melting point with the other acid fraction showed no depression. Rojahn[12] reports the melting point of 1-methyl-5-pyrazolecarboxylic acid as 222°.

The yield of acid melting at 223–224° from this metalation was 54%. The neutralization equivalent of the metalation acid was 127; the theoretical value for 1-methyl-5-pyrazolecarboxylic acid is 126.

KNOXVILLE, TENN.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER & CO.]

The Lithium–Amine Reduction of Derivatives of Isoquinoline and Quinoline. A Route to *trans*-Decahydroisoquinoline

BY ALLAN P. GRAY AND DONALD E. HEITMEIER

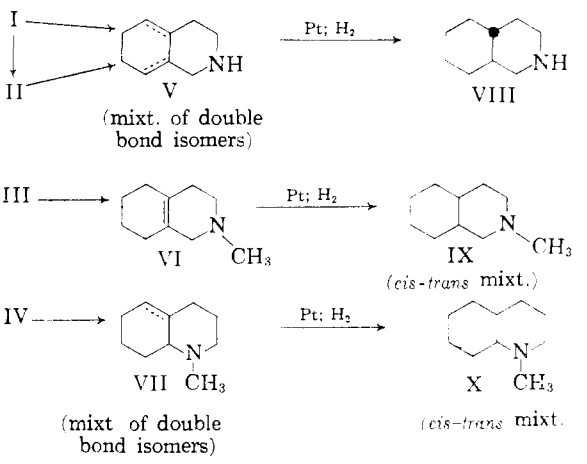
RECEIVED MAY 14, 1958

Isoquinoline, tetrahydro- and N-methyltetrahydro-isoquinoline, and N-methyltetrahydroquinoline have been reduced to octahydro derivatives by lithium in either propylamine or ethylenediamine. Subsequent catalytic hydrogenation afforded the corresponding decahydro bases. In this two-step process the N-methyl starting materials yielded mixtures of *cis* and *trans* fused decahydro isomers; however, relatively pure *trans*-decahydroisoquinoline was obtained from isoquinoline and from tetrahydroisoquinoline.

It is known to be difficult to effect catalytic hydrogenation of the isoquinoline nucleus beyond the tetrahydro stage.[1] Notably, Witkop[1] found it necessary to use one gram of platinum oxide catalyst and a medium of glacial acetic acid containing concentrated sulfuric acid in order to hydrogenate one gram of isoquinoline to a mixture containing predominantly *cis*-decahydroisoquinoline. A mixture in which the *trans* isomer predominated was obtained in excellent yield by the use of Raney nickel,[2] but the quite high temperatures and pressures required limit the usefulness of this method insofar as derivatives having labile substituents are concerned. Recently, the *amino acid*, tetrahydroisoquinoline-3-carboxylic acid, *but not its ethyl ester* (cf. footnote[1]), was reported to be smoothly reduced to the *cis*-decahydro derivative by a rhodium-on-alumina catalyst.[3] Bz-hydroisoquinolines have, however, most frequently been synthesized by methods involving ring closure.

Since the recently developed, lithium–primary amine reducing systems[4] have been found to reduce benzenoid rings readily to both the tetrahydro and hexahydro stage, it thus became of interest to examine their action on derivatives of isoquinoline and, for purposes of comparison, quinoline. The less powerful agent, sodium and liquid ammonia, entirely analogously to its effect on benzenoid systems, has been reported to yield py-dihydro derivatives as the primary products of the reduction of quinoline[5] and isoquinoline,[6] and to reduce N-methyl-6-methoxy-py-tetrahydroisoquinoline to a bz-dihydro derivative.[7]

Quite in accord with the results on carbocyclic substances,[4] lithium dissolving in *n*-propylamine smoothly converted isoquinoline (I), tetrahydro- (II) and N-methyltetrahydro-isoquinoline (III) and N-methyltetrahydroquinoline (IV) to octahydro derivatives V–VII. Ethylenediamine in



place of *n*-propylamine gave comparable results, but the propylamine reaction mixtures were found more convenient to work up. Except in the case of III, which afforded 61% of 2-methyl-1,2,3,4,5,6-7,8-octahydroisoquinoline (VI), the crude octahydro products apparently were mixtures of double bond isomers. Yields of these were reasonably good but were considerably diminished in abortive attempts at purification.

