dark yellow oil (1.65 g.), obtained after treatment with sodium carbonate solution, extraction with chloroform and evaporation, was shaken with 6.5 ml. of 2 *N* sodium hydroxide for 4 hr. The aqueous solution was extracted with chloroform, passed through a column of Amberlite CG-120[21] in the hydrogen form, decolorized with Norit and freeze-dried. The tan solid (1.61 g.) was crystallized from ethyl acetate to yield 276 mg. (10.5%) of product, m.p. 91–94°. Another recrystallization afforded small colorless prisms, m.p. 95.5–96.5° (lit.[19] 97°), no depression with an authentic sample.[19]

Dibenzyl Acetamidomalonate. (a) **By Acetylation of Dibenzyl Aminomalonate.**—Dibenzyl aminomalonate (7.14 g.), prepared by Kissman and Witkop's[25] procedure, was treated with 5 ml. of acetic anhydride. The mixture rapidly solidified to a magma, which after 3 hr. at room temperature was boiled with 15 ml. of ethanol for a few moments. The solution, when treated with water to incipient turbidity, deposited 7.39 g. (91%) of colorless needle-shaped prisms, m.p. 111–113°. Recrystallization from ethyl acetate–hexane yielded 6.89 g. of colorless prismatic needles, m.p. 112.6–113.3°. A sample, recrystallized from methylene chloride–pentane, had m.p. 112.8–113.3°.

Anal. Calcd. for $C_{19}H_{19}O_5N$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.55; H, 5.67; N, 3.99.

(25) H. M. Kissman and B. Witkop, THIS JOURNAL, **75**, 1967 (1953).

(b) **By Transesterification.**—Following essentially Bowman's technique,[8] a magnetically stirred suspension of 2.40 g. of sodium hydride in 50 ml. of dry benzene was treated dropwise with 5 ml. of absolute ethanol, then with 21.71 g. of I and 21.65 g. of benzyl alcohol, which were rinsed in with 100 ml. of dry benzene. The mixture was stirred for 15 min., then slowly distilled (with continued stirring) through a Fenske column until the temperature at the head reached 79°. The residue was cooled and treated with 7 ml. of glacial acetic acid, then with water. The organic layer was washed with sodium chloride solution, dried over sodium sulfate, evaporated, and the residue crystallized from ethyl acetate–hexane to yield 17.23 g. (50%) of colorless crystalline solid, m.p. 108.5–110°. Recrystallization from 50% methanol provided colorless needles, m.p. 112.6–113.7°, which did not depress the melting point of material prepared by method (a).

An attempt to obtain the benzoyl derivative of this ester by the procedure used in the preparation of II and VII resulted in a crystalline product, m.p. 75–86°, the melting point of which was raised to 86–91° by recrystallization from 75%, then from absolute methanol, but which could not be obtained pure. Hydrogenolysis of this material with palladium-on-strontium carbonate[8] or with palladium-on-carbon,[25] followed by heating failed to yield any α-acetamidoacetophenone (VIII).

BETHESDA 14, MD.

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Formation of Homopiperazine Rings by the Lithium Aluminum Hydride Catalyzed Rearrangement of Some Piperidone Oximes in the Phenothiazine Series

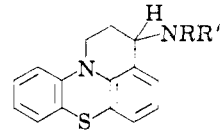
BY M. HARFENIST AND E. MAGNIEN

RECEIVED JUNE 6, 1958

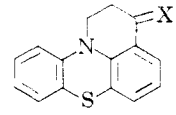
Lithium aluminum hydride reduction of the 4-piperidone oxime (II) gave only the homopiperazine IIIa, with ring enlargement. Similarly, lithium aluminum hydride reduction of the piperidinedione monoxime IVa and of 2-acetylphenothiazine oxime gave the homopiperazine IIIc and 2-ethylaminophenothiazine, respectively, as the only detectable bases. The compound Ia was prepared by two different methods for comparison of its pK'a value with those of the compounds III. Aqueous dimethyl sulfoxide was found to be a most satisfactory solvent for the titrations which were required. The pK'_a of N-*n*-propylaniline hydrochloride in this solvent mixture and in water were nearly identical.

