental Section

Dihydroquinoxalines (Table I).—2-Bromoacetophenone, 2-chloro-3′-nitroacetophenone, 2-bromo-4′-nitroacetophenone, and 2,4′-dibromoacetophenone were commercial materials, used as received. All were obtained from the Eastman Kodak Co. except 2-chloro-3′-nitroacetophenone, which was purchased from the Aldrich Chemical Co. 2-Bromo-4′-methoxyacetophenone was prepared from anisole and bromoacetyl bromide.[6]

General Procedure.—A mixture of 10.8 g (0.10 mole) of *o*-phenylenediamine, 10 g of anhydrous sodium acetate, and 0.10 mole of the α-haloacetophenone[7] in 100 ml of methanol was stirred for 1–2 hr under nitrogen. The product was filtered, washed with water, and purified (see Table I) by crystallization or washing with solvents.

All of the dihydroquinoxalines show a sharp absorption peak in the infrared at 3300–3400 cm^{-1} (N–H stretching).

The nmr spectrum[8,9] of 3-phenyl-1,2-dihydroquinoxaline in deuterated acetone contains a singlet at δ = 4.44 ppm (two methylene protons) and bands at δ = 8.0 ppm and δ = 7.0 ppm (nine aromatic protons). A broad band at δ = 5.3 ppm disappeared after addition of D_2O (one exchangeable proton, N–H).

Quinoxalines (Table II). **A. Oxidation with Benzoquinone.—2-(4-Bromophenyl)quinoxaline** and **2-(4-nitrophenyl)quinoxaline** were prepared as follows. The crude dihydroquinoxaline (0.15 mole), prepared as just described, was dissolved in 450 ml of acetone, and 23.8 g (0.22 mole) of benzoquinone was added. The reaction mixture was warmed gently on a steam bath, diluted with 500 ml of water, and filtered. The crude material was recrystallized from a suitable solvent (see Table II).

Treatment of 3-phenyl-1,2-dihydroquinoxaline with benzoquinone, as described, gave a 44% yield of **2-phenylquinoxaline–hydroquinone complex**, mp 164–165°. This material was identical (mixture melting point and infrared determinations) with an authentic sample prepared from 1.04 g (0.005 mole) of 2-phenylquinoxaline and 0.55 g (0.005 mole) of hydroquinone in 10 ml of ethanol. The authentic sample (1.26 g, 91% yield based on a 1:0.6 complex) precipitated as pale yellow needles, mp 165–166°. Elemental analysis of the authentic sample (Found: C, 78.6; H, 4.8; N, 10.2.) corresponded to a 2-phenylquinoxaline–hydroquinone ratio of 1.0:0.6.[10] The mass spectrum of the complex[11] showed intense peaks at *m/e* 206 (2-phenylquinoxaline) and 110 (hydroquinone).

3-(4-Methoxyphenyl)-1,2-dihydroquinoxaline was oxidized, as just described, with benzoquinone. The quinoxaline was released from its hydroquinone complex with aqueous ethanolic sodium hydroxide to give a poor yield (20%) of **2-(4-methoxyphenyl)quinoxaline**, mp 99–100.5° (recrystallized from acetonitrile).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.2; H, 5.1; N, 11.9. Found: C, 75.8; H, 4.9; N, 12.3.

B. Oxidation with Ferric Chloride. 2-(4-Methoxyphenyl)-quinoxaline.—A solution of 24 g (0.089 mole) of ferric chloride hexahydrate in 100 ml of methanol was added to a suspension of 9.5 g (0.040 mole) of 3-(4-methoxyphenyl)-1,2-dihydroquinoxaline in 100 ml of methanol. Concentrated hydrochloric acid, 10 ml, was added to the deep red solution. The reaction mixture was stirred for 5 min. The product was isolated by pouring the alcohol solution onto 300 g of cracked ice. The product was filtered and recrystallized from ethanol (see Table II).

C. Oxidation with *m*-Nitrobenzoic Acid. 2-Phenylquinoxaline.—A suspension of 14.0 g (0.067 mole) of 3-phenyl-1,2-dihydroquinoxaline in 100 ml of methanol containing 5.7 g (0.34 mole) of *m*-nitrobenzoic acid (Eastman Grade) was treated with 10 ml of concentrated hydrochloric acid. After 10 min, the solution was poured onto 400 g of ice. The mixture was made neutral with dilute aqueous sodium hydroxide and filtered. The yellow solid was triturated with 5% aqueous sodium hydroxide and filtered. The solid was recrystallized from cyclohexane to give 2-phenylquinoxaline (Table II). The filtrate from the alkaline wash, after acidification with hydrochloric acid, gave 1.25 g (26%) of 3,3′-dicarboxyazoxybenzene, mp 345° dec (lit.[12] m.p. 345° dec).

Anal. Calcd for $C_{14}H_{10}N_2O_5$: C, 58.7; H, 3.5; N, 9.8. Found: C, 58.5; H, 3.5; N, 9.7.

