Bromination of dimesitoylmethylethylene gave a *cis*-monobromo derivative from which the *trans*-isomer was made by inversion. The use of sodium bicarbonate in preventing secondary reactions during bromination is described.

CHARLOTTESVILLE, VA. RECEIVED JULY 6, 1942

[CONTRIBUTION FROM NICHOLS LABORATORY, NEW YORK UNIVERSITY]

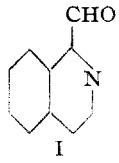
Condensation Reactions of Isoquinaldaldehyde

BY ROBERT S. BARROWS AND H. G. LINDWALL

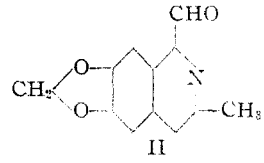
The successful use of lepidine as a source of cinchoninaldehyde[1] suggested that 1-methylisoquinoline might similarly be oxidized through the action of selenium dioxide to yield isoquinaldaldehyde (I). The method of Späth,[2] with modification, was used for the preparation of 1-methylisoquinoline. The modification involved the substitution of Raney nickel for platinized asbestos in the dehydrogenation of 1-methyl-3,4-dihydroisoquinoline. The 1-methylisoquinoline thus obtained was characterized by the preparation of several known derivatives.

The oxidation of 1-methylisoquinoline by selenium dioxide was carried out in dioxane solution with vigorous stirring; an excess of selenium dioxide was avoided. The product (I), which is volatile with steam, reacts with Tollens reagent, gives a sodium bisulfite addition product, and forms an oxime, a phenylhydrazone and a semicarbazone. The aldehyde (I) formed no hydrate.

A similar oxidation of 1,3-dimethyl-6,7-methylenedioxy-isoquinoline was carried out. The product, an aldehyde, formed a monoxime, and is tentatively assigned the structure 3-methyl-6,7-methylenedioxy-isoquinaldaldehyde (II).



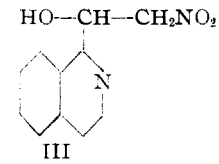
I



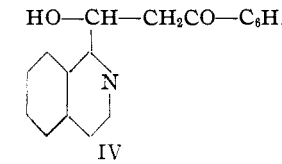
II

The condensation reactions of compound I with a series of "active methylene" compounds were studied. Condensation with nitromethane was accomplished readily to yield α-nitro-β-hydroxy-β-(isoquinolyl-1)-ethane (III).

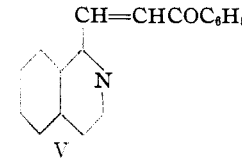
Initial attempts at condensation with acetophenone gave a mixture of products; with varied conditions, however, either IV, V, or VI could be obtained as the principal product. If the condensation of equimolecular quantities of isoquinaldaldehyde and acetophenone was carried out in the presence of sodium hydroxide for a short period of time, IV was obtained, but if longer time was allowed or if sodium ethylate was used, compound V resulted. With an excess of acetophenone and either sodium hydroxide or sodium ethylate, VI was the principal product.



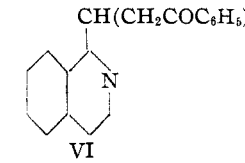
III



IV

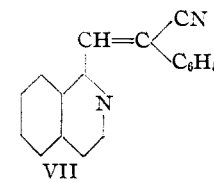


V

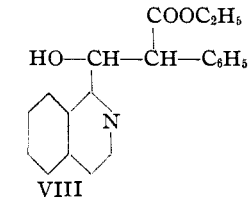


VI

No product could be obtained from isoquinaldaldehyde and phenylacetic acid under conditions of the Perkin condensation, but two derivatives of phenylacetic acid were condensed under other conditions. Phenylacetonitrile and compound I yielded VII in the presence of diethylamine or sodium ethylate; ethyl phenylacetate and I gave VIII when sodium ethylate was used as the catalyst.



