[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Cinnolines. V. Bz-tetrahydrocinnolines and -Quinazolines[1,2]

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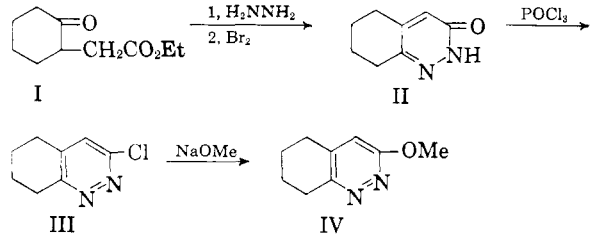
Several bz-tetrahydrocinnolines have been synthesized by the dehydrogenation of the condensation products of hydrazine with ethyl 2-oxocyclohexylacetate (I) or with the 2-oxocyclohexylmethyl ketones (II). The latter have been prepared by an extension of the Stork alkylation procedure to α-halo ketones. Several bz-tetrahydroquinazolines have been synthesized by the condensation of an amidine with hydroxymethylenecyclohexanone or with 2-carboethoxycyclohexanone.

In one useful synthesis of pyridazines and pyridazones a γ-keto acid, ester or ketone is treated with hydrazine or a monosubstituted hydrazine and the resultant dihydropyridazine derivative is aromatized by dehydrogenation or by bromination and simultaneous dehydrobromination.[4] This sequence has seen some but not extensive use[5] in the synthesis of bz-tetrahydrocinnolines, probably because the starting γ-keto acids, esters or ketones have been prepared of necessity by rather tedious routes. Inasmuch as the recently described alkylation of ketones by Stork and co-workers[6,7] appeared to obviate the multistep preparations of the requisite starting materials, we have examined the synthesis of the several new bz-tetrahydrocinnolines described in this communication, which were needed for comparison with their fully aromatized analogs. While this work was in progress Horning and Amstutz[8] reported their preparation of several bz-tetrahydrocinnolines by the same general route although they did not utilize the Stork procedure for the preparation of their intermediates.

Also described are the preparations of several bz-tetrahydroquinazolines by an extension of the classical Pinner synthesis of pyrimidines.

The condensation of ethyl bromoacetate with the pyrrolidine enamine of cyclohexanone was reported by Stork, Terrell and Szmuszkovicz[6] to give a "good" yield of ethyl 2-oxocyclohexylacetate (I). In the present work a 58% yield of I was obtained by the Stork procedure, whereas the older procedure of Chuang and Mai[9] gave a maximum over-all yield of 31% (based on cyclohexanone).[10,11] The reaction of I with hydrazine hydrate in the presence of acetic acid followed by aromatization without isolation of the resultant dihydropyridazone gave a 51–70% yield of 5,6,7,8-tetrahydro-3-cinnolinol (II).[12]

Treatment of II with *fresh* phosphorus oxychloride gave an 83% yield of 3-chloro-5,6,7,8-tetrahydrocinnoline (III),[13] and reaction of the latter with sodium methoxide gave 3-methoxy-5,6,7,8-tetrahydrocinnoline (IV) in 71% yield.



Although the application of the Stork procedure to α-halo ketones has not been described previously, two of these substances, α-bromoacetone and phenacyl bromide, reacted smoothly with the pyrrolidine enamine of cyclohexanone to give the C-alkylated products, α-(2-oxocyclohexyl)-acetone (Va) and α-(2-oxocyclohexyl)-acetophenone (Vb) in 40 and 55% yields, respectively. The yield of Va showed a considerable dependence on the choice of solvent. Thus, the yields of Va obtained in boiling methanol, benzene, dioxane and toluene were 0, 9, 19 and 40%, respectively. Although these results appear to indicate a dependence on the temperature at which the reaction is run, the polarity of the solvent may be of some importance as well. An attempt to substitute the ethylene acetal of bromoacetone for the free ketone gave none of the desired alkylation product.