A recent publication[1] gave the details of the preparation in excellent yield of what was quite reasonably presumed to be the tetracyclic amine Ia, made by lithium aluminum hydride reduction of the oxime IIA. Since compound I might be looked on as a "tied-back" 3-(10-phenothiazinyl)-propylamine and therefore would be related to a number of useful and interesting drugs, we wished to prepare some dialkylamino analogs of this substance.

Our reduction of the oxime IIa by means of lithium aluminum hydride gave the presumed Ia in 85% yield. This was monoacetylated readily, presumably to Ib. The monoacetyl compound was reduced by lithium aluminum hydride to a monoethyl compound, presumed to be Ic. However, an attempt to acetylate the presumed Ic gave no acetyl compound.



Ia, R = R′ = H
Ib, R = CH_3CO, R′ = H
Ic, R = C_2H_5, R′ = H
Id, R = R′ = CH_3



IIa, X = NOH
IIb, X = O

Since no obvious reason for this failure could be found in the chemical properties which would be anticipated for the structure Ic, it seemed likely that Beckmann-like rearrangement[2a] of the oxime II had occurred during the reduction procedure, leading to ring expansion to an intermediate having a 7-membered ring. The latter then must have been reduced to the homopiperazine IIIa.

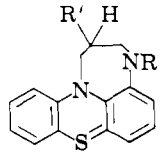
The structure of the product III could best be corroborated by comparison of the pK'_a values for any of the compounds IIIa-c with pK'_a values for compounds known to be of type I.

The corresponding compound I with its six-membered ring still intact was prepared for comparison purposes, both by the Bouveault–Blanc re-

(1) E. F. Godefroi and E. L. Wittle, *J. Org. Chem.*, **21**, 1163 (1956). Since this work was written up for publication, summaries of two pertinent Japanese papers have become available. In one [H. Kano, Y. Makizumi and K. Ozata, *C. A.*, **51**, 6644 (1957)] procedures similar to those of Godefroi and Wittle have been reported, and the structures Ia and 10-(or 4-)chloro Ia (from 2-chlorophenothiazine) have been ascribed to the products. In another publication [K. Fujii, *C. A.*, **52**, 5417 (1958)] the compounds Ia and 10-chloro-Ia were reported as made by a formamide procedure similar to that reported below. The corresponding compounds by the two methods are reported to have similar melting points, well within the reproducibility which we have found for these high-melting salts, and no mention is made of the fact that different products are obtained by the different methods.

(2) (a) R. E. Lyle and H. J. Troscianiec, *J. Org. Chem.*, **20**, 1757 (1955); E. Larsson, *C. A.*, **44**, 1898 (1950). (b) D. R. Smith, M. Maienthal and J. Tipton, *J. Org. Chem.*, **17**, 294 (1952).

duction of the oxime II with sodium in 1-butanol and by treatment of the ketone IIb with refluxing formamide. Neither reaction would be expected to lead to rearrangement. The products of both the Bouveault–Blanc and the formamide preparations had identical titration curves (see below) and infrared absorption spectra, but the Bouveault–Blanc product, formed in poor yield, appeared by its melting point range to be contaminated by an impurity which was not removed completely by two recrystallizations.



IIIa, R = R′ = H
IIIb, R = C_2H_5, R′ = H
IIIc, R = H, R′ = C_2H_5

Neither the hydrochlorides nor the free bases of the lithium aluminum hydride reaction products IIIa and IIIb were sufficiently soluble even in 50% aqueous methanol for convenient determination of their titration curves. A 50% aqueous dimethyl sulfoxide solution was found to be a satisfactory solvent for nearly all of the hydrochlorides of interest. The pK'_a of N-*n*-propylaniline hydrochloride was determined in this solvent mixture as a check on its suitability. The result, 4.65, was sufficiently close to that found in water alone, 4.75, to allow use of the pK'_a values to distingush the aromatic amines III from the benzylamines I.

The pertinent pK'_a values[3] are given in Table I. It will be seen that all of the lithium aluminum hydride reduction products are of type III, formed by rearrangement before or during reduction.

