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.

[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

BY IRVING ALLAN KAYE, HOWARD C. KLEIN AND WILLIAM J. BURLANT[1]

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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.

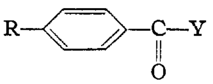
[8] Samples of *p*-chlorobenzoyl chloride and anisoyl chloride were generously supplied by the Heyden Chemical Corporation.

[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).

TABLE I

KETONES OF FORMULA



R^{a}	Y	Iodine, g.	Reflux time, hr.	Method	Yield,^{b} %	M.p., °C.	B.p. °C.	B.p. Mm.
OCH_3 (1:2)	*p*-Anisyl	7.7	15	A	84	142–144^{c}		
H (0.5:1)	*p*-Xenyl	15.0	14	B	50	102–103^{d}	156–158	0.1
Cl (1.1:1)	*p*-Anisyl	25	15	A	93	124–125		
NO_2 (1:2)	*p*-Anisyl	40	15	B	57	126–128^{e}	192–194	0.9
H (1.1:1)	Veratryl	2	15	^{f}	81^{g}	102–103^{h}	162–170	2.0
H (0.5:1)	2-Mesityl	20	10	B	65		141–143^{i}	0.03
H (1:2)	*p*-Ethoxyphenyl	8	15	B	83^{j}		129^{j}	0.6
H (1:1.5)	2-Methoxynaphthyl	15	7.5	B	72	124–125^{k}	200–205	2.0
OCH_3 (1:2)	2-Thienyl	2	8	A	76^{l}	76–77		
Cl (1:1)	2-Thienyl	6	8	A	50^{m}	99.5–100^{m}		
H (1:1)	2-(5-Chlorothienyl)	20	9	A	34^{n}	63–64^{k}		
Cl (1:1)	2-(5-Chlorothienyl)	20	15	A	58	105–106^{o}		

[a] Figures in parentheses refer to mole ratios of reactants, the first number representing the moles of acylating agent, *p*-R—C_6H_4COCl. [b] All compounds were recrystallized from isopropyl alcohol unless otherwise stated. [c] H. Schnackenberg and R. Scholl, *Ber.*, **36**, 654 (1903), using aluminum chloride, reported no yield. [d] L. Long and H. Henze, THIS JOURNAL, **63**, 1939 (1941), obtained a 75% yield with aluminum chloride as condensing agent. [e] *Anal.* Calcd. for $C_{14}H_{11}NO$: N, 5.45. Found: N, 5.38. N. Böeseken, *Rec. trav. chim.*, **19**, 25 (1900), found a melting point of 121°. [f] At the end of the reflux period, the reaction mixture was distilled *in vacuo*. [g] A small amount (2.3 g.) of a higher boiling fraction, b.p. 207–210° (0.04 mm.), was also obtained. This presumably dibenzoylated veratrole gave a mono-2,4-dinitrophenylhydrazone which melted at 190–191° after recrystallization from ethanol. *Anal.* Calcd. for $C_{28}H_{24}N_2O_4$: C, 63.86; H, 4.07. Found: C, 63.04; H, 3.93. [h] Recrystallized from hexane. B. König and St. V. Kostanecki, *Ber.*, **39**, 4027 (1906), gave no yield for their product. [i] P. J. Montagne, *Rec. trav. chim.*, **27**, 327 (1908). [j] Although C. Torres, *Anales soc. españ. fís. quím.*, **24**, 82 (1926); *C. A.*, **20**, 2158 (1926), reported that the oxime of his product melted at 135–136°, the ketoxime melted at 151–152° after recrystallization from isopropyl alcohol. *Anal.* Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27. Found: C, 74.53; H, 6.21. [k] Recrystallized from heptane. [l] Employing equimolecular quantities of the reactants, the product was obtained in 62% yield. *Anal.* Calcd. for $C_{12}H_{10}O_2S$: S, 14.65. Found: S, 14.28. The compound has recently been prepared by Ng. D. Buu-Hoï, Ng. Hoán and Ng. D. Xuong, *Rec. trav. chim.*, **69**, 1083 (1950), in 80% yield. [m] The yield dropped to 35% when 2.0 g. of iodine was employed. The product was recrystallized from hexane. There was also isolated 13.0 g. of di-(4-chlorobenzoyl)-thiophene, m.p. 238–239° after recrystallization from isopropyl alcohol. *Anal.* Calcd. for $C_{18}H_{10}Cl_2O_2S$: Cl, 19.62. Found: Cl, 19.38. Buu-Hoï and co-workers (*cf.* preceding reference) obtained a 71% yield of 2-(4-chlorobenzoyl)-thiophene. [n] *Anal.* Calcd. for $C_{11}H_7ClOS$: C, 59.32; H, 3.06; Cl, 15.95. Found: C, 59.24; H, 3.17; Cl, 15.95. Buu-Hoï, Hoán and Xuong [*cf.* note (*l*)] reported a 53% yield. [o] *Anal.* Calcd. for $C_{11}H_6Cl_2OS$: C, 51.38; H, 2.35; Cl, 27.58; S, 12.47. Found: C, 51.48; H, 2.44; Cl, 27.40; S, 12.43. The conventional Friedel–Crafts procedure [*cf.* note (*l*)] afforded a 77% yield.