It is interesting to note that the only simple diketone of this series previously described was Va, which had been prepared by a more conventional route by Ebel, Huber and Brunner[14] in something less than 3% yield. They had prepared Va as a starting material for the preparation of 2-methyl-4,5,6,7-tetrahydrobenzo[b]furan (VII), although their subsequent efforts in this direction were unsuccessful. In the present work when the hydrolysis of the intermediate pyrrolidinium bromide was carried out in more concentrated acid solution than

(1) Paper IV, THIS JOURNAL, **80**, 1981 (1958).

(2) This work was supported in part by grant G-1090 of the National Science Foundation.

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(4) T. L. Jacobs in R. C. Elderfield's, "Heterocyclic Compounds," Vol. 6, John Wiley and Sons, Inc., New York, N. Y., 1957, Chap. 4.

(5) C. F. H. Allen and J. A. VanAllan, THIS JOURNAL, **73**, 5850 (1951).

(6) G. Stork, R. Terrell and J. Szmuszkovicz, *ibid.*, **76**, 2029 (1954).

(7) G. Stork and H. K. Landesman, *ibid.*, **78**, 5128 (1956).

(8) R. H. Horning and E. D. Amstutz, *J. Org. Chem.*, **20**, 707 (1955).

(9) C. Chuang and C. Mai, *Ber.*, **68B**, 871 (1935); *cf.* R. Ghosh, *J. Indian Chem. Soc.*, **12**, 601 (1935); N. Chatterjee, *ibid.*, **12**, 591 (1935).

(10) Chuang and Mai reported a 26% yield. The slightly higher yield was obtained by substituting sodium hydride for sodium ethoxide in the alkylation of ethyl 2-carbethoxycyclohexanone. Benzene was used as the reaction solvent.

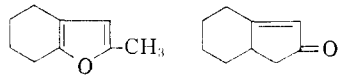
(11) The Stork procedure was also more rapid and more adaptable to large scale runs.

(12) Numerous attempts were made to dehydrogenate II to 3-cinnolinol (using palladium, palladium-on-charcoal in the presence and absence of various diluents, palladium-on-charcoal plus maleic acid, sulfur, selenium, N-bromosuccinimide and chloranil) without success.

(13) If *aged* phosphorus oxychloride was used, the starting material dissolved and formed a complex with the reagent as observed in successful reactions, but on neutralization the starting material was recovered almost quantitatively. These observations are interesting contrast to those of H. E. Baumgarten (THIS JOURNAL, **77**, 5109 (1955)) and A. R. Osborn, K. Schofield and L. N. Short (*J. Chem. Soc.*, 4191 (1956)), who found *aged* phosphorus oxychloride to be necessary to effect similar reactions.

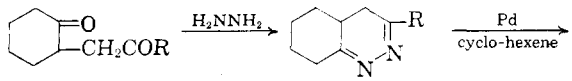
(14) F. Ebel, F. Huber and A. Brunner, *Helv. Chim. Acta*, **12**, 16 (1929).

that found to be the optimum for the preparation of Va, a neutral by-product was isolated in yields of up to 29%. In acid solution Va could be expected to undergo two significantly different reactions. One would be an intramolecular aldol condensation and cyclization giving bicyclo[4.3.0]non-6-en-8-one (VI). The other would be the formation of the furan VII sought by Ebel, Huber and Brunner.[14] Both products are known, having been prepared by other routes.[15,16] Comparison of the physical data for the hydrolysis product and its maleic anhydride adduct with those of VI and VII indicated it to be the furan VII. The infrared spectrum of the hydrolysis product supported the identification.