It is instructive to compare these reductions. Compounds I and II both provided approximately the same mixture of octahydroisoquinolines (V). This, and the finding of a small amount of tetrahydroisoquinoline among the products obtained from isoquinoline, support the reasonable assumption that reduction of I proceeds *via* II. Of particular interest is the fact that catalytic hydrogenation in glacial acetic acid smoothly reduced the mixture of octahydro isomers V to *trans*-

(1) B. Witkop, THIS JOURNAL, **70**, 2617 (1948). It is suggestive to note that: (1) this refractory behavior appears to be general for phenethylamines (see M. Freifelder and G. R. Stone, Abstracts of Papers, 133rd Meeting of the American Chemical Society, San Francisco, Calif., April 13–18, 1958, p. 1-M); and (2) acetylation of the nitrogen of a tetrahydroisoquinoline circumvents the difficulty (R. B. Woodward and W. E. Doering, THIS JOURNAL, **67**, 860 (1945)). Speculation as to an effect of transannular interaction between the basic nitrogen and the aromatic ring seems in order.

(2) B. Witkop, *ibid.*, **71**, 2559 (1949).

(3) R. T. Rapala, E. R. Lavagnino, E. R. Shepard and E. Farkas, *ibid.*, **79**, 3770 (1957). The authors mention, without elaboration, successful preliminary experiments on the hydrogenation of bz-substituted isoquinolines with this catalyst.

(4) R. A. Benkeser, R. E. Robinson, D. M. Sauve and O. H. Thomas, *ibid.*, **77**, 3230 (1955); L. Reggel, R. A. Friedel and I. Wender, *J. Org. Chem.*, **22**, 891 (1957).

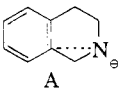
(5) W. Huckel and L. Hagedorn, *Chem. Ber.*, **90**, 752 (1957).

(6) W. Huckel and G. Graner, *ibid.*, **90**, 2017 (1957).

(7) A. Marchant and A. R. Pinder, *J. Chem. Soc.*, 327 (1956).

decahydroisoquinoline (VIII). Thus, this constitutes an attractive route to the *trans* isomer. The formation of VIII as the sole isolated product of the hydrogenation of V makes it plausible to suggest that the octahydroisoquinolines most likely to be present in V are the $\Delta^{5,10}$ and $\Delta^{8,9}$-isomers.[8] This is in accord with considerations regarding the course of the chemical reduction.[4,9]

In contrast, as already noted, reduction of the N-methyl derivative III led to VI as the only isolable product. This process, therefore, offers promise as a means to N-substituted $\Delta^{9,10}$-octahydroisoquinolines, compounds which are useful synthetic intermediates. Catalytic hydrogenation of VI yielded a mixture of the *cis* and *trans* isomers of N-methyldecahydroisoquinoline (also *cf.* ref. 8). The difference in the outcome of the lithium–amine reduction of III and of that of II (or I) would appear to indicate that the anion (A) is involved in the reduction of II, and influences its course.



A

Support for this is found in the observation that, although the N-methyl derivative IV was reduced to a mixture of N-methyloctahydroquinolines (VII), quinoline itself could not be reduced beyond the tetrahydro stage under the conditions used here (also *cf.* ref. 9). Although salt derivatives of VII were crystalline and sharp melting, the appearance of the infrared spectrum of VII·methiodide, particularly the broad, weak absorption in the 1600-1700 cm.$^{-1}$ (max. at about 1640 cm.$^{-1}$) double bond stretching region, suggests a mixture of C–C double bond isomers. The appearance of the spectrum in this region further indicates the virtual absence of absorption ascribable to a $>C{=}\overset{+}{N}<$ group. Therefore, the methiodide contained very little, if any, immonium salt and, accordingly, it is unlikely that there was very much enamine present in VII.[10] On this basis the $\Delta^{5,10}$-isomer is probably an important component of the mixture VII.

In a rough, qualitative way (*i.e.*, in terms of yield), the ease of reduction of these compounds with the lithium reagent appears to decrease in the expected[9] order: III > IV > II. Further extensions of this reduction are being explored.

Experimental[11]

Preparation of Intermediates.—Isoquinoline, Matheson, Coleman & Bell "Practical" grade, was used without purification. Tetrahydroisoquinoline and N-methyltetrahydroisoquinoline were prepared essentially as previously described.[12] N-Methyltetrahydroquinoline, b.p. 120–124° (16 mm.), n^{25}D 1.5800,[13] was obtained by the catalytic (Adams platinum oxide) hydrogenation of quinoline methobromide in ethanol.

