[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Substituted Isoquinolines

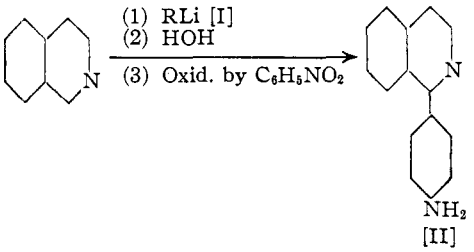
BY HENRY GILMAN AND GORDON C. GAINER[1]

In connection with the pharmacological action of some aminophenyl compounds, a need arose for 1-(*p*-aminophenyl)-isoquinoline. A convenient procedure for the synthesis of this compound was the addition to isoquinoline of the organolithium compound formed by a halogen-metal interconversion reaction with *p*-bromoaniline.[1,3]

$$p\text{-}NH_2C_6H_4Br + n\text{-}C_4H_9Li \longrightarrow p\text{-}NH_2C_6H_4Li + n\text{-}C_4H_9Br$$
[I]

The N-lithio salt of the compound [I] is formed to an extent of at least 68%[1a]; and although three equivalents of *n*-butyllithium were used it is unknown whether both active hydrogens of the amino group are replaced by lithium under the mild conditions employed.

Addition of the RLi compound to isoquinoline, followed by oxidation of the intermediate dihydro compound, gave the *p*-(aminophenyl)-isoquinoline in about 70% yield.



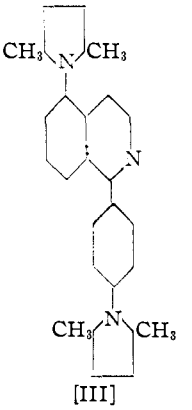
[II]

It was necessary to establish the structure of [II] for two reasons. First, there was the possibility of the amino group being *ortho* rather than *para* because of a self-metalation of the kind previously observed in the formation of the RLi compound from *p*-bromoanisole.[2] Second, there was the possibility that the *p*-aminophenyl group might not be in the 1-position.[3] The earlier studies[4] on the addition of phenyllithium to isoquinoline indicated, but did not rigorously establish, that the phenyl group was in the 1-position.

Our product from the RLi reaction was shown, by the method of mixed melting points, to be identical with an authentic specimen of 1-(*p*-aminophenyl)-isoquinoline prepared by the following sequence of reactions. First, the directions of Rodinov and Yavorskaya[5] were checked for the preparation of 1-(*p*-nitrophenyl)-3,4-dihydroisoquinoline by the Bischler–Napieralski reaction. Second, this compound was dehydrogenated to 1-(*p*-nitrophenyl)-isoquinoline. Third, reduction with Raney nickel catalyst gave the 1-(*p*-aminophenyl)-isoquinoline.

An attempt to dehydrogenate 1-(*p*-nitrophenyl)-3,4-dihydroisoquinoline by oxidation with dilute nitric acid in acetic acid, as was done in the preparation of 1-phenylisoquinoline,[5] was without success. Equally unsuccessful was an attempted dehydrogenation by potassium permanganate in dilute sulfuric acid in accordance with a general procedure for the preparation of various 1-substituted isoquinolines.[6] Dehydrogenation was effected by palladium black in accordance with a general procedure described by Späth.[7]

In view of certain special properties noted in antimalarial studies of some 2,5-dimethyl-1-pyrryl types,[8] several isoquinolines containing this substituted-pyrryl nucleus were prepared. One among them, having two of these nuclei, is 1-[*p*-(2,5-dimethyl-1-pyrryl)-phenyl]-5-(2,5-dimethyl-1-pyrryl)-isoquinoline [III], prepared by reaction of 5-(2,5-dimethyl-1-pyrryl)-isoquinoline with *p*-(2,5-dimethyl-1-pyrryl)-phenyllithium. Another novel type prepared by means of organolithium compounds is 1-(*p*-mercaptophenyl)-isoquinoline. This compound is prepared by the addition of *p*-$LiSC_6H_4Li$ to isoquinoline, and the RLi compound was obtained by a facile halogen–metal interconversion reaction starting with *p*-bromothiophenol.



[III]

The authors are grateful to Parke, Davis and Company for arranging for the tests.

