with methanol. The m.p. of this material, 16.3 g., was 67–72° (unsharp). Since repeated recrystallizations from methanol did not give a substance with sharp m.p., we dissolved the material in petroleum ether and chromatographed it on alumina, collecting fractions of 50 ml. Fractions 5–8 gave a crystalline residue of m.p. 86–87°, which upon recrystallization from isopropyl alcohol formed yellow cubes of m.p. 87°.

Anal. Calcd. for $C_{16}H_{11}OCl_3$: C, 59.0; H, 3.4. Found: C, 59.1; H, 3.4.

The ketone II did not react with any of the usual carbonyl reagents.

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Reductions with Hydrazine Hydrate Catalyzed by Raney Nickel. I. Aromatic Nitro Compounds to Amines[1,2]

BY D. BALCOM AND ARTHUR FURST

RECEIVED APRIL 13, 1953

Hydrazine, though a powerful reducing agent is not used extensively to reduce aromatic nitro compounds to amines. The rate of reaction is too slow. If employed in a sealed tube[3] or in high boiling solvents[4] almost all functional groups are reduced.

With the addition of a small amount of Raney nickel catalyst, hydrazine hydrate will selectively reduce an aromatic nitro compound to an amine at room or steam-bath temperature. Yields are excellent ranging from 80 to 99%. Under these conditions other functional groups, namely, carbonyls, will not be affected. To eliminate loss due to foaming a large excess of solvent alcohol is necessary. We have confirmed Kuhn's[5] observation that no reduction takes place even after 18 hours if no catalyst is added. The mechanism of the reaction is unknown, but hydrazine when catalytically decomposed liberates only water and gases[6] so that elimination of by-products is not a problem.

Experimental

As all of the aromatic nitro compounds listed here were reduced by the same method, only a general procedure is given. In each case the amino compound listed was also obtained by the reduction of the nitro compound by a procedure obtained from the literature. Mixed melting points as well as fusion analysis[7] helped prove the identity of the amino compound. In some cases the hydrochloride rather than the free amine was isolated.

Generalized Procedure.—To the nitro compound dissolved in alcohol (10 ml./g.) was added 2–3 molar ratios of hydrazine hydrate 100%. The solution was placed on the steam-bath and when just warm a small amount of Raney Ni was added. The solution frothed. As the reaction proceeded (5 to 60 min.) the color changed from yellow to almost colorless. More catalyst was added to decompose the excess hydrazine and the solution was heated to boiling to drive off the dissolved gases. The hot solution was filtered to remove the Ni, boiled with decolorizing carbon and filtered again. The free amine was isolated by cooling the solution to *ca.* 50° and then pouring into a large excess of water; or the hydrochloride salt was obtained by evaporating the solvent to *ca.* 5–10 ml., adding *ca.* of 5 ml. ofconcentrated hydrochloric acid and cooling the mixture. The precipitates were isolated and dried.

Amines.—By this procedure *p*-aminobiphenyl ether[8] was obtained in 96.5% yield. Other amines obtained in yield between 80 and 99% were *p*-aminocinnamic acid,[9] *m*-aminobenzophenone,[10] 2-methyl-4′-aminobiphenyl,[11] 4,4′-diaminodiphenyl ether[12] and aniline.

Biological Testing.—These compounds were tested for their effect on the mouse Sarcoma-37. No inhibitory action was noted.[13]

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(2) This investigation was supported in part by a research grant from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service, and from the Catherine Stern Memorial Fund.

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Preparation of 1-Methyl-3-phenyl-3-(γ-dimethylaminopropyl)-piperidine

BY F. F. BLICKE AND EU-PHANG TSAO

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Phenyldi-(γ-dimethylaminopropyl)-acetonitrile, prepared from phenylacetonitrile, γ-dimethylaminopropyl chloride and sodamide, was hydrolyzed to the corresponding acetic acid. The latter compound was refluxed with thionyl chloride, the excess thionyl chloride removed and the residue heated until the evolution of methyl chloride stopped. The 1-methyl-3-phenyl-3-(γ-dimethylaminopropyl)-2-piperidone was reduced with lithium aluminum hydride to the corresponding piperidine.

Experimental

Phenyldi-(γ-dimethylaminopropyl)-acetonitrile.—Phenylacetonitrile (35.2 g.) in 50 cc. of toluene was added, gradually, to a stirred mixture of 29.3 g. of sodamide in 100 cc. of toluene at 40–50°. The mixture was stirred for 1 hour, then 90 g. of γ-dimethylaminopropyl chloride[1] was added, dropwise, to the stirred mixture at 40–50°. The material was refluxed for 6 hours and treated in the usual manner. After fractionation 70.0 g. (81.3%) of nitrile was obtained, b.p. 155–158° (1 mm.).

The dihydrochloride, prepared from an ethereal solution of the base and hydrogen chloride, melted at 280–282° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{18}H_{31}N_3Cl_2$: N, 11.66; Cl, 19.72. Found: N, 11.55; Cl, 19.71.

Phenyldi-(γ-dimethylaminopropyl)-acetic Acid.—A mixture of 57.4 g. of the nitrile, 94 cc. of concd. sulfuric acid and 63 cc. of water was refluxed for 2 hours. The cold mixture was poured into water and sodium hydroxide was added until the mixture was only slightly acidic. It was then decolorized with Norite. The filtered solution was made alkaline whereupon an oil separated. A further amount of oil was obtained by extraction of the aqueous solution with chloroform and removal of the solvent. When the oil was warmed under 16 mm. pressure for some time, it be-

(1) A. Mercer, *Helv. Chim. Acta*, **24**, 209 E (1941).

came crystalline; m.p. 116–117° after recrystallization from acetone. This material was found to be the acid amide.

