[CONTRIBUTION FROM THE LABORATORY OF THE AMERICAN PHARMACEUTICAL CO.]

Acetic Acid–Ammonium Acetate Reactions. 2-Isoimidazoles as Intermediates in Imidazole Formation[1]

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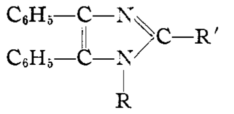
The reaction of ketones with benzil in the presence of acetic acid and ammonium acetate results in derivatives of the as yet unknown 2-isoimidazole. Certain of such isoimidazoles are rearranged by heat, in the presence or absence of a solvent, to imidazoles, while acid hydrolysis yields the original reactants. The seemingly unusual acid hydrolysis of 2,2-dibenzyl-4,5-diphenylisoimidazole to form 2-benzyl-4,5-diphenylimidazole is offered as additional proof of structure.

In a preceding article,[2] the reactions of various carbonyl compounds to form nitrogen heterocycles with acetic acid and ammonium acetate were correlated and reviewed. It can be shown by indirect means that the active form of ammonium acetate in such multiple condensations is the free ammonia base.[3]

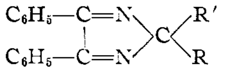
The action of acetic acid and ammonium acetate on benzil yields largely 2,4,5-triphenylimidazole (lophine) (Ia) along with a minor amount of 2,4,5-triphenyloxazole. Investigation[4] clearly demonstrated that the action of alcoholic ammonia on benzil results in the intermediate formation of N-desylbenzamide, but while this intermediate (not a necessary one) was shown to cyclize to lophine with acetic acid and ammonium acetate, its presence in the acetic acid–ammonium acetate reaction on benzil was never detected. Therefore, it was felt that additional information might be gleaned about imidazole, and possibly oxazole formation from the condensation of benzil with simple ketones and ammonium acetate in acetic acid.

The interaction of benzil and benzophenone in this medium produces a compound which has the correct analysis for tetraphenylimidazole but which melts 20 degrees below the known 1,2,4,5-tetraphenylimidazole (Ib). The only other possible arrangement of phenyl groups is that present in 2,2,4,5-tetraphenylisoimidazole (IIa). This was especially interesting since 2-isoimidazole intermediates have long been postulated in imidazole formation from aldehydes or amidines with diketones, for example, although no such intermediates have ever been isolated or synthesized.



I

a, R = H; R′ = phenyl
b, R = R′ = phenyl
c, R = benzyl; R′ = phenyl
d, R = benzoyl; R′ = phenyl



II

a, R = R′ = phenyl
b, R + R′ = spirocyclohexane
c, R = benzoyl; R′ = phenyl

The early work of Japp and Meldrum[5] may provide a partial explanation of such failures. In the reaction of acetone with phenanthrenequinone and ammonia, an acetonylaminophenanthrone is obtained, that is, the methyl group of acetone is activated in preference to its carbonyl group. This prompted a trial with dibenzyl ketone and benzil in the acetic acid–ammonium acetate medium, and a compound whose composition was that of 2,2-dibenzyl-4,5-diphenylisoimidazole (III) was found to form in excellent yield. However, this product showed a low melting point and crystallized with a molecule of water. Therefore, a series of compounds was synthesized, using desoxybenzoin, acetone and cyclohexanone.

Hydrolysis with hydrochloric acid in acetic acid yielded the original reactants from the isoimidazoles obtained from benzophenone, acetone and cyclohexanone, but surprisingly the desoxybenzoin derivative resisted hydrolysis, and the dibenzyl compound (III) was cleaved quantitatively into 2-benzyl-4,5-diphenylimidazole (IV) and benzyl chloride. In addition, solution of the dibenzyl compound (III) in formic acid resulted in two imidazoles, 1,2-dibenzyl-4,5-diphenylimidazole (V) and 2-benzyl-4,5-diphenylimidazole (IV). The rearranged benzyl group could not be removed from the ring nitrogen by boiling in strong acids.