Experimental

1-(*p*-Aminophenyl)-isoquinoline from RLi Compound.—In a nitrogen amosphere, there was added dropwise and with stirring 0.66 mole of *n*-butyllithium in one liter of ether to 38 g. (0.22 mole) of *p*-bromoaniline in 200 cc. of ether. When 300 cc. of the *n*-butyllithium had been added, refluxing ceased and the color of the solution

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(1a) Gilman and Stuckwisch, THIS JOURNAL, **64**, 1007 (1942), and **63**, 2844 (1941).

(2) Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938).

(3) See, Gilman and Gainer, THIS JOURNAL, **69**, 877 (1947), for other possible modes of addition of RM compounds to quinoline.

(4) Ziegler and Zeiser, *Ann.*, **485**, 174 (1931); Bergmann, Blum-Bergmann and von Christiani, *ibid.*, **483**, 80 (1930).

(5) Rodinov and Yavorskaya, *J. Gen. Chem., U. S. S. R.*, **11**, 446 (1941) [*C. A.*, **35**, 6592 (1941)].

(6) Pictet and Kay, *Ber.*, **42**, 1973 (1909).

(7) Späth and Polgar, *Monatsh.*, **51**, 190 (1929); Späth, Berger and Kunatra, *Ber.*, **63**, 134 (1930).

(8) (a) Gilman, Stuckwisch and Nobis, THIS JOURNAL, **68**, 326 (1946); (b) for the preparation of some isomeric (methoxy)-(2,5-dimethyl-1-pyrryl)-quinolines, see, Gilman and Fullhart, *ibid.*, **68**, 978 (1946); (c) Walsh, *J. Chem. Soc.*, 726 (1942); Coates, Cook, Heilbron and Lewis, *ibid.*, 419 (1943); Gilman and Karmas, THIS JOURNAL, **67**, 343 (1945); Gilman and Tolman, *ibid.*, **67**, 1847 (1945); Gilman, Tolman, Yeoman, Woods, Shirley and Avakian, *ibid.*, **68**, 427 (1946).

TABLE I

1-(ARYLSUBSTITUTED)-ISOQUINOLINES

Product	RLi compound	M. p., °C.	Formula	N Analyses, % Calcd.	Found
1-(*p*-Tolyl)-isoquinoline[a]	*p*-$CH_3C_6H_4Li$	71–72	$C_{16}H_{13}N$	6.40	6.60
1-(*p*-Dimethylaminophenyl)-isoquinoline[b]	*p*-$(CH_3)_2NC_6H_4Li$	114.5–115	$C_{17}H_{16}N_2$	11.29	11.20
1-[*p*-(2,5-Dimethyl-1-pyrryl)-phenyl][c]	*p*-$(C_6H_8N)C_6H_4Li$	159–160	$C_{21}H_{19}N_2$	9.36	9.59
1-(*p*-Anisyl)-5-(2,5-dimethyl-1-pyrryl)-isoquinoline[d]	*p*-$CH_3OC_6H_4Li$	[d]	$C_{22}H_{20}ON_2$	8.53	8.74
See Formula [III][e]	*p*-$(C_6H_8N)C_6H_4Li$	214–215	$C_{27}H_{25}N_3$	10.74	10.91
1-(*p*-Mercaptophenyl)-isoquinoline (Hydrochloride)[f]	*p*-$LiSC_6H_4Li$	271–272	$C_{15}H_{12}NClS$	11.62	11.80 11.90