Anal. Calcd. for $C_{18}H_{31}ON_3$: N, 13.77. Found: N, 13.58.

The amide was refluxed with 150 cc. of 70% sulfuric acid for 48 hours. The mixture was poured onto ice, the solution was decolorized with Norite, filtered and the filtrate made alkaline with sodium hydroxide (*p*H 8–9). After the precipitated oil had been warmed under 16 mm. pressure, it became crystalline. The product was dissolved in absolute alcohol, the solution was filtered and the filtrate evaporated to dryness. The acid melted at 197–198° after recrystallization from dioxane.

Anal. Calcd. for $C_{18}H_{30}O_2N_2$: N, 9.15. Found: N, 8.96.

1-Methyl-3-phenyl-3-(γ-dimethylaminopropyl)-2-piperidone.—A mixture of 24.5 g. of the acid and 75 cc. of thionyl chloride was refluxed for 1.5 hours. The excess thionyl chloride was removed and the solid residue was heated in an oil-bath (200–205°) for 40 minutes when the evolution of gas practically stopped. The cold residue was dissolved in water, the solution was made alkaline and extracted with ether. Upon fractionation 12.5 g. (57%) of product was obtained, b.p. 148–150° (0.01 mm.).

The hydrochloride, obtained by the use of hydrogen chloride, melted at 182–183° after recrystallization from methyl ethyl ketone.

Anal. Calcd. for $C_{17}H_{27}ON_2Cl$: N, 9.02; Cl, 11.40. Found: N, 9.06; Cl, 11.61.

1-Methyl-3-phenyl-3-(γ-dimethylaminopropyl)-piperidine.—The piperidone (9.6 g.), dissolved in 30 cc. of ether, was reduced with 1.4 g. of lithium aluminum hydride dissolved in 70 cc. of ether. The mixture was stirred and refluxed for 5 hours, 3 cc. of water was added and the product was isolated in the usual manner; b.p. 122–124° (0.5 mm.), yield 7.8 g. (86%).

Since both the hydrochloride and the methobromide were hygroscopic, the methiodide was prepared. One gram of the base, dissolved in ether was treated with 2 g. of methyl iodide. After 2 hours the precipitated methiodide was recrystallized from methyl ethyl ketone; m.p. 172–173°.

Anal. Calcd. for $C_{18}H_{31}N_2I$: N, 6.97; I, 31.58. Found: N, 6.93; I, 31.50.

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The Significance of Basicity and Acidity of Nuclei in Cyanine Type Condensations

BY L. G. S. BROOKER, S. G. DENT, JR., D. W. HESELTINE AND E. VAN LARE

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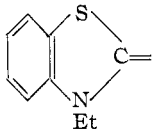
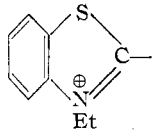
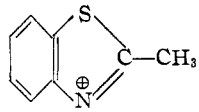
The gain in stabilization in passing from the net-uncharged form to the positively charged form of certain heterocyclic rings (*e.g.*, from I to II) is a quantity (the "basicity") that has considerable

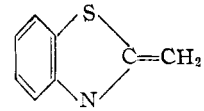

I


II

significance for the absorptions of cyanine and related dyes containing these nuclei.[1] It is now suggested that this "basicity" has an equal significance in reactions leading to these dyes.

These reactions commonly employ quaternary salts of heterocyclic bases containing a reactive methyl group (III is a typical cation), the cations losing a proton to give methylene bases (*e.g.*, IV)


III


IV

which are the reactive intermediates.[2] The formulas show that the formation of methylene base by the process III → IV involves the same loss of ring stabilization as in II → I, and, as a general proposition, a methylene base will be liberated from the corresponding cation the more readily, the lower the basicity of the nucleus in the sequence established by the "deviation" and similar procedures.[1] The *availability* of methylene base in a given reaction (which will in large measure determine whether that reaction will take place or not) therefore depends partly on the basicity of the particular nucleus and partly on the basic nature of the reaction medium.

By this reasoning it becomes possible to correlate a great many hitherto unrelated empirical observations and to account for many seeming anomalies, of which the following examples are illustrative.

Salts of a number of the less basic cations in the sequence[1] referred to react directly with *p*-dimethylaminobenzaldehyde in ethanol solution to give high yields of styryl dyes, whereas salts of more basic cations require piperidine as catalyst. For the first group, the aldehyde is itself sufficiently basic to liberate methylene base, but not for the second group. Again, salts of highly basic nuclei, such as α-picoline ethiodide, fail completely to give carbocyanine by the pyridine–ethyl orthoformate method. Here the nucleus is so basic that an insufficient concentration of methylene base is reached under the conditions of the experiment. Similarly, the low yields of carbocyanines given by salts of certain thiazoles (*e.g.*, 2,4-dimethylthiazole ethiodide)[3] are a consequence of the high basicity of these nuclei.[1] Introduction of a negative substituent (as in 5-ethoxycarbonyl-2,4-dimethylthiazole ethiodide) increases the apparent reactivity of the 2-methyl group[4] (*i.e.*, the yields of certain dyes are higher) by lowering the basicity of the nucleus and increasing the availability of the methylene base.

Less is known about the actual reactivity of a methylene base, as distinct from its availability. It is possible that the reactivity increases with increasing basicity of the ring, though this is still uncertain.

By somewhat similar reasoning, the yields of dyes of the merocyanine and oxonol types may be correlated with the "acidity" of the ketomethylene compounds that give them.[5] Such condensations also take place under basic conditions, and it is reasonable to suppose that the first step is the loss

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