

of sodium iodide was added and the mixture was refluxed for three hours at atmospheric pressure. After cooling, the precipitate of sodium *p*-toluenesulfonate and excess sodium iodide was separated by filtration. The filtrate was concentrated *in vacuo* and worked up according to Compton.⁵ Our product weighed 8.5 g., representing 38.3% of the theoretical yield from the methyl glucoside used. It melted at 148.5–150° (cor.).

Methyl 6-Iodo-6-desoxy- α -D-glucopyranoside.—Methyl 2,3,4-triacetyl-6-iodo-6-desoxy- α -D-glucopyranoside (6 g.) was dissolved in 20 cc. of 95% ethyl alcohol. Fifty cc. of approximately 5% HCl (6 cc. of concd. HCl diluted to 50 cc.) was added and the mixture was heated under reflux on the steam-bath for two hours. After cooling, the solution was shaken with eleven grams of freshly prepared silver carbonate. The precipitate was filtered off and the solution was gassed with hydrogen sulfide, filtered, decolorized, and concentrated at reduced pressure to a thick sirup which immediately crystallized. The solid was heated on the steam-bath with 15 cc. of ethyl acetate to which absolute ethyl alcohol was added dropwise until complete solution occurred. The solution was decolor-

ized and filtered. On cooling, colorless crystals (2.5 g.), melting at 136.9–137.4° (cor.) and rotating⁶ +93.9° (C, 0.3192; H₂O; 20.9°) were obtained.

Anal. Calcd. for C₇H₁₃O₅I: C, 27.6; H, 4.28; I, 41.77. Found: C, 27.9; H, 4.47; I, 41.7.

Summary

A method is described for removal of the acetyl groups from methyl 2,3,4-triacetyl-6-iodo-6-desoxy- α -D-glucopyranoside without other changes. Methyl 6-iodo-6-desoxy- α -D-glucopyranoside is described and the use of methyl isobutyl ketone as a vehicle for the replacement of *p*-toluenesulfonate groups by iodide is recorded.

(6) Rotations refer to specific rotations of the D line of sodium. Concentrations refer to the weight of sample in one hundred cubic centimeters of solution.

CAMBRIDGE, MASS.

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[CONTRIBUTION FROM THE NICHOLS LABORATORY, NEW YORK UNIVERSITY]

Syntheses and Certain Reactions of 1-Isoquinolyl and 4-Isoquinolyl Methyl Ketones

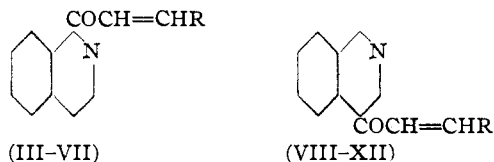
BY JOHN J. PADBURY¹ AND H. G. LINDWALL

1-Isoquinolyl methyl ketone (I) was prepared by two methods. It was obtained by the method of Kaufman² from 1-cyanoisoquinoline and methylmagnesium iodide. However, since 1-cyanoisoquinoline could be obtained pure only with difficulty, another method was sought. The ethyl ester of isoquinaldinic acid was condensed with ethyl acetate under Claisen conditions, and the ketone (I) was obtained by hydrolysis of the intermediate β -keto ester. Grosheintz and Fischer³ have observed that in the preparation of aldehydes from 1-acyl-1,2-dihydroquinolindonitriles by treatment with sulfuric acid quinaldinic acid can be obtained in good yield as a by-product. Using a similar procedure, 1-cyano-2-benzoyl-1,2-dihydroisoquinoline⁴ gave isoquinaldinic acid which was then converted to the ethyl ester.

4-Isoquinolyl methyl ketone (II) was prepared in an analogous manner by condensation of ethyl 4-isoquinolinecarboxylate with ethyl acetate.⁵ This ketone could not be obtained from 4-cyanoisoquinoline and methylmagnesium iodide.

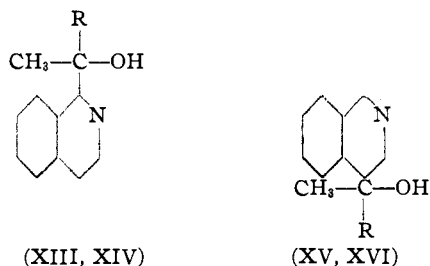
The condensation reactions of I and II with a series of aromatic aldehydes were studied. Using sodium hydroxide or diethylamine as catalysts

condensation products of the unsaturated type were obtained (III–XII).