TABLE I

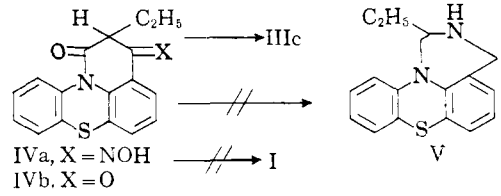
ACIDITIES (pK'_a) OF AMINE HYDROCHLORIDES

Compound	Ia	Id	IIIa	IIIb	IIIc[a]	[b]
pK'_a	8.11	7.10	3.75	3.35	3.2	4.05

[a] Approximate value due to low solubility in titration medium. [b] 2-(Ethylamino)-phenothiazine from reduction of 2-acetylphenothiazine ketoxime.

To study the scope of this rearrangement somewhat more fully in the phenothiazine series, 2-acetylphenothiazine ketoxime,[4] which has its "oximino carbon" *para* to the phenothiazine sulfur, was reduced with lithium aluminum hydride. The only amine which was isolated, in about 65% yield, was shown by its pK'_a to be the rearranged product 2-(ethylamino)-phenothiazine.

The other phenothiazinyl ketoxime whose reduction was studied was the C-ethyl compound IVa. The keto-amide IVb required to prepare IVa was made by heating phenothiazine with ethyl ethylmalonate, by a procedure modified from that reported for carbazole.[5]



IVa, X = NOH
IVb, X = O

This quite acidic ketone-amide IVb gave a poor yield of an oxime IVa. This, on lithium aluminum hydride reduction, gave a comparatively low yield of an amine whose hydrochloride had a melting point which was not raised on further recrystallization. It appeared to be entirely aromatic amine hydrochloride IIIc, within the precision of the titration curve. Thus neither the primary amine related to I, nor the benzylamine, V, which might be formed by the alternative Beckmann-like rearrangement with migration of the presumably anionic C-ethyl group, was detectable.

The fact that only the amines resulting from rearrangement were isolated from the reductions of these phenothiazinyl oximes is perhaps a bit surprising,[6] since a moderate proportion of unrearranged amine had been found previously[2a] even for the reduction of *p*-methoxyacetophenone oxime. It is not possible to compare the migratory aptitude to be expected from the aryl residuum in the oxime II with that of the *p*-methoxyphenyl group since the requisite Hammett σ-values for *m*-thioaryl (probably near zero), and the *o*-arylamino groups, have not been reported. To reason backwards from our results, it would seem, not surprisingly, that a large negative value of the σ-constant would be found for the *o*-arylamino group if it were possible to measure it.

Presumably these charge distribution effects are augmented in these compounds by the "*ortho* effect" which has been found[7] to accelerate the rate of Beckmann rearrangement (as compared to hydrolysis) of certain *o*-substituted acetophenone oximes. The Beckmann rearrangement of some of the same *o*-substituted oximes in concentrated sulfuric acid is much faster than the rate found for the *p*-isomers[8] bearing the same substituents.

The reductions of the last two oximes, IVa and 2-acetylphenothiazine oxime, are similar to each other in that probably they occur only after replacement of an "active hydrogen" (other than that of the oximino group) in each instance. In the case of the 2-acetylphenothiazine ketoxime there is a diarylamine "active hydrogen," and in IVa there is the "active hydrogen" flanked by the carbonyl and ketoximino groups. In the former case, it is easy to understand that a highly electron-rich benzene ring would be produced by such a replacement in the ketoxime, leading to rapid and complete rearrangement. However, the reason for the isolation of only IIIc in the reduction of IVa is not as obvious. Possibly the re-

(3) These were taken as the *p*H of the solutions in 50% dimethyl sulfoxide at the mid-points of the titrations of the amine hydrochlorides by aqueous sodium hydroxide.

(4) R. Baltzly, M. Harfenist and F. J. Webb, THIS JOURNAL, **68**, 2673 (1946).

(5) P. Baumgarten and M. Riedel, *Ber.*, **75B**, 984 (1942).

(6) It should be noted that essentially the same proportion of rearrangement has been reported on lithium aluminum hydride reduction with acetophenone oxime as with propiophenone oxime[2b] so that at least in that case an additional substituent in the carbon alpha to the oximino group did not have a noticeable effect on the ratio of isomers.

