methylamine hydrochloride, m.p. and admixture m.p. 222–224°. The recovery by extraction in this manner is only 33%. Calculated from the quantity of diazomethane eventually obtained (below) from the crude sodium chloride–methylamine hydrochloride mixture, however, the reduction proceeds to the monoamine to the extent of at least 85% (see also Hershberg, *et al.*[4]). Quantitative separation of pure methylamine at this stage requires distillation (gas rack) of the free amine liberated with alkali from the crude reduction residue and collection in hydrochloric acid.

Nitroso-C^{14}-methylurea.—The hydrogenation residue from 205 mg. (4.18 mmoles) of $NaC^{14}N$, in water (1 ml.), was refluxed (3 hours) with 711 mg. (11.85 mmoles) of urea. An aqueous solution (5.6 ml.) of carrier methylurea (790 mg., 10.7 mmoles), and sodium nitrate (1.3 g.), were added, and to this, sulfuric acid (0.65 ml. in 7.1 g. of ice–water mixture) was added dropwise and with stirring (15 minutes). The precipitated dried (vacuum) nitroso-C^{14}-methylurea (1.04 g., 10.0 mmoles) had m.p. and admixture m.p. 120–123°. The yield is 55%, calculated from cyanide and ascertained gravimetrically from trial runs from $NaC^{12}N$ without addition of methylurea.

Plated (1.0 μg./cm.^{2}), from methanol, the product showed 4.75×10^7 cts./min./mmole against 6.65×10^8 for the diazomethane-C^{14} generated (below) from the same material. Nitroso-methylurea thus decomposes with almost complete loss of methyl carbon on thin plating. Attempts to count under an end window G.M. tube led to contamination of the latter from volatile decomposition product(s).

Diazomethane-C^{14}.—The nitroso-C^{14}-methylurea (1.04 g.) was decomposed in the usual manner[3] with potassium hydroxide solution (3 ml. of 50%), and the liberated diazomethane-C^{14} (319 mg., 7.6 mmoles) distilled in ether (50 ml.).

For determination of specific activity, 50 mg. of 3-keto-Δ^4-etiocholenic acid was esterified with an aliquot (1.0 ml.) of the above ethereal solution of diazomethane-C^{14}. The corresponding C^{14}-methyl ester, separated and purified by alumina chromatography, had m.p. and admixture m.p. 132–133°, and 6.65×10^8 cts./min./mmole.

The over-all yield of diazomethane from cyanide is 41–42%, as determined in trial runs from $NaC^{12}N$ and estimated by back titration of excess standard benzoic acid solution.

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Phenylquinolines[1]

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Several phenylquinolines were prepared for the purpose of studying orientation in nitration. 6-Phenylquinoline (I) and 8-phenylquinoline (II) have been prepared previously[3] by the Skraup reaction on *o*- and *p*-aminobiphenyl. The decomposition of benzenediazonium hydroxide in quinoline has also been used to prepare 8-phenylquinoline.[4] The Conrad–Limpach reaction has been used to obtain 8-phenyl-4-hydroxyquinaldine.[5]

The yield of I by the Skraup reaction on the acetyl derivative[6] of *p*-aminobiphenyl was considerably greater than from the free amine. In the case of II, there seemed to be little difference in the yield. However, in both instances the use of *o*-nitrophenol as the oxidizing agent gave a better yield than did arsenic acid. 8-Phenyl-4-hydroxyquinaldine (V) was obtained by the Conrad–Limpach reaction but unlike most ring closures of this type the crude methyl β-(*o*-biphenylamino)-crotonate underwent ring closure by merely heating in vacuum at 180–190°. The melting point of V however was 207–209°, much lower than the 280° reported by Hughes and Lions.[5] A product of the same melting point (207–209°) was obtained when some of the crude aminocrotonate, which had not previously been subjected to a high temperature, was added to boiling phenyl ether. This melting point, however, is lower than one would predict.

