383. *The Synthesis of Some Dimethyl- and Ethyl-isoquinolines.*

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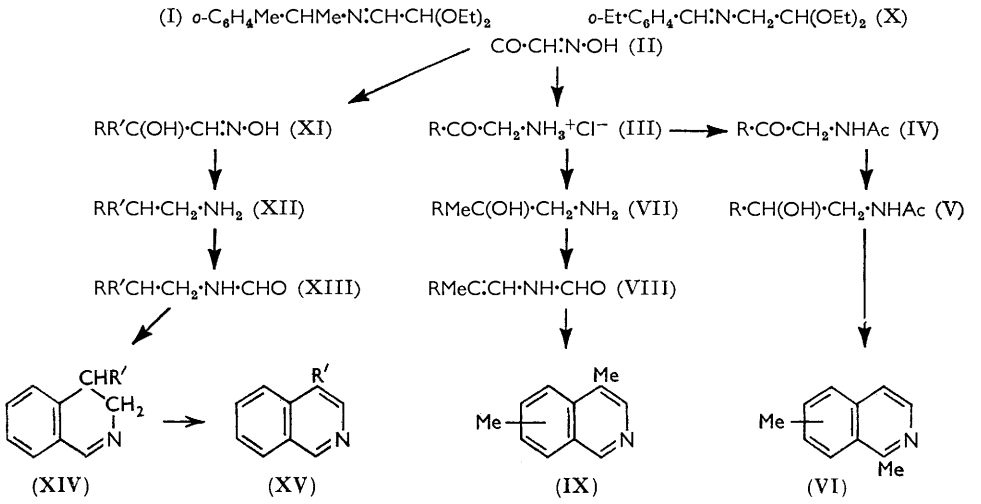
The synthesis of 1,6-, 1,7-, 1,8-, 4,6-, and 4,7-dimethylisoquinoline, and of 4- and 8-ethylisoquinoline by established routes is described. The ultraviolet absorption spectra of the monomethylisoquinolines and of some dimethylisoquinolines are reported; the spectra of the monoethylisoquinolines are compared with those of the corresponding monomethyl derivatives.

WHEN this work was started, the alicyclic portion of the alkaloid gelsemine was assumed to contain an *exo*-methylene group,[1] and distillation of gelsemine with zinc dust had been shown [2] to give (among other products) a base $C_{11}H_{11}N$, isolated as its picrate (A), m. p. 186—187°. From the formula the base could be a dimethyl- or an ethyl-quinoline or -isoquinoline, but the reported presence of an *exo*-methylene group in gelsemine suggested that the base was a dimethyl derivative. All the dimethylquinoline picrates were known,[3] but relatively few dimethylisoquinolines and the work reported below was concerned with the synthesis of some of the more likely possibilities. During the course of this work Gibson reported [4] the synthesis of the unknown 5,*x*-dimethylisoquinoline picrates ($x = 4$, 6, 7, and 8), none of which was identical with picrate (A). When five dimethylisoquinoline picrates had been prepared Marion and Sargeant reported [5] that the double bond in gelsemine was present as a vinyl residue and not as a methylene group, and this suggested that the picrate (A) was that of an ethyl and not a dimethyl derivative. The most likely bases on biogenetic grounds appeared to be 4- or 8-ethylisoquinoline, and these were synthesized, but the picrates had m. p. lower than that reported for picrate (A).

The complete structure of gelsemine has recently been reported,[6,7] and Conroy and Chakrabarti [7] note that " the 4,7-dimethylisoquinoline skeleton is present intact in the

[1] Goutarel, Janot, Prelog, and Taylor, *Helv. Chim. Acta*, 1951, **34**, 1139.
[2] Witkop, *J. Amer. Chem. Soc.*, 1948, **70**, 1424.
[3] Manske, Marion, and Leger, *Canad. J. Res.*, 1942, **20***B*, 133.
[4] Gibson, *J.*, 1956, 808.
[5] Marion and Sargeant, *J. Amer. Chem. Soc.*, 1956, **78**, 5127.
[6] Lovell, Pepinsky, and Wilson, *Tetrahedron Letters*, 1959, No. 4, p. 1.
[7] Conroy and Chakrabarti, *Tetrahedron Letters*, 1959, No. 4, p. 6.

molecule." The synthesis of 4,7-dimethylisoquinoline picrate is reported below and this is not identical with Witkop's picrate (A).