(7) K. v. Auwers, M. Lechner and H. Bundesmann, *Ber.*, **58**, 36 (1925).

(8) D. E. Pearson and W. E. Cole, *J. Org. Chem.*, **20**, 488 (1955).

duction of oximes without rearrangement occurs by nucleophilic attack at the C=N bond, and so is slowed by accession of electrons to that bond, whatever their source. The competing Beckmann-like rearrangement would seem to require electrophilic attack on the oxime hydroxyl group.

Acknowledgment.—It is a pleasure to acknowledge helpful discussions with Dr. R. Baltzly of these laboratories. Elemental analyses were done by Mr. S. Blackman and Mr. C. Marr.

Experimental

Homopiperazino-[3,2,1-kl]phenothiazine Hydrochloride (IIIa).—Fifty-two grams (0.194 mole) of oxime IIA was placed in the extraction thimble of a Soxhlet extractor, and allowed to drop into 15.2 g. (0.4 mole) of lithium aluminum hydride in 1.2 l. of absolute ether during 48 hours. The reaction mixture was decomposed with the theoretical amount of water, filtered, and the cake thoroughly washed with ether. The ethereal solution was dried over sodium hydroxide and filtered. An excess of dry hydrogen chloride was then bubbled into the solution and the amine hydrochloride was removed by filtration to yield 47.9 g. (85%) of crude hydrochloride, m.p. 235–238° dec. Recrystallization from methanol did not raise the m.p.

Anal. Calcd. for $C_{15}H_{15}ClN_2S$: C, 62.00; H, 5.20. Found: C, 61.80; H, 5.58.

4-Acetylhomopiperazino[3,2,1-kl]phenothiazine.—A solution of 32.6 g. of IIIa in absolute ethanol was treated with an excess of 45% sodium hydroxide and then diluted with water. The crystals were filtered off and dried to yield 31.5 g. of base. This was heated under reflux for 2 hours in 50 ml. of acetic anhydride. On cooling, there was obtained 28 g. (76.5% yield), m.p. 177–178°.[9] A second crop of 6.4 g. was obtained of m.p. 156–157° which was unchanged on recrystallization from absolute ethanol. The first crop was recrystallized from absolute alcohol for analysis, m.p. 177–178°.

Anal. Calcd. for $C_{17}H_{16}N_2OS$: C, 68.90; H, 5.41. Found: C, 69.12; H, 5.37.

4-Ethyl homopiperazino[3,2,1-kl]phenothiazine (IIIb).—N-Acetyl-IIIa (26.5 g., 0.089 mole) was reduced, with 5.7 g. (0.15 mole) of lithium aluminum hydride in 1.2 l. of absolute ether by the Soxhlet procedure. The mixture was stirred and heated under reflux for 24 hours. The excess reagent was decomposed carefully with the theoretical amount of water. The mixture was filtered and the ether solution was dried over magnesium sulfate. On filtering and evaporating to dryness, 25.5 g. of a light brown viscous liquid was obtained. This was dissolved in about 300 ml. of absolute ether and an excess of hydrogen chloride was bubbled through the solution. The hydrochloride was removed by filtration to yield 27.5 g. (96% yield), m.p. 178–180°. On recrystallization from absolute ethanol–ether (yield 24.6 g.) the m.p. was 178–182°.

Anal. Calcd. for $C_{17}H_{19}ClN_2S$: C, 64.10; H, 5.70; Cl^-, 11.1. Found: C, 64.29; H, 5.92; Cl^-, 10.9.

3-Amino-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (Ia)(Bouveault-Blanc Method).—Six and three-tenths grams of II (0.0234 mole) was refluxed with 50 ml. of 1-butanol, which previously had been distilled from calcium hydride, while 3.8 g. (0.16 mole) of sodium was added over 15 minutes. The mixture was heated under reflux for one hour, cooled, absolute ether was added, and the solution was filtered. The ether–butanol solution was washed several times with water, dried over magnesium sulfate and the solvents removed *in vacuo* to leave 1.9 g. (32%) of a light brown liquid which solidified on standing. This material was dissolved in ether and methanol, acidified with hydrochloric acid, and distilled to dryness. The crude hydrochloride was dissolved in methanol and several volumes of absolute ether was added to precipitate 0.77 g. of a reddish material, m.p. 195–210°. This was twice recrystallized from ethanol–ether. It seemed to melt unsharply in the range 197–240°.