The ring closure of *p*-phenylacetoacetanilide by the customary reagent, concentrated sulfuric acid, always produced either a sulfur containing substance or did not cause ring closure. Phosphoric acid did not give satisfactory results either, only small amounts of a material believed to be 6-phenyl-4-methylcarbostyril was obtained. Rather unexpectedly, the addition of *p*-phenylacetoacetanilide to mineral oil at 275° gave a 70% yield of a substance (m.p. 213–214°) which did not depress the melting point of the compound obtained by the phosphoric acid ring closure. As in the case of V, melting point of 6-phenyl-4-methylcarbostyril is much lower than expected. Attempts at ring closure of *o*-phenylacetoacetanilide gave only oils and other intractable material.

o-Aminobiphenyl and *p*-aminobiphenyl were condensed with ethyl sodioethoxalylacetate according to the procedure of Lisk and Stacy[7] then ring closure to the 8- and 6-phenyl-4-hydroxy-2-carbethoxyquinoline was brought about in boiling phenyl ether. Saponification and decarboxylation proceeded without difficulty.

Experimental

6-Phenylquinoline (I).—A solution of 67.3 g. (0.4 mole) of 4-aminobiphenyl in 200 ml. of methanol was treated at room temperature with 46.6 ml. (0.48 mole) of acetic anhydride. After precipitation seemed to be complete, the *p*-phenylacetanilide was removed by filtration, washed with 50-ml. portions of ethyl alcohol and dried at 100°. The yield was 72 g. (88%), m.p. 168–172°. Recrystallization from methyl alcohol gave a substance which melted at 171–172°. The melting point recorded in literature is 171°.[8]

A mixture of 21.1 g. (0.10 mole) of crude *p*-phenylacetanilide, 8.3 g. (0.06 mole) of *o*-nitrophenol, 6.5 g. of boric acid and 37.5 g. (0.40 mole) of anhydrous glycerol was heated in an oil-bath to about 110° and 18 ml. of concentrated sulfuric acid was added in small portions while the solution was stirred mechanically. The rate of addition was regulated so as to keep the temperature of the reaction mixture at 125–130°. After the addition of sulfuric acid, the solution was maintained at 130–133° for two hours and finally refluxed for five hours. After cooling, ice was added, then the reaction mixture was neutralized with concentrated sodium hydroxide and the solid removed by filtration. The dark colored substance was dissolved in 30 ml. of ethyl alcohol, treated with Norite, filtered and the boiling alcohol solution diluted with water to the cloud point. The yield of gray colored solid was 8.6 g. (42%); the substance melted at 103–106°. Recrystallization from 50% ethyl alcohol raised the melting point 109–110°. The melting point recorded for 6-phenylquinoline is 110–111°.[3]

8-Phenylquinoline (II).—This substance was prepared from *o*-aminobiphenyl, instead of its acetyl derivative, by essentially the same method as was used for 6-phenylquinoline, except that the substance was extracted with benzene

(1) Contribution No. 505 from the Chemistry Laboratory of Indiana University.

(2) Abstracted from a thesis submitted by Mason Hayek to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree, Doctor of Philosophy, in the Department of Chemistry, Indiana University, June, 1947.

(3) W. La Coste and C. Sorger, *Ann.*, **230**, 1 (1885).

(4) R. Mohlau and R. Berger, *Ber.*, **26**, 1994 (1893).

(5) G. K. Hughes and F. Lions, *C.A.*, **33**, 611 (1939).

(6) R. F. H. Manske, F. Leger and G. Gallagher, *Can. J. Research*, **19B**, 318 (1941).

(7) G. F. Lisk and G. W. Stacy, THIS JOURNAL, **68**, 2686 (1946).

(8) F. Heusler, *Ann.*, **260**, 234 (1890).

and distilled in vacuum since it is a liquid. The yield, after two fractional distillations was 11.8 g. (57.6%) and the distillation temperature was 198–200° at 13 mm. pressure. The boiling point recorded in literature[4] is 270–276° at 80 mm. pressure.