Reaction of N,N-Dimethylaniline with Benzoyl Chloride.—A solution of 20.0 g. of iodine, 70.3 g. (0.50 mole) of benzoyl chloride and 121.2 g. (1.0 mole) of N,N-dimethylaniline was refluxed for 10 hours, cooled, washed with dilute sodium hydroxide, dried over anhydrous potassium carbonate and distilled *in vacuo*. The yellow oil, b.p. 189° (0.9 mm.), weighing 45.0 g., crystallized on cooling and was recrystallized from hexane. The white crystals, m.p. 164–165°, showed no depression in melting point on admixture with an authentic sample of benzanilide.[11]

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.18; H, 5.57; N, 7.30. Found: C, 79.23; H, 5.58; N, 7.13.

In a similar manner there was obtained 35.3 g. of a red oil, b.p. 121° (1.0 mm.), from a mixture of 24.2 g. (0.20 mole) of the tertiary amine, 42.2 g. (0.30 mole) of benzoyl chloride and 0.8 g. of iodine. The amide, crystallized from heptane and recrystallized to constant melting point from the same solvent, melted at 63.5–64.5°.[11]

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.13. Found: C, 79.54; H, 6.28; N, 6.24.

Hydrolytic cleavage with hydrochloric acid[11] afforded benzoic acid, identified by the fact that its melting point was not depressed when mixed with an authentic sample, and N-methylaniline, identified similarly as its hydrochloride, m.p. 121–123°.

Reaction of N,N-Dimethylaniline with Iodine.—A mixture of 24.2 g. (0.2 mole) of N,N-dimethylaniline and 8.0 g. of iodine, refluxed for 3 hours, deposited, by sublimation in an air condenser during the reflux period, 6.0 g. of the methiodide of N,N-dimethylaniline, m.p. 213–214°. Mixed with an authentic sample, there was no depression in melting point.

Anal. Calcd. for $C_9H_{14}IN$: C, 41.22; H, 5.34. Found: C, 40.99; H, 5.35.

Benzylation of Anisole.—From a mixture of 32.4 g. (0.3 mole) of anisole, 18.9 g. (0.15 mole) of benzyl chloride and 6.0 g. of iodine, refluxed 14 hours, there was isolated (Method B) 15.0 g. (51%) of a yellow oil, b.p. 106–108° (0.04 mm.). A sample of the distillate, after hydrobromic acid demethylation, yielded *p*-benzylphenol, m.p. 84.5–85.5°.[12]

There was also obtained 9.6 g. (22%) of a higher boiling fraction, b.p. 165–167° (0.09 mm.), presumed to be 2,4-dibenzylanisole.

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.04; H, 6.67.

From mixtures of 1.0 mole of thiophene or 2-chlorothiophene, 0.5 mole of benzyl chloride and 7.5 g. of iodine which were refluxed 14 hours, only starting materials could be recovered.

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(11) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Thomas Y. Crowell Company, New York, N. Y., 1947, pp. 185, 403 and 413.

(12) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 3rd edition, 1948, p. 272.

Use of 2-Aminopyridine in the Voigt Reaction

BY IRVING ALLAN KAYE, CHESTER L. PARRIS AND WILLIAM J. BURLANT

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The synthesis of the two stereochemical isomers of N-(2-pyridyl)-1,2-diphenyl-2-aminoethanol (I)