[a] The crude product (55%) distilled between 174–183° (5 mm.); the m. p. of this crude material was 65–68°, and purification was effected by crystallization from a benzene–petroleum ether (b. p., 60–68°) mixture. The *p*-tolyllithium was prepared in a 90% yield (see Gilman, Zoellner and Selby, THIS JOURNAL, **54**, 1957 (1932)]. [b] The orange-red, glassy product (55%) distilled at 196–199° (4 mm.) and purification was effected by crystallization from methanol. The picrate of 1-(*p*-dimethylaminophenyl)-isoquinoline, prepared from a hot dioxane solution of the isoquinoline compound and a hot ethanolic solution of picric acid, formed scarlet-red glistening crystals which melted at 220–221°. *Anal.* Calcd. for $C_{23}H_{19}O_7N_5$: N, 14.68. Found: N, 14.95. [c] The dark-red, viscous liquid (45%) distilled over the range 203–208° (4 mm.), and was purified by crystallization from a benzene–petroleum ether (b. p. 60–68°) mixture. The *p*-(2,5-dimethyl-1-pyrryl)-phenyllithium was prepared in 70% yield from *p*-(2,5-dimethyl-1-pyrryl)-phenyl bromide in accordance with the directions of Gilman and O'Donnell, THIS JOURNAL, **66**, 840 (1944). [d] The product (38%) distilled between 222–228° (2 mm.) as a dark red viscous oil. A small quantity of 5-(2,5-dimethyl-1-pyrryl)-isoquinoline was recovered in the forerun. [e] The 1-[*p*-(2,5-dimethyl-1-pyrryl)-phenyl]-5-(2,5-dimethyl-1-pyrryl)-isoquinoline (31%) was obtained as a dark red, brittle glass which distilled over the range 220–230° (0.05 mm.). The compound crystallized from benzene as tan-colored, microscopic needles. [f] This product was isolated as the hydrochloride (20%) which melted, when crude, at 241–246° with decomposition. Recrystallization from dilute hydrochloric acid (1:1) gave pale yellow needles which melted at 271–272° with decomposition. A 50-cc. aliquot of the product resulting from the reaction of 53 g. (0.28 mole) of *p*-bromothiophenol in 100 cc. of ether with 0.45 mole of *n*-butyllithium in 500 cc. of ether (followed by refluxing and stirring for one-half hour) gave a 75% yield of crude *p*-mercaptobenzoic acid. A related procedure has been used by Russell N. Clark.

changed from a deep violet to a pale yellow. The remaining 700 cc. of solution was added more rapidly; and the mixture was refluxed and stirred, with external heating, for one and one-fourth hours. Then 57 g. (0.44 mole) of freshly distilled isoquinoline, dissolved in an equal volume of ether, was added at a slow rate to maintain refluxing. The solution immediately assumed a deep orange color, and a finely divided granular precipitate formed. The mixture was then stirred and refluxed for twelve hours, at the end of which time all of the solid had dissolved. Subsequent to hydrolysis, drying, removal by distillation of material boiling up to 110° (0.5 mm.), the orange colored residue was heated at 190° for one-half hour with 40 cc. of nitrobenzene. Distillation at 178–190° (0.02 mm.) gave a very viscous oil in a yield of 23 g. (67%, based on a 70% halogen–metal interconversion). From another preparation the yield was 70%. The 1-(*p*-aminophenyl)-isoquinoline melted at 191–192° after crystallization from benzene.

Anal. Calcd. for $C_{15}H_{12}N_2$: N, 12.70. Found: N, 12.63.

Preparation from 1-(*p*-Nitrophenyl)-isoquinoline.—A mixture of 2 g. (0.008 mole) of 1-(*p*-nitrophenyl)-3,4-dihydroisoquinoline[5] and one gram of palladium black[9] was heated for two hours in a metal-bath kept between 190–200°, with occasional shaking. The cooled reaction mass was extracted with boiling acetone, from which was obtained 1.2 g. (60%) of compound melting at 150–151°. On recrystallization the compound melted at 155–156°.

Anal. Calcd. for $C_{15}H_{10}O_2N_2$: N, 11.18. Found: N, 11.10.

Reduction of 0.72 g. (0.0029 mole) of the 1-(*p*-nitrophenyl)-isoquinoline in 50 cc. of absolute ethanol in one hour over Raney nickel under three atmospheres of hydrogen at 95–100° gave 0.45 g. (70%) of fine needles melting at 185–190°. The melting point after one crystallization from benzene was 191–192°, and there was no depression in a mixed melting point determination with the compound prepared by the RLi reaction.

(9) Prepared in accordance with directions of Willstätter and Waldschmidt-Leitz, *Ber.*, **54**, 123 (1921).

1-(Arylsubstituted)-isoquinolines.—Table I lists a series of 1-(arylsubstituted)-isoquinolines. These were prepared in essential accordance with the directions given for the synthesis of 1-(*p*-aminophenyl)-isoquinoline. The appropriate RLi compound was added to isoquinoline or a substituted isoquinoline, and then the intermediately formed dihydro compound was oxidized by nitrobenzene.

