**6-*o*-Carboxyphenylthiopurine (Method D).**—A mixture of 5.35 g. (38.8 mmoles) of anhydrous potassium carbonate and 3.30 g. of *o*-mercaptobenzoic acid (Eastman technical grade) in 20 ml. of dimethylformamide was stirred mechanically for 5 minutes. 6-Chloropurine (3.00 g., 19.4 mmoles) then was added, and when no temperature rise occurred during 15 minutes of vigorous stirring, the mixture was heated at 40–50° in a warm water-bath for an hour. The resulting thin suspension was poured into 120 ml. of water, and the clear solution was partially neutralized with 5 ml. of concentrated hydrochloric acid. The *p*H now was adjusted to 3 with 1 *N* hydrochloric acid. The tan solid that precipitated was collected by filtration, washed thoroughly with water and dried *in vacuo* over phosphorus pentoxide at 61°; yield 5.15 g. (97.5%), m.p. 235–237°. This material was twice precipitated from 1 *N* sodium hydroxide solution with 1 *N* hydrochloric acid; recovery, 4.12 g. of light tan solid, m.p. 238–239°.

**9-Benzyl-6-benzylthiopurine.**—α-Chlorotoluene (0.12 ml., 1.03 mmoles) was added to a well-stirred mixture of 250 mg. (1.03 mmoles) of 9-benzyl-6-mercaptopurine,[11] 137 mg. (1.03 mmoles) of anhydrous potassium carbonate and 3 ml. of dimethylformamide. The mixture was stirred at room temperature (23–25°) for 15 minutes and then heated between 40 and 53° for about 30 minutes. Then the mixture was cooled and poured into 25 ml. of water: a tan solid precipitated. The resulting mixture (*p*H 8–9) was cooled in an ice–water-bath and the solid was collected, washed with water and dried *in vacuo* over phosphorus pentoxide at room temperature; yield 308 mg. of a tan powder (90%), m.p. 108° with softening from 102°. Recrystallization of *ca.* 295 mg. from *ca.* 20 ml. of cyclohexane gave 240 mg. of matted white needles after drying *in vacuo* at room temperature; m.p., needles fused at 100° forming a solid that melted at 108°; spectral data: $\lambda_{max}$ in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 295 (18.9); *p*H 7, 289 (shoulder), 294 (20.4); *p*H 13, 289 (shoulder), 294 (20.5); EtOH, 286 (21.3), 290 (shoulder). *Anal.* Calcd. for $C_{19}H_{16}N_4S$: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.49; H, 4.84; N, 16.81 (Dumas).

**7-Benzyl-6-benzylthiopurine** was prepared from 74 mg. of 7-benzyl-6-mercaptopurine ($C_{12}H_{10}N_4S \cdot {}^1/_4H_2O$)[11] in a manner similar to that described for the 9-isomer above; the reaction mixture was heated at 50° for one hour; yield 91 mg. (91%) of a tan powder, m.p. *ca.* 120°. Recrystallization from *ca.* 20 ml. of cyclohexane gave 51 mg. of near-white fine matted needles (dried *in vacuo* at 61°), m.p. 120° with collapse of crystal structure at 118° forming an opaque melt; spectral data: $\lambda_{max}$ in mμ ($\epsilon \times 10^{-3}$): *p*H 1, 305 (13.1); *p*H 7, 252–254 (5.34), 297–301 plateau, 13.8); *p*H 13, 252–254 (5.31), 297–301 (plateau, 13.7); EtOH, 295 (14.9), 299 (shoulder). *Anal.* Calcd. for $C_{19}H_{16}N_4S$: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.56; H, 4.81; N, 16.26 (Kjeldahl).