Anal. Calcd. for $C_{15}H_{15}ClN_2S$: C, 62.00; H, 5.20. Found: C, 61.90; H, 5.41.

Ia by Leuckart Reaction.—Three grams (0.119 mole) of 2,3-dihydro-3-keto-1H-pyrido[3,2,1-kl]-phenothiazine[10] was heated under reflux with 10 ml. (0.253 mole) of 99% formamide for 7 hours. The mixture was cooled and water was added slowly to precipitate 2.1 g. of the supposed formylamine. This was refluxed for 1.5 hours with 1:1 aqueous hydrochloric acid. On cooling the solution, a purple material precipitated and was removed by filtration. The material was stirred with an excess of aqueous sodium hydroxide and then extracted once with ether and five times with hot benzene. The yellow solution of the base was dried over sodium hydroxide pellets and filtered. A slight excess of alcoholic hydrogen chloride was added to precipitate 1.0 g. of purple crystals of m.p. 190–210° dec. Recrystallization from methanol–ether gave material of m.p. 228–232° dec.

Anal. Calcd. for $C_{15}H_{15}ClN_2S$: C, 62.00; H, 5.20. Found: C, 61.83; H, 4.85.

3-Dimethylamino-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine hydrochloride (Id).—Five and eight-tenths grams of Ia was mixed with 4.65 g. of 99% formic acid and 3.3 ml. of formalin. After the vigorous bubbling had ceased, the solution was heated on a steam-bath (condenser) for 19.5 hours; 3 ml. of concd. hydrochloric acid was added and the solution was distilled to dryness *in vacuo* on the steam-bath. The residue was dissolved in water and made basic with a slight excess of sodium hydroxide solution. A light green material was removed by filtration and washed with water until alkali free. This material weighed 5.2 g. and had a melting point of 62–72°. This was converted to the hydrochloride in dry benzene–ether solution with dry gaseous HCl. The dry hydrochloride melted over a wide range and so was put through another alkali-acid treatment to yield 4.0 g. of the hydrochloride of m.p. 180–190° dec. This material was recrystallized twice from isopropyl alcohol–methyl isobutyl ketone–ether, in each case the first dark precipitate being discarded. The yield was 0.81 g. of hydrochloride of m.p. 200–204° dec.

Anal. Calcd. for $C_{17}H_{19}ClN_2S$: C, 64.10; H, 6.02; N, 8.80. Found: C, 64.52; H, 6.06; N, 8.48.

Reduction of 2-Acetylphenothiazine Oxime with Lithium Aluminum Hydride.—Twenty-four and a half grams (0.094 mole) of the oxime was added to a slurry of 7.6 g. (0.2 mole) of lithium aluminum hydride in 1.5 l. of absolute ether. The mixture was stirred and heated under reflux for 24 hours, cooled and decomposed with the theoretical amount of water. The slurry was filtered and washed thoroughly with ether. An excess of hydrogen chloride was passed into the dried ether solution. The cooled suspension was filtered to yield 17.1 g. (65%) of pink platelets of m.p. 215–220° dec. Three crystallizations from methanol-ether raised the m.p. to a constant 220–222° dec.

Anal. Calcd. for $C_{14}H_{15}ClN_2S$: C, 60.39; H, 5.43. Found: C, 59.96; H, 5.40.

2-Ethyl-1,3-diketo-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (IVb).—Twenty grams (0.1 mole) of phenothiazine and 20.8 g. (0.11 mole) of ethyl ethylmalonate were placed in a flask equipped with an air condenser 15 cm. in height. The mixture was heated (bath *ca.* 262°) for 15 hours at a heat input sufficient to keep the reading of a thermometer about one-third of the way down the air condenser at 78°. It then was cooled, and partitioned between an excess of 5% aqueous sodium hydroxide and ether. The resulting tan opalescent aqueous phase was warmed to remove ether, cooled, and acidified with hydrochloric acid to give a solid which was reprecipitated from aqueous 10% sodium carbonate to give 16 g., m.p. 216–217°. This on recrystallization from ethanol–water had constant m.p. 223–224°.

