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

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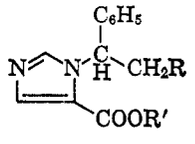
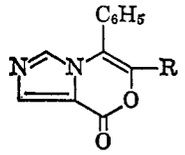
The synthesis of DL-1-(α-carboxybenzyl)imidazole-5-carboxylic acid (X) is described. This compound reacts with acetic and propionic anhydride to give enol lactones IIa and b, respectively. Reduction of the corresponding keto acids XIa and b with sodium borohydride, gives, upon heating, lactones XIIIa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



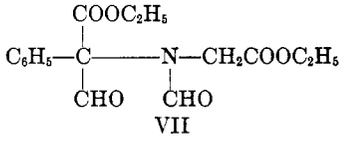
I, R = H, CH_3, C_2H_5; R′ = lower alkyl



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

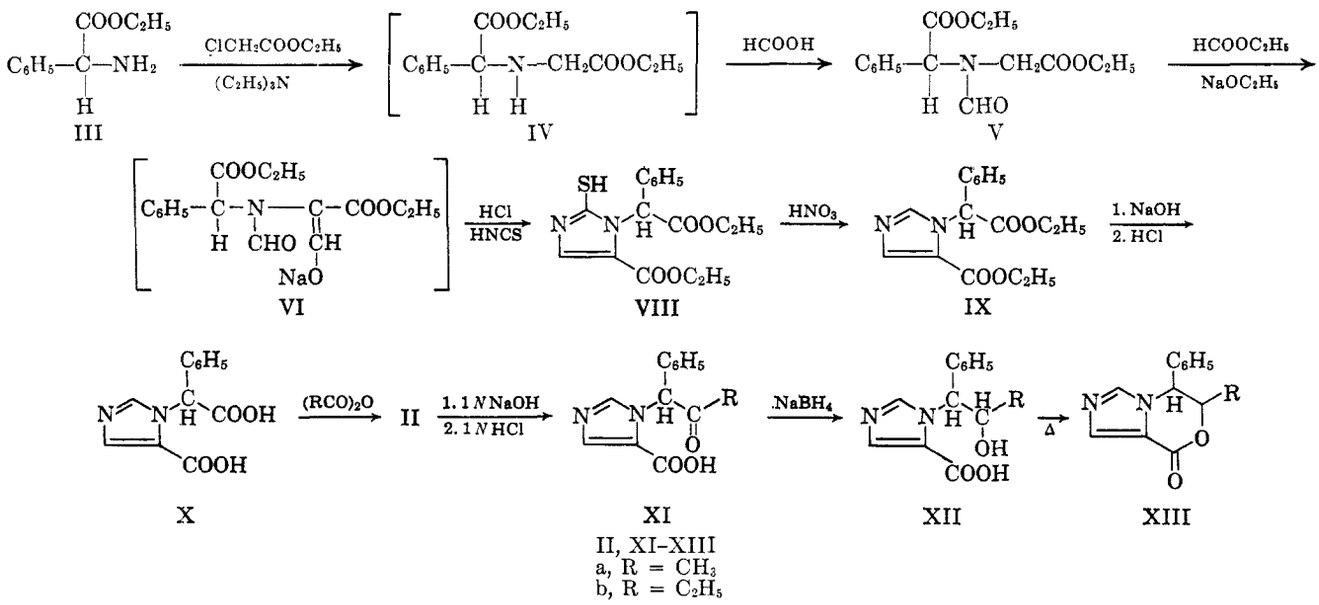
(1) E. F. Godefroi, P. A. J. Janssen, C. A. M. Van der Eycken, A. H. M. T. van Heertum, and C. J. E. Niemegeers, *J. Med. Chem.*, **8**, 220 (1965).

(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).

SCHEME I



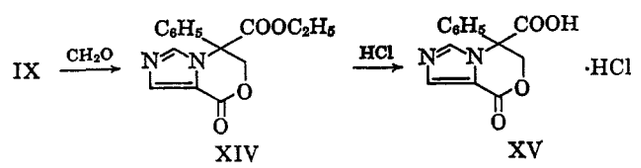
II, XI–XIII
a, R = CH_3
b, R = C_2H_5

is base catalyzed, as exemplified by the role of pyridine in the conversion of phenylacetic acid to phenylacetone.[4b] In our own case one may assume inter- or intramolecular catalysis to be effected by the imidazole nucleus.