VII



VIII

Experimental

1-Methylisoquinoline.—To 1-methyl-3,4-dihydroisoquinoline (15 g.) was added an excess of Raney nickel and the mixture was heated under reflux for fifteen to twenty minutes or until the temperature of the mixture had reached 248° (the boiling point of 1-methylisoquinoline); yield, 70–75%; boiling point 124–126° (at 10 mm.). **Melting points of derivatives:** picrate, 230–232°; sul-

(1) Kwartler and Lindwall, THIS JOURNAL, **59**, 524 (1937).

(2) Späth, Berger and Kuntara, *Ber.*, **63**, 134 (1930); Späth and Polgar, *Monatsh.*, **51**, 190 (1929).

fate, 246–248°; hydrochloride 200–205°; chloroplatinate, 233–234°; methiodide, 208°.

Isoquinaldaldehyde (I).—To a solution of 1-methylisoquinoline (10 g.) in dioxane (17 cc.) was added, drop by drop, a solution of selenium dioxide (8.9 g.) in dioxane (90 cc.); the solutions were mixed over a period of one-half hour with agitation and gentle warming. The final mixture was then heated, with agitation, on the steam-bath for three hours. At the end of this time the solution was cooled and the precipitated selenium was removed; the bulk of the dioxane was removed under diminished pressure; the residual material was then steam distilled. The product (I) crystallized from the distillate after several hours at ice-box temperature; long white needles, m. p. 55–55.5°; yield, 42%. The product reduces Tollens reagent and forms a bisulfite addition product slowly. It is soluble in acetone, ligroin, benzene, but it is only slightly soluble in water.

Anal. Calcd. for $C_{10}H_7NO$: C, 76.49; H, 4.46; N, 8.92. Found: C, 76.40; H, 4.80; N, 8.90.

Semicarbazone of I.—Yellow plates from ethyl alcohol; m. p. 195–197°.

Anal. Calcd. for $C_{11}H_{10}N_4O$: N, 26.17. Found: N, 25.95, 26.41.

Oxime of I.—White needles from 50% ethyl alcohol; m. p. 171–172°.

Anal. Calcd. for $C_{10}H_8N_2O$: N, 16.27. Found: N, 16.01.

Phenylhydrazone of I.—Yellow needles from ethyl alcohol; m. p. 174–175°.

Anal. Calcd. for $C_{16}H_{13}N_3$: N, 17.00. Found: N, 17.19.

3-Methyl-6,7-methylenedioxy-isoquinaldaldehyde (II).—To a solution of 2.2 g. of 1,3-dimethyl-6,7-methylenedioxy-isoquinoline in 20 cc. of dioxane was added, drop by drop, a solution of 1.3 g. of selenium dioxide in 20 cc. of dioxane. The mixture was stirred and warmed gently during the addition which required one-half hour. One and one-half hours of further heating on the steam-bath were allowed. The precipitated selenium was filtered from the hot mixture and the filtrate was steam-distilled. When the bulk of the dioxane had been removed in the course of this distillation, the product (II) began to separate from the residue; yield, 34% after crystallization from toluene. Light yellow needles from ethyl alcohol; m. p. 186.5–188.5°. The product (II) reduces Tollens reagent.

Anal. Calcd. for $C_{12}H_9NO_3$: N, 6.51. Found: N, 6.64.

Oxime of II.—Needles from 50% ethyl alcohol; m. p. 215–216°.

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: N, 12.17. Found: N, 11.90.

α-Nitro-β-hydroxy-β-(isoquinolyl-1)-ethane (III).—To a mixture of 0.3 g. of nitromethane and 0.32 g. of I was added diethylamine (2 drops). The solution, which became warm, was cooled and allowed to stand for two hours. A small amount of water was then added and an oil separated. Vigorous scratching caused the oil to solidify. The crude product (III) was dried on a porous tile; crude yield, 71%. The product may be crystallized from ligroin but heating in solvents causes apparent gradual decomposition; m. p. 106–107°, approx.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: N, 12.84; Found: N, 12.75.