The infrared spectra of the quinoxalines show little or no absorption at 3330–3400 cm^{-1} (N–H stretching).

1-Acetyldihydroquinoxalines (Table I).—The dihydroquinoxaline, 0.025 mole, was dissolved in 30 ml of acetic anhydride. After 5–10 min, the solution was poured into water (100 ml) containing a few drops of pyridine. The suspension was stirred until the organic phase solidified. The solid was filtered, washed with water, and recrystallized from a suitable solvent (see Table I).

Attempts to prepare the acetyl derivative from 3-(4-bromophenyl)-1,2-dihydroquinoxaline gave mixtures, which were not investigated.

The acetyl derivatives absorb in the infrared at 1650 cm^{-1} (amide carbonyl) and show little or no absorption in the N–H region (3300 cm^{-1}) characteristic of the starting materials.

The nmr spectrum of 1-acetyl-3-phenyl-1,2-dihydroquinoxaline has sharp peaks at δ = 2.24 ppm (three methyl protons) and δ = 4.82 ppm (two methylene protons) and a multiplet centered at δ = 7.54 ppm (nine aromatic protons). The spectrum did not change after addition of D_2O, confirming the absence of exchangeable protons.

2-Phenyl-1,2,3,4-tetrahydroquinoxaline.—A suspension of 4.16 g (0.020 mole) of 3-phenyl-1,2-dihydroquinoxaline in 75 ml of methanol was shaken under hydrogen (3 atm) with 0.1 g of palladium catalyst (15% palladium on charcoal). The theoretical

(6) F. Kunckell and F. Johannssen, *Ber.*, **31**, 169 (1898).

(7) In the case of 2-chloro-3′-nitroacetophenone, 1 g of potassium iodide was added to promote reaction.

(8) The nmr spectra were determined with a Varian Model 60 nmr spectrometer. We are indebted to Dr. T. Regan for obtaining and interpreting the spectra.

(9) The nmr spectrum of 3-phenyl-1,2-dihydroquinoxaline was obtained from a sample stored *in vacuo* over Drierite. A sample exposed to the atmosphere had a slightly different spectrum: the N–H band at δ = 5.3 ppm broadened and moved slightly up field, the methylene singlet at δ = 4.44 ppm split into a doublet, and a spurious peak of variable intensity (0.2–0.3 proton) appeared at δ = 2.73 ppm. The original spectrum was recovered if the sample was stored *in vacuo* over Drierite. The splitting of the methylene singlet after exposing the compound to the atmosphere was probably the consequence of changes in coupling between the N–H proton and the contiguous methylene protons. This was confirmed by exchange with D_2O, which caused the doublet to collapse to a singlet.

(10) Taylor and Hand[5] found a ratio of 1.0:0.5 for the components of this complex.

(11) Mass spectra were determined by Mr. David F. Maier, of these laboratories.

(12) M. P. Carre, *Compt. Rend.*, **141**, 594 (1905).

amount of hydrogen (0.020 mole) was consumed in 0.5 hr at room temperature. The catalyst was removed by filtration, and the solvent was stripped *in vacuo* in a rotary evaporator. The residual oil solidified on scratching. The product was crystallized from cyclohexane to give 3.32 g (77%) of white product, mp 77–78°.

Anal. Calcd. for $C_{14}H_{14}N_2$: C, 80.0; H, 6.7; N, 13.3. Found: C, 79.7; H, 6.9; N, 13.2.

The nmr spectrum of 2-phenyl-1,2,3,4-tetrahydroquinoxaline contains multiplets at δ = 7.28 ppm (five aromatic protons) and δ = 6.48 ppm (four aromatic protons). The rest of the spectrum is composed of an ABX pattern consisting of a quartet of lines centered at δ = 4.34 ppm and a group of seven lines centered at δ = 3.3 ppm (two methylene protons). The absorption due to the protons on nitrogen appeared as a broad peak superimposed on the quartet; when these protons were exchanged for deuterium, the integrated intensity of the quartet corresponded to one (methine) proton, and a water peak appeared corresponding in integrated intensity to two (N–H) protons.

Characterization of 1-Acetyl-2-hydroxy-3-phenyl-1,2-dihydroquinoxaline (6).—A 3-month-old sample (6.0 g) of 1-acetyl-3-phenyl-1,2-dihydroquinoxaline was treated with 100 ml of boiling cyclohexane. The insoluble material, mp 151–153°, weighed 3.3 g. A small sample was recrystallized for analysis to give pale yellow needles, mp 153–154°.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.1; H, 5.3; N, 10.5. Found: C, 71.9; H, 5.3; N, 10.7.

Infrared examination indicated the presence of hydroxyl (weak, broad absorption at 3100 cm^{-1}) and amide (absorption at 1670 cm^{-1}).