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 69.15; H, 4.44. Found: C, 68.67; H, 4.89.

2-Ethyl-3-oximino-1-keto-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine(IVa).—Seventy-five grams (0.254 mole) of (IVb), 35.4 g. (0.508 mole) of hydroxylamine hydrochloride and 27 g. (0.254 mole) of sodium carbonate were heated under reflux in 1 l. of 95% ethanol for 16 hours after which an additional 13.5 g. of sodium carbonate was added. After

(9) M.p. 172–173° was given in ref. 1 for what was presumed to be compound Ib.

(10) Prepared by procedure of N. L. Smith, *J. Org. Chem.*, **15**, 1125 (1950).

another 5 hours under reflux, the solution was slightly acidic. A saturated sodium carbonate solution was added until the solution was slightly alkaline after which it was heated under reflux an additional hour. The solution was cooled and water was added slowly to precipitate the oxime which amounted to 22.9 g. (29%), m.p. 149–155°. Recrystallization from isopropyl alcohol or acetone–water resulted in material melting unsharply from 149–163°.

Anal. Calcd. for $C_{17}H_{14}N_2O_2S$: C, 65.85; H, 4.55. Found: C, 65.72; H, 4.43.

2-Ethyl-3-amino-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine Hydrochloride (IIIc).—We reduced 13.8 g. (0.0445 mole) of IVa with 6.35 g. (0.167 mole) of lithium aluminum hydride in 2 l. of absolute ether by the Soxhlet procedure. The mixture was heated for 21 hours, and then the excess of hydride was decomposed with water. The slurry was filtered and washed thoroughly with dry ether. Dry hydrogen chloride was passed into the solution and the amine hydrochloride was removed by filtration to yield 4.0 g. (28%) of product, of m.p. 249–253°. Recrystallization from ethanol–ether did not raise the melting point.

Anal. Calcd. for $C_{17}H_{19}ClN_2S$: C, 64.15; H, 5.69. Found: C, 63.97; H, 5.83.

TUCKAHOE 7, N. Y.

[CONTRIBUTION FROM ABBOTT LABORATORIES]

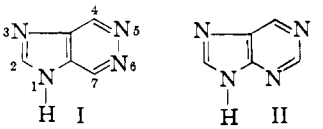
The Preparation of Several 4-Substituted Imidazo[4,5-d]pyridazines as Possible Purine Antimetabolites

BY JOHN A. CARBON

RECEIVED JUNE 23, 1958

A number of 4-substituted imidazo[4,5-d]pyridazines have been prepared for testing as antitumor agents. 1-Benzylimidazo[4,5-d]pyridazin-4(5H),7(6H)-dione (IV, R = $CH_2C_6H_5$) was found to react smoothly with phosphorus oxychloride to give 1-benzyl-4,7-dichloroimidazo[4,5-d]pyridazine (V, R = $CH_2C_6H_5$). Treatment of the latter compound with a variety of nucleophilic reagents gave a series of 1-benzyl-4-substituted-7-chloroimidazo[4,5-d]pyridazines, which were reduced readily with sodium in liquid ammonia to the 4-substituted imidazo[4,5-d]pyridazines. A similar reaction sequence has been applied to 1-methylimidazo[4,5-d]pyridazin-4(5H),7(6H)-dione (IV, R = CH_3) to give 4-amino-1-methylimidazo[4,5-d]pyridazine (XIX) and 7-amino-1-methylimidazo[4,5-d]pyridazine (XX).

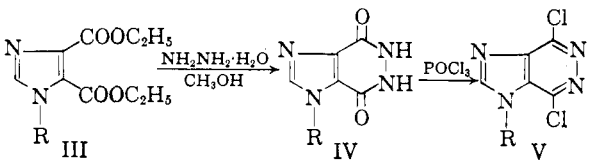
The chemistry of compounds which are structurally related to the naturally occurring purines has received a great deal of attention recently, largely because of the search for more effective antitumor and antileukemic agents. Due to the marked similarity of the imidazo[4,5-d]pyridazine (I) and purine (II) ring systems, we have prepared a series of compounds containing the system I as potential antagonists of purine metabolism.



