After warming on the steam-bath for one and one-half minutes, the reaction mixture was acidified with a slight excess of 1 *N* hydrochloric acid. Water was added and the mixture extracted with ether and the ether soluble portion washed with 5% sodium bicarbonate. The base soluble material crystallized from aqueous methanol in short needles, 0.95 g. (90%) of IV, m.p. 96.5–98.0°. There was no depression of the melting point when admixed with an authentic sample of IV. No acidic material (III) could be isolated from the bicarbonate extracts.

**Acidic Methanolysis of I.**—A solution of 2-(2-hydroxyphenoxy)-benzoic acid lactone (I) (75 mg.) in 30 ml. of methanol and 1 ml. of concentrated hydrochloric acid was heated under reflux for five hours. At the end of this time the solution was carefully neutralized with 1 *N* sodium hydroxide, and evaporated. The residue was dissolved in ether and extracted with 5% sodium bicarbonate and 1 *N* sodium hydroxide. Acidification of the bicarbonate extracted afforded 22 mg. (26%) of 2-(2-hydroxyphenoxy)-benzoic acid (III) m.p. 124–125° (mixed m.p. undepressed). Immediate acidification of the sodium hydroxide extracts afforded on crystallization from aqueous methanol 48 mg. (70%) of IV, m.p. 95.5–97.5° (mixed m.p. undepressed). From the remaining ether solution there was obtained 5 mg. of crude I, m.p. 55–59°.

**Methanolysis of Phenyl Benzoate.**—Phenyl benzoate (1 g.), 40 ml. of methanol and 10 ml. of 1 *N* sodium hydroxide were heated on the steam-bath 1.5 minutes, and then acidified. Isolation in the usual manner afforded 0.42 g. (90%) of phenol; the neutral fraction yielded 0.69 g. of methyl benzoate.

**Methanolysis of *p*-Methoxyphenyl Benzoate.**—*p*-Methoxyphenyl benzoate (100 mg.) was treated as above and worked up in the same manner. There was obtained in this fashion, 1 mg. of acidic material, 41 mg. (74%) of phenolic material, m.p. 50–53° (lit.[17] for hydroquinone monomethyl ether 53°), benzoate, m.p. 86–88° (mixed m.p. undepressed), and 63 mg. of neutral material, saponification equivalent 159. Assuming that the neutral fraction is composed of only methyl benzoate and *p*-methoxyphenyl benzoate, 68% of the theoretical amount of methyl benzoate was formed and 32% of *p*-methoxyphenyl benzoate was recovered.

(17) H. Hlasiwetz and J. Habermann, *Ann.*, **177**, 339 (1875).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

# N,N-Dimethyl-N'-benzohydryl-N'-(2-pyridyl)-ethylenediamine and Related Compounds as Histamine Antagonists

BY IRVING ALLAN KAYE, IRVING C. KOGON AND CHESTER L. PARRIS

N,N-Dimethyl-N'-benzohydryl-N'-(2-pyridyl)-ethylenediamine and some similar compounds were prepared by the reaction of 2-benzohydrylaminopyridine and related secondary amines with dimethylaminoethyl chloride hydrochloride and lithium amide. Since N-benzohydrylaniline behaved anomalously, N,N-dimethyl-N'-benzohydryl-N'-phenylethylenediamine was synthesized by alkylating N,N-dimethyl-N'-phenylethylenediamine with benzohydryl chloride. The products decomposed somewhat during distillation, losing the benzohydryl group which dimerized to form *sym*-tetraphenylethane. In the presence of hydrogen chloride this dissociation predominated so that none of the desired salts could be isolated. The intermediate secondary amines were prepared for the most part either by alkylating 2-aminopyridine, 2-aminopyrimidine and 2-aminolepidine with benzohydryl chloride in the presence of lithium amide or by the reductive alkylation of some 2-aralkylideneaminopyridines with phenylmagnesium bromide. In the absence of condensing agent, only the N-substituted heterocyclic amine was isolated from benzohydryl chloride and either 2-aminopyridine or 2-aminothiazole, rather than the ring-alkylated compound. Some of the products have been screened for pharmacological activity.