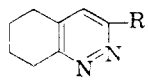
VI VII

Treatment of the 1,4-diketones with hydrazine in ethanol solution apparently gave the hexahydrocinnolines (VIII) but these were unstable in air and did not form simple stable derivatives. Aromatization of the crude VIII by hydrogen exchange with cyclohexene in the presence of palladium-on-charcoal[17] gave 3-methyl-(IXa) and 3-phenyl-5,6,7,-



Va, R = CH_3
Vb, R = C_6H_5

VIII

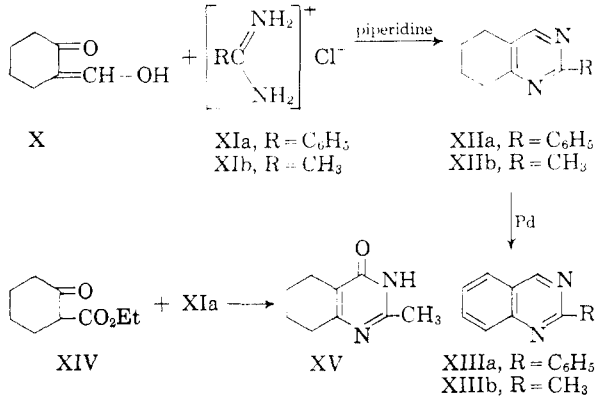


IXa, R = CH_3
IXb, R = C_6H_5

8-tetrahydrocinnoline (IXb) in 56 and 88% yields, respectively.[18]

Mitter and Bhattacharya[19] have described a synthesis of bz-tetrahydroquinazolines involving in the examples of interest here the condensation of hydroxymethylenecyclohexanone (X) or 2-carbethoxycyclohexanone (XIV) with an amidine XI. We have confirmed their yield of 48% of 2-phenyl-5,6,-7,8-tetrahydroquinazoline (XIIa) obtained from X and benzamidine hydrochloride (XIa) and have extended the reaction to acetamidine hydrochloride (XIb), which gave 2-methyl-5,6,7,8-tetrahydroquinazoline (XIIb) in 23–43% yield. The reaction of XIV with acetamidine hydrochloride gave 2-methyl-5,6,7,8-tetrahydro-4-quinazolinol (XV) in 54% yield.

Several procedures for the dehydrogenation of XIIa were examined. The best results were obtained by heating XIIa at *ca.* 300° with palladium-on-charcoal, whereby 2-phenylquinazoline (XIIIa) was formed in 80% yield. The over-all yield of



X

XIa, R = C_6H_5
XIb, R = CH_3

XIIa, R = C_6H_5
XIIb, R = CH_3

XIV XV

XIIIa, R = C_6H_5
XIIIb, R = CH_3

XIIIa (38%) compares favorably with those reported previously for this compound.[20,21] Attempts to dehydrogenate XIIb by this same procedure were not successful. Although nearly the theoretical amount of hydrogen was evolved, no satisfactory yield of 2-methylquinazoline could be isolated from the crude product.

Experimental[22]

Cyclohexanonepyrrolidine enamine was prepared by a procedure similar to that used by Heyl and Herr[23] for the preparation of some steroidal pyrrolidine enamines. A mixture of 98 g. (1 mole) of cyclohexanone, 119 g. (1.67 moles) of technical pyrrolidine and 200 ml. of dry benzene was heated under reflux in an apparatus fitted with a moisture trap as long as water collected in the trap (about 4 hr.). The benzene and excess pyrrolidine were removed by distillation at atmospheric pressure. The distillate could be used as part of the starting material in subsequent preparations. The residue was distilled through a 15-cm. Vigreux column under reduced pressure, and the fraction boiling at 69–74° (0.10 mm.), 127–128° (30 mm.), was collected as the pyrrolidine enamine of cyclohexanone. The average yield was 140 g. (92%). The material was sufficiently pure for use in the following preparations.

Ethyl 2-Oxocyclohexylacetate (I).—To a solution of 116 g. (0.768 mole) of the pyrrolidine enamine of cyclohexanone in 200 ml. of absolute methanol, stirred and heated under reflux, 193 g. (1.5 × 0.768 mole) of ethyl bromoacetate was added dropwise over a period of 0.75 hr. Heating and stirring were continued for 2 hr.; then 100 ml. of water was added through the reflux condenser and heating was continued for another 2 hr., after which time 150 ml. of methanol was removed by distillation. After cooling the mixture in an ice-bath, another 100 ml. of water was added and the resultant mixture was extracted with three 100-ml. portions of ether. (At this point the *p*H of the aqueous layer was 2.) The combined ether extracts were dried over anhydrous magnesium sulfate, filtered and distilled through a 15-cm. Vigreux column. After a sizeable forerun consisting mainly of ethyl bromoacetate, the pressure was lowered and the fraction boiling from 95–101° (1.5 mm.) (lit.[9] b.p. 130° (10 mm.)), 81.4 g. (58%), was collected. When one equivalent of ethyl bromoacetate was used per equivalent of the pyrrolidine enamine of cyclohexanone, only 40% of the product was obtained.

