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

Amino Ketones. III.* β-Tetrahydroisoquinolino Ketones and Derivatives. Reaction with Grignard Reagents[1]

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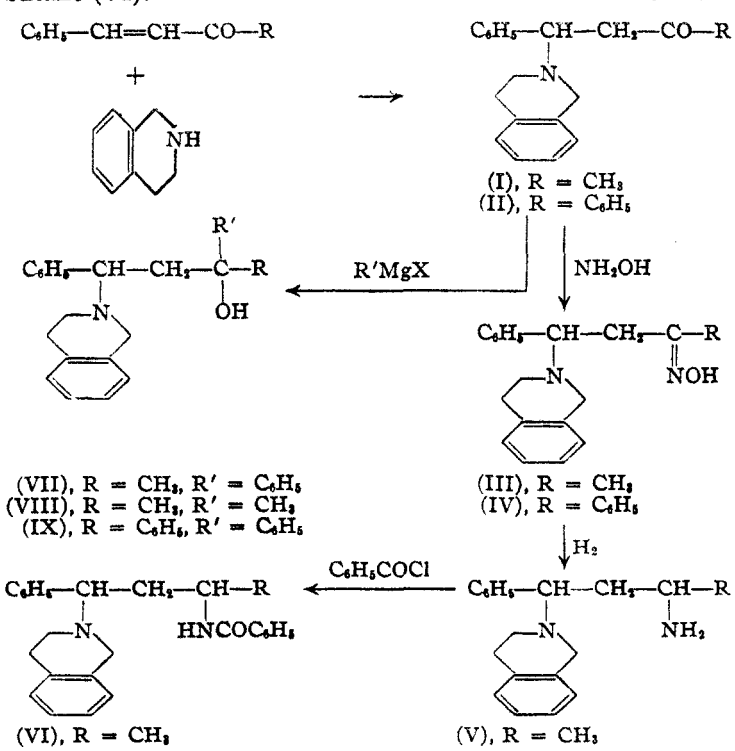
While extending our investigations of the chemistry of β-amino ketones,[2] it seemed important to introduce the interesting base tetrahydroisoquinoline into these molecules. Buck and Ide[3] reported N-alkyl tetrahydroisoquinolines to show slight depressor action and to be strong sympatholytics. Allewelt and Day[4] reported that 1-phenyl-2-tetrahydroisoquinolino ethanol hydrochloride showed mild local anesthetic activity.

Tetrahydroisoquinoline was found to add readily to benzalacetone and benzalacetophenone to give the β-amino ketones (I) and (II), respectively. The oxime (III) of (I) was reduced with sodium and alcohol to 1-phenyl-1-tetrahydroisoquinolino-3-aminobutane, (V). This reduction was accompanied by some cleavage of the tetrahydroisoquinolino nitrogen to β-carbon bond, thereby reducing the yield of diamine. (V) reacted with benzoyl chloride to give low yields of 1-phenyl-1-tetrahydroisoquinolino-3-benzamidobutane (VI).



Apparently the only previous study of the reaction of a β-amino ketone with a Grignard reagent is the addition of methylmagnesium iodide to diacetone amine, reported by Kohn.[5] Since the β-amino ketones (I) and (II) could be obtained in a pure dry state it was of interest to compare their reactivities with Grignard reagents. Moreover, the resulting amino alcohols should be of interest pharmacologically.

Phenylmagnesium bromide and methylmagnesium iodide both added readily to (I) to give good yields of the corresponding amino alcohols (VII) and (VIII), respectively. Only a very slow and incomplete reaction was experienced in adding phenylmagnesium bromide to (II). This might be expected because of the hindering and electron attracting effect of the phenyl group attached to the carbonyl group, along with the similar effect of the tetrahydroisoquinolino group in the beta position. However, methylmagnesium iodide added readily to this same amino ketone (II) to give a good yield of the amino alcohol (VII).

The pharmacological investigations of these compounds will be reported elsewhere.

Experimental[6]

β-Tetrahydroisoquinolinobenzylacetone (I).—To a solution of 60.8 g. (0.416 mole) of benzalacetone in 100 ml. of 95% ethyl alcohol was added 58.2 g. (0.437 mole) of tetrahydroisoquinoline.[7] This solution was heated to boiling and then allowed to stand at room temperature for two days and in an ice-chest four days. The white crystalline product was filtered and washed with a 70% alcohol solution; yield 69.0 g. (59%); m. p. 71–72°. Recrystallization from low boiling petroleum ether or methyl alcohol and water solutions did not change the melting point of the white product.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.58. Found: C, 81.70; H, 7.83.

Attempts to prepare this amino ketone in a petroleum ether solution gave a mixed product that resisted purification.

β-Tetrahydroisoquinolinobenzylacetone Oxime (III).—To a solution of 11.2 g. (0.162 mole) of hydroxylamine hydrochloride and 16.6 g. (0.202 mole) of sodium acetate in 180 ml. of methyl alcohol and 40 ml. of water was added 29.0 g. (0.104 mole) of (I), dissolved in 300 ml. of methanol. This mix-

* Paper II: Cromwell and Hoeksema, THIS JOURNAL, 66, 870 (1944).

(1) Presented before a session of the Division of Organic Chemistry, 107th Meeting of the American Chemical Society, Cleveland, Ohio, April 4, 1944.

(2) Cromwell, Wiles and Schroeder, *ibid.*, 64, 2432 (1942).

(3) Buck and Ide, *ibid.*, 60, 2101 (1938).

(4) Allewelt and Day, *J. Org. Chem.*, 6, 385 (1941).

(5) Kohn, *Sitzungsber.*, 116[2b], 953 (1907).