In view of this behavior, the effect of heat on the compounds of this series was examined. It was found that while the tetraphenylisoimidazole (IIa) and the dibenzyldiphenylisoimidazole (III) did rearrange to the corresponding imidazoles (Ib and V), the other products were recovered unchanged, with the exception of the spirocyclohexane isoimidazole (IIb) which underwent decomposition. This finding cast suspicion on the structure of the product derived from desoxybenzoin since if it contained a phenyl and benzyl group on the second carbon, it should, by analogy, both hydrolyze and rearrange.

The rearrangement of a benzyl group during the original reaction of desoxybenzoin with benzil would lead to 1-benzyl-2,4,5-triphenylimidazole (Ic) and this substance was therefore synthesized from N-desylbenzamide and benzylamine in acetic acid. It was found to be identical with the desoxybenzoin derivative in melting point and ultraviolet

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[1] Presented at the Meeting-in-Miniature, N. Y. Section, February, 1952.

[2] M. Weiss, THIS JOURNAL, **74**, 200 (1952).

[3] The blue-green color of a solution of cupric acetate and ammonium acetate in acetic acid becomes increasingly blue as heat is applied, and fades as the solution is cooled. This color transition is best described as a competition of dissociation against ionization, or a rivalry between Cu^{++} and H^+ for NH_3. See for example H. H. Sisler, A. W. Davidson, R. Stoenner and L. L. Lyon, *ibid.*, **66**, 1888 (1944).

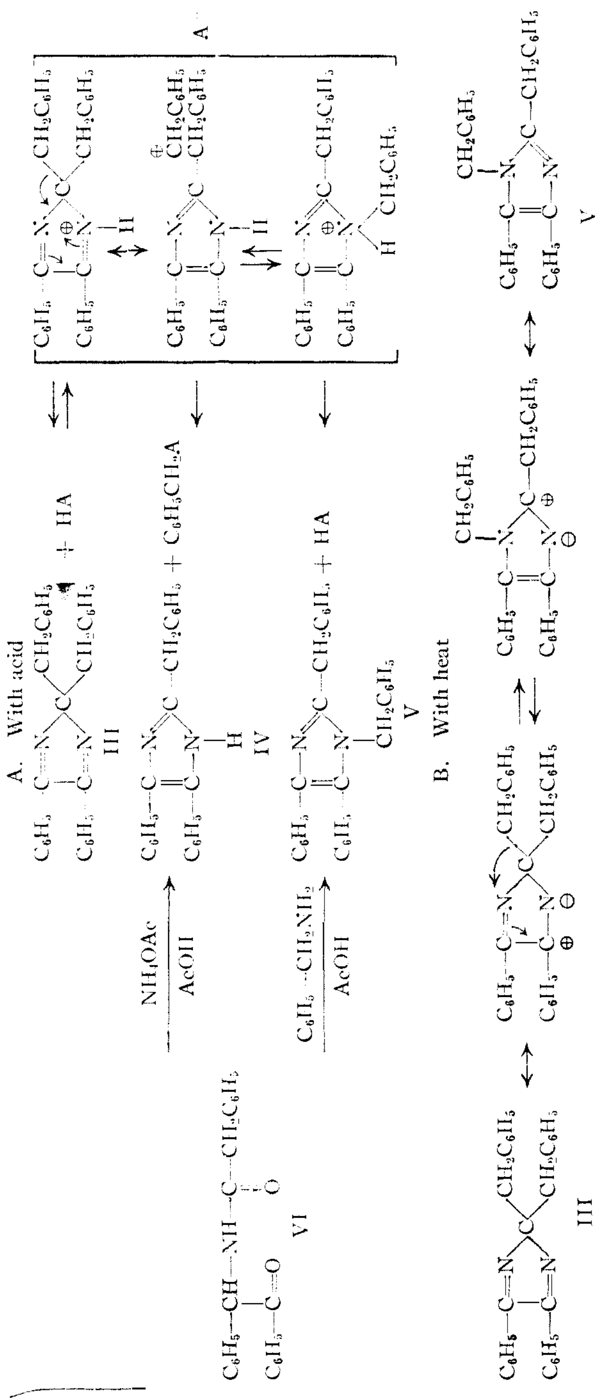
If a drop of aniline (a weak base) is added to Davidson's B-I indicator reagent, which is 0.05 N HCl in glacial acetic acid containing the indicator benzeneazodiphenylamine [D. Davidson, *J. Chem. Ed.*, **19**, 221 (1942)], the color will change from magenta to yellow. Upon the addition of acetic anhydride (a neutral substance) only a few seconds are required for the magenta color to return. If the test is repeated with ammonia or methylamine (intermediate bases) approximately 5 hours are necessary for the indicator color to revert. Acetic anhydride obviously acetylates the free base and not its ion, or reacts faster with the more dissociable acetate.