5,6,7,8-Tetrahydro-3-cinnolinol (II).—4,4a,5,6,7,8-Hexahydro-3-cinnolinol was prepared and aromatized essentially as described by Horning and Amstutz.[8] However, the details of the aromatization procedure were taken from a preparation of pyridazones by Overend and Wiggins.[24] This procedure gave an essentially quantitative yield (measured 101%) of 5,6,7,8-tetrahydro-3-cinnolinol hydrobromide, m.p. 193–197° dec. (lit.[8] m.p. 193–199° dec., yield 82%).

(15) T. Morel and P. E. Verkade, *Rec. trav. chim.*, **70**, 35 (1951).
(16) A. M. Islam and R. A. Raphael, *J. Chem. Soc.*, 4086 (1952).
(17) C. G. Overberger, N. R. Byrd and R. B. Mesrobian, THIS JOURNAL, **78**, 1964 (1956).
(18) During aromatization the completely reduced decahydrocinnolines may have been formed[17]; however, they have not been isolated.
(19) P. C. Mitter and A. Bhattacharya, *Quart. J. Indian Chem. Soc.*, **4**, 149 (1927).
(20) A. Bischler and M. Lang, *Ber.*, **28**, 279 (1895).
(21) M. T. Bogert and F. P. Nabenhauer, THIS JOURNAL, **46**, 1932 (1924).
(22) Melting points are corrected; boiling points are uncorrected. Analyses by Micro-Tech Laboratories, Skokie, Ill.
(23) F. W. Heyl and M. E. Herr, THIS JOURNAL, **75**, 1919 (1953).
(24) W. G. Overend and L. F. Wiggins, *J. Chem. Soc.*, 3508 (1950).

The free base, 5,6,7,8-tetrahydro-3-cinnolinol, was recovered by neutralization of the salt with sodium acetate[24] and was recrystallized from hot water (charcoal), giving over-all yields of 67–70% of thick, colorless rods, m.p. 192–194° (lit.[8] m.p. 192–194°, yield unspecified), in reactions on a 0.1-mole scale. One run on a larger scale (0.44 mole) gave a 51% yield. Repeated recrystallization from water raised the melting point to 194.5–196.5°.

The general procedure of Steck, Brundage and Fletcher[25] could also be used and was somewhat more convenient, but it gave lower yields (40%) of the product.

3-Chloro-5,6,7,8-tetrahydrocinnoline (III) was prepared by a procedure similar to that used by Horning and Amstutz[8] except that about one-half as much *fresh* phosphorus oxychloride[13] per equivalent of 5,6,7,8-tetrahydro-3-cinnolinol (5 ml./g.) was used and the excess phosphorus oxychloride was removed by distillation under reduced pressure before adding the crude product to crushed ice. On distillation of the crude product through a 15-in. Vigreux column, 3-chloro-5,6,7,8-tetrahydrocinnoline was obtained in 83% yield as a colorless liquid, b.p. 123–127° (0.5 mm.) (lit.[8] b.p. 135–137° (2 mm.), 65% yield). On standing the oil crystallized and, after one recrystallization from Skellysolve B,[26] the product was obtained as colorless needles, m.p. 29–29.5°.

Anal. Calcd. for $C_8H_9N_2Cl$: C, 56.98; H, 5.38; N, 16.62. Found: C, 56.85; H, 5.43; N, 16.90.