BIRMINGHAM, ALA.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

# The Metalation of 1-Phenyl- and 1-Methylpyrazole with *n*-Butyllithium

BY PEGGY W. ALLEY AND DAVID A. SHIRLEY

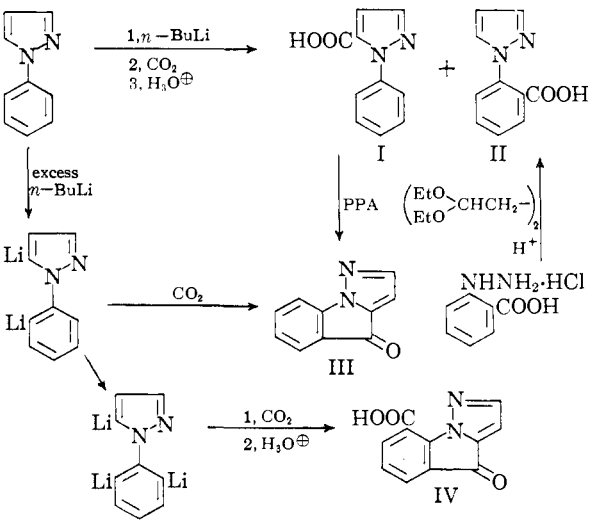
RECEIVED JULY 18, 1958

1-Phenylpyrazole is monometalated in 80% yield. Substitution occurs in the 5-position and in the *o*-position of the phenyl group in a ratio of about 4:1, as shown by reaction of the organolithium compound with carbon dioxide. Treatment of 1-phenylpyrazole with excess *n*-butyllithium gave dimetalation (8%) and trimetalation (26%) as indicated by the formation, upon carbonation, of the cyclic ketone 4-oxopyrazolo[1,5-a]indoline and a monocarboxylic acid derivative of the ketone. 1-Methylpyrazole is metalated in the 5-position with *n*-butyllithium in 54% yield.

The metalation reaction of simple N-substituted pyrazoles with *n*-butyllithium was undertaken to find the position of attack of the metalating agent. Electrophilic substitution of the pyrazole ring occurs predominantly in the 4-position.[1] It is well established[2] that metalation occurs at positions adjacent to heteroatoms. Two such positions (the 3- and 5-positions) are present in the pyrazole nucleus, and it was of interest to determine the points of attack by *n*-butyllithium in the pyrazole ring.

There are few reported examples of metalation of monocyclic systems containing two hetero atoms. These are the metalation of thiazole[3] and 4,5-dimethylthiazole[4] in the 2-position with phenyllithium, the metalation of 1-phenyl-3-methylpyrazole[5] in the 5-position with *n*-butyllithium and the metalation of 1-methyl-, 1-benzyl- and 1-phenylimidazole[6] in the 2-position with *n*-butyllithium.

The metalation of 1-phenylpyrazole with an equivalent of *n*-butyllithium followed by reaction with carbon dioxide gave in 80% yield a mixture of monocarboxylic acid derivatives. The acid mixture gave upon fractional crystallization from water two pure acids, m.p. 185–186.5° (39% yield) and m.p. 140–142° (10%). All possible monocarboxylic acid derivatives of 1-phenylpyrazole are known with the exception of 1-(*m*-carboxyphenyl)-pyrazole. 1-Phenyl-5-pyrazolecarboxylic acid (I) is reported to melt at 183°[7] and 185–186°[8] and none




(1) T. L. Jacobs in R. C. Elderfield, editor, "Heterocyclic Compounds," Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 45–161.

(2) Henry Gilman and J. W. Morton, *Org. Reactions*, **8**, 258 (1954).

(3) J. Metzger and B. Koether, *Bull. soc. chim. France*, 702 (1953).

(4) M. Erne and H. Erlenmeyer, *Helv. Chim. Acta*, **31**, 652 (1948).

(5) H. R. Snyder, F. Verbanac and D. B. Bright, THIS JOURNAL, **74**, 3246 (1952).

(6) D. A. Shirley and P. W. Alley, *ibid.*, **79**, 4922 (1957).

(7) L. Claisen, *Ann.*, **278**, 261 (1894).

(8) C. Ainsworth and R. G. Jones, THIS JOURNAL, **76**, 3173 (1954).

of the other known isomers melts near this temperature. The methyl ester of the higher melting acid melted at 63–64°, and the methyl ester of the 1-phenyl-5-pyrazolecarboxylic acid is reported[7] to melt at 67°. The conversion of the carboxylic acid I into the cyclic ketone III (4-oxopyrazolo-[1,5-a]indoline) with polyphosphoric acid in conjunction with the synthesis of 1-(*o*-carboxyphenyl)-pyrazole (see above) established conclusively the structure of I as 1-phenyl-5-pyrazolecarboxylic acid.