The benzohydryl group is found in a number of substituted amines which are therapeutically useful[1,2]; several of these have been described as potent histamine antagonists.[3,4] It seemed worthwhile therefore to prepare for pharmacological evaluation a series of compounds related to the Pyribenzamine[5] type of antihistaminic wherein the latter's benzyl moiety is replaced by a benzohydryl or similar substituent. A description of the preparation and of some properties of such structures (I) constitutes the subject of this report.

$$C_6H_5—CHR—NR'—CH_2—CH_2N(CH_3)_2$$

I

| | | | |
|---|---|---|---|
| R = | (A) phenyl | R' = | (F) phenyl |
| | (B) 4-methoxyphenyl | | (G) 2-pyridyl |
| | (C) 4-chlorophenyl | | (H) 2-pyrimidyl |
| | (D) 2-thienyl | | (I) 2-thiazolyl |
| | (E) 2-furyl | | (J) 2-lepidyl |

(1) D. W. Adamson, *J. Chem. Soc.*, Suppl. Issue, No. 1, S144 (1949).

(2) M. M. Klenk, C. M. Suter and S. Archer, THIS JOURNAL, **70**, 3846 (1948).

(3) F. Leonard and C. P. Huttrer, "Histamine Antagonists," National Research Council Chemical-Biological Coördination Center, Washington, D. C., 1950, p. 31.

(4) M. V. Patwardhan, N. L. Phalnikar and B. V. Bhide, *J. Univ. Bombay*, **18**, 22 (1950); N. V. Bringi, N. L. Phalnikar and B. V. Bhide, *ibid.*, **18**, 25 (1950); [*C. A.*, **45**, 1986 (1951)].

(5) C. P. Huttrer, C. Djerassi, W. L. Beears, R. L. Mayer and C. R. Scholz, THIS JOURNAL, **68**, 1999 (1946).

Most of the products were obtained by condensing a secondary amine of structure $C_6H_5$–CHR–NR'H (II, where R and R' have the same significance as in I) with dimethylaminoethyl chloride hydrochloride, in the presence of lithium amide (Method C).[5,6] The results of nitrogen analyses of the distilled products were generally significantly lower than the theoretical. The analytical values were not raised by redistilling the bases; this frequently resulted in even greater deviations from the calculated figures. In one instance (I AH), a small amount of 1,1,2,2-tetraphenylethane, apparently formed by cleavage and dimerization of the benzohydryl group, was isolated. It may be assumed that the poor nitrogen analyses are due to hydrocarbon contaminants. This lability of the benzohydryl group has been demonstrated by others. For example, *sym*-tetraphenylethane has been prepared by gently warming benzohydryl chloride.[7] Fox and Wenner[8] recently described a similar example of benzohydryl cleavage in a reaction between N-benzohydrylglycine ethyl ester with ethylenediamine. Instead of the desired imidazoline, *sym*-tetraphenylethane and 2-methylimidazoline were obtained. It was found most

(6) I. A Kaye, *ibid.*, **71**, 2322 (1949).

(7) L. A. R. Hall and J. H. Burckhalter, *ibid.*, **73**, 473 (1951).

(8) H. H. Fox and W. Wenner, *J. Org. Chem.*, **16**, 225 (1951).

convenient to characterize the products as oxalates which were purified by washing with either hot benzene or isopropyl acetate and then recrystallized from isopropyl alcohol.

After some of our products had been prepared, a note[7] appeared containing a description of an unsuccessful attempt to prepare I AG by the same procedure which had previously been used for the preparation of N,N-dimethyl-N′-benzyl-N′-(2-pyridyl)-ethylenediamine (Pyribenzamine).[3] The authors had attempted to prepare the hydrochloride directly by saturating an ethanolic solution of the crude amine with dry hydrogen chloride gas. Concentration of the solution gave only the dihydrochloride of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine (III), and *sym*-tetraphenylethane; this is apparently another example of benzohydryl scission.