The first dimethylisoquinolines prepared were the remaining unknown 1,*x*-dimethylisoquinolines (*x* = 6, 7, and 8). For the synthesis of 1,8-dimethylisoquinoline the Schlittler–Müller modification [8] of the Pomerantz–Fritsch method was used; condensation of glyoxal hemiacetal with 1-*o*-tolylethylamine gave the aldimine acetal (I), which was cyclised in poor yield to 1,8-dimethylisoquinoline. The picrate melted at 224—226°. The route used to prepare 1,6- and 1,7-dimethylisoquinolines is shown by formulæ (II) ⟶ (VI). Using ω-hydroxyimino-4-methylacetophenone (II; R = *p*-tolyl) led to 1,7-dimethylisoquinoline, whose picrate melted at 223—224°; ω-hydroxyimino-3-methylacetophenone (II; R = *m*-tolyl) similarly gave 1,6-dimethylisoquinoline (picrate, m. p. 225—227°). The ultraviolet absorption of the 1,6-dimethylisoquinoline obtained by this method differed appreciably from that of the 1,8-dimethylisoquinoline prepared by the unambiguous route described above (see Table); hence in this case, as in others,[9] the Bischler–Napieralski cyclodehydration proceeds predominantly *para*- to the *o*,*p*-directing group already present.

For the synthesis of 4,7-dimethylisoquinoline the modified route shown by formulæ (II) ⟶ (IX) above was adopted. Mills and Grigor [10] have shown that reaction of a keto-amine hydrochloride with a large excess of a Grignard reagent gives a hydroxy-amine of type (VII). Using methylmagnesium iodide and ω-amino-4-methylacetophenone hydrochloride (III; R = *p*-tolyl) [obtained by reduction of the hydroxyimino-compound (II; R = *p*-tolyl)] afforded the hydroxy-amine (VII; R = *p*-tolyl); this, when heated with 90% formic acid, gave the styrylamide (VIII; R = *p*-tolyl), cyclized to give 4,7-dimethylisoquinoline (picrate, m. p. 223°). A similar series of reactions starting from ω-hydroxyimino-3-methylacetophenone (II; R = *m*-tolyl) gave a very small yield of a picrate, m. p. 228—229°, which was assumed to be 4,6-dimethylisoquinoline picrate. The material was not prepared on a larger scale because of the widely different melting points of this picrate and of picrate (A).

8-Ethylisoquinoline picrate was obtained after a normal Pomeranz–Fritsch reaction [11] from the imine (X); the picrate melted at 158—160°. A compound prepared from

[8] Schlittler and Müller, *Helv. Chim. Acta*, 1948, **31**, 914.
[9] Gulland and Virden, *J.*, 1929, 1791.
[10] Mills and Grigor, *J.*, 1934, 1568.
[11] Gensler, " Organic Reactions," Wiley, New York, 1951, Vol. VI, p. 200.

1,2,3,4-tetrahydro-4,4-dimethyl-1,3-dioxoisoquinoline has been formulated [12] as 4-ethylisoquinoline, but is in fact 3,4-dimethylisoquinoline.[13] Orékhoff and Tiffeneau have reported [14] that a hydroxyimino-derivative such as (II) will react with a Grignard reagent to give a hydroxy-oxime (XI). When ω-hydroxyiminoacetophenone was added to a solution of ethylmagnesium bromide the hydroxy-oxime (XI; R = Ph, R′ = Et) was formed. An attempt to reduce this to a β-hydroxyphenethylamine derivative by sodium in ethanol gave instead the saturated amine (XII; R = Ph, R′ = Et), the benzylic hydroxyl group being hydrogenolysed. This saturated amine was used to prepare the formamide (XIII; R = Ph, R′ = Et), and this underwent Bischler–Napieralski cyclodehydration to give 4-ethyl-3,4-dihydroisoquinoline (XIV; R′ = Et). Dehydrogenation gave 4-ethylisoquinoline, whose picrate melted at 163—164°.