Reduction of N-Methyltetrahydroisoquinoline (III).—Into a flask equipped with a mechanical stirrer and reflux condenser was introduced, under nitrogen, 700 ml. of *n*-propylamine followed by 17.0 g. (2.4 gram atoms) of lithium shot (previously washed with ether containing a small amount of ethanol) and 41.8 g. (0.28 mole) of III. The mixture was stirred at room temperature. After a period of about 15 minutes the propylamine began to reflux gently and the reaction mixture developed a milky green color. Refluxing ceased in 30 minutes but stirring was continued for an additional 4 hours. The solution was decanted from the excess lithium metal, which had clumped together, and treated with enough solid ammonium chloride (approximately 50 g.) to neutralize the lithium salts. (In more recent experiments it has been found more satisfactory to distil the decanted solution at atmospheric pressure until the lithium salt precipitate becomes copious, dilute the residual mixture with ether, and then to treat the ether solution with ammonium chloride. In this way more than half of the *n*-propylamine can be recovered.) The neutralized mixture was diluted with water and exhaustively extracted with ether. Drying and removal of the ether left an oil which was distilled to yield 26.4 g. (61%) of **2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (VI)**, b.p. 59–62° (2 mm.), n^{25}D 1.4975. The picrate, recrystallized from ethanol, showed m.p. 187–188° (lit.[14] reports b.p. 94° (10 mm.), n^{18}D 1.5009, picrate m.p. 187°).

Anal. Calcd. for $C_{10}H_{17}N$: N, 9.26. Found: N (basic), 8.88.

A solution of 25.0 g. (0.16 mole) of VI in 200 ml. of glacial acetic acid was shaken with 1.0 g. of platinum oxide in an Adams–Parr apparatus at room temperature and 50 p.s.i. One equivalent of hydrogen was absorbed in three hours, after which no further uptake was noted. The filtered solution was concentrated under reduced pressure and the residue was treated with 20% sodium hydroxide and extracted with ether. The organic layer was dried and distilled to yield 21.3 g. (84%) of **2-methyldecahydroisoquinoline (IX)**, b.p. 78° (8 mm.), n^{25}D 1.4788. An aqueous acid solution of IX did not decolorize a 2% potassium permanganate solution. The melting points of the hydrochloride salt (185–187°), picrate (215°) and picrolonate (207–208°) indicated IX to be a mixture of the *cis* and *trans* isomers.[15]

Anal. Calcd. for $C_{10}H_{19}N$: N, 9.14. Found: N (basic), 9.06.

Reduction of Tetrahydroisoquinoline (II). (a) **In *n*-Propylamine.**—To a slurry of 13.8 g. (2.0 gram atoms) of cleaned lithium shot in 450 ml. of *n*-propylanine, stirred under nitrogen, was added 30.0 g. (0.23 mole) of II in one portion. After approximately 20 minutes at room temperature, refluxing began and continued for 45 minutes. The dark reaction mixture was stirred for 3 hours and then refluxed on a steam-bath for an additional hour. Work-up essentially as before, fractional distillation and redistillation of the product afforded 10.1 g. of a basic oil, distilling over the range 90–105° (12 mm.), n^{25}D 1.5050–1.5265, apparently a mixture of isomeric **octahydroisoquinolines** (V). The fraction of highest refractive index possibly contained some unreacted II (n^{25}D 1.5618[12]). Fractions with indices of refraction above the given range were discarded after attempts at purification had failed.

(b) **In Ethylenediamine.**—A solution of 30.0 g. of II in 400 ml. of ethylenediamine was stirred under nitrogen and heated to 90° on a steam-bath. Over a period of 1.5 hours 12.7 g. (1.8 gram atoms) of clean lithium shot was added in small portions. The solvent began to reflux vigorously and the color of the reaction mixture went from yellow to blue to brown. Stirring and heating was continued for an additional 3 hours. The excess lithium was removed, the solution was treated with about 50 g. of ammonium chloride, diluted with water and exhaustively extracted with ether. Drying and removing of the ether left an oil. This was

(8) See R. L. Burwell, Jr., *Chem. Revs.*, **57**, 895 (1957), for an excellent review of the stereochemistry of catalytic hydrogenation.