III, VIII, R = C₆H₅—
 IV, IX, R = 4-CH₃OC₆H₄—
 V, X, R = 3,4-(CH₃O)₂C₆H₃—
 VI, XI, R = 2-ClC₆H₄—
 VII, XII, R = 2,3-(OCH₃)₂C₆H₃—

The Grignard reagent was found to react normally with I and II to give tertiary alcohols (XIII–XVI).



XIII, XV, R = CH₃—
 XIV, XVI, R = C₆H₅—

Experimental⁶

(1) Present address: American Cyanamid Co., Stamford, Connecticut.
 (2) Kaufman, Dändliker and Burkhardt, *Ber.*, **46**, 2934 (1913).
 (3) Grosheintz and Fischer, *THIS JOURNAL*, **63**, 2021 (1941).
 (4) Reissert, *Ber.*, **38**, 3427 (1905).
 (5) Since this work was completed the preparation of 4-isoquinolyl methyl ketone has been reported by Koelsch (*J. Org. Chem.*, **10**, 34 (1945)) who obtained the ketone (II) by the same reaction. As he has pointed out, the ethyl ester of 4-isoquinolinecarboxylic acid undergoes the Claisen condensation comparatively poorly. This observation finds confirmation in our work. The lesser activity of the carboxy group in the 4-position is demonstrated by a comparison of the yields of 4-isoquinolyl methyl ketone (40%) and 1-isoquinolyl methyl ketone (85%).

1-Cyano-2-benzoyl-1,2-dihydroisoquinoline.—This compound was prepared by a modification of the procedure used by Reissert.⁴ To a solution of 294 g. (6 moles) of sodium cyanide in 2.5 liters of water was added 258 g. (2 moles) of isoquinoline, and the mixture was stirred rapidly

(6) All melting points are corrected. Boiling points are uncorrected.

to form an emulsion. Benzoyl chloride (560 g., 4.0 moles) was added over a period of three hours, with vigorous stirring. The dark oil which separated solidified to form small hard spheres, after one hour of additional stirring. A small temperature rise was noted during the reaction. The dark solid was collected by suction filtration, washed thoroughly with water, then with 10% hydrochloric acid, and again with water. Recrystallization from ethyl alcohol (charcoal) gave 303 g. (58%) of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline; m. p. 124–126°.

1-Cyanoisoquinoline. Method A.—From 130 g. of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline and 130 g. of phosphorus pentachloride, following the procedure of Kaufmann,⁷ there was obtained after steam distillation 62 g. of material; m. p. 67–85°. Two recrystallizations from ligroin–benzene gave 41 g. (53%) of 1-cyanoisoquinoline; m. p. 88–89°. Recrystallized a third time the m. p. was 89–89.5°, which was unchanged by further recrystallization from this mixture of solvents, or from a mixture of dioxane and water.

Anal. Calcd. for $C_{10}H_8N_2$: N, 18.2. Found: N, 18.0.

Method B.—A mixture of 0.2 g. of oxime of isoquinaldaldehyde⁸ and 1.5 ml. of acetic anhydride was heated under reflux for one-half hour. Twenty milliliters of water was added and the mixture was heated to boiling. Upon cooling fine white needles were deposited; 0.123 g.; m. p. 86–89°. Recrystallization from aqueous dioxane gave material of m. p. 83.7–89.5°, which showed no depression of the m. p. when mixed with a sample of 1-cyanoisoquinoline prepared by Method A.

Isoquinaldinic Acid.—1-Cyano-2-benzoyl-1,2-dihydroisoquinoline (150 g.) and 500 ml. of 10% sulfuric acid were boiled under reflux for one and one-half hours. Steam was then passed through the mixture to remove benzaldehyde. The mixture was cooled and the small amount of solid (21 g., composed for the most part of benzoic acid) was filtered off. Sodium hydroxide solution (10%) was added to the filtrate until the solution was almost neutral (acid to litmus), and the mixture was again filtered to remove a very small amount of solid which had separated. The clear solution was heated to boiling and excess copper sulfate solution was added. The gray copper salt was collected, washed thoroughly with hot water, and suspended in 1.5 liters of hot water. Hydrogen sulfide was passed in until precipitation of copper sulfide was complete. Evaporation of the filtrate, after removal of copper sulfide and treatment with decolorizing charcoal, gave 65 g. (65%) of light-colored acid, m. p. 158.5–161.5° (dec.). This material was used without further purification for the preparation of the ester. A sample of the acid recrystallized from benzene gave fine white crystals; m. p. 162° (dec.) [lit.,⁴ m. p. 161° (dec.)].