Ultraviolet Absorption Spectra.—In the Table the spectra of the seven monomethyliso-

Ultraviolet absorption maxima (mμ) (log ε *in parentheses*) *of substituted isoquinolines in hexane.*

Subst.	*x′*-Band	*y*-Band		*x*-Band		
1-Me	217(4·80)	270(3·71)	295(3·20)	306_5(3·37)	314(3·30)	320(3·45)
3-Me	218(4·87)	267(3·62)	298(3·14)	311(3·42)	319_5(3·38)	324(3·53)
4-Me	216_5(4·74)	271(3·67)	296(3·22)	308(3·43)	315(3·44)	321_5(3·54)
5-Me	220(4·89)	272(3·68)		307(3·32)	314_5(3·26)	3200(3·43)
6-Me	221(4·78)	277(3·58)	300 † (3·26)	307(3·25)	316(3·19)	321(3·23)
7-Me	223(4·77)	279_5(3·66)		314(3·51)	322(3·50)	327(3·69)
8-Me	219(4·78)	272(3·64)	296(3·24)	308(3·46)	316(3·42)	322(3·60)
			302(3·28)			
1-Et	218 * (4·79)	270(3·73)		306(3·41)	314(3·33)	320(3·51)
4-Et	216_5(4·78)	271(3·66)	296(3·24)	308(3·43)	315(3·39)	321(3·53)
1,6-Me_2 ...	220(4·73)	273(3·66)		304(3·30)	310 † (3·19)	318(3·40)
1,7-Me_2 ...	220(4·81)	270(3·74)	300(3·20)	312(3·47)	321(3·38)	326(3·57)
1,8-Me_2 ...	220(4·82)	275(3·75)		310(3·50)	318(3·45)	324(3·63)
3,4-Me_2 ...	221(4·85)	273_5(3·68)	302_5(3·30)	314(3·54)	323(3·53)	328_5(3·68)
4,6-Me_2 ...	219(4·82)	275(3·57)	306(3·27)	312(3·31)	319_5(3·41)	325(3·34)
4,7-Me_2 ...	219(4·82)	270(3·70)	301(3·25)	314(3·49)	322(3·45)	328(3·63)

* In ethanol. † Inflexion.

quinolines are reported, together with those of 1- and of 4-ethylisoquinoline and of some dimethylisoquinolines, all in hexane. The spectra of the monomethylisoquinolines are sufficiently distinctive to be used in the characterisation of any monomethylisoquinoline on a milligram scale. The spectra of 1- and 4-ethylisoquinoline resemble very closely those of the corresponding monomethyl derivatives, and it seems that the position of substitution of the alkyl substituent in any monoalkylisoquinoline could be tentatively assigned by reference to the spectra of the monomethyl derivatives recorded above. The spectrum of an *a,b*-dimethylisoquinoline seems to bear no simple relation to those of the *a*- and *b*-monomethylisoquinolines, and a hope that it might be possible to predict the position of the substituents in a dialkylisoquinoline has not been fulfilled.

Experimental

M. p.s were determined on a Kofler block. For spectroscopy the isoquinolines were regenerated from the pure picrates by lithium hydroxide or by ethanolamine and then distilled.

