Methyl 3-Nitrobiphenyl-2-carboxylate.—Methyl 6-nitro-2-aminobenzoate was diazotized and subjected to the Gomberg reaction with benzene as described previously for the analogous case of methyl 5-nitro-2-aminobenzoate.[19] A 7% yield of colorless crystals, m.p. 121°, was obtained; Chase and Hey[2] record m.p. 121.5–122.5°. 0.3 g. of this substance was converted directly to yield 50 mg. of 1-nitrofluorenone by heating in 5 cc. of concentrated sulfuric acid for one hour at 100°.

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(19) I. M. Heilbron, D. H. Hey and R. Wilkinson, *J. Chem. Soc.*, 115 (1938).

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A Novel N-Alkylation Reaction

BY IRVING ALLAN KAYE, CHESTER L. PARRIS AND NATHAN WEINER

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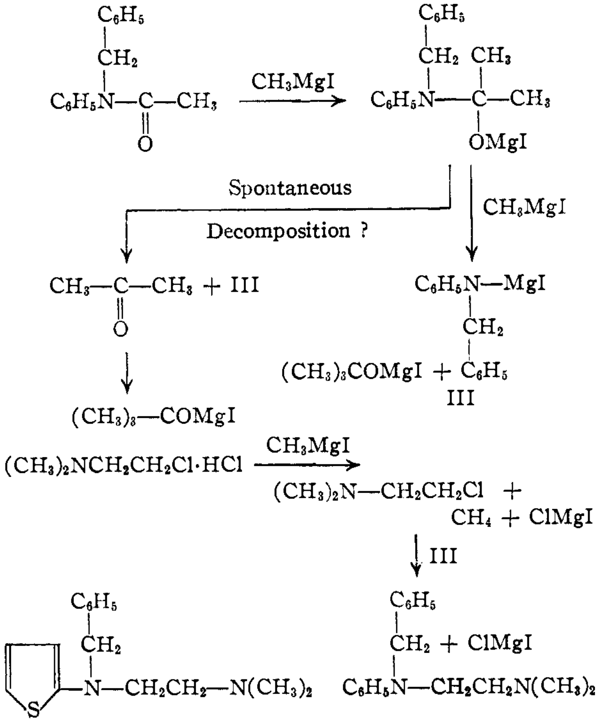
Attempts to prepare the thiophene analog (II) of Antergan (I)[1] by methods which have been successfully employed in the synthesis of its thiazole[2] and pyridine[3] isosteres have not been found practical due to the low reactivity of the halogen in 2-bromothiophene[4] and the extreme air-sensitivity of 2-thienylamines.[5] Stability of the latter in air is enhanced considerably by acetylation and the amides, in the form of N-sodio derivatives, can be alkylated.[5] Since N-benzyl-N-(2-thienyl)-acetamide, obtained in good yield by heating 2-acetamidothiophene and benzyl chloride in toluene solution in the presence of lithium amide, was on hand, a method was sought whereby this amide could be converted directly to the tertiary amine (II) without isolation of the presumably unstable 2-benzylaminothiophene. It appeared possible to accomplish this by interaction of the amide with a Grignard reagent, a method available for the preparation of ketones[6] which yields the corresponding halomagnesium amide (RR′N–MgX) as a by-product. Treatment of the reaction mixture with an alkyl halide should form the desired tertiary amine.

The preparation of Antergan by this method was undertaken as a model experiment. N-Benzyl-N-phenylacetamide was treated with an excess of methylmagnesium iodide followed by dimethylaminoethyl chloride hydrochloride. The quantity of the Grignard reagent employed was sufficient to liberate the aminoalkyl halide from its salt. The product, Antergan (I), was obtained in 53.5% yield. Its picrate was identical with that obtained from a product prepared by the alkylation of N-benzylaniline with dimethylaminoethyl chloride hydrochloride in the presence of lithium amide.

When the reaction was repeated with N-benzyl-N-(2-thienyl)-acetamide in a nitrogen atmosphere, a pale yellow oil was obtained which remained unchanged for weeks when kept at room temperature in an inert atmosphere but which decomposed rapidly when exposed to air. Its elementary analysis revealed that it was not the desired diamine (II) and attempts to establish its structure have been unsuccessful thus far.