5-(2,5-Dimethyl-1-pyrryl)-isoquinoline.—The 5-aminoisoquinoline was obtained from 5-nitroisoquinoline[10] by catalytic reduction.[11] Condensation of 50 g. (0.35 mole) of 5-aminoisoquinoline and 39.9 g. (0.35 mole) of acetonylacetone (using two drops of 1:1 hydrochloric acid) was effected in accordance with the general procedure of Lions and co-workers.[12] The crude product (95%) melted at 78–80°, and crystallization from 95% ethanol gave 65 g. (83%) melting at 83–84°. In subsequent preparations with other amines it was found helpful to use an excess of acetonylacetone.

Anal. Calcd. for $C_{15}H_{14}N_2$: N, 12.61. Found: N, 12.61.

The picrate was obtained as yellow platelets melting at 174–175° after crystallization from 95% ethanol.

Anal. Calcd. for $C_{21}H_{17}O_7N_5$: N, 15.58. Found: N, 15.59.

4-(2,5-Dimethyl-1-pyrryl)-isoquinoline.—A mixture of 6 g. (0.042 mole) of 4-aminoisoquinoline and 10 g. (0.088 mole) of acetonylacetone and 2 drops of 1:1 hydrochloric acid was refluxed for three hours. After pouring the cooled solution on ice there was obtained 9 g. (97%) of product melting at 76–77°. Recrystallization from methanol raised the melting point to 77–78°.

Anal. Calcd. for $C_{15}H_{14}N_2$: N, 12.61. Found: N, 12.50.

The 4-aminoisoquinoline was prepared[11] by heating 4-bromoisoquinoline with concd. aqueous ammonia and

(10) Le Fèvre and Le Fèvre, *J. Chem. Soc.*, 1470 (1935).

(11) Craig and Cass, THIS JOURNAL, **64**, 783 (1942).

(12) Lions and co-workers, *J. Proc. Roy. Soc., N. S. Wales*, **74**, 443 (1941) [*C. A.*, **35**, 4771 (1941)]. Earlier references can be obtained from this citation.

copper sulfate in a rocking autoclave. The 4-bromoisoquinoline was obtained (445 g. or 71.5%) as a crude product (m. p., 39–42°) which on recrystallization from petroleum ether (b. p., 60–68°) melted at 42–42.5°. We observed that the yield was improved by completely mixing the molten isoquinoline perbromide hydrobromide prior to the prolonged heating.[11,13]

4-Hydroxyisoquinoline.—A mixture of 10.5 g. (0.05 mole) of 4-bromoisoquinoline, 5 g. (0.02 mole) of copper sulfate, 4.1 g. of copper bronze and 31.3 g. (0.75 mole) of sodium hydroxide in 17 cc. of water was heated in an autoclave at 210° for twelve hours. After cooling, the dark brown residue was extracted with hot water, and to the aqueous filtrate was added Dry Ice. The 4.5 g. (61%) of light brown 4-hydroxyisoquinoline which precipitated melted between 210–214°. Recrystallization from a 1:2 mixture of glacial acetic acid and ethyl ether raised the melting point to 223°. The yield of crude product using double the quantities of reactants was 60%.

Anal. Calcd. for C_9H_7ON: N, 9.65. Found: N, 9.67.

The yellow, crystalline *picrate* melted at 243–244° after recrystallization from 95% ethanol.

Anal. Calcd. for $C_{15}H_{10}O_8N_4$: N, 14.97. Found: N, 15.20.

***p*-(γ-Diethylaminopropylamino)-phenyl Bromide.**—This compound was prepared incidental to an orienting experiment concerned with the synthesis of 1-[*p*-(γ-diethylaminopropylamino)-phenyl]-isoquinoline by a procedure like that described earlier for the preparation of 1-(*p*-aminophenyl)-isoquinoline.