3-Methoxy-5,6,7,8-tetrahydrocinnoline (IV).—A solution of 10.0 g. (0.059 mole) of 3-chloro-5,6,7,8-tetrahydrocinnoline in 25 ml. of anhydrous methanol was added rapidly (5 min.) to a refluxing solution of 6.8 g. (5 × 0.059 mole) of sodium metal in 100 ml. of anhydrous methanol. Sodium chloride began to precipitate almost immediately, but refluxing was continued for 5 hr. to ensure a complete reaction. Water (25 ml.) was added to the cooled mixture to hydrolyze the excess sodium methoxide, the sodium chloride was removed by filtration, and the methanol was evaporated under reduced pressure. The residue was diluted with 75 ml. of water and was extracted with four 50-ml. portions of ether. After washing the ether extracts with 25 ml. of water, drying the solution (magnesium sulfate) and evaporating the solvent, the residue was distilled through a 15-cm. Vigreux column, giving 6.9 g. (71%) of 3-methoxy-5,6,7,8-tetrahydrocinnoline, b.p. 94–98° (0.4 mm.). The product solidified on standing in the refrigerator and, after one recrystallization from Skellysolve B,[26] was obtained as colorless needles, m.p. 17–18°.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.35; H, 7.24; N, 17.68.

In a similar reaction 3-chloro-5,6,7,8-tetrahydrocinnoline hydrochloride was treated with five equivalents of sodium methoxide from which 73% of crude 3-methoxy-5,6,7,8-tetrahydrocinnoline was isolated as the hydrochloride, m.p. 187–192°. This hydrochloride was purified with difficulty and gave no cleanly defined analytical sample. It is not recommended as a derivative.

The picrate of the product formed yellow needles from ethanol, m.p. 161–163°.

Anal. Calcd. for $C_{15}H_{15}N_5O_8$: C, 45.80; H, 3.84; N, 17.81. Found: C, 45.86; H, 3.71; N, 18.24.

α-(2-Oxocyclohexyl)-acetone (Va).—To a solution of 38.1 g. (0.25 mole) of the pyrrolidine enamine of cyclohexanone[23] in 100 ml. of dry toluene, stirred and heated to reflux, was added a solution of 34.3 g. (0.25 mole) of bromoacetone[27] in 50 ml. of dry toluene over a period of 30 min. Stirring and heating were continued for another 2 hr., after which time a two-phase reaction mixture was obtained. Following the addition of 100 ml. of water, heating and stirring were continued for an additional 3 hr. The mixture was steam distilled and 500 ml. of distillate was collected. The toluene layer (distillate) was separated and the aqueous phase was extracted with three 100-ml. portions of ether. After drying the combined organic layers (magnesium sulfate) and distilling the solvents under reduced pressure, the residue was distilled through a 15-cm. Vigreux column. A total of 15.3 g. (40%) of α-(2-oxocyclohexyl)-acetone was obtained as a fragrant, pale yellow oil, b.p. 64–75° (0.10 mm.) (lit.[14] b.p. 112°, pressure unspecified). After distillation through a 2-ft. Podbielniak column,[28] the diketone was obtained as a colorless liquid, b.p. 91–93° (1.1 mm.), $n^{25}D$ 1.4655.

The bis-2,4-dinitrophenylhydrazone[29] formed fine needles from methanol–chloroform, m.p. 209.5–211° dec.

Anal. Calcd. for $C_{21}H_{22}N_8O_8$: C, 49.03; H, 4.31; N, 21.78. Found: C, 48.69; H, 4.38; N, 21.74.

The compound gave a solid oxime (m.p. 133–135°) and semicarbazone (m.p. 195–199°), but these were not characterized.

2-Methyl-4,5,6,7-tetrahydrobenzo[b]furan (VI).—When 100 ml. of 10% sulfuric acid was added to the enamine intermediate in preparation of Va instead of the 100 ml. of water specified and the hydrolysis was conducted as described above, 9.8 g. (29%) of 2-methyl-4,5,6,7-tetrahydrobenzo[b]-furan, b.p. 36–41° (0.20 mm.), and 3.3 g. (9%) of α-(2-oxocyclohexyl)-acetone, b.p. 78–80° (0.20 mm.), were obtained. The furan obtained from two such reactions was combined and redistilled through a 30-plate, spinning band column, giving a colorless liquid with a pungent, naphthalene-like odor, b.p. 80–81° (20 mm.) (lit.[15] b.p. 77–79° (17 mm.)), $n^{25}D$ 1.4896, d^{20}_4 0.990. A microdetermination of the boiling point indicated a value of about 185–190°.