The second monocarboxylic acid, m.p. 140–142°, was indicated by its melting point to be either 1-phenyl-3-pyrazolecarboxylic acid, reported to melt at 146°[7] and 142–143°,[5] or 1-(*o*-carboxyphenyl)-pyrazole, m.p. 138.5–139°.[9] The latter compound (III) was synthesized from *o*-carboxyphenylhydrazine hydrochloride and 1,1,3,3-tetraethoxypropane. Comparison of the synthetic acid and its hydrazide with the metalation acid and its hydrazide *via* melting points and mixed melting points demonstrated the structure II for the second metalation acid.

Apparently the 3-position of the pyrazole ring is not involved in the metalation. 1-Phenyl-3-pyrazolecarboxylic acid should form a chelate ring compound of low solubility with Cu(II) ion as observed with the corresponding imidazole derivative.[6] We tested the mother liquors from separation of I and II with Cu(II) ion and failed to obtain evidence for chelate ring formation.

Metalation of 1-phenylpyrazole with slightly more than a twofold excess of *n*-butyllithium followed by carbonation yielded two products. The first was a bright yellow neutral ketone, formed in 8% yield, which was shown to be 4-oxopyrazolo-[1,5-a]indoline (III) by elemental analyses and identity of the infrared spectrum with that of the compound obtained by the action of polyphosphoric acid on 1-phenyl-5-pyrazolecarboxylic acid. The formation of the ketone III occurred *via* dimetalation of 1-phenylpyrazole. Similar cyclic ketones have been isolated from dimetalation of 1-phenylindole,[10] 1-phenylpyrrole[11] and 1-phenylimidazole.[6]

The second product from metalation of 1-phenylpyrazole with excess *n*-butyllithium was a bright yellow acidic ketone. This had the composition and neutralization equivalent for a carboxylic acid derivative of the cyclic ketone III. This product (IV) was isolated in 26% yield and represents an unusual and perhaps unique example of *trimetalation* of a simple aromatic system. We have tentatively assigned the carboxylic group to the 8-position, but no structural proof has been obtained. This assignment is based on: (1) the failure to observe 3-position metalation on 1-phenylpyrazole, (2) the observed metalation of 1-phenylpyrazole in the *o*-position on the phenyl ring and (3) the quite general tendency of metalation to occur at positions adjacent to a heteroatom. The infrared spectrum of the acid showed a strong absorption at 13.28 $\mu$ which is just above the 13.0–13.2 $\mu$ range commonly designated for 1,2,3-trisubstitution on a benzene ring.

The metalation of 1-methylpyrazole with one equivalent of *n*-butyllithium and then carbonation gave a single monocarboxylic acid, m.p. 223–224°, in 54% yield. 1-Methyl-5-pyrazolecarboxylic acid has been prepared by Rojahn[12] and reported to melt at 222°. 1-Methyl-3-pyrazolecarboxylic acid has been reported[13] to melt at 222°, but later work has indicated that the acid was quite likely the 5-carboxylic acid and not the 3-acid.[14] 1-Methyl-3-pyrazolecarboxylic acid apparently has never been prepared. In view of the tendency of 1-phenylpyrazole to metalate in the 5-position, and the correspondence in melting point of the acid from the metalation with the known 1-methyl-5-pyrazolecarboxylic acid, we are assigning the position of metalation of 1-methylpyrazole as the 5-position.

**Acknowledgment.**—We wish to acknowledge the financial support of the Eli Lilly Co. in the form of a research fellowship under which this work was carried out.

## Experimental[15]

1-Methyl- and 1-phenylpyrazole were prepared by the condensation of 1,1,3,3-tetraethoxypropane with methylhydrazine and phenylhydrazine, respectively. The procedure used is similar to one by Jones[16] for the preparation of pyrazole. 1-Methylpyrazole was obtained in 83% yield and 1-phenylpyrazole in 64% yield by this method.