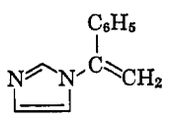
In an analogous fashion, bisacid X, upon treatment with propionic anhydride, furnished enol lactone IIb.

Vigorous basic hydrolysis of IIa resulted not only in lactone rupture, but was accompanied by deacetylation to yield a carboxylic acid, $C_{11}H_{10}N_2O_2$, mp 229–230°. This compound proved to be 1-benzylimidazole-5-carboxylic acid, being in all respects (melting point, mixture melting point, and infrared spectrum) identical with the saponification product of 1-benzylimidazole-5-carboxylic acid methyl ester prepared by Jones.[3] The treatment of IIa with 1 equiv of 1 *N* sodium hydroxide, followed by neutralization, gave keto acid XIa. This material was then reduced with sodium borohydride producing hydroxy acid XIIa. Thermal lactonization was readily effected to furnish XIIIa. Similarly, compound IIb was converted to XIIIb. In these lactonization reactions, the formation of *cis–trans* mixtures is likely. Whereas compound XIIIa was isolated as crystalline material, the initial presence of a mixture cannot be precluded. Lactone XIIIb failed to surrender crystalline components and was obtained as a high-boiling, viscous oil.

Of additional interest is the fact that bisester IX reacted with 37% formaldehyde, giving rise to structure XIV. This approach was prompted by recent work of Bohlmann, *et al.*,[5] who prepared β-(2-pyridyl)-β-carbomethoxybutyrolactone by a comparable reaction. Acid hydrolysis of the latter was accompanied by decarboxylation. In our own case, acid hydrolysis



of XIV gave the carboxylic acid XV. Heating the free base of XV to 220° drove off *two* molecules of CO_2. Titration data of the residue showed a molecular weight of *ca.* 170. This, in addition to the presence of a C=C band in the infrared spectrum, plus styrene-type conjugation in the ultraviolet spectrum, leads us to believe that the material was, in fact, enamine XVI. The corresponding *hydrochloride salt*, mp 167–168°, proved to be unstable.



XVI

Experimental Section[6]

N-(α-Carbethoxybenzyl)-N-formylglycine Ethyl Ester (V).—To a solution of 179 g (1.0 mole) of *dl*-α-phenylglycine ethyl ester in 150 ml of dimethylformamide containing 101 g (1.0 mole) of triethylamine was added with stirring 122.5 g (1.0 mole) of ethyl chloroacetate. The temperature was kept at 35–40° for 1 hr, whereupon the mixture was stirred overnight at room temperature. One liter of ether was added and most of the triethylamine was filtered off. The filtrate was washed thoroughly, dried, and stripped, leaving crude N-benzyl-α-carbethoxyglycine ethyl ester as an oily residue. This was dissolved in 600 ml of xylene, 50 g of formic acid was added, and the solution was refluxed in an apparatus equipped with a water trap. Water evolution was complete within 2 hr. Scrubbing of the cooled solution with 20% formic acid, water, sodium bicarbonate and water, respectively, followed by drying and evaporation of the solvent, gave crude product. Fractionation gave 153 g (52%) of product, bp 194–198° (0.8 mm).

DL-1-(α-Carbethoxybenzyl)-2-mercaptoimidazole-5-carboxylic Acid Ethyl Ester (VIII).—Sodium ethoxide, 0.45 mole, was freshly prepared in tetrahydrofuran by addition of 21.6 g of absolute ethanol in 100 ml of tetrahydrofuran to 21.6 g of 50% sodium hydride dispersion in 300 ml of tetrahydrofuran. To this suspension at 5° was added in one portion and with stirring a solution of 130 g (0.45 mole) of V in 100 g (1.36 moles) of ethyl formate. After stirring at 5° for 1 hr, the reaction was allowed to proceed overnight. The solvent was stripped and replaced with 400 ml of water; the paraffin was washed out with ether. Concentrated HCl (84 ml.) was added, followed by 500 ml of ethanol. After the temperature was kept at 40° for 15 min,

(5) F. Bohlmann, E. Winterfeldt, D. Schumann, U. Zarnack, and P. Wandrey, *Ber.*, **95**, 2365 (1962).