[4] D. Davidson, M. Weiss and M. Jelling, *J. Org. Chem.*, **2**, 319 (1937).

[5] F. R. Japp and A. N. Meldrum, *J. Chem. Soc.*, **75**, 1032 (1899).

spectrum. This substance had been prepared earlier[6] by the action of benzylamine on benzil, and a repetition of this reaction in acetic acid gave the same compound.

The picture for imidazole formation in acetic acid and ammonium acetate now becomes clear. Under these conditions the isoimidazole forms first. This isoimidazole structure contains a strongly electron attracting nitrogen adjacent to a quaternary carbon >C=N—[7] which is known to favor rearrangement. A simple mechanism consistent with the observed facts is



One can visualize benzil reacting in acetic acid with ammonium acetate to form a transitory 2-benzoyl-2,4,5-triphenylisoimidazole (IIc) which may in accord with the above mechanism A form lophine (Ia) and benzamide, or rearrange to 1-benzoyl-2,4,5-triphenylimidazole (N-benzoyllophine) (Id), which then may undergo a subsequent reaction to yield lophine and benzamide. In harmony with this, N-benzoyllophine was prepared and was found to react immediately when heated with acetic acid and ammonium acetate (loss of yellow color), while in acetic acid alone it was necessary to boil under reflux 15 minutes to produce the same result.

The imidazoles resulting from the rearrangement and hydrolysis of 2,2-dibenzyl-4,5-diphenylisoimidazole (III) were unknown. Accordingly N-desylphenylacetamide (VI) was synthesized and in a reaction with ammonium acetate in acetic acid yielded 2-benzyl-4,5-diphenylimidazole (IV) and with benzylamine in acetic acid formed 1,2-dibenzyl-4,5-diphenylimidazole (V).

The infrared spectra of these isoimidazoles and related imidazoles are being investigated at the present time and will be reported in the near future.

Experimental

2,2-Dibenzyl-4,5-diphenylisoimidazole Hydrate (III).—A mixture of 10.5 g. (0.05 mole) of dibenzyl ketone, 10.5 g. (0.05 mole) of benzil, 40 g. of ammonium acetate and 100 ml. of acetic acid was boiled under reflux for one hour. At the start of the reflux period, a brilliant green color developed, which gradually deepened.[8] At the end of the reflux period, the solution was poured into 150 ml. of water causing a separation of a deep green oil which crystallized very gradually. After the separation was complete, the supernatant liquid was decanted,[9] the residue washed with water, and the water decanted. The addition of 200 ml. of hot methanol containing 10 ml. of water dissolved the residue and upon cooling, crystals formed. Filtration yielded colorless crystals with a pinkish cast. These were washed with 70% methanol. Combining filtrate and washings yielded a second crop of deep pink crystals. The combined yield was 16.7 g. or 80% of 2,2-dibenzyl-4,5-diphenylisoimidazole hydrate. One or more recrystallizations from aqueous methanol or aqueous pyridine was necessary to obtain colorless crystals. The m.p. of the hydrate was indefinite, melting between 88 and 105°. A sample held in an oil-bath at 120° until all water of crystallization was removed and then recrystallized from petroleum ether melted at 88°.