Ethyl Isoquinaldinate.—A mixture of 75 g. of isoquinaldinic acid, 150 g. of absolute ethyl alcohol and 150 g. of concd. sulfuric acid was heated under reflux on the steam-bath for eleven hours. The reaction mixture was poured over ice and made alkaline with concd. ammonium hydroxide. The oily ester which separated was taken up in ether, and the aqueous layer was extracted with ether. The ether extracts were combined and distilled. The yield was 56.6 g. (65%); b. p. 197–199° (20 mm.) (lit.,¹⁰ b. p. 188–190° (13 mm.)).

1-Isoquinolyl Methyl Ketone (I). Method A.—To a suspension of 0.5 mole of sodium ethylate in 300 ml. of toluene was added 50 g. (0.25 mole) of ethyl isoquinaldinate followed by 66 g. (0.75 mole) of ethyl acetate. The mixture was heated on the steam-bath, with stirring, for five hours. To the cooled reaction mixture was added 400 ml. of dil. hydrochloric acid, and the mixture was stirred thoroughly to extract the toluene layer. The aqueous layer was separated and boiled for one hour to decompose the

β -keto ester. The solution was made alkaline with saturated potassium carbonate solution, and the brown oil which was liberated was taken up in ether. The ether solution was dried over anhydrous potassium carbonate, the ether evaporated, and the residue distilled. The yield was 36.2 g. (85%) of pale yellow ketone: b. p. 148–149° (11 mm.). A sample of this material was redistilled twice and melted at 14–15°. This m. p. was unchanged by two recrystallizations from petroleum ether.

Anal. Calcd. for $C_{11}H_9NO$: C, 77.2; H, 5.3; N, 8.2. Found: C, 77.0; H, 5.4; N, 8.1.

Method B.—Prepared from 1-cyanoisoquinoline and methylmagnesium iodide according to the method of Kaufmann.² The yield of (I) was 50%; b. p. 148–148.5° (11 mm.); m. p. 14–15° (lit.,² b. p. 149–150° (12 mm.); m. p. 48°).

Oxime of I.—Colorless rhomboids from 50% ethyl alcohol; m. p. 211.5–213.5°.

Anal. Calcd. for $C_{11}H_{10}N_2O$: N, 15.1. Found: N, 15.0.

Phenylhydrazone of (I).—Orange needles from ethyl alcohol; m. p. 165–167° (dec.) (lit.,² m. p. 160°).

Anal. Calcd. for $C_{17}H_{14}N_2$: N, 16.1. Found: N, 16.0.

Semicarbazone of I.—Fine white needles from 50% ethyl alcohol; m. p. 208°.

Anal. Calcd. for $C_{12}H_{12}N_4O$: N, 24.5. Found: N, 24.4.

4-Bromoisquinoline.—This preparation was adapted from the procedure of Bergstrom and Rodda,¹¹ as modified by Craig and Cass.¹² To 155 g. (1.2 moles) of isoquinoline was added 97 ml. of concd. hydrochloric acid, and the resulting solution was evaporated nearly to dryness, under vacuum, on the steam-bath. To the white pasty salt was added 208 g. (1.3 moles) of bromine, in several portions. The stiff mass was stirred occasionally during the addition of the bromine. After addition of all the bromine, the material was transferred to a large mortar and ground to reduce the hard lumps present. The material was returned to the flask, an air condenser was attached and the flask was heated on an oil-bath maintained at 210–215° for seven hours. During the early part of the heating the mass was liquid and there was vigorous evolution of gas. The oil-bath was cooled to about 100°, 500 ml. of water was added to the reaction flask, and the mixture was heated to boiling to dissolve the solid. The dark solution was filtered and made alkaline with 20% sodium hydroxide solution. The heavy oil which was liberated was taken up in benzene, and the aqueous layer was extracted once with benzene. The benzene was removed on the steam-bath and the residue was distilled. The product condensed in the receiver as white solid, after a small forerun of unchanged isoquinoline had passed over. The yield was 178 g. (71%); b. p. 140–148° (15 mm.). This material was used without further purification for the preparation of 4-cyanoisoquinoline. A sample of the distillate recrystallized from petroleum ether melted at 38–40°.

4-Bromoisquinoline was converted into 4-cyanoisoquinoline according to the method of Tyson,¹³ and 4-isoquinolinecarboxylic acid was prepared according to the method of Bergstrom and Rodda.¹¹

Ethyl 4-Isoquinolinecarboxylate.—The procedure for the preparation of this material was the same as that for ethyl isoquinaldinate. The yield was 85%; b. p. 132–137° (1 mm.); m. p. 47–49° (lit.,¹¹ m. p. 47–48°).