(6) Melting points were taken on a Fisher-Johns block.

there was introduced a solution of 48 g of potassium thiocyanate in 100 ml of water. Stirring was continued and within a few hours product started crystallizing out. The reaction was allowed to proceed overnight at room temperature, whereupon filtration afforded 45 g of product. The filtrate was stripped of alcohol at atmospheric pressure to give a second crop of product, which was brown and was rendered colorless by trituration with ice-cold ethanol. The combined batches, 78.5 g (52%), melted at 182–183°. An analytical sample, prepared from 95% ethanol, melted at 182–183°.

Anal. Calcd for $C_{16}H_{18}N_2O_4S$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.32; H, 5.52; N, 8.63.

DL-1-(α-**Carbethoxybenzyl)imidazole-5-carboxylic Acid Ethyl Ester Hydrochloride** (**IX**).—Compound VIII (77 g, 0.23 mole) was added portionwise and with stirring to a solution of 80 ml. of nitric acid in 225 ml of water containing 1 g of sodium nitrite, keeping the temperature at 47–52°. After addition of *ca.* 20 g of the mercaptoimidazole, the **nitrate salt** of the product started crystallizing out. The mixture was finally stirred at room temperature for an additional hour. Cooling and filtration afforded the **nitrate salt**, which was dissolved in hot water, brought to pH 9 (sodium carbonate) and extracted with ether. Addition of isopropanolic HCl to the dried organic phase yielded 72 g (93%) of product, mp 140–142°. A recrystallized sample (ethanol–ether) had mp 143–144°.

Anal. Calcd for $C_{16}H_{18}N_2O_4 \cdot HCl$: C, 56.72; H, 5.65; N, 8.27. Found: C, 56.68; H, 5.73; N, 8.47.

The corresponding free base had mp 56–57°.

DL-1-(α-**Carboxybenzyl)imidazole-5-carboxylic Acid** (**X**).—A mixture of 20 g of sodium hydroxide, 18 g (0.053 mole) of ester IX in 50 ml of water was refluxed for 1 hr. Water, 100 ml, was added, and the solution was neutralized with hydrochloric acid giving 12.6 g of bisacid, mp 235–236°, yield 97%. Recrystallization from 50% dimethylformamide failed to raise the melting point.

Anal. Calcd for $C_{12}H_{10}N_2O_4$: C, 58.53; H, 4.09; N, 11.38. Found: C, 58.48; H, 4.21; N, 11.55.

5-Phenyl-6-methyl-8-oxo-8H-imidazo[5,1-*c*][1,4]oxazine (**IIa**).—A mixture of 40 g (0.162 mole) of bisacid X and 400 ml of acetic anhydride was refluxed for 15 hr. About 375 ml of acetic anhydride were removed at atmospheric pressure. Cooling the residue and addition of 300 ml of isopropyl ether gave, upon refrigeration, 26 g of product, mp 123–124°. This represents a 71% yield. An additional 5 g (14%) could be gained by stripping of the mother liquors and distillation of the residue, the lactone coming over at 140–160° (0.2 mm). An analytical sample (benzene–heptane) had mp 123–124°.

Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.38. Found: C, 68.90; H, 4.55; N, 12.45.

5-Phenyl-6-ethyl-8-oxo-8H-imidazo[5,1-*c*][1,4]oxazine (**IIb**).—A solution of 45 g (0.183 mole) of X in 400 ml. of propionic anhydride was refluxed for 4 hr. Removal of the solvent and distillation of the residue gave 29 g of an oil, bp 190–200° (1 mm). The material was dissolved in 60 ml of isopropyl ether, from which was deposited 23 g (52% yield) of IIb, mp 78–80°. Recrystallization from benzene–hexane furnished the analytical sample, mp 79–80°.

Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.88; H, 5.02; N, 11.62.

Drastic Hydrolysis of IIa to 1-Benzylimidazole-5-carboxylic Acid.—Three grams (0.0133 mole) of IIa was refluxed for 0.5 hr in 10 ml of 10 *N* sodium hydroxide. Cooling, dilution, and neutralization of the mixture yielded 1.9 g of a carboxylic acid, mp 229–230°. Recrystallization from 50% dimethylformamide did not raise the melting point.

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.47; H, 4.91; N, 13.62.