Since their starting compound, 2-benzohydrylaminopyridine, was prepared by heating a mixture of benzohydryl bromide and 2-aminopyridine, a method which leaves some uncertainty as to the validity of the structure, an attempt was made to establish the identity of the product. It has been shown that when 2-aminopyridine is heated with a lower alkyl halide, the pyridine compound reacts to a large extent in the tautomeric imine form.[9] Interaction of the base with higher alkyl halides has been described as yielding mixtures of the two isomers which become progressively richer in the 2-alkylaminopyridine component with increasing chain length of the alkyl halide.[10] In the case of the aralkyl halides, benzyl chloride has been found to give predominantly the imino compound[10] and triphenylmethyl chloride, as well as triphenylcarbinol (in the presence of a trace of acid), a good yield of 2-triphenylmethylaminopyridine.[11] Since benzohydryl bromide represents a sort of midway state between these two compounds, it would seem as though, in reacting with 2-aminopyridine, the product might consist of a mixture of 1-benzohydryl-2-pyridoneimine and II AG.

In the presence of a condensing agent, as sodium hydride, sodamide or lithium amide, 2-aminopyridine behaves as though the imine form were entirely absent and yields only N-substituted 2-aminopyridines. Our benzohydrylaminopyridine (II AG), synthesized in this manner (Method A), was identical with the product obtained by the reductive alkylation (Method B) of 2-benzylideneaminopyridine with phenylmagnesium bromide (*vide infra*). Contrary to our expectations, the compound prepared from the reactants in the absence of a condensing agent (Method F, a modification of the method of Hall and Burckhalter[7]) proved to be the same as our II AG. Similar results were obtained with 2-aminothiazole. From a mixture of this amine and benzohydryl chloride, a poor yield of II AI was obtained.

Hall and Burckhalter had inferred that the base (I AG) had been formed and had subsequently decomposed as the hydrochloride. We attempted to substantiate this mechanism. An alcoholic solution of the distilled amine (I AG) was saturated with hydrogen chloride and then concentrated to one-third its original volume. The same two products, N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine (III) and *sym*-tetraphenylethane, were obtained, thus confirming their hypothesis. That the displacement was caused by the excess hydrogen chloride may be inferred from the fact that purified dihydrochloride, prepared by adding ethereal hydrogen chloride to a solution of I AG in dry ether, could be recovered unchanged after prolonged refluxing in ethanol.

We had previously attempted to isolate some products as hydrochlorides by saturating the reaction mixtures, after removal of insoluble lithium compounds, with gaseous hydrogen chloride (Method E). In each case results paralleled those of Hall and Burckhalter. From 2-(4-methoxybenzohydryl)-aminopyridine and dimethylaminoethyl chloride hydrochloride the only base obtained was III; from dimethylaminoisopropyl chloride hydrochloride and both 2-benzohydrylaminopyridine and 2-benzohydrylaminopyrimidine the amines isolated were 2-(dimethylaminoisopropyl)-aminopyridine and -pyrimidine, respectively.[12]

The benzohydryl group is not the only substituent which can be removed from alkyldiamines by treatment with hydrogen chloride. All attempts of Leonard and Solmssen[13] to form either hydrochlorides or hydrobromides of $N^2$,$N^2$-dimethyl-$N^1$-phenyl-$N^1$-(2-thenyl)-1,2-propanediamine (IV) and $N^2$,$N^2$-dimethyl-$N^1$-(2-pyridyl)-$N^1$-(2-thenyl)-1,2-propanediamine resulted in decomposition of the compounds, although they were successful in preparing stable picrates and bisuccinates. Addition of the calculated amount of ethanolic hydrochloric acid to an ether solution of IV gave, in addition to recovered IV, $N^2$,$N^2$-dimethyl-$N^1$-phenyl-1,2-propanediamine and 2-thenyl ethyl ether. The authors postulated the formation of the latter by the reaction of either a thenyl carbonium ion or thenyl chloride with the ethanol of the reaction medium. Hall and Burckhalter assumed in an analogous manner that their benzohydryl group was removed as benzohydryl chloride which then formed *sym*-tetraphenylethane.[14]

Although tertiary amines were prepared successfully from II (A-E)G, II AH, II AI and II AJ by Method C, only starting material could be isolated from N-benzohydrylaniline and either dimethylaminoethyl chloride hydrochloride or dimethylaminoisopropyl chloride hydrochloride in the presence of either lithium amide or potassium bicarbon-

(9) For leading references, see F. F. Blicke and M. U. Tsao, THIS JOURNAL, **68**, 905 (1946).

(10) T. M. Sharp, *J. Chem. Soc.*, 1855 (1939).