H I H II

Aside from the preparation of imidazo[4,5-d]-pyridazin-4(5H),7(6H)-dione (IV, R = H) and a few of its 1-substituted derivatives (IV, R = CH_3 and C_6H_5),[1] the chemistry of these compounds has received little attention.[2] We have found that the cyclic hydrazides (IV) of 1-substituted imidazole-4,5-dicarboxylic acids are convenient intermediates for the synthesis of a large variety of imidazo-[4,5-d]pyridazines.

Preliminary attempts to convert imidazo[4,5-d]-pyridazin-4(5H),7(6H)-dione (IV, R = H) to 4,7-dichloroimidazo[4,5-d]pyridazine (V, R = H) by treatment with phosphorus oxychloride or phosphorus pentachloride were without success, IV (R = H) being completely inert to these reagents. The use of a phosphorus oxychloride–N,N-dimethylaniline mixture, a procedure which has been successful in reactions of this type,[3] was also unsatisfactory.[4] However, when 1-phenylimidazo[4,5-d]pyridazin-4(5H), 7(6H)-dione (IV, R = C_6H_5) was treated with refluxing phosphorus oxychloride, a smooth conversion to 4,7-dichloro-1-phenylimidazo[4,5-d]pyridazine (V, R = C_6H_5) was realized in high yield. This remarkably facile replacement of both oxygen functions by chlorine could be extended to produce 4,7-dichloro-1-methylimidazo[4,5-d]pyridazine (V, R = CH_3) and 1-benzyl-4,7-dichloroimidazo[4,5-d]pyridazine (V, R = $CH_2C_6H_5$) from the corresponding imidazo[4,5-d]pyridazin-4(5H),7(6H)-diones.



As might be predicted from the excellent work of Druey, *et al.*,[5] on the behavior of 3,6-dichloropyridazine toward nucleophilic reagents, one of the chlorine atoms in compounds of type V could be replaced with a variety of groups with ease, while the replacement of both chlorine atoms was accomplished only with difficulty. Most of these replacement reactions were carried out on 1-benzyl-4,7-dichloroimidazo[4,5-d]pyridazine (V, R = $CH_2C_6H_5$) since the benzyl grouping can be cleaved easily from an imidazole nitrogen by reduction with sodium in liquid ammonia.[6]

(1) R. G. Jones, THIS JOURNAL, **78**, 159 (1956).

(2) A recent paper (R. N. Castle and W. S. Seese, Abstracts of Papers, 133rd Meeting, American Chemical Society, San Francisco, Calif., April 13–18, 1958, p. 28M) has reported the synthesis of some 4,7-disubstituted imidazo[4,5-d]pyridazines.

(3) (a) J. Baddiley and A. Topham, *J. Chem. Soc.*, 678 (1944); (b) P. Bitterli and H. Erlenmeyer, *Helv. Chim. Acta*, **34**, 835 (1951); (c) J. R. Marshall and J. Walker, *J. Chem. Soc.*, 1004 (1951); (d) N. Whittaker, *ibid.*, 1565 (1951); 1646 (1953); (e) J. Davoll and B. A. Lowy, THIS JOURNAL, **73**, 2936 (1951); (f) A. Bendich, P. J. Russell, Jr., and J. J. Fox, *ibid.*, **76**, 6073 (1954).

(4) Castle and Seese (ref. 2) have been able to isolate a small quantity of 4,7-dichloroimidazo[4,5-d]pyridazine (V, R = H) from the reaction of imidazo[4,5-d]pyridazin-4(5H),7(6H)-dione (IV, R = H) with phosphorus oxychloride–N,N-diethylaniline.

(5) J. Druey, K. Meier and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121, 510, 837 (1954).

(6) (a) V. duVigneaud and O. K. Behrens, *J. Biol. Chem.*, **117**, 27 (1937); (b) R. G. Jones, THIS JOURNAL, **71**, 383 (1949).