1-o-*Tolylethylamine.*—Sodium (13 g.) was added rapidly to a boiling solution of 2-methylacetophenone oxime (7·2 g.) in dry ethanol (100 ml.). When all the sodium had dissolved, the solution was cooled, poured into water, and extracted with ether. The ethereal solution was extracted with 2N-hydrochloric acid, and the aqueous acid extracts were combined, basified,

[12] Heilbron and Bunbury, " Dictionary of Organic Compounds," Eyre and Spottiswoode, revised edn., 1953, p. 513.
[13] Jones, following paper.
[14] Orékhoff and Tiffeneau; *Bull. Soc. chim. France*, 1927, **41**, 841.

and extracted with ether. The dried (K_2CO_3) ethereal solution was distilled, giving the amine, b. p. 204—206°/732 mm. (4·4 g., 67·5%). *The picrate* crystallised from ethanol as yellow prisms, m. p. 211—212° (Found: C, 49·5; H, 4·4. $C_{15}H_{16}O_7N_4$ requires C, 49·5; H, 4·4%). The toluene-*p*-sulphonate crystallized from aqueous ethanol as leaflets, m. p. 108·5—109·5°.

1,8-*Dimethylisoquinoline*.—The 1-*o*-tolylethylamine (1·8 g.) and glyoxal hemiacetal [8] (2 g.) were heated together at 110° for 1 hr. Further acetal (0·25 g.) was added, and heating continued at 125—130° for 1 hr. The cooled mixture was dissolved in ether, dried (Na_2SO_4), and distilled. The ketimine (I) had b. p. 94°/0·15 mm.

Cyclisation.—(*a*) The ketimine (I) (2·33 g.), dissolved in concentrated sulphuric acid (10 ml.) at 0—5°, was added to concentrated sulphuric acid (20 ml.) at 120°; the mixture was kept at 120° for several minutes, then cooled, and treated with ice. The aqueous solution was basified with sodium hydroxide and steam-distilled. The distillate was extracted with ether, dried (Na_2SO_4), and distilled, giving the impure isoquinoline (0·15 g., 10·2%), b. p. 155°/15 mm. The *picrate* crystallised from ethanol as yellow prisms, m. p. 224—226° (Found: C, 53·0; H, 3·6. $C_{17}H_{14}O_7N_4$ requires C, 52·9; H, 3·65%). The pure picrate was shaken with saturated aqueous lithium hydroxide and ether, and the ether layer was separated, washed with water, dried (Na_2SO_4), and distilled, giving pure 1,8-*dimethylisoquinoline*, m. p. 49—51° (Found: C, 84·3; H, 7·5. $C_{11}H_{11}N$ requires C, 84·0; H, 7·1%).

(*b*) The ketimine (3·0 g.) was added to a mixture of phosphoric oxide (10 g.) and syrupy phosphoric acid (10 ml.) at 160°. The mixture was held at 160° for several minutes, then cooled, and worked up as described above. The isoquinoline (once-distilled) weighed 0·22 g. (11·6%).

3-*Methylacetophenone*.—(*a*) Acetonitrile (freshly distilled from phosphoric oxide) (13·5 g.) was added slowly to the stirred Grignard reagent from *m*-bromotoluene (157 g.) in ether (1·5 l.). The mixture was boiled under reflux for 6 hr., cooled, and treated with ice-water, followed by concentrated hydrochloric acid (100 ml.). The ether was distilled off and the resulting aqueous mixture was stirred at 95° for 1 hr., cooled, and separated. The aqueous layer was extracted with ether, and the combined organic material extracted with aqueous sodium hydrogen carbonate, and then with water. The ethereal solution was dried (Na_2SO_4) and distilled at atmospheric pressure. When the distillation temperature reached 130° the pressure was reduced, and distillation continued at 15 mm. The yield of 3-methylacetophenone, b. p. 108—112°/15 mm., was 24 g. (54·4%).

(*b*) Acetaldehyde (25 g.) was added slowly in the cold to the Grignard reagent from *m*-iodotoluene (109 g.) in ether (1·1 l.). The Grignard complex was decomposed by ice and 2N-sulphuric acid, and the ethereal layer separated, and shaken with aqueous sodium hydrogen carbonate and then with water. The dried (Na_2SO_4) ethereal solution was evaporated; the residue was freed from traces of ether by heating it *in vacuo*, and dissolved in glacial acetic acid (190 ml.). This mixture was treated slowly with a solution of chromic anhydride (19 g.) in acetic acid (100 ml.) and water (10 ml.). The mixture was heated for a few minutes on a boiling-water bath, concentrated under reduced pressure, diluted with water, and extracted with ether. The ethereal solution was shaken with aqueous sodium hydrogen carbonate, then with water, dried (Na_2SO_4), and distilled. The yield of 3-methylacetophenone, b. p. 108—110°/15 mm., was 27 g. (40·3%).