The procedure is illustrated as



II Antergan (I)

Experimental[7]

N,N-Dimethyl-N′-benzyl-N′-phenylethylenediamine (I). **Alkylation of N-Benzylaniline.**—A mixture of 9.2 g. (0.05 mole) of N-benzylaniline, 8.7 g. (0.06 mole) of dimethylaminoethyl chloride hydrochloride, 2.8 g. (0.12 mole) of lithium amide (98% purity) and 100 ml. of dry benzene was refluxed for 25 hours. The reaction mixture was then filtered and the residue washed with benzene. The solvent was removed from the filtrate by distillation and the residue distilled *in vacuo*. There was obtained 11.8 g. (92%) of a pale yellow oil distilling at 159–163° (2 mm.). The picrate prepared in ether and recrystallized once from isopropyl alcohol, melted at 149–150°. Huttrer[8] reported a boiling point of 195–196° (0.03 mm.) and a melting point of 149–154° (dec.) for the picrate; Carrara[9] found that his product distilled at 157–158° (1 mm.).

From **N-Benzyl-N-phenylacetamide.**—To 200 ml. of an ether solution of methylmagnesium iodide, prepared from 8.5 g. (0.35 mole) of magnesium turnings and 49.7 g. (0.35 mole) of methyl iodide, 21.3 g. of N-benzyl-N-phenylacet-

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(1) Antergan is the trade mark for N,N-dimethyl-N′-benzyl-N′-phenylethylenediamine, Rhône-Poulenc.

(2) C. W. Sondern and P. J. Breivogel, U. S. Patent 2,440,703 (May 4, 1948), prepared N,N-dimethyl-N′-benzyl-N′-(2-thiazolyl)-ethylenediamine by heating 2-bromothiazole with N,N-dimethyl-N′-benzylethylenediamine.

(3) C. P. Huttrer, C. Djerassi, W. L. Beears, R. L. Mayer and C. R. Scholz, THIS JOURNAL, **68**, 1999 (1946), prepared Pyribenzamine [N,N-dimethyl-N′-benzyl-N′-(2-pyridyl)-ethylenediamine] and other 2-pyridyl tertiary, as well as secondary, amines by alkylating a 2-pyridylamine with an alkyl halide in the presence of either sodamide or lithium amide.

(4) Employing the same conditions which were used successfully in condensing 2-bromopyridine [N. Weiner and I. A. Kaye, *J. Org. Chem.*, **14**, 868 (1949)] with ethanolamine, no product could be isolated from a mixture of 2-bromothiophene and the aminoalcohol. The reactants were recovered even after prolonged heating at 250° in the presence of copper powder.

(5) I. W. Steinkopf, "Die Chemie Des Thiophens," reprinted by Edwards Brothers, Inc., Ann Arbor, Mich., 1944, pp. 59–60.

(6) W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., New York, N. Y., 1948, p. 276.

(7) Melting points are corrected, boiling points are not.

(8) C. P. Huttrer, *Enzymologia*, **12**, 278 (1947).

(9) G. Carrara, *et al.*, *Chimica e Industria (Milan)*, **28**, 9 (1946); *C. A.*, **40**, 7241 (1946)

amide[10] was added in small portions. The mixture was refluxed, with stirring, for 1.5 hours. After chilling in an ice-bath, 21.6 g. (0.15 mole) of dimethylaminoethyl chloride hydrochloride was added in small quantities to the stirred reaction mixture which was then refluxed for an additional 2 hours. Fifty-five ml. of a saturated aqueous ammonium chloride solution was added to the stirred suspension. The magnesium salts were removed by filtration and washed with ether. The filtrate was dried over anhydrous potassium carbonate and then distilled, initially at atmospheric pressure to remove the ether and afterwards *in vacuo*. The product, collected at 98–107° (0.05 mm.), weighed 13.8 g. (53.5%). The picrate melted at 147.5–149° after two recrystallizations from isopropyl alcohol. Mixed with a sample prepared by alkylating N-benzylaniline, the melting point was not depressed (147.5–149.5°).