Methyl β-(*p*-Biphenylamino)-crotonate (III).—A solution of 169 g. (1.0 mole) of *p*-aminobiphenyl and 131.5 g. (1.1 moles) of methyl acetoacetate in 375 ml. of chloroform, acidified with 4 drops of dilute hydrochloric acid, was refluxed under a heavier-than-water liquid separator until no more water collected. After cooling, the crystalline mass in the flask was diluted with 200 ml. of petroleum ether and the solid removed by filtration. The yield was 235.5 g. (88.5%) and the substance melted at 164–165.5°. Two grams of III was purified by recrystallization from ethyl alcohol. Pure III was obtained as white platelets which melted at 165–166.5°.

Anal. Calcd. for $C_{17}H_{17}NO_2$: N, 5.24. Found: N, 5.24.

6-Phenyl-4-hydroxyquinaldine (IV).—Diphenyl ether (130 ml.) was heated to boiling and 32.3 g. (0.12 mole) of crude III was added in one portion. The solution was boiled until no more methyl alcohol distilled. After the solution cooled to room temperature, it was diluted with 25–30 ml. of petroleum ether, filtered and the solid washed first with ethyl ether then with petroleum ether. The yield of IV was 23.5 g. (83%) and it melted at 315–316°. Recrystallization from isopropyl alcohol, with decolorizing charcoal, did not change the melting point.

Anal. Calcd. for $C_{16}H_{13}NO$: N, 5.95. Found: N, 5.96.

8-Phenyl-4-hydroxyquinaldine (V).—Methyl acetoacetate and *o*-aminobiphenyl were condensed in chloroform solution as in the preparation of III. The crude liquid methyl β-(*o*-biphenylamino)-crotonate could not be caused to solidify. In an attempt to remove the excess methyl acetoacetate, the liquid was heated in an oil-bath at 180–190° at a pressure of 13 mm. After cooling, the contents of the flask congealed. Recrystallization of the solid from dilute ethyl alcohol and from benzene gave 106 g. (45%) of V which melted at 207–209°. A mixed melting point with V which was produced by ring closure of a small amount of the above crude liquid *o*-biphenylaminocrotonate in boiling phenyl ether, showed no depression. The melting point for V recorded by Hughes and Lions[5] is 280°.

Anal. Calcd. for $C_{16}H_{13}NO$: N, 5.95. Found: N, 6.08.

6-Phenyl-4-methylcarbostyril (VI).—*p*-Phenylacetoacetanilide was prepared in an 85% yield from *p*-aminobiphenyl and diketene in benzene according to the general procedure described by Kaslow and Sommer.[9] The substance melted at 147–148.5°. Eighteen grams (0.07 mole) of *p*-phenylacetoacetanilide was added to 150 ml. of mineral oil at 275° and the heating continued for two minutes. After cooling, 100 ml. of petroleum ether was added, the solid removed by filtration and washed with ether. The yield of brown colored crude VI was 11.7 g. (70.5%) which melted at 187–196°. After recrystallization from ethyl alcohol and cellosolve, the substance melted at 213–214.5°.

Anal. Calcd. for $C_{16}H_{13}NO$: N, 5.95. Found: N, 5.72.

6-Phenyl-4-hydroxy-2-quinolinecarboxylic Acid (VII).—A mixture of 41 g. (0.2 mole) of *p*-aminobiphenyl hydrochloride and 43.5 g. (0.22 mole) of ethyl sodioethoxalylacetate in 250 ml. of absolute ethyl alcohol was stirred for 40 hours at room temperature with 60 g. of anhydrous sodium sulfate. The solution was diluted with 1.5 liters of water, the solid which separated was washed, dissolved in ether then shaken with 125 ml. of 10% hydrochloric acid. The ether layer was next washed with 2% sodium bicarbonate solution, and dried over sodium sulfate. After removal of the ether, the oily residue weighed 57 g. Five grams of the above oil was added in one portion to 40 ml. of boiling phenyl ether and after 5 minutes the solution allowed to cool. The solid was removed by filtration, washed with successive portions of ether and petroleum ether and dried. This procedure was repeated in 5-g. portions for the remainder of the crude ethyl β-carbethoxy-β-(*p*-biphenylamino)-crotonate. The yield of the light yellow crystalline 6-phenyl-4-hydroxy-2-carbethoxyquinoline (VIII) was 37 g. (63%). The substance melted at 226–227°; recrystallization did not raise the melting point. The ester (10 g., 0.034 mole) was refluxed with 75 ml. of 10% sodium hydroxide solution for one hour, filtered and then diluted with about 400 ml. of water and acidified with phosphoric acid. The yield of light cream-colored solid was 8.5 g. (94%). The substance melted at 261–261.5° with decomposition.