2-Methylacetophenone, prepared by method (*a*), had b. p. 102—106°/15 mm. (70% yield).

4-*Methylphenacylamine Hydrochloride* (III; R = *p*-tolyl).—ω-Hydroxyimino-4-methylacetophenone (30 g.) in the minimum of ethanol was added to a cold stirred solution of stannous chloride (105 g.) in concentrated hydrochloric acid (150 ml.). Further hydrochloric acid (45 ml.) was added, and the mixture kept overnight at −5°. The solid salt was collected, dissolved in warm water, and treated with hydrogen sulphide. Filtration and evaporation of the filtrate to dryness gave 4-methylphenacylamine hydrochloride, m. p. 210° (from absolute ethanol) (lit.,[15] m. p. 206°) (22·5 g., 66%).

3-*Methylphenacylamine Hydrochloride* (III; R = *m*-tolyl).—3-Methylacetophenone (22 g.) was added to a cold solution of sodium (4 g.) in absolute ethanol (100 ml.). To the stirred mixture was added pentyl nitrite (20 g.), and the dark red solution was kept at 0° for 4 hr. during which a chocolate-brown solid separated. Ice-water was added, and the alkaline mixture was extracted with ether. The aqueous layer was acidified with ice-cold 5N-hydrochloric acid, and the crude hydroxyimino-compound (10 g.) was collected and reduced as

[15] Ryan, *Ber.*, 1898, **31**, 2133.

described above, to give 3-methylphenacylamine hydrochloride (3·4 g.), m. p. 175—176° (from ethanol–ether). The *picrate* crystallized from 95% ethanol as yellow prisms, m. p. 170—170·5° (Found: C, 47·7; H, 3·7. $C_{15}H_{14}O_8N_4$ requires C, 47·6; H, 3·7%).

N-*Acetyl*-β-*hydroxy*-4-*methylphenethylamine* (V; R = *p*-tolyl).—4-Methylphenacylamine hydrochloride was converted into *N*-acetyl-4-methylphenacylamine as described by Buu-Hoï, Xuong, and Khoï.[16] This (4·1 g.) in 95% ethanol (100 ml.) was shaken with Adams catalyst (0·115 g.) and hydrogen at atmospheric temperature and pressure until 1·1 mol. of hydrogen had been absorbed. The solution was then filtered and evaporated under reduced pressure. The *hydroxy-amide* (3·0 g., 72%) crystallized from tetrahydrofuran as rhombs, m. p. 150—151° (Found: C, 68·5; H, 7·6. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8%).

1,7-*Dimethylisoquinoline*.—The amide (V; R = *p*-tolyl) (2·5 g.) in dry xylene (50 ml.) was added to phosphoric oxide (20 g.) and phosphorus oxychloride (5 ml.), the mixture was boiled under reflux for 1 hr., then treated with ice, and the aqueous layer was separated and basified. The oil which separated was extracted with ether, dried (K_2CO_3), and distilled, giving 1,7-*dimethylisoquinoline*, b. p. 148—150°/15 mm., m. p. 35—37° (0·89 g., 44%) (Found: C, 83·8; H, 7·4; N, 8·9. $C_{11}H_{11}N$ requires C, 84·0; H, 7·1; N, 8·9%). The *picrate* crystallized from ethanol as yellow prisms, m. p. 223—224° (Found: C, 53·3; H, 4·3. $C_{17}H_{14}N_4O_7$ requires C, 52·9; H, 3·7%).

1,6-*Dimethylisoquinoline*.—3-Methylphenacylamine hydrochloride (2 g.) gave its *N*-acetyl derivative, needles, m. p. 79—80° (from ethyl acetate–light petroleum) (1·05 g.).