The other isoimidazoles were prepared in a similar manner. Their properties are given in Table I.

1,2-Dibenzyl-4,5-diphenylimidazole (V). A. By Rearrangement of (III).—Two grams of 2,2-dibenzyl-4,5-diphenylisoimidazole hydrate was placed in a test-tube and heated at 250° for one-half hour in an oil-bath. Forty ml. of hot pyridine was added to the cooled mixture to dissolve the plastic mass. The solution was then poured into a beaker and 32 ml. of hot water added. Upon stirring and cooling 1.35 g. (67% yield) was obtained. Recrystallization from aqueous pyridine yielded a product having a m.p. 147–148°. The same rearrangement was found to occur when (III) was refluxed in Dowtherm for 15 minutes.

Anal. Calcd. for $C_{29}H_{24}N_2$: C, 86.96; H, 6.04; N, 7.00. Found: C, 86.95; H, 6.04; N, 7.04.

2,2,4,5-Tetraphenylisoimidazole (IIa) when heated at 320° for one-half hour rearranged to the known 1,2,4,5-

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(6) F. R. Japp and W. B. Davidson, *J. Chem. Soc.*, **67**, 39 (1895).

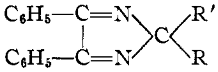
(7) B. Witkop and H. B. Patrick, THIS JOURNAL, **73**, 2196 (1951).

(8) The intensely colored compound that formed to the extent of only a few milligrams, was not investigated further beyond determining that it behaved as an indicator by turning a dull pink with alkali. Only those ketones containing two methylene groups adjacent to the carbonyl formed derivatives having different colors, but similar properties.

(9) The supernatant liquid if made alkaline will precipitate lophine.

TABLE I

2-ISOIMIDAZOLES



R	R′	Yield, %	M.p., °C.[c]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C[a]	Found, % H[a]	Found, % N[b]
Phenyl	Phenyl	20	199–201	$C_{27}H_{20}N_2$	87.06	5.41	7.52	87.03	5.45	7.45
Benzyl	Benzyl	80	88 (anhyd.)	$C_{29}H_{26}N_2O$ (hydrate)	83.22	6.26	6.70	83.07	6.20	6.64
Methyl	Methyl	58	79–80	$C_{17}H_{16}N_2$	82.22	6.50	11.28	82.11	6.55	11.24
Spirocyclohexane		76	107–108	$C_{20}H_{20}N_2$	83.29	6.99	9.72	83.24	6.99	9.69

[a] The C and H analyses were performed by Mrs. Mildred Libowitz of the Cornell microanalytical laboratory. [b] Kjeldahl nitrogen analyses were performed by Mr. Michel Margosis of this Laboratory. [c] All melting points in this paper are corrected.

tetraphenylimidazole (Ib) and was identified by mixed m.p. and ultraviolet curve.

B. From N-Desylphenylacetamide.—A mixture of 0.66 g. of N-desylphenylacetamide (VI); 3 ml. of benzylamine and 10 ml. of acetic acid was boiled under reflux for 2 hours. Upon the addition of dilute ammonia to the cooled solution an oil precipitated which gradually solidified. The supernatant liquid was decanted and the residue dissolved in 40 ml. of methanol. The filtered solution was diluted with water to an incipient precipitate. The yield was 0.3 g. melting at 146°.

Anal. Calcd. for $C_{29}H_{24}N_2$: N, 7.00. Found: N, 7.18.

2-Benzyl-4,5-diphenylimidazole (IV). A. By Acid Hydrolysis of (III).—A solution of 4.2 g. of 2,2-dibenzyl-4,5-diphenylisoimidazole hydrate in 50 ml. of methanol containing 20 ml. of hydrochloric acid was boiled under reflux for one-half hour. The flask was then chilled and cold dilute ammonia added to precipitate the crude imidazole, which was filtered. The imidazole weighed 3.1 g. (theoretical yield) and when recrystallized from aqueous ethanol melted at 239–240°.