(6) Micro-Dumas analyses for nitrogen and semi-micro analyses for carbon and hydrogen by the Analytical Laboratory, Department of Chemistry, University of Nebraska, under the supervision of H. Armin Pagel.

(7) Cromwell and Cram, THIS JOURNAL, 65, 301 (1943).

ture was heated to boiling and allowed to stand one day at room temperature and two days in the ice-chest. The white, needle-shaped crystals were filtered and washed with 50% methyl alcohol and recrystallized from 95% alcohol, wt. 25.8 g. (84% yield), m. p. 155–157°.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53. Found: C, 77.52; H, 7.68.

β-Tetrahydroisoquinolinobenzylacetophenone (II).—To 100 ml. of 95% alcohol were added 26.8 g. (0.129 mole) of benzalacetophenone and 17.8 g. (0.134 mole) of tetrahydroisoquinoline. Using the same procedure as with (I), the yield was 36.7 g. (83%), recrystallized from an alcohol–ether mixture, m. p. 90–91°.

Anal. Calcd. for $C_{24}H_{23}NO$: C, 84.42; H, 6.79. Found: C, 84.24; H, 7.04.

The oxime (IV) of (II) was prepared by the procedure used for (III); yield 10%, recrystallized from absolute alcohol, m. p. 173–175°.

Anal. Calcd. for $C_{24}H_{24}N_2O$: C, 80.86; H, 6.79. Found: C, 80.82; H, 6.87.

1-Phenyl-1-tetrahydroisoquinolino-3-aminobutane (V).—The oxime (III) was reduced in boiling ethanol with sodium and the diamine isolated by the method outlined in the first paper of this series.[8] The product was a thick, pale-green oil that flowed only when warm and refused to solidify or crystallize, b. p. 178–180° (1 mm.), yield 32%.

Anal. Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 80.95; H, 8.73; N, 10.06.

From this reduction mixture was also isolated tetrahydroisoquinoline identified as its benzene sulfonamide, m. p. 154°,[8] benzalacetone oxime, m. p. 113–116°,[9] and benzylacetone oxime, m. p. 85–88°.[10]

The benzamide (VI) of (V) was prepared by the method outlined in the first paper in this series.[8] The yield was comparatively low, however (30%); recrystallized from 95% alcohol, m. p. 159–161°.

Anal. Calcd. for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.34. Found: C, 80.89; H, 7.32.

4-Tetrahydroisoquinolino-2,4-diphenylbutanol-2 (VII).—To an ethereal solution of phenylmagnesium bromide, prepared from 3.5 g. (0.144 mole) of magnesium, was added as rapidly as possible, a solution of 10 g. (0.036 mole) of (I) in 75 ml. of dry ether. The solution was stirred during addition and refluxed for four hours thereafter, a white precipitate forming during this time. The reaction mixture was decomposed by pouring it onto ice and 10 g. of ammonium chloride. The product was separated from the water layer with ether–benzene extractions. This ether–benzene layer was washed with four 50-ml. portions of 0.03 *N* hydrochloric acid to remove any free tetrahydroisoquinoline.

Evaporation of the solvent and recrystallization of the residual oil from low boiling petroleum ether gave 5.5 g. (43% yield) of white crystals, m. p. 115–116°.

Anal. Calcd. for $C_{25}H_{27}NO$: C, 83.99; H, 7.61. Found: C, 83.94; H, 7.64.

This same amino alcohol (VII) was obtained in 45% yields by adding methylmagnesium iodide to the β-amino ketone (II).

4-Tetrahydroisoquinolino-2-methyl-4-phenylbutanol-2 (VIII).—This carbinol was prepared from (I) by the method outlined for (VII), using methylmagnesium iodide. The mixture was refluxed for three hours even though an addition product had precipitated in ten minutes. The ether–benzene extractions containing the product were freed of tetrahydroisoquinoline by adding a small amount of acetic anhydride. After standing at room temperature for twelve hours this acetic anhydride reaction mixture was extracted with ten 60-ml. portions of 0.2 *N* hydrochloric acid. The combined acid extracts were made basic with sodium hydroxide and the liberated amino alcohol extracted with benzene. Evaporation of the benzene left a brown oil which was crystallized from low-boiling petroleum ether, yield 46%, m. p. 95–96°. This product was considerably more soluble in dilute hydrochloric acid than was (VII).

Anal. Calcd. for $C_{20}H_{25}NO$: C, 81.31; H, 8.53. Found: C, 81.25; H, 8.60.

3-Tetrahydroisoquinolino-1,1,3-triphenylpropanol-1 (IX).—The amino ketone (II) was refluxed for seven hours with phenylmagnesium bromide. Only a small amount of white addition product was precipitated. The product was isolated in the manner outlined for (VII). Only a small amount of the amino alcohol was obtained (5% yield), recrystallized from absolute alcohol, m. p. 78–80°. A mixed melting point experiment with (II) gave m. p. 73–78°.

Anal. Calcd. for $C_{30}H_{29}NO$: C, 85.88; H, 6.97. Found: C, 85.82; H, 7.20.

Summary

1. β-Tetrahydroisoquinolinobenzylacetone and the corresponding benzylacetophenone have been prepared and their reactions with Grignard reagents compared.

2. 1-Phenyl-1-tetrahydroisoquinolino-3-aminobutane and the benzamide have been prepared starting with the β-amino ketone.

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(8) Von Braun, *Ber.*, **57B**, 910 (1924).

(9) Zelinsky, *ibid.*, **20**, 923 (1887).

(10) Vavon, *Compt. rend.*, **154**, 1706 (1912).