N-Benzyl-N-(2-thienyl)-acetamide.[11]—A mixture of 70.6 g. (0.5 mole) of 2-acetamidothiophene,[5] 75.9 g. (0.6 mole) of benzyl chloride and 14.1 g. (0.6 mole) of lithium amide (98% purity) in 500 ml. of dry toluene was refluxed for 24 hours. The suspended solids were removed by filtration and washed with toluene. The filtrate was stripped of solvent and the residue distilled *in vacuo*. The pale yellow distillate, b.p. 137–143° (0.5 mm.), weighed 96.7 g. (84%). On redistillation, the fraction (78.7 g.) distilling at 133–137° (0.4 mm.) was collected and analyzed.

Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.48; H, 5.66; N, 6.06; S, 13.86. Found: C, 67.60; H, 5.68; N, 6.15; S, 13.82.

Attempts to Prepare N,N-Dimethyl-N'-benzyl-N'-(2-thienyl)-ethylenediamine (II) from N-Benzyl-N-(2-thienyl)-acetamide.—Prepared in exactly the same manner and on the same scale as I, except that the reaction was performed in an atmosphere of nitrogen, the product which was obtained distilled at 129–132° (0.09 mm.) and weighed 12.1 g. On redistillation, the light yellow oil, collected at 118–122° (0.08 mm.), weighed 9.1 g. No salt could be prepared which was stable in air. *Anal.* (under nitrogen). Calcd. for $C_{15}H_{20}N_2S$: C, 69.17; H, 7.74; N, 10.76; S, 12.31; mol. wt., 260.4; neut. equiv., 260.4. Found: C, 72.40, 72.59; H, 8.36, 8.34; N, 5.73, 5.71; S, 13.42, 13.68; mol. wt.,[12] 284; neut. equiv.,[12] 262.0.

Acknowledgment.—The authors wish to thank Endo Products, Inc., for support (in part) of this investigation.

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[10] Prepared by refluxing N-benzylaniline with a 3 molar excess of acetic anhydride for 4 hours. The product was obtained in 91% yield as a colorless oil, b.p. 110–125° (0.04 mm.). On chilling in a bath of solid carbon dioxide and trichloroethylene, the distillate solidified. After washing with cold hexane and air-drying, the solid melted at 57–58°. The m.p. has been given as 58° (N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Thomas Y. Crowell Co., New York, N. Y., 1947, p. 406).

[11] The authors are indebted to Mr. Dave Regenbogen for carrying out the initial preparation of this compound.

[12] The validity of these two results is questionable. In the Rast molecular weight determination darkening occurred on heating which made it difficult for the analyst to determine the melting point. The end-point in the neutralization equivalent titration [method of J. S. Fritz, *Anal. Chem.*, **22**, 1028 (1950)] was similarly obscured.

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Iodine-catalyzed Benzoylations

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In connection with another investigation[2] involving the condensation of some benzohydryl chlorides with heterocyclic amines, several substituted benzophenones and 2-benzoylthiophenes[3] were prepared, in yields comparable with those obtained by the Friedel–Crafts method, using the iodine-catalyzed acylation procedure of Hartough and Kosak.[4]

N,N-Dimethylaniline and benzoyl chloride, in the presence of iodine, yielded, instead of the expected *p*-benzoylated product, demethylated derivatives of aniline; the extent of demethylation depended upon the amount of condensing agent employed.[5]

In addition to catalyzing acylation reactions, it has been found that iodine can promote the benzylation of anisole.[6] This, however, does not seem to be a very general reaction, for no product was obtained from reactions with thiophene or 2-chlorothiophene, although these compounds are easily benzoylated in the presence of iodine.