The cloudy supernatant liquid was decanted and extracted with petroleum ether. The petroleum ether layer was dried and evaporated under reduced pressure. The residual oil, consisting mostly of benzyl chloride, was converted to its S-benzylthiouronium chloride derivative, whose m.p. was compared with that of a known sample.

B. From N-Desylphenylacetamide.—A mixture of 0.83 g. of N-desylphenylacetamide, 3 g. of ammonium acetate and 10 ml. of acetic acid was boiled under reflux for one hour. Excess water and ammonia were added to precipitate the oily product which soon solidified. The crude imidazole was filtered, washed with water and then dissolved in ethanol. Upon addition of a small amount of water, crystals appeared very slowly after scratching. The mixed m.p. and ultraviolet curve checked with the compound from method A.

Anal. Calcd. for $C_{22}H_{18}N_2$: C, 85.13; H, 5.84; N, 9.03. Found: C, 85.14; H, 5.82; N, 8.98.

N-Desylphenylacetamide.—A suspension of 5 g. of desylamine in 80 ml. of water containing some acetic acid and ammonium acetate was cooled to 10° in an ice-bath. A solution of 4 ml. of phenylacetyl chloride in 200 ml. of benzene was added, followed by stirring in 100 ml. of 10% sodium hydroxide solution. After stirring for one-half hour the benzene solution was separated from the water and washed with dilute ammonia. The benzene layer was dried with anhydrous sodium sulfate and filtered and evaporated. Crystallization from ethanol yielded 5.9 g., m.p. 140–142°.

Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.30; H, 5.82; N, 4.21.

1-Benzyl-2,4,5-triphenylimidazole. A. From Desoxybenzoin.—A mixture of 2 g. (0.01 mole) of desoxybenzoin, 2.1 g. (0.01 mole) of benzil, 8 g. of ammonium acetate and 20 ml. of acetic acid was boiled under reflux for one hour. The solution was then poured into excess water, and the precipitate filtered, then dissolved in 40 ml. of hot pyridine and 25 ml. of hot water was added to the filtered hot pyridine solution, yielding 1.02 g. (26.5%) of crystals melting at 163–164°.

Anal. Calcd. for $C_{28}H_{22}N_2$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.00; H, 5.73; N, 7.26.

B. From N-Desylbenzamide.—A mixture of 0.79 g. of N-desylbenzamide,[4] 3 ml. of benzylamine and 10 ml. of acetic acid was boiled under reflux for one hour. Excess water was added and the precipitate filtered. Crystallization from aqueous methanol yielded 0.35 g. melting at 163–164°. The m.p. was not depressed by mixing with a sample from method A.

C.—The method of Japp and Davidson[6] was modified by boiling under reflux 1.05 g. of benzil, 3 ml. of benzylamine and 10 ml. of acetic acid for one hour. The addition of a small amount of water precipitated some tetraphenylpyrazine, which was removed by filtration. The addition of excess water and dilute ammonia to the filtrate precipitated a brownish substance, which when recrystallized from methanol, yielded a product identical in all respect with the compounds from methods A and B.

1-Benzoyl-2,4,5-triphenylimidazole (N-Benzoyllophine) (Id).—A mixture of 2 g. of lophine and 10 ml. of benzoyl chloride was boiled under reflux for 40 minutes, during which time the color of the solution turned brown. Sixty ml. of ethanol containing 10 ml. of 10% aqueous ammonia was added to the cooled solution forming a precipitate. Excess acid was neutralized by stirring in concentrated ammonia. Two grams of a dark yellow precipitate was filtered. Crystallization from ethanol yielded bright yellow spherical crystals melting at 150–151°.

Anal. Calcd. for $C_{28}H_{20}N_2O$: N, 7.00. Found: N, 7.05.

Hydrolysis of N-Benzoyllophine.—A mixture of 0.25 g. of N-benzoyllophine, 1.0 g. of ammonium acetate and 5 ml. of acetic acid was boiled under reflux for one minute. Upon cooling and neutralizing with ammonia a quantitative yield of lophine was obtained (0.18 g.) melting at 275–276°.

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