(11) (a) R. Adams and J. B. Campbell, THIS JOURNAL, **71**, 3539 (1949); (b) R. Dahlbom and T. Ekstrand, *Svensk. Kem. Tid.*, **56**, 304 (1944) [*C. A.*, **40**, 3415 (1946)].

(12) There is some doubt as to the structure of these compounds since there are several recorded instances in which isomers have been isolated from alkylations with dimethylaminopropyl chlorides. For further discussion and leading references, the reader is referred to an article by W. B. Reid, J. B. Wright, H. G. Kolloff and J. H. Hunter, THIS JOURNAL, **70**, 3100 (1948); *cf.* also P. Ofner, *J. Chem. Soc.*, 1800 (1951).

(13) F. Leonard and U. V. Solmssen, THIS JOURNAL, **70**, 2064 (1948).

(14) Both papers (references 7 and 13) should be consulted for more detailed descriptions of the mechanisms postulated by the authors. It is noteworthy that 2-triphenylmethylamino-pyridine, -pyrimidine and -thiazole lose their trityl groups also in acid solution (11b).

ate. This was rather unexpected, especially since N-benzylaniline, dimethylaminoethyl chloride hydrochloride and lithium amide gave a 93% yield of N,N-dimethyl-N'-phenyl-N'-benzyl-ethylenediamine (Antergan).[15] The product (I AF), containing a considerable amount of 1,1,2,2-tetraphenylethane, was obtained in low yield by treatment of N,N-dimethyl-N'-phenylethylenediamine with benzohydryl chloride and lithium amide (Method D). A similar reaction between III and either 4-chloro-, 4-methoxy-, 4,4'-dichloro- or 4,4'-dimethoxybenzohydryl chloride failed to yield any of the expected products. Though this may have been due to an instability inherent in some substituted benzohydryl chlorides, it seems more likely that the desired amines were formed and subsequently cleaved when the reaction mixtures were extracted with dilute hydrochloric acid. In each case only III could be isolated from the basic fraction. Hall and Burckhalter[7] also recovered III and some *sym*-tetraphenylethane from a mixture of III, benzohydryl bromide and sodamide.

It is interesting to compare our N-alkylation of N,N-dimethyl-N'-phenyl-ethylenediamine with benzohydryl chloride with the difficulty experienced by Cromwell and Fitzgibbon[16] in preparing N-phenyl-N-benzohydrylethanolamine from benzohydryl bromide and phenylethanolamine. They attributed this to a low reactivity of the amino group combined with steric difficulties involved in the approach of the benzohydryl group toward this nitrogen which is attached to both phenyl and ethanol groups.

The intermediate pyrimidine and lepidine secondary amines (II AH and II AJ) were prepared from 2-aminopyrimidine and 2-aminolepidine[6] and benzohydryl chloride in the presence of lithium amide (Method A). Since we were unable to synthesize N-monosubstituted 2-aminothiazoles in the same manner, 2-benzohydrylaminothiazole (II AI) was prepared by total synthesis. Benzohydrylamine was converted to benzohydryl isothiocyanate which, on treatment with ammonia, formed N-benzohydrylthiourea. The latter, heated with dimethyl chloroacetal, yielded II AI[17,18] (Method G). In the latter reaction N-aralkylthioureas have been shown to form only 2-aralkylaminothiazoles.

Catalytic hydrogenation of benzophenone anil gave an excellent yield of N-benzohydrylaniline. The Schiff base was obtained in 96% yield by heating a mixture of benzophenone and aniline until almost the theoretical amount of water had been collected.[19a] Under the same conditions, neither 2-aminopyridine nor 2-aminopyrimidine gave any evidence of reaction, even in the presence of small amounts of hydrogen chloride.[19b] Upon the addition of iodine, and at a higher reaction temperature (280°), less than half the theoretical amount of water was collected, but the reaction mixtures had undergone such extensive decomposition that no products could be isolated.