**Metalation of 1-Phenylpyrazole with *n*-Butyllithium.**—To a solution of 7.0 g. (0.049 mole) of 1-phenylpyrazole in 200 ml. of dry ether was added dropwise at 0° a solution of 0.050 mole of *n*-butyllithium in 50 ml. of dry ether. The cooling bath was removed, and the reaction was stirred for two hours at room temperature. At the end of this period the ether solution was dark red, and solid was present. The combined reaction mixture was carbonated by pouring it over a slurry of crushed solid carbon dioxide in ether. After the excess carbon dioxide had evaporated, 150 ml. of water was added, and the aqueous layer was separated from the ether layer. The aqueous layer was cooled in an ice–salt bath and barely acidified to precipitate 3.0 g. of a solid melting from 171 to 180°. The filtrate was further acidified to *p*H 2 and additional solid, 2.4 g., melting from 150 to 182°, was collected by filtration. The filtrate from the last fraction was maintained at 15° overnight, and 2.0 g. of additional product, melting from 126–141°, slowly precipitated. By the fractional crystallization of these three fractions from water, there were obtained 3.6 g. (39% yield) of 1-phenyl-5-pyrazolecarboxylic acid, m.p. 186–187°,[7,8] neutralization equivalent 192, and 1.85 g. of another impure acid fraction, m.p. 127–131°, neutralization equivalent 191.

A second acid was isolated from another experiment conducted as above except 2.43 g. (0.0168 mole) of 1-phenylpyrazole was used and the aqueous layer from hydrolysis of the reaction mixture was brought immediately to *p*H 2, filtered, and the filtrate extracted continuously for 24 hours with ether. The ether solution was evaporated yielding a brown residue (0.8 g.). This was dissolved in dilute sodium hydroxide solution, the solution treated with charcoal, filtered, cooled, and acidified to give 0.3 g. (10% yield) of white product, m.p. 140–142°. A mixed melting point of this acid and an authentic sample (see below) of 1-(*o*-carboxyphenyl)-pyrazole,[9] m.p. 138–139°, showed no depression.

1-Phenyl-5-pyrazolecarboxylic acid was isolated in 32% yield from the latter experiment.

**The methyl ester** of 1-phenyl-5-pyrazolecarboxylic acid was prepared from an ether solution of diazomethane in

(9) L. Balbiano, *Gazz. chim. ital.*, **19**, 134 (1889); *Chem. Zentr.*, **60, II**, 78 (1889).

(10) D. A. Shirley and P. A. Roussel, THIS JOURNAL, **75**, 375 (1953).

(11) D. A. Shirley, B. H. Gross and P. A. Roussel, *J. Org. Chem.*, **20**, 225 (1955).

(12) C. A. Rojahn, *Ber.*, **59**, 609 (1926).

(13) H. A. D. Jowett and C. E. Potter, *J. Chem. Soc.*, **83**, 464 (1903).

(14) K. von Auwers and H. Hollmann, *Ber.*, **59**, 606 (1926).

(15) Microanalyses by Galbraith Microanalytical Laboratories of Knoxville, Tenn., and Weiler and Strauss of Oxford, England. All melting and boiling points are uncorrected.

(16) R. G. Jones, THIS JOURNAL, **71**, 3997 (1949).

normal manner. The product m.p. 63–64° was formed in nearly quantitative yield; Claisen[7] reports m.p. 67°.

**1-(*o*-Carboxyphenyl)-pyrazole.**—*o*-Carboxyphenylhydrazine hydrochloride, m.p. 205°, was prepared in high yield by diazotization of anthranilic acid and reduction of the diazonium salt with sodium bisulfite. The product is reported to melt at 189–190°[17] and 207°.[18]

Five grams of crude *o*-carboxyphenylhydrazine hydrochloride was dissolved in 100 ml. of 50% ethanol. Two grams of concentrated sulfuric acid was added, and then 5.5 g. (0.025 mole) of 1,1,3,3-tetraethoxypropane. The resulting yellow solution was heated on the steam-bath for two hours. This solution was extracted with an equal volume of ether. From the ether extract there was obtained 3.1 g. of crude light yellow 1-(*o*-carboxyphenyl)-pyrazole, m.p. 132–138°. An 0.80-g. portion of this was treated with decolorizing charcoal in 10 ml. of absolute ethanol. An equal volume of water was added to the colorless ethanol filtrate, and the ethanol removed on the steam-bath. The solution was cooled in an ice-bath, and a white solid precipitate slowly formed. This was collected by filtration and weighed 0.60 g., m.p. 138–139°; Balbiano[9] reports m.p. 138.5–139°. The yield of crude acid product based on 0.025 m. of 1,1,-3,3-tetraethoxypropane was 66%.