The nmr spectrum of this material in dimethyl sulfoxide contains a multiplet at δ = 7.5 ppm (nine aromatic protons), a singlet at δ = 1.60 ppm (methyl protons of the acetyl group), and an A–B splitting pattern from –CH–OH, occurring at δ = 6.60, 6.70, 6.96, and 7.07 ppm (two protons). Addition of D_2O caused replacement of the A–B pattern with a singlet at δ = 6.70 ppm having half the integrated intensity of the original signal, as a result of exchange to give –CH–OD.[13]

The mass spectrum of 6 is a pattern composed of superimposed spectra of acetic acid and 2-phenylquinoxaline, owing to decomposition of 6 at the heated inlet (230°) of the mass spectrometer. Compound 6 was recovered unchanged after treatment with 10% aqueous sodium bicarbonate, establishing that the compound was not simply a salt of 2-phenylquinoxaline and acetic acid.

(13) Coupling between O–H and C–H protons in dimethyl sulfoxide was observed by O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

Imidazoles as Hypnotic Agents. II. The Synthesis of Certain 5,6-Disubstituted 8-Oxo-8H-imidazo[5,1-*c*][1,4]oxazines

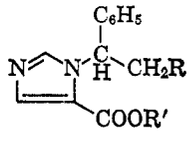
ERIK F. GODEFROI, CYRIEL A. M. VAN DER EYCKEN, AND PAUL A. J. JANSSEN

Janssen Pharmaceutica n.v., Research Laboratoria, Beerse, Belgium

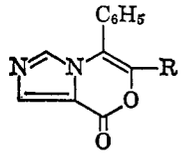
Received October 22, 1965

The synthesis of DL-1-(α-carboxybenzyl)imidazole-5-carboxylic acid (X) is described. This compound reacts with acetic and propionic anhydride to give enol lactones IIa and b, respectively. Reduction of the corresponding keto acids XIa and b with sodium borohydride, gives, upon heating, lactones XIIIa and b.

The unexpected observation by our Pharmacology Department that DL-1-(1-arylalkyl)imidazole-5-carboxylic acid esters (I) possessed strong hypnotic properties[1] made the preparation of cyclic variations of type II and their 5,6-dihydro-derivatives desirable. Whereas the synthesis of the ring system of type II has been



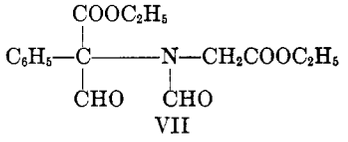
I, R = H, CH_3, C_2H_5; R′ = lower alkyl



II, R = CH_3, C_2H_5

described recently,[2] examination of the literature failed to reveal the preparation of other imidazo[5,1-*c*][1,4]oxazines. It was felt, however, that earlier work by Jones,[3] in addition to our own experience, might make the unknown DL-1-(α-carboxybenzyl)-imidazole-5-carboxylic acid (X) readily accessible. This material would then serve as starting material for the desired compounds.

To this effect α-phenylglycine ethyl ester (III) was condensed with ethyl chloroacetate in dimethylformamide containing 1 equiv of triethylamine. The resulting crude N-(α-carbethoxybenzyl)glycine ethyl ester (IV) was then treated with formic acid–xylene, furnishing N-formyl derivative V. The over-all yield was 52%. Claisen formylation of V (sodium ethoxide–ethyl formate) yielded a water-soluble, enolized *sodium salt*, VI; the water solubility precluded, of necessity, the formation of nonenolizable VII. Compound VI



VII

was subsequently transformed to DL-1-(α-carbethoxybenzyl)-2-mercaptoimidazole-5-carboxylic acid ethyl ester (VIII) by means of HCl–HNCS. When VIII was treated with warm, dilute nitric acid, the desulfurized product IX was produced in 93% yield. Vigorous saponification of the latter provided bisacid X. (See Scheme I.)

Numerous efforts to induce this bisacid to undergo anhydride formation met with failure. Instead, X reacted smoothly with acetic anhydride to give an enol lactone (IIa) in good yield. This reaction constitutes, in fact, a modified Dakin–West reaction,[4] proceeding presumably *via* the α-acylated carboxylic acid which, in turn, almost certainly would decarboxylate. Subsequent enolization and ring closure gives rise to IIa. Normally the Dakin–West reaction

(1) E. F. Godefroi, P. A. J. Janssen, C. A. M. Van der Eycken, A. H. M. T. van Heertum, and C. J. E. Niemegeers, *J. Med. Chem.*, **8**, 220 (1965).

(2) E. F. Godefroi, C. A. M. Van der Eycken, and C. Van der Westeringh, *J. Org. Chem.*, **29**, 3707 (1964).

(3) R. G. Jones, *J. Am. Chem. Soc.*, **71**, 644 (1949).

(4) (a) H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 91 (1928); (b) J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, **73**, 4911 (1951); (c) G. G. Smith, *ibid.*, **75**, 1134 (1953).