Anal. Calcd. for $C_9H_{12}O$: C, 79.43; H, 8.89. Found: C, 79.03; H, 8.82.

The maleic anhydride adduct was prepared in 50% yield by adding a benzene solution of the furan to a benzene solution of maleic anhydride. The adduct melted at 83–84° (lit.[15] m.p. 82.5–83°) after recrystallization from Skellysolve B.[26]

α-(2-Oxocyclohexyl)-acetophenone (Vb).—To a solution of 30.5 g. (0.20 mole) of the pyrrolidine enamine of cyclohexanone[23] in 100 ml. of dry toluene, stirred and heated to reflux, was added a solution of 39.8 g. (0.20 mole) of phenacyl bromide in 100 ml. of toluene over a period of 45 min. Stirring and heating were continued for another 2 hr. before adding 100 ml. of water to hydrolyze the enamine intermediate. The stirred, heterogeneous mixture was heated to reflux for 2 hr., then steam distilled to remove the toluene. The product, which was only slightly steam volatile, remained in the still-pot. The cooled aqueous reaction mixture was extracted with three 100-ml. portions of ether, the combined extracts were washed with water and dried over magnesium sulfate. After removing the spent drying agent and solvent, the residue was distilled through a 30-cm. Vigreux column, giving 21.9 g. (55%) of α-(2-oxocyclohexyl)-acetophenone, b.p. 149–151° (0.05 mm.), as a thick, pale yellow oil which crystallized on standing. The product was obtained as colorless prisms, m.p. 45–46°, on recrystallization from ether–petroleum ether (1:1).

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.75; H, 7.46. Found: C, 77.93; H, 7.37.

The bis-semicarbazone was obtained as colorless cubes from ethanol, m.p. 197.5–198.5° dec.

Anal. Calcd. for $C_{16}H_{22}N_6O_2$: C, 58.16; H, 6.71; N, 25.44. Found: C, 58.11; H, 6.70; N, 25.82.

The bis-2,4-dinitrophenylhydrazone[29] was obtained as fine, orange needles from methanol–chloroform, m.p. 234.5–236° dec.

Anal. Calcd. for $C_{26}H_{24}N_8O_8$: C, 54.16; H, 4.20; N, 19.44. Found: C, 53.61; H, 4.53; N, 19.15.

3-Methyl-5,6,7,8-tetrahydrocinnoline (XIIIa).—To a solution of 11.6 g. (0.075 mole) of α-(2-oxocyclohexyl)-acetone and 0.5 ml. of acetic acid in 50 ml. of methanol was added, in one lot, 5.9 g. (0.075 mole) of 64% hydrazine hydrate. The solution warmed noticeably and, after it had stood overnight at room temperature, the methanol was distilled under reduced pressure. The residue was dissolved in 50 ml. of cyclohexene, 0.25 g. of 10% palladium-on-charcoal was added and the mixture was heated under reflux for 24 hr.[30] The catalyst was removed and the cyclohexene was distilled under reduced pressure. The residue yielded 6.2 g.

(25) E. A. Steck, R. P. Brundage and L. T. Fletcher, THIS JOURNAL, **75**, 1117 (1953).

(26) A hydrocarbon solvent, b.p. 60–69°.

(27) P. A. Levene, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 88.

(28) J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice Hall, Inc., New York, N. Y., 1950, p. 237.

(29) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Thos. Y. Crowell Co., New York, N. Y., 1947, p. 247.

(30) Based on procedure found in ref. 17.

(56%) of 3-methyl-5,6,7,8-tetrahydrocinnoline, m.p. 53.5–54.5°, after several recrystallizations from Skellysolve B.[26]

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.94; H, 8.16; N, 18.90. Found: C, 73.06; H, 7.95; N, 18.91.