Anal. Calcd. for $C_{16}H_{11}NO_3$: N, 5.28. Found: N, 5.54.

6-Phenyl-4-hydroxyquinoline (IX).—Sixty-five milliliters of phenyl ether was heated to boiling and 7.5 g. (0.028 mole) of VIII was added in 0.2–0.4 g. portions over a period of 5–10 minutes and the heating continued for an additional 5–10 minutes. After cooling, the crude IX was removed by filtration and washed with successive portions of diethyl ether and petroleum ether. The crude IX was recrystallized from ethyl alcohol giving 3.9 g. of light gray colored needles which melted at 279–281°.

Anal. Calcd. for $C_{15}H_{11}NO$: N, 6.33. Found: N, 6.35.

8-Phenyl-4-hydroxy-2-quinolinecarboxylic Acid (X).—This substance was prepared from *o*-aminobiphenyl and ethyl sodioöxaloacetate by exactly the same procedure as was employed for VII. The yield of the intermediate ester, 8-phenyl-4-hydroxy-2-carbethoxyquinoline (XI), was 29 g. (49%) from 0.2 mole of *o*-aminobiphenyl. XI melted at 154.5–156°. Saponification of XI (8 g.) was carried out as in the case of VIII but on acidification with phosphoric acid, the precipitated acid contained a large amount of the sodium salt. Acidification of the hot solution gave pure X as a voluminous white solid. The yield was 5.2 g. (71.5%). X melted at 236–238° with decomposition.

Anal. Calcd. for $C_{16}H_{11}NO_3$: N, 5.28. Found: N, 5.53.

8-Phenyl-4-hydroxyquinoline (XII).—Decarboxylation of XI was carried out in the same manner as for VIII; 4.8 g. of XI gave 2.4 g. (60%) of pure XII after recrystallization from aqueous ethyl alcohol. The substance melted at 203.5–204°.

Anal. Calcd. for $C_{15}H_{11}NO$: N, 6.33. Found: N, 6.10.

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(9) C. E. Kaslow and N. B. Sommer, THIS JOURNAL, **68**, 644 (1946).

Totally Synthetic Lumiestrone

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In our total synthesis of estrone[1] three of the seven possible racemic stereoisomers of estrone were also produced. For reasons which were implied[1] (and are now stated below) we suggested that one of these isomers, estrone "g," m.p. 240°, represented the *dl* modification of lumiestrone. More recently Anner and Miescher[2] dismissed this hypothesis, and presented the counter proposal that their estrone "f" (m.p. 190°), which is clearly different from our "g," was indeed *dl*-lumiestrone. The arguments which they presented in support of this thesis are, in our opinion, inconclusive. The low reactivity of the carbonyl group toward Girard reagent would not be expected to be unique for lumiestrone. Moreover, there is no assurance that those reactions to produce estrone "f" from "keto ester B" and those leading to lumidoisynolic acid (from the same keto ester) take the same stereochemical course. Even if this is the case, however, the fact that only single substances were isolated in each series cannot be taken to mean that they were the exclusive products formed.

In the preparation of estrone "g" the β form of the benzylidene derivative I was methylated with potassium *t*-butoxide and methyl iodide. This treatment gave two products, β^1 and β^2, which by analogy to the established structure of the methyla-

(1) W. S. Johnson, D. K. Banerjee, W. P. Schneider and C. D. Gutsche, THIS JOURNAL, **72**, 1426 (1950).

(2) G. Anner and K. Miescher, *Helv. Chim. Acta*, **33**, 1379 (1950).