**Hydrazide of 1-(*o*-Carboxyphenyl)-pyrazole.**—An ethereal solution of crude 1-(*o*-carboxyphenyl)-pyrazole (0.5 g.) was treated with an ethereal solution of diazomethane. After a short reaction period, the excess diazomethane was expelled and the ether solution filtered. The ether was evaporated from the filtrate, and the oily residue was refluxed with 0.5 ml. of hydrazine hydrate (99–100%) and 2 cc. of absolute ethanol for 4 hours. The resulting solution was evaporated nearly to dryness on the steam-bath. The air-dried solid which had formed weighed 0.4 g. One-half of this solid was sublimed *in vacuo* (1 to 2 mm.) and the sublimate melted at 131–133°. After two recrystallizations from benzene the melting point was raised to 135–137°.

The acid, of m.p. 140–142°, obtained from the metalation of 1-phenylpyrazole was converted to a hydrazide by the same method. The hydrazide obtained from this sequence of reactions melted at 134–135° and a mixed melting point with the hydrazide prepared above was 134–137°.

*Anal.* Calcd. for $C_{10}H_{10}N_4O$: C, 59.39; H, 4.98; N, 27.7. Found: C, 59.61, 59.70; H, 5.12, 5.25; N, 27.5.

**Metalation of 1-Phenylpyrazole with Excess *n*-Butyllithium.**—A solution of 2.0 g. (0.014 mole) of 1-phenylpyrazole in 30 ml. of dry ether was cooled in an ice-bath, and a solution of 32 meq. of *n*-butyllithium in 30 ml. of ether was added dropwise over a period of 5 minutes. The mixture became bright yellow, and after 30 minutes a solid began to form. The ice-bath was removed and stirring was continued for 7 hours. The reaction mixture was carbonated by pouring into a slurry of powdered carbon dioxide in dry ether. After the excess carbon dioxide had evaporated, the mixture was hydrolyzed with 75 ml. of water. The dark orange aqueous layer was separated from the bright yellow ether layer. The ether was evaporated and the yellow oily residue slowly solidified. The resulting solid was recrystallized from dilute ethanol, and 0.154 g. of yellow needles was obtained which melted from 100–101°. Concentration of the filtrate yielded an additional 0.039 g. of the same solid (total yield 8%). A sample sublimed for analysis melted at 107–109°. The infrared spectrum shows an intense band at 5.78 $\mu$ due to the carbonyl group. The structure assigned to this compound is 4-oxopyrazolo[1,5-a]indoline (III).

*Anal.* Calcd. for $C_{10}H_6N_2O$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.41; H, 3.82; N, 16.20.

The aqueous solution was cooled in an ice-bath and acidified to *p*H 2 with concentrated hydrochloric acid. A bright yellow solid formed. The mixture was chilled overnight at 15° and the solid was separated by filtration. The product weighed 0.90 g. and decomposed from 210 to 240°. The acid was washed with an acetone–ethanol mixture, treated with 10 ml. of 10% sodium hydroxide and the solid (0.32 g.) which did not dissolve was removed by filtration. The basic filtrate was treated with decolorizing charcoal and refiltered. On acidification with concentrated hydrochloric acid, a yellow solid, 0.22 g., m.p. 239°, was obtained. The first fraction of solid (0.32 g.) showed a residue on ignition and was found to be the sodium salt of the second fraction by solution in hot water and acidification. A yellow solid precipitated which melted at 238–239.5°, and a mixed melting point with the second fraction above showed no depression.

The yellow acid was not appreciably soluble in acetone or ethanol, but could be recrystallized from methanol. A portion of the acid was washed with water and recrystallized three times from methanol, which raised the melting point to 241–242°. The yield was 26%. An analytical sample was sublimed *in vacuo* and the melting point was unchanged. Analysis indicated the product to be a monocarboxylic acid derivative of 4-oxopyrazolo[1,5-a]indoline (IV).

*Anal.* Calcd. for $C_{11}H_6N_2O_3$: C, 61.68; H, 2.82; N, 13.08; neut. equiv., 214. Found: C, 60.84; H, 3.26; N, 12.55; neut. equiv., 213.

The yellow acid gave a colorless derivative with hydroxylamine by refluxing 0.10 g. of acid, 0.10 g. of hydroxylamine hydrochloride, 3 ml. of absolute ethanol and 3 ml. of pyridine for 9 hours. The derivative was insoluble in water, chloroform, methanol, ethanol, acetone and ethyl acetate and could not be purified sufficiently for analysis.