The picrate formed bright yellow needles from ethanol, m.p. 139.5–141.5°.

Anal. Calcd. for $C_{15}H_{15}N_5O_7$: C, 47.75; H, 4.01; N, 18.56. Found: C, 47.77; H, 4.27; N, 18.76.

Attempts to isolate 3-methyl-4,4a,5,6,7,8-hexahydrocinnoline from the ethanolic hydrazine–diketone reaction mixture yielded colorless needles on cooling, but the solid was not stable in air. In addition no stable picrate nor hydrochloride could be prepared. No attempt was made to isolate the decahydrocinnoline which was probably formed[17] along with the tetrahydrocinnoline during the dehydrogenation.

3-Phenyl-5,6,7,8-tetrahydrocinnoline (XIIIb).—The procedure was identical with that described for 3-methyl-5,6,7,8-tetrahydrocinnoline. The product was obtained in an 88% yield after recrystallization from Skellysolve B.[26] The 3-phenyl-5,6,7,8-tetrahydrocinnoline formed colorless leaflets, m.p. 86–87.5°.

Anal. Calcd. for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.32. Found: C, 80.26; H, 6.75; N, 12.97.

The picrate formed bright yellow leaflets from ethanol, m.p. 174–175° dec.

Anal. Calcd. for $C_{20}H_{17}N_5O_7$: C, 54.67; H, 3.90; N, 15.94. Found: C, 54.58; H, 3.97; N, 16.15.

2-Phenyl-5,6,7,8-tetrahydroquinazoline (XIIa) was prepared by the condensation of hydroxymethylenecyclohexanone[31] with benzamidine hydrochloride[32] in absolute ethanol using piperidine as a catalyst following the method of Mitter and Bhattacharya,[19] from which a 48% yield of the crude product was obtained. Although the product could be purified by careful recrystallization from dilute ethanol, a better product could be obtained by steam distillation. The compound was sparingly volatile with steam and, when the distillate was collected in a cooled receiver, fine white crystals, m.p. 52–53° (lit.[19] 52–53°), were obtained.

The hydrochloride, m.p. 175–177°, was formed by passing anhydrous hydrogen chloride into an ethereal solution of the base.

Anal. Calcd. for $C_{14}H_{14}N_2Cl$: C, 68.14; H, 6.13; N, 11.36. Found: C, 67.74; H, 6.10; N, 11.02.

In another experiment 7.0 g. (0.045 mole) of benzamidine hydrochloride was added in small portions with shaking to 100 ml. of an aqueous solution containing 5.6 g. (0.045 mole) of hydroxymethylenecyclohexanone as the sodium salt. After about 10 minutes small yellow crystals began to appear in the solution. After standing overnight the mixture was filtered and the crystals were washed with water and dried, giving 16 g. of yellow crystals, m.p. 153–155°. The crude product was insoluble in cold water, ether, ethanol and Cellosolve. It dissolved in all of these solvents at the boiling point, but chilling of the solutions yielded no solid product. The substance dissolved readily in dilute hydrochloric acid, but neutralization precipitated only an infusible, voluminous precipitate. A 2-g. portion of the yellow solid was heated under reflux for two hours with a solution of 1 ml. of piperidine in absolute ethanol. The white crystalline solid obtained by steam distillation of the residue left after removal of the alcohol melted at 51–53°, and its hydrochloride melted at 175–177°. Mixed melting points of these products with 2-phenyl-5,6,7,8-tetrahydroquinazoline and its hydrochloride, respectively, were not depressed. Steam distillation of 2.0 g. of the yellow solid without prior treatment gave no solid product. It was concluded from these observations that the yellow solid was an intermediate in the formation of 2-phenyl-5,6,7,8-tetrahydroquinazoline, but the nature of this intermediate was not determined.[33]