Experimental[7]

4-Chloro-4'-methoxybenzophenone. Method A.—A mixture of 10.8 g. (0.10 mole) of anisole, 19.3 g. (0.11 mole) of *p*-chlorobenzoyl chloride[8] and 2.5 g. of iodine was refluxed for 15 hours. Refluxing was continued for 15 minutes longer after the cautious addition of 120 ml. of isopropyl alcohol. The chilled mixture was then filtered and the precipitate washed with the cold solvent and air-dried. One recrystallization of the tan solid, weighing 23.0 g. (93%), from isopropyl alcohol, raised the melting point from 115–119° to 124–125°.[9]

When the reactants were refluxed for 1, 5 and 24 hours, the product was obtained in yields of 43, 84 and 85%, respectively. In the presence of 6.0, 6.4, 12.8, 25.0, 30.0 and 40.0 g. of iodine, a mixture of 1.0 mole of anisole and 0.5 mole of *p*-chlorobenzoyl chloride, heated 15 hours, gave yields of 20, 29, 62, 72, 57 and 56%, respectively.

1-Benzoyl-2-methoxynaphthalene. Method B.—A mixture of 71.1 g. (0.45 mole) of 2-methoxynaphthalene, 42.3 g. (0.30 mole) of benzoyl chloride and 4.5 g. of iodine, was refluxed 7.5 hours and subsequently dissolved in 200 ml. of ether. The brown solution was washed twice with 50-ml. portions of 10% aqueous potassium carbonate solution and twice more with 50 ml. of 10% sodium bisulfite solution. After drying over anhydrous potassium carbonate, the ether was removed and the residual liquid distilled *in vacuo*. The colorless distillate, b.p. 200–205° (2 mm.), weighing 56.5 g. (72%), solidified on cooling. The product melted at 124–125° after two recrystallizations from heptane.[10]

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[1] From the M.A. Thesis of W. J. Burlant submitted to the Graduate Faculty of Brooklyn College, September, 1951.

[2] I. A. Kaye, I. C. Kogon and C. L. Parris, THIS JOURNAL, **74**, 403 (1952).

[3] No evidence of ability to retard the growth of sarcoma 180 in mice was shown by 2-(*p*-methoxybenzoyl)-thiophene, 2-(*p*-chlorobenzoyl)-thiophene, 2,4,6-trimethylbenzophenone, 4-chloro-4'-methoxybenzophenone, 4-chlorobenzohydryl chloride, 4-methoxybenzohydryl chloride and 4,4'-dimethoxybenzohydryl chloride. The authors wish to thank Dr. C. Chester Stock of the Sloan-Kettering Institute for Cancer Research for this information.

[4] H. D. Hartough and A. I. Kosak, THIS JOURNAL, **68**, 2639 (1946), acylated thiophene and furan. More recently S. Chodroff and H. C. Klein, *ibid.*, **70**, 1647 (1948), and D. L. Turner, *ibid.*, **71**, 612 (1949), prepared some aromatic ketones by a similar procedure.

[5] Since N,N-dimethylaniline has been found to undergo nuclear iodination with the liberation of hydrogen iodide under conditions similar to those employed in this reaction (*cf.* W. Militzer, E. Smith and E. Evans, *ibid.*, **63**, 436 (1941)), the hydroiodide of some of the unreacted compound may have been formed initially and subsequently undergone thermal decomposition with the formation of methyl iodide and either aniline or N-methylaniline. Our isolation of the methiodide of N,N-dimethylaniline by heating this amine with iodine, in the absence of an acylating agent, would tend to substantiate this inference.

[6] C. D. Nenitzescu, D. A. Isacescu and C. N. Ionescu, *Ann.*, **491**, 210 (1931), have obtained *p*-methoxydiphenylmethane in unstated yield by condensation of benzyl chloride with anisole in the absence of a catalyst.

[7] Melting points are corrected; boiling points are not.

[8] Samples of *p*-chlorobenzoyl chloride and anisoyl chloride were generously supplied by the Heyden Chemical Corporation.

[9] P. P. Peterson, *Am. Chem. J.*, **46**, 325 (1911), obtained an 85% yield using aluminum chloride.

[10] R. R. Galle, *J. Gen. Chem.* (*U.S.S.R.*), **8**, 402 (1938); *C. A.*, **32**, 7910 (1938).