(9) See A. J. Birch, *J. Chem. Soc.*, 430 (1944); *Quart. Revs.*, **4**, 69 (1950), for discussions of the sodium–ammonia reduction, which certainly involves qualitatively the same electronic processes; also see *ibid.*, **12**, 17 (1958).

(10) *Cf.* N. J. Leonard and V. W. Gash, THIS JOURNAL, **76**, 2781 (1954); N. J. Leonard, L. A. Miller and P. D. Thomas, *ibid.*, **78**, 3463 (1956); G. Stork, R. Terrell and J. Szmuszkovicz, *ibid.*, **76**, 2029 (1954).

(11) Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill. Melting points are corrected for stem exposure.

(12) A. P. Gray, W. L. Archer, D. C. Schlieper, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **77**, 3536 (1955).

(13) "Beilstein" gives b.p. 130–131° (17 mm.), n^{23}D 1.5802.

(14) R. Grewe, R. Hamann, G. Jacobsen, E. Nolte and K. Riecke, *Ann.*, **581**, 104 (1953).

(15) *Cf.* B. Witkop, references 1 and 2.

thrice distilled to give 7.4 g. of mixed **octahydroisoquinolines** (V) having properties comparable to those of the material obtained in propylamine, boiling range 85–100° (12 mm.), $n^{25}D$ 1.4980–1.5230.

The V mixtures obtained by both procedures were separately hydrogenated in glacial acetic acid over Adams platinum oxide. In each case one equivalent of hydrogen was absorbed and there was obtained 60–70% of ***trans*-decahydroisoquinoline (VIII)**, b.p. 84–87° (12 mm.), $n^{25}D$ 1.4897. The picrate showed m.p. 173–174°; the hydrochloride melted at 222–223° (Witkop[1] reports VIII picrate, m.p. 177°; hydrochloride, m.p. 224°).

Methylation of VIII by the Eschweiler–Clarke process provided **2-methyl-*trans*-decahydroisoquinoline**, b.p. 75–80° (9 mm.), $n^{25}D$ 1.4785. The picrate melted at 233–234°; the hydrochloride melted at 221–222°; the picrolonate showed m.p. 215–216° (*cf.* ref. 2).

Reduction of Isoquinoline (I).—A mixture of 33.0 g. (0.25 mole) of I, 20.1 g. (2.9 gram atoms) of clean lithium shot and 450 ml. of *n*-propylamine was stirred at room temperature under nitrogen. Within 30 minutes the solvent began to reflux and the reaction mixture turned red and then, gradually, milky green. Refluxing continued for approximately 2 hours. The reaction mixture was stirred at room temperature for an additional 2 hours and then refluxed for 2 hours on the steam-bath. The product was worked up as before and twice distilled to give 7.4 g. of a crude **octahydroisoquinoline** (V) fraction similar to those obtained from II, boiling range 80–100° (12 mm.), $n^{25}D$ 1.5170–1.5270.

Redistillation of a higher boiling fraction afforded 2 g. of not quite pure II, b.p. 107–111° (12 mm.), identified *via* its hydrochloride salt (*cf.* ref. 12).

Hydrogenation of the V material obtained from I gave, as before, ***trans*-decahydroisoquinoline** (VIII).

Reduction of N-Methyltetrahydroquinoline (IV).—A mixture of 24.0 g. (0.16 mole) of IV, 8.9 g. (1.3 gram atoms) of lithium shot and 400 ml. of *n*-propylamine was stirred for 6 hours without external source of heat and then refluxed for 1 hour; IV reacted much less vigorously than III. The pale green reaction mixture was worked up as before to yield 12.2 g. (50%) of what was apparently a mixture of **1-methyloctahydroquinolines** (VII), boiling range 97–106° (13 mm.), $n^{25}D$ 1.5168–1.5240. The picrate, recrystallized from ethanol, melted at 126–127° (*cf.* Leonard, Miller and Thomas[10]).

Anal. Calcd. for $C_{10}H_{17}N$: N, 9.26. Found: N (basic), 9.42.

VII. Methiodide, prepared in ether and recrystallized from ethanol, showed m.p. 200–201°. The infrared spectrum[16] of this salt exhibited a diffuse, weak absorption band in the 1600–1700 cm.$^{-1}$ region, maximum centered at about 1640 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{20}IN$: C, 45.06; H, 6.87. Found: C, 44.92; H, 6.84.