β-Hydroxy-β-(isoquinolyl-1)-propiophenone (IV).—A few small pieces of ice were added to a solution of 0.2 g. of I and 0.17 g. of acetophenone in 8 cc. of ethyl alcohol. Then 15 cc. of 10% sodium hydroxide solution was added slowly. The solution soon became milky and after fifteen to twenty minutes a yellow crystalline product (IV) appeared; recrystallized from ethyl alcohol; m. p. 114.5–115°; yield, 85%.

Anal. Calcd. for $C_{18}H_{15}NO_2$: N, 5.05. Found: N, 4.76.

β-(Isoquinolyl-1)-acrylophenone (V). **Method A.**—Compound I (0.25 g.) was dissolved in 15 cc. of ethyl alcohol, and to this solution was added an excess of acetophenone (0.38 g.) and a small amount of ice. After then adding 6 cc. of 10% sodium hydroxide solution, the mixture was allowed to stand for one hour at room temperature. At the end of this time the product had appeared as fine yellow needles; yield, 60%; recrystallized from ethyl alcohol, m. p. 144–146°. **Method B.**—Equimolecular amounts of I (0.5 g.) and acetophenone (0.33 g.) were dissolved in 2 cc. of absolute alcohol and to this was added 5 drops of a solution of sodium ethylate in alcohol (0.05 g. of sodium per 1 cc.). At first the solution became warm and turned green but after standing the color changed to yellow and finally solidified to a crystalline mass. Treatment with bone black and crystallization from alcohol gave light yellow needles, m. p. 145.5–146°; yield 77%. A melting point determination when mixed with the product of method A showed no depression.

Anal. Calcd. for $C_{18}H_{13}NO$: C, 83.38; H, 5.04; N, 5.40. Found: C, 83.32, 83.23; H, 5.14, 4.99; N, 5.50, 5.44.

Bis-acetophenonyl-(isoquinolyl-1)-methane (VI).—Compound I (0.25 g.) and acetophenone (0.35 g.) were dissolved in 2 cc. of absolute ethyl alcohol and to this solution was added 0.5 cc. of a solution of sodium ethylate in alcohol (0.05 g. of sodium per 1 cc.). The product (VI) was removed by filtration after twenty hours. White plates from alcohol, m. p. 133–133.5°; yield, 42%. A small amount of VI was also obtained from the residual liquid after the removal of compound V in method "A" above.

Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 80.90; H, 5.73; N, 3.69; mol. wt., 277. Found: C, 81.26; H, 5.57; N, 3.68, 3.84; mol. wt. (micro-cryoscopic, with camphor), 264.

α-Phenyl-β-(isoquinolyl-1)-acrylonitrile (VII).—A solution was prepared consisting of 0.4 g. of phenylacetonitrile 0.5 g. of isoquinaldaldehyde and 1 cc. of absolute ethyl alcohol. To this was added a small amount of sodium ethylate solution (three drops of solution containing 0.05 g. of sodium per 1 cc. of ethyl alcohol). After cooling and scratching the product separated as light yellow needles; recrystallized from ethyl alcohol, m. p. 96.5–97°; yield, 92%.

Anal. Calcd. for $C_{18}H_{12}N_2$: C, 84.36; H, 5.13; N, 10.93. Found: C, 84.44; H, 4.83; N, 10.94.

Ethyl Ester of α-Phenyl-β-hydroxy-β-(isoquinolyl-1)-propionic Acid (VIII).—Compound VIII was prepared by a method similar to that used in the preparation of VII.

employing ethyl phenylacetate with isoquinaldaldehyde; recrystallized from ethyl alcohol as white needles, m. p. 134.5–135.5°; yield, 45%.

Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.72; H, 5.98; N, 4.36. Found: C, 74.46; H, 5.61; N, 4.47.

Summary

1. 1-Methylisoquinoline and 1,3-dimethyl-6,7-methylenedioxyisoquinoline are oxidized by selenium dioxide to yield isoquinaldaldehyde and 3-methyl-6,7-methylenedioxy-isoquinaldaldehyde, respectively.