2-Phenylquinazoline (XIIIa).—A 1.0-g. sample of 2-phenyl-5,6,7,8-tetrahydroquinazoline was mixed with 0.5 g. of 10% palladium-on-charcoal and heated in an air-bath in an apparatus equipped to pass all evolved gases into an inverted buret filled with 50% potassium hydroxide solution. Carbon dioxide was passed through the apparatus to sweep out the gases. When the temperature reached 285°, hydrogen began to collect rapidly, 150 ml. being collected over a period of 45 min. The theoretical volume of hydrogen was 228 ml. The reaction mixture was cooled, and the solid cake that formed was broken up and dissolved in ether. Dry hydrogen chloride was passed into the filtered solution and the crude, brown hydrochloride, 1.0 g. (87%), m.p. 154–157°, was collected. The brown solid was dissolved in water, the solution was neutralized with dilute sodium hydroxide and the canary-yellow solid that formed was collected and recrystallized from dilute ethanol, giving 0.8 g. (80%) of 2-phenylquinazoline, m.p. 98–100° (lit.[20,21] m.p. 100–101°), as long, shining, greenish-white needles. The identity of the product was confirmed by oxidizing it in 65% yield with chromium trioxide in glacial acetic acid[20] to 2-phenyl-4-quinazolinol, m.p. 234–236° (lit.[20] m.p. 235–236°).

2-Methyl-5,6,7,8-tetrahydroquinazoline (XIIb).—A solution of 67.5 g. (0.535 mole) of hydroxymethylenecyclohexanone,[31] 60 g. (0.635 mole) of acetamidine hydrochloride (H. and S. Chemical Co.), 90 ml. (*ca.* 0.65 mole) of triethylamine and 300 ml. of ethanol was heated under reflux for 12 hr. The ethanol was removed by distillation and the solid residue was dissolved in a solution of 100 ml. of concentrated hydrochloric acid in 600 ml. of water. The acidic solution was extracted with three 100-ml. portions of ether and the ether was discarded. The aqueous solution was made strongly alkaline with 33% potassium hydroxide and was extracted with three 100-ml. portions of ether. The ethereal solution was dried over magnesium sulfate and distilled through the Podbielniak column,[28] giving 22.5 g. (29%) of 2-methyl-5,6,7,8-tetrahydroquinazoline, b.p. 112.5–113° (11.5 mm.), $n^{25}D$ 1.5273. The product had a strong, clinging, mouse-like odor. Other experiments gave yields of 23–43%.

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.93; H, 8.17; N, 18.91. Found: C, 72.68, 72.63; H, 8.20, 8.08; N, 18.80, 18.41.

2-Methyl-5,6,7,8-tetrahydro-4-quinazolinol (XV).—To a solution of 15 g. (0.28 mole) of sodium methoxide in 200 ml. of methanol was added 23.6 g. (0.25 mole) of acetamidine hydrochloride (H. and S. Chemical Co.). The precipitated sodium chloride was removed by filtration and washed with a small amount of methanol. To the combined filtrates was added 42.5 g. (0.25 mole) of 2-carbethoxycyclohexanone.[34] The solution turned pale yellow and warmed slightly. After the solution had stood overnight, it was evaporated to half volume, chilled in ice and filtered, giving 19 g. (46%) of crude 2-methyl-5,6,7,8-tetrahydro-4-quinazolinol. Evaporation of the filtrate to a small volume and dilution with water gave a solution which, after extraction with ether to remove oily by-products, formed a second crop of product, 8.5 g. (21%), on cooling in ice. The combined crude products were recrystallized from *ca.* 175 ml. of water (charcoal), forming long, colorless needles, 22 g. (54%), m.p. 207–208°, which turned chalk white on drying.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.82; H, 7.35; N, 17.66.

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(31) V. Prelog, L. Ruzicka and O. Metzler, *Helv. Chim. Acta*, **30**, 1885 (1947).

(32) A. W. Dox, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 5.

(33) Mitter and Bhattacharya[19] reported obtaining a crude supposed intermediate in the condensation of benzamidine hydrochloride with acetylcyclohexanone in the presence of potassium carbonate.

(34) H. R. Snyder, L. A. Brooks and S. H. Shapiro, ref. 27, p. 531.