Compound VII, hydrogenated in acetic acid solution over Adams catalyst, absorbed 1 equivalent of hydrogen to give 63% of a mixture of the *cis* and *trans* isomers of **1-methyldecahydroquinoline** (X), b.p. 79–81° (10 mm.), $n^{25}D$ 1.4815. The picrate melted at 183–184°; the picrolonate at 196–198°; the hydrochloride melted over the range 170–210°; the methiodide showed m.p. 258°.[17]

Anal. Calcd. for $C_{10}H_{19}N$: C, 78.37; H, 12.50; N, 9.14. Found: C, 78.52; H, 12.36; N (basic), 9.16.

ADDED IN PROOF.—It already has been noted briefly (*vide supra*) that tetrahydroquinoline apparently was not reduced by the lithium–amine system, and that tetrahydroisoquinoline was more difficult to reduce and gave different products than its N-methyl derivative. These observations were taken to indicate that the N–H compounds underwent proton loss in the strongly basic reaction medium. In each case the resulting anion, the negative charge of which would be in resonance with the aromatic ring, was presumed to be the species being acted upon by the reagent. A similar interpretation recently has been advanced by R. A. Benkeser and R. F. Lambert, who studied the reduction of substituted anilines [Abstracts of Papers, 134th Meeting of the American Chemical Society, Chicago, Illinois, Sept. 7–12, 1958, p. 80-P].

Acknowledgment.—The authors wish to thank Mr. D. F. Cortright for the basic nitrogen analyses.

(16) Sadtler Laboratories, Philadelphia, Pa.

(17) *Cf.* Leonard, Miller and Thomas,[10] and references cited therein.

DECATUR, ILL.

[CONTRIBUTION NO. 19 FROM THE L. G. RYAN RESEARCH LABORATORIES OF MONSANTO CANADA LTD.]

Amino Nitriles. I. Cyclization of α-Cyanoalkylureas

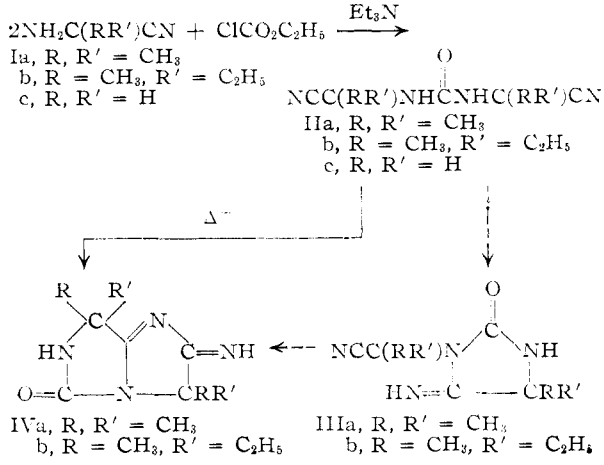
BY A. F. MCKAY, G. Y. PARIS AND D. L. GARMAISE

RECEIVED JUNE 19, 1958

A novel cyclization reaction is described which provides a method for preparing derivatives of the new heterocyclic ring system 7(H)-imidaz[3,4-a]imidazole. The evidence for the structure of this bicyclic system is presented together with a description of the reactions of symmetrical and unsymmetrical α-cyanoalkylurea derivatives.

The cyclization of certain 1,3-bis-(α-cyanoalkyl)-urea derivatives to a bicyclic ring system was observed during a recent study of the chemistry of amino nitriles. This reaction gives substituted 2-imino-5-oxo-2,3,5,6-tetrahydro-7(H)-imidaz[3,4-a]-imidazoles (IV). In addition, some of the 1-(β-cyanoethyl)-3-(α-cyanoalkyl)-ureas were cyclized to substituted 4-imino-2-imidazolidones. α-Cyanoalkylureas have been employed[1,2] for a long time in the synthesis of hydantoins, and Herbst and Johnson[3] demonstrated that 4-imino-2-imidazolidones (or the tautomeric 2-amino-2-imidazolones) were intermediates in their formation.

α-Aminoisobutyronitrile (Ia) combined with ethyl chloroformate in the presence of triethylamine to give a good yield (80%) of 1,3-bis-(α-cyanoiso-



(1) F. Urech, *Ann.*, **164**, 255 (1872).

(2) R. M. Herbst and T. B. Johnson, THIS JOURNAL, **54**, 2463 (1932).

(3) R. M. Herbst and T. B. Johnson, *ibid.*, **52**, 3676 (1930).