In the first reaction, 34.4 g. (0.2 mole) of *p*-bromoaniline and 30 g. (0.2 mole) of freshly distilled γ-diethylaminopropyl chloride[14] were heated between 150–160° (internal temperature) for six hours. After cooling the dark brown solution, water was added, and the neutralization was effected by 20% sodium hydroxide. The ether extracts were dried, and after removal of the ether fractional distillation yielded 30 g. (52%) of a colorless liquid which boiled at 135–137° (0.2 mm.); $n^{20}D$ 1.5530; d^{20}_{20} 1.1178.

In a second preparation, to a melt of 156 g. (0.5 mole) of crude N-(*p*-bromophenyl)-benzenesulfonamide[15] and 41.5 g. (0.3 mole) of anhydrous potassium carbonate heated at 150° was added cautiously 90 g. (0.6 mole) of γ-diethylaminopropyl chloride. Heating was continued between 150–160° for six hours, and on pouring into cold water a brown, viscous oil separated. The oil was hydrolyzed by refluxing for twelve hours with 600 cc. of concentrated hydrochloric acid. Subsequent to neutralization by 40% sodium hydroxide solution and extraction with ether, there was obtained 88.5 g. (62%) of compound distilling at 155–157° (0.5 mm.); $n^{20}D$ 1.5528; d^{20}_{20} 1.1181.

Anal. Calcd. for $C_{13}H_{21}N_2Br$: N, 9.92. Found: N, 10.19.

The **dihydrochloride**, prepared by adding an excess of ethereal hydrogen chloride to a dry ether solution of *p*-(γ-diethylaminopropylamino)-phenyl bromide, melted at 185–186° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{13}H_{23}N_2BrCl_2$: N, 7.83. Found: N, 7.72.

(13) Edinger and Bossung, *J. prakt. Chem.*, **43**, 191 (1891); Bergstrom and Rodda, THIS JOURNAL, **62**, 3030 (1940).

(14) Gilman and Shirley, *ibid.*, **66**, 888 (1944).

(15) v. Braun, *Ber.*, **40**, 3926 (1907).

Summary

1-(*p*-Aminophenyl)-isoquinoline has been prepared by the addition of the lithium salt of *p*-aminophenyllithium to isoquinoline and shown to be identical with a compound prepared by cyclization. By the use of appropriate RLi compounds, other 1-(arylsubstituted)-isoquinolines have been synthesized in which some of the aryl groups are *p*-mercaptophenyl and *p*-(2,5-dimethyl-1-pyrryl)-phenyl.

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Studies in the Terpene Series. VII. Destructive Hydrogenation of Bicyclic Dihydroterpenic Hydrocarbons[1,2]

BY V. N. IPATIEFF, HERMAN PINES AND MICHAEL SAVOY

The structure of bicyclic dihydroterpenic hydrocarbons, which are often formed during the catalytic treatment of mono- and bicyclic terpenes, is difficult to prove by heretofore described methods. It was of especial importance during our study to find a means of determining the type of rings present in bicyclic dihydroterpenic hydrocarbons. For that reason the study of the destructive hydrogenation of bicyclic dihydroterpenic hydrocarbons was undertaken with the purpose of splitting one of the rings and converting these dihydroterpenes to monocyclic hydrocarbons; the structure of the latter can usually be determined by means of dehydrogenation.

For that reason the following compounds were submitted to a ring rupture by means of destructive hydrogenation: pinane, isocamphane and isobornylane. The reaction was carried out in a rotating autoclave in the presence of a nickel–kieselguhr catalyst and under an initial hydrogen pressure of 100 atmospheres, measured at 25–28°. It was found that the temperature at which the fission of one of the rings takes place depends upon the size of the rings. In pinane, which is composed of a four- and a six-carbon atom ring, the rupture of the ring occurs as low as 175°. Bicyclic hydrocarbons composed of a six-carbon atom ring containing a bridge in the 1,4-position linked through a carbon atom are more stable toward hydrogenation than pinane; the cleavage of one of the rings takes place at 210–220°.

The destructive hydrogenation of pinane causes the rupture of the following bonds: 6–8 (I), 4–8 (II), 4–5 (III) and 5–6 (IV)

(1) This work was made possible through financial assistance of the Universal Oil Products Company, Riverside, Illinois.

(2) For Paper VI of this series see V. N. Ipatieff, H. Pines, V. Dvorkobitz, R. C. Olberg and M. Savoy, *J. Org. Chem.*, **12**, 34 (1947).