The material was spectrally identical with authentic 1-benzylimidazole-5-carboxylic acid, mp 229–230°, with which it failed to give a melting point depression.

Mild Hydrolysis of IIa to DL-1-(α-**Acetylbenzyl)imidazole-5-carboxylic Acid** (**XIa**).—A suspension of 22.6 g (0.10 mole) of IIa in 105 ml of 1 *N* sodium hydroxide was stirred at room temperature for 0.5 hr, whereupon all the material had gone into solution. Addition of 105 ml of 1 *N* HCl afforded, upon filtration, 24 g (98%) of keto acid, mp 242–243°. A recrystallized sample (60% dimethylformamide) melted at 243–243.5°.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 64.12; H, 5.06; N, 11.54.

DL-1-(α-**Propionylbenzyl)imidazole-5-carboxylic Acid** (**XIb**).—This compound, mp 226–227°, was prepared analogously to the method offered for XIa.

Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46. Found: C, 65.06; H, 5.60.

DL-**5-Phenyl-5,6-dihydro-6-methyl-8-oxo-8H-imidazo[5,1-*c*][1,4]oxazine** (**XIIIa**).—To a stirred slurry of 7.3 g (0.03 mole) of XIa in 70 ml of water was added portionwise 2.4 g (0.06 mole) of sodium borohydride. Upon stirring for 1 hr at room temperature, some insoluble material was filtered off, and the pH was adjusted to 7. Refrigeration caused deposition of 6 g of crude hydroxy acid (XIIa) which was recrystallized from water to give 3.7 g of material, mp *ca* 100°. The material was finally heated for 15 min to 170° to give, upon addition of isopropyl alcohol–isopropyl ether to the residue, 1.8 g of lactone XIIIa, mp 148–150°. An analytical sample prepared from isopropyl alcohol–isopropyl ether melted at 150–151°.

Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.36; H, 5.40; N, 12.35.

DL-1-(**1-Phenyl-2-hydroxybutyl)imidazole-5-carboxylic Acid** (**XIIb**).—Treatment of 13.4 g (0.052 mole) of XIb with 3.2 g of sodium borohydride in 150 ml of water, in a fashion analogous to directions for XIIa, provided after prolonged standing 9.2 g of product, mp 191–192°. An analytical sample from water melted at 192–193°.

Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.40; H, 6.12; N, 10.71.

DL-**5-Phenyl-5,6-dihydro-6-ethyl-8-oxo-8H-imidazo[5,1-*c*][1,4]oxazine** (**XIIIb**).—Ten grams (0.39 mole) of XIIb was heated for *ca.* 20 min to 230° to expel the formed water. Distillation of the residue gave 8.0 g of a thick oil, bp 195–205° (0.2 mm).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.89; H, 6.04; N, 11.67.

DL-**5-Carbethoxy-5-phenyl-5,6-dihydro-8-oxo-8H-imidazo-[5,1-*c*][1,4]oxazine** (**XIV**).—A mixture of 41 g (0.136 mole) of the free base of bisester IX, 400 ml of 37% formaldehyde, and 1 ml of piperidine was refluxed for 4 hr. The solution was then poured onto 1.5 l. ice–water. Isopropyl ether (*ca.* 200 ml) was added, whereupon the oily product slowly solidified. It was filtered off, washed with fresh isopropyl ether, and then dissolved in *ca.* 150 ml of benzene. The solution was washed three times with water and the organic phase was dried and stripped. Addition of isopropyl ether to the oily residue provided 23 g (59%) of product, mp 88–89°. An analytical sample from isopropyl alcohol–isopropyl ether melted at 88–89°.

Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.99; H, 4.87; N, 9.96.

DL-**5-Carboxy-5-phenyl-5,6-dihydro-8-oxo-8H-imidazo[5,1-*c*][1,4]oxazine** (**XV**).—A solution of 18 g (0.063 mole) of ester XIV in 100 ml of concentrated hydrochloric acid was refluxed overnight. Cooling of the solution brought about deposition of 15.1 g (82%) of hydrochloride product, mp 203–206°, with vigorous foaming. For analytical purposes a sample was converted to the free base, which crystallized slowly from water and which melted at 196–197°.

Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.90; N, 10.85. Found: C, 60.37; H, 3.56; N, 10.77.

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