The amide (IV; R = *m*-tolyl) (1·0 g.), reduced catalytically as described above, gave an oily hydroxy-amide (V; R = *m*-tolyl). This was dried at 95°/15 mm., and cyclized in xylene to 1,6-dimethylisoquinoline, b. p. 145—150° (bath temp.)/15 mm. (0·5 g., 61·5%). The picrate crystallized from ethanol as yellow needles, m. p. 225—227° (Found: C, 52·5; H, 3·4%).

β-*Hydroxy*-β,4-*dimethylphenethylamine* (VII; R = *p*-tolyl).—Dry 4-methylphenacylamine hydrochloride (11·5 g.) was added to the stirred Grignard reagent from methyl iodide (60 g.), in ether (600 ml.). The mixture was stirred at the b. p. for 4 hr., then cooled and treated with ice-water, followed by 5N-hydrochloric acid. The aqueous layer was basified with aqueous ammonia (*d* 0·88), and the liberated base was extracted with ether. The dried (Na_2SO_4) ethereal solution was distilled, giving the hydroxyamine, b. p. 148—150°/20 mm. (2·6 g., 25·4%). The *picrate* crystallized from water as yellow prisms, m. p. 180—181° (Found: C, 49·1; H, 4·4. $C_{16}H_{18}O_8N_4$ requires C, 48·75; H, 4·6%).

A solution of this hydroxy-amine (2·3 g.) in 90% formic acid (50 ml.) was heated on a boiling-water bath for 3 hr. The solution was concentrated under reduced pressure and diluted. The precipitated N-*formylstyrylamide* (VIII; R = *p*-tolyl) crystallized from ethyl acetate–light petroleum as prisms, m. p. 157—157·5° (0·25 g.) (Found: C, 75·0; H, 7·2. $C_{11}H_{13}ON$ requires C, 75·4; H, 7·5%), $\lambda_{max.}$ 278 mμ ($\log_{10}$ ε 4·32) in 95% EtOH.

The acid filtrate, after separation of the amide, was basified to give some amine, and this was further heated with 90% formic acid to give more amide (0·15 g.). Total yield of amide was 0·4 g. (16·4%).

4,7-*Dimethylisoquinoline*.—The amide (VIII; R = *p*-tolyl) (0·4 g.) was cyclized (as described for 1,7-dimethylisoquinoline above) to give 4,7-dimethylisoquinoline, b. p. 140° (bath-temp.)/15 mm. (0·13 g., 36%). The *picrate* crystallized from ethanol as yellow prisms, m. p. 223° (Found: C, 52·6; H, 3·4%).

o-*Ethylbenzaldehyde*.—Ethyl *N*-phenylformimidate [17] (8·5 g.) was added slowly, at room temperature, to the stirred Grignard reagent from *o*-ethyliodobenzene (14·8 g.) in ether (150 ml.), and the mixture was then boiled for 30 min. A mixture of ice and 5N-hydrochloric acid was added, and the ether was distilled off, the aqueous residue being heated on a boiling-water bath for 30 min. The cooled mixture was extracted with ether, and the combined ethereal extracts were dried (Na_2SO_4) and distilled. The yield of *o*-ethylbenzaldehyde, b. p. 88—90°/11 mm., was 3·5 g. (40·8%).

8-*Ethylisoquinoline*.—*o*-Ethylbenzaldehyde (1·3 g.) was mixed at room temperature with amino-acetal (2 g.) and then heated on a boiling-water bath for 1 hr. Ether (10 ml.) was added to the cooled mixture, the water was separated, and the dried (Na_2SO_4) ethereal solution was distilled, giving the aldimine (X), b. p. 148°/2·5 mm. (1·56 g., 68·3%).