4-Isoquinolyl Methyl Ketone (II).—This compound was obtained according to Method A for the preparation of 1-isoquinolyl methyl ketone, from 0.5 mole of sodium ethylate, 0.25 mole of ethyl 4-isoquinolinecarboxylate, and 0.75 mole of ethyl acetate. After evaporation of the ether the product was distilled. The material boiling 160–164° (8 mm.) solidified in the receiver. Recrystallization from ligroin gave 17 g. (40%) of II; white needles; m. p. 70–

(7) Kaufmann and Dändliker, *Ber.*, **46**, 2928 (1913).

(8) Recorded melting points are: Kaufmann and Dändliker (ref. 7), m. p. 74°; Zincke and Krollpfeiffer, *Ann.*, **408**, 338 (1915), m. p. 93°.

(9) Barrows and Lindwall, *This Journal*, **64**, 2430 (1942).

(10) Kindler, *Ber.*, **69**, 2792 (1936).

(11) Bergstrom and Rodda, *This Journal*, **63**, 3030 (1940).

(12) Craig and Cass, *ibid.*, **64**, 783 (1942).

(13) Tyson, *ibid.*, **61**, 183 (1939).

TABLE I

COMPOUNDS OBTAINED BY CONDENSATION OF ISOQUINOLYL METHYL KETONES WITH AROMATIC ALDEHYDES

	Isoquinoline	M. p., °C.	Yield, %	Formula	Nitrogen, %		Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
III	1-Cinnamoyl-	78 - 79 (dec.) ^a	73	C ₁₅ H ₁₃ NO	5.4	5.5	83.4	83.6	5.1	5.3
IV	1-(4'-Methoxycinnamoyl)-	100 - 100.5 (dec.) ^b	88	C ₁₅ H ₁₅ NO ₂	4.8	4.7	78.9	78.8	5.2	5.2
V	1-(3',4'-Methylenedioxcinnamoyl)-	129 - 130 (dec.) ^c	74	C ₁₅ H ₁₃ NO ₃	4.6	4.6	75.2	75.5	4.3	4.4
VI	1-(2'-Chlorocinnamoyl)-	114.5-115 (dec.) ^d	93	C ₁₅ H ₁₃ ClNO	4.8	4.8	73.6	73.6	4.1	4.1
VII	1-(2',3'-Dimethoxycinnamoyl)-	107 - 107.5	90	C ₁₇ H ₁₇ NO ₃	4.4	4.4	75.2	75.1	5.4	5.4
VIII	4-Cinnamoyl-	96.5-98 ^d	52	C ₁₅ H ₁₃ NO	5.4	5.5	83.4	83.0	5.1	5.2
IX	4-(4'-Methoxycinnamoyl)-	137.5-138.5 ^d	76	C ₁₅ H ₁₅ NO ₂	4.8	5.1	78.9	78.5	5.2	5.1
X	4-(3',4'-Methylenedioxcinnamoyl)-	166.5 ^c	95	C ₁₅ H ₁₃ NO ₃	4.6	4.5	75.2	74.8	4.3	4.3
XI	4-(2'-Chlorocinnamoyl)-	127 - 128 ^d	71	C ₁₅ H ₁₃ ClNO	4.8	4.9	73.6	73.3	4.1	4.3
XII	4-(2',3'-Dimethoxycinnamoyl)-	115.5-117 ^d	66	C ₁₇ H ₁₇ NO ₃	4.4	4.3	75.2	74.9	5.4	5.2

^a Recrystallized from ligroin. ^b Recrystallized from isopropyl ether. ^c Recrystallized from ethyl alcohol. ^d Recrystallized from 50% ethyl alcohol.

71° (lit.,⁵ m. p. 72-74°). The yield was not improved when the reaction time was increased from five to twelve hours.

Anal. Calcd. for C₁₁H₉NO: C, 77.2; H, 5.3; N, 8.2. Found: C, 77.4; H, 5.3; N, 8.2.

Oxime of II.—Needles from 50% ethyl alcohol; m. p. 194.5-195.5°.

Anal. Calcd. for C₁₁H₁₀N₂O: N, 15.1. Found: N, 15.3.

Phenylhydrazone of II.—Orange plates from ethyl alcohol; m. p. 173.5-176° (dec.).

Anal. Calcd. for C₁₇H₁₅N₃: N, 16.1. Found: N, 16.1.

Semicarbazone of II.—Fine white crystals from 50% ethyl alcohol; m. p. 211.5-212°.

Anal. Calcd. for C₁₂H₁₂N₄O: N, 24.5. Found: N, 23.9.

Condensation Reactions of Isoquinolyl Methyl Ketones.