The acid was converted to its **methyl ester** by treating 0.1 g. of acid with an ethereal solution of diazomethane. The excess diazomethane was expelled and the ether solution of the ester was filtered. The filtrate was concentrated to a volume of 10 ml., and low boiling petroleum ether was added until the solution became cloudy. The yellow needles which precipitated on cooling were separated by filtration and recrystallized from dilute methanol. The product weighed 0.050 g. and melted at 139–140°.

*Anal.* Calcd. for $C_{12}H_8N_2O_3$: C, 63.16; H, 3.53; N, 12.28; mol. wt., 228. Found: C, 63.27, 63.26; H, 3.39, 3.40; N, 12.1, 12.2; mol. wt. (Rast), 217.

**Action of Polyphosphoric Acid on 1-Phenyl-5-pyrazolecarboxylic Acid.**—A mixture of 0.1 g. of 1-phenyl-5-pyrazolecarboxylic acid, m.p. 186–187°, and 2 ml. of polyphosphoric acid was heated in an oil-bath to 200° and maintained at this temperature for two hours. The bath temperature was reduced and the temperature of the mixture fell to 120° during the next two hours. The mixture was cooled and hydrolyzed with ice-water. The aqueous solution was yellow and was separated by centrifugation from 0.085 g. of unreacted starting material, which had precipitated on the addition of water. The decantate was neutralized with solid sodium carbonate and extracted with ether. Evaporation of the ether left a small amount of bright yellow solid which was recrystallized from aqueous ethanol to yield 4-oxopyrazolo[1,5-a]indoline, m.p. 107–110°. The infrared spectrum of this material was identical with the spectrum of the ketone from dimetalation of 1-phenylpyrazole.

**Metalation of 1-Methylpyrazole.**—To a solution of 2.2 g. (0.027 mole) of 1-methylpyrazole in 150 ml. of dry ether was added dropwise a solution of 0.03 mole of *n*-butyllithium in 25 ml. of ether. A light yellow precipitate formed and the ether solution became yellow. The resulting mixture was stirred at room temperature for three hours and then cooled in an acetone–solid carbon dioxide-bath. Crushed solid carbon dioxide suspended in dry ether was added cautiously with rapid stirring followed by powdered solid carbon dioxide alone until a large excess was present. The orange color of the reaction mixture was slowly discharged, and stirring was continued until the carbon dioxide had evaporated. After hydrolysis with 50 ml. of water, the ether layer was separated. The aqueous layer was cooled to 0–5° in an ice–salt-bath and acidified to *p*H 2. A solid slowly precipitated and after 3 hours at 15°, the solid was removed by filtration and air-dried. It weighed 1.80 g. and melted in the range 210–220° dec. The acid was dissolved in ethanol, treated with charcoal, and the ethanol filtrate was concentrated to 50 ml.; 20 ml. of water was added and the solution cooled. In this manner there was obtained 1.4 g. of white crystalline product which melted at 224° with some prior sublimation. Concentration of the filtrate from the recrystallization yielded an additional 0.10 g. of the acid. To the original aqueous filtrate of the acid was added several drops of concentrated hydrochloric acid and the solution held at about 15° overnight. Additional solid was filtered off and after treatment with charcoal, 0.30 g. of acid was obtained which melted at 223°. A mixture

(17) K. Pfannstiel and J. Janecke, *Ber.*, **75**, 1096 (1942).

(18) S. F. Acree, *Am. Chem. J.*, **37**, 361 (1907).

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.

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[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

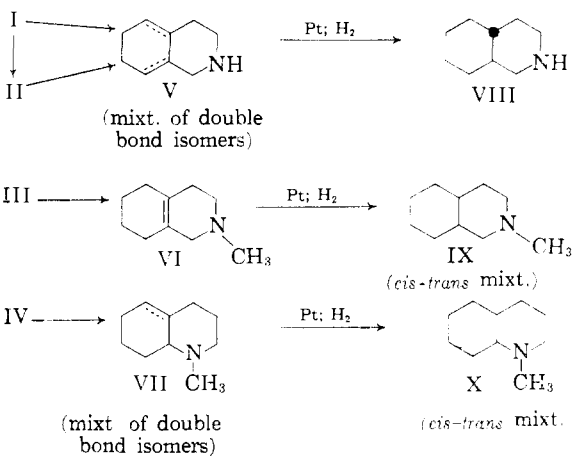
RECEIVED MAY 14, 1958

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).