The aldimine (2·5 g.), dissolved in concentrated sulphuric acid (22 g.) at 0—5°, was added

[16] Buu-Hoï, Xuong, and Khoï, *J.*, 1951, 255.
[17] Roberts, *J. Amer. Chem. Soc.*, 1949, **71**, 3848.

slowly to a mixture of concentrated sulphuric acid (3 g.) and phosphoric oxide (5 g.) at 180°. The mixture was then cooled, diluted, and extracted with ether. The aqueous acid layer was basified and extracted with ether, evaporation of the ethereal extracts giving a small quantity of oil. This oil, with ethanolic picric acid, gave 8-*ethylisoquinoline picrate*, crystallizing from absolute ethanol as yellow prisms, m. p. 158—160° (some needles formed in the melt; these vanished at 183—184°) (Found: C, 52·9; H, 3·5%).

β-*Methylphenethylamine* (XII; R = Ph, R′ = Me).—ω-Hydroxyiminoacetophenone (10 g.) was added to the stirred solution of the Grignard reagent from methyl iodide (50 g.) in ether (500 ml.). The mixture was boiled for 1 hr., cooled, and treated with ice-water and then with 2N-hydrochloric acid. The ethereal layer was separated, shaken with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and distilled. The hydroxy-oxime (XI; R = Ph, R′ = Me) (9 g., 82%) had b. p. 136—140°/0·1 mm.

Sodium (18 g.) was added to the vigorously boiling solution of the hydroxy-oxime (XI; R = Ph, R′ = Me) (9 g.) in dry ethanol (150 ml.). When all the sodium had dissolved the solution was concentrated and then poured into water. The amine was extracted by ether, dried (K_2CO_3), and distilled. The amine (XII; R = Ph, R′ = Me) had b. p. 112°/27 mm. (3 g., 40·7%). The picrate had m. p. 181° (lit.,[18] m. p. 179—181°), and the benzoate had m. p. 84° (lit.,[18] m. p. 85—87°).

β,2-*Dimethylphenethylamine* (XII; R = *o*-tolyl, R′ = Me).—Prepared as above from *o*-tolylmagnesium bromide and hydroxyiminoacetone, the hydroxy-oxime had b. p. 132—134°/0·5 mm. (yield 42·7%). Reduction with sodium in ethanol gave the amine (XII; R = *o*-tolyl, R′ = Me), b. p. 86—88°/1·5 mm. (40%). The *picrate* crystallized from ethanol as yellow prisms, m. p. 173—173·5° (Found: C, 50·3; H, 4·65. $C_{16}H_{18}O_7N_4$ requires C, 50·8; H, 4·8%).

β-*Ethylphenethylamine* (XII; R = Ph, R′ = Et). Prepared as described above from hydroxyiminoacetophenone and ethylmagnesium bromide, the hydroxy-oxime (XI; R = Ph, R′ = Et) had b. p. 128—130°/0·2 mm. (yield 42%). Reduction with sodium in ethanol gave the amine, b. p. 114—120°/20 mm. (40%). The N-*formyl derivative* (XIII; R = Ph, R′ = Et), prepared by heating the amine and 98% formic acid at 190° for 4 hr., had b. p. 150—152°/1·5 mm. (Found: N, 7·9. $C_{11}H_{15}ON$ requires N, 7·9%).

4-*Ethylisoquinoline* (XV; R′ = Et).—The amide (XIII; R = Ph, R′ = Et) (1·5 g.) was cyclized, as previously described, by means of phosphoric oxide (10 g.) in xylene (50 ml.). Working up gave the dihydroisoquinoline (XIV; R′ = Et) (0·3 g.), b. p. 110—115° (bath-temp.)/13 mm.

The dihydroisoquinoline (0·3 g.) and palladized charcoal (0·3 g.) were heated together at 190° for 4 hr. Distillation gave the isoquinoline (XV; R′ = Et), b. p. 145° (bath-temp.)/15 mm. The *picrate* crystallized from ethanol as yellow prisms, m. p. 163—164° (Found: C, 53·2; H, 4·1%).

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[*Received, November 13th*, 1959.]

[18] Tsukervanik and Grebenyuk, *Doklady Akad. Nauk S.S.S.R.*, 1951, **76**, 223 (*Chem. Abs.*, 1951, **45**, 6604).