2. Isoquinaldaldehyde has been found to undergo condensation reactions with nitromethane, acetophenone, phenylacetonitrile and ethyl phenylacetate.

NEW YORK, N. Y. RECEIVED JULY 17, 1942

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Amino Ketones. I. Synthesis of Amino Alcohols and 1,3-Diamino Compounds from β-Amino Ketones

BY NORMAN H. CROMWELL, Q. T. WILES[1] AND O. C. SCHROEDER[2]

Although many previous investigations[3] have been concerned with the addition of various amines to α,β-unsaturated ketones, few studies have been made with the resulting β-amino ketones.

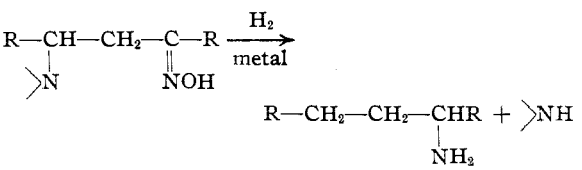
It seemed of interest to attempt the preparation of certain amino alcohols and the corresponding 1,3-diamino compounds of possible pharmacological value from such β-amino ketones by the application of certain known reactions.

The present investigation deals with the addition of certain amines to benzalacetone and benzalacetophenone and the conversion of the products to amino alcohols and 1,3-diamino compounds.

It has been found that both morpholine and piperidine add readily to benzalacetone to give, respectively, β-morpholinobenzylacetone (I) and β-piperidinobenzylacetone (II), isolated as the hydrochlorides. The preparation of β-amino ketones using high boiling, water soluble amines is best accomplished in water insoluble solvents. This allows the removal of the excess reactant amine by water washing. Conversely, the preparation of β-amino ketones from water insoluble amines such as aniline is easiest to manipulate in a water soluble solvent such as alcohol.

The oximes (III) and (IV) of the amino ketones (I) and (II) were prepared in good yields but it was necessary to take certain precautions to obtain these results. The best yields were obtained when the reaction medium was strongly basic. It was necessary that the amino ketone hydrochloride be added only after the hydroxylamine was available in the reaction medium to react immediately with the amino ketone before it could decompose to the α,β-unsaturated ketone. These amino ketoximes were amphoteric. The oximes (XIII) and (XIV), respectively, of β-morpholinobenzylacetophenone[3f] and of β-anilinobenzylacetophenone[3a] were also prepared.

Attempts to reduce these various amino ketoximes with catalytic hydrogen to the corresponding 1,3-diamino compounds were not successful. In all cases the following reaction was noted



The oximes (III) and (IV) however, were reduced in fair yields to the 1,3-diamino compounds (V) and (VI) using sodium and alcohol according to the method of Kohn.[4] The benzamides (VII) and (VIII) of these diamines were also prepared.

In order to obtain possible ephedrine-like amino alcohols the β-amino ketones (I) and (II) were reduced with sodium amalgam according to the method of Kohn.[5] These amino ketone hydrochlorides were not stable to catalytic hydrogenation though various conditions were employed.

(1) Present address: Shell Development Co., Emeryville, Calif.

(2) Present address: E. I. du Pont de Nemours and Co., Charleston, W. Va.

(3) (a) Tambor and Wildi, *Ber.*, **31**, 352 (1898); (b) Smith and Adkins, THIS JOURNAL, **60**, 407 (1938); (c) Georgi and Schwyzer, *J. prakt. Chem.*, **86**, 273 (1912); (d) Kohn and Morgenstern, *Monatsh.*, **24**, 773 (1903); **28**, 479 (1907); (e) Pollard and Stewart, THIS JOURNAL, **58**, 1980 (1936); (f) **59**, 2006, 2702 (1937); (g) Macovski and Silberg, *J. prakt. Chem.*, **137**, 131 (1933); (h) Jones and Kerner, *J. Chem. Soc.*, 363 (1933).

(4) Kohn, *Monatsh.*, **29**, 519 (1908).

(5) Kohn, *ibid.*, **28**, 423 (1907).