—Data for products obtained by condensation of the ketones with aromatic aldehydes are summarized in Table I. The procedure below for the preparation of 1-(2',3'-dimethoxycinnamoyl)-isoquinoline (VII) was followed, except for the preparation of compound VIII. To a solution of 2.2 g. of (I) and 2.5 g. of 2,3-dimethoxybenzaldehyde in 40 ml. of 70% ethyl alcohol was added 5 ml. of 10% sodium hydroxide solution. A yellow precipitate began to form immediately. After standing at room temperature for several hours, the solid was collected and washed with 50% ethyl alcohol. The product (VII), 4.1 g., m. p. 106-107°, was recrystallized from a mixture of ligroin and benzene, giving bright yellow crystals (3.7 g.); m. p. 107-107.5°.

4-Cinnamoyl-isoquinoline (VIII).—When sodium hydroxide was used as the catalyst in the preparation of this compound, a high-melting white solid was obtained, which could not be purified. To a solution of 0.5 g. of II and 0.5 g. of benzaldehyde in 3 ml. of ethyl alcohol was added 0.5 ml. of diethylamine. The solution was heated under reflux for two hours, after which the solvent was evaporated. The oil remaining was taken up in ether and was shaken with sodium bisulfite solution to remove benzaldehyde. Evaporation of the ether left an oil which solidified after several hours. Recrystallization from ligroin gave 0.4 g. of VIII; yellow crystals, m. p. 96.5-98°.

α,α-Dimethyl-1-isoquinolinemethanol (XIII).—The Grignard reagent was prepared in 50 ml. of anhydrous ether from 0.72 g. (0.03 atom) of magnesium, and 4.26 g. (0.03 mole) of methyl iodide. 1-Isoquinolyl methyl ketone (1.71 g., 0.01 mole) in 25 ml. of ether was added to the Grignard reagent with stirring. The light colored granular precipitate which formed settled to the bottom of the reaction flask. The mixture was heated under reflux for one and one-half hours and allowed to stand at room temperature overnight. Saturated ammonium chloride solution was

added to decompose the mixture; the ether layer was separated and dried over anhydrous potassium carbonate. The yellow oil remaining after evaporation of the ether was heated for one-half hour on the steam-bath under vacuum. The oil did not crystallize directly, but after standing for several days in a vacuum desiccator, crystals had separated. The crystals were pressed on a clay plate to remove adhering oil, giving 1.38 g. of material; m. p. 53-56°. Recrystallization from ligroin (decolorizing charcoal) gave 1.05 g. (56%) of XIII; colorless crystals; m. p. 56-56.5°.

Anal. Calcd. for C₁₂H₁₃NO: C, 77.0; H, 7.0; N, 7.5. Found: C, 77.1; H, 7.3; N, 7.5.

α-Methyl-α-phenyl-1-isoquinolinemethanol (XIV).—Following the same procedure, from 0.03 mole of phenylmagnesium bromide and 1.71 g. (0.01 mole) of I in 30 ml. of anhydrous ether there was obtained 2.24 g. of crude product. Recrystallization from ligroin (decolorizing charcoal) gave XIV; yield, 1.92 g. (77%); fine white crystals, m. p. 93-95°.

Anal. Calcd. for C₁₇H₁₅NO: C, 81.9; H, 6.1; N, 5.6. Found: C, 81.5; H, 6.2; N, 5.7.

α,α-Dimethyl-4-isoquinolinemethanol (XV).—From 0.0075 mole of methylmagnesium iodide and 0.472 g. (0.0025 mole) of II there was obtained 0.43 g. of crude XV. Recrystallization from ligroin gave colorless prisms; 0.35 g. (75%); m. p. 108-109°.

Anal. Calcd. for C₁₂H₁₃NO: C, 77.0; H, 7.0; N, 7.5. Found: C, 77.1; H, 6.8; N, 7.4.

α-Methyl-α-phenyl-4-isoquinolinemethanol (XVI).—From 0.03 mole of phenylmagnesium bromide and 1.71 g. (0.01 mole) of II there was obtained, after recrystallization from ligroin containing a small amount of benzene, 1.74 g. (70%) of XVI; colorless cubes, m. p. 168.5-170°.

Anal. Calcd. for C₁₇H₁₅NO: C, 81.9; H, 6.1; N, 5.6. Found: C, 82.1; H, 5.9; N, 5.5.

Summary

1. 1-Isoquinolyl and 4-isoquinolyl methyl ketones have been prepared by condensation of the appropriate esters with ethyl acetate, followed by hydrolysis of the intermediate β-keto esters.

2. The isoquinolyl methyl ketones have been found to undergo condensation reactions with aromatic aldehydes.

3. Several tertiary alcohols have been obtained by reaction of isoquinolyl methyl ketones with Grignard reagents.

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