One of the methods which has been described for the preparation of N-benzohydrylaniline involves a reaction between phenylmagnesium bromide and benzalaniline.[20] Some of our intermediates [II (A-E)G] were synthesized in this manner. In the preparation of 2-benzohydrylaminopyridine, the product was obtained in better yield when an excess of Grignard reagent was employed. This procedure has been used recently for the preparation of two similarly constituted 2-aminopyridines and a 2-aminothiazole.[18,21]

**Pharmacological Activity.**—Neither II AG nor I AG have shown any evidence of ability to retard the growth of sarcoma 180.[22a] The latter (I AG) appeared to offer some protection in mice against electric shock.[22b] Preliminary studies on the isolated guinea pig ileum strip indicate that I CG is the most potent histamine antagonist of the series, showing about 15% of the activity of Pyribenzamine. Of the other compounds, I BG, I AG, I EG, I AJ and I AI are, respectively, 4, 2.5, 1.5, 0.4 and 0.1% as active.[22c] Against acetylcholine little or no activity was observed.[22c]

## Experimental[23]

**Preparation of Secondary Amines [II A(G, H and J)] in the Presence of Lithium Amide. Method A.**—These compounds were prepared in the same way as was 2-benzylaminolepidine[6] except that benzene, rather than toluene, was used as solvent.

**2-Monosubstituted Aminopyridines [II (A-E)G] by Reductive Alkylation of Schiff Bases with Phenylmagnesium Bromide. Method B.**—To a stirred ethereal solution of phenylmagnesium bromide, prepared from 48.6 g. (2.0 g. atoms) of magnesium and 314.0 g. (2.0 moles) of bromobenzene, was added dropwise 0.5 mole of the Schiff base[24] dissolved in 300 ml. of cumene. Ether was removed through a take-off tube attached to the condenser until the temperature of the mixture reached about 140°. Stirring was continued, and this temperature maintained, for 3 hours longer. After chilling, the reaction mixture was decomposed by the cautious addition of 300 ml. of saturated aqueous ammonium chloride solution. The solid which precipitated was separated by filtration and washed thoroughly with ether. The product was obtained by vacuum distillation, after prior removal of ether and cumene from the filtrate. It was then recrystallized from an appropriate solvent.

In one preparation of 2-benzohydrylaminopyridine, 2-benzylideneaminopyridine was prepared by refluxing a cumene solution of benzaldehyde (2.0 moles) and 2-aminopyridine (2.0 moles) until the volume of water collected in a Dean–Stark moisture trap remained constant at 34.5

(15) I. A. Kaye and C. L. Parris, THIS JOURNAL, in press.

(16) N. H. Cromwell and W. E. Fitzgibbon, *ibid.*, **70**, 387 (1948).

(17) R. H. Wiley, D. C. England and L. C. Behr, "The Preparation of Thiazoles" in "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 378–379.

(18) This compound could probably have been prepared, too, from 2-benzylideneaminothiazole and phenylmagnesium bromide. Subsequent to this investigation, 2-(1,2-diphenylethyl)-aminothiazole was prepared in this fashion.

(19) (a) F. J. Moore, *Ber.*, **43**, 564 (1910), obtained a 59% yield after heating the reactants at 210° for one hour; (b) G. Reddelien, *ibid.*, **46**, 2720 (1913); **48**, 1469 (1915), obtained 71% as his maximum yield, m.p. 113°, after three-quarters of an hour at 200° in the presence of a hydrogen halide. The compound has also been reported as melting at 112° by P. Grammaticakis, *Compt. rend.*, **204**, 502 (1937), and 114–115° by Rosser and Ritter (reference 20).

(20) C. M. Rosser and J. J. Ritter, THIS JOURNAL, **59**, 2179 (1937), obtained this compound in 50% yield, b.p. 233° (20 mm.), by the method of M. Busch and A. Rinck, *Ber.*, **38**, 1761 (1905), from benzalaniline and phenylmagnesium bromide. The melting point has been given as 58° [P. Grammaticakis, *Compt. rend.*, **210**, 716 (1940)].

(21) K. Hayes, G. Gever and J. Orcutt, THIS JOURNAL, **72**, 1205 (1950).

(22) The authors are grateful to (a) Dr. C. Chester Stock of the Sloan-Kettering Institute for Cancer Research, (b) Dr. Irwin H. Slater of the School of Medicine and Dentistry of the University of Rochester and to (c) Dr. Harold Blumberg and Mr. Eric Meyer of Endo Products, Inc., for this information.

(23) All melting points are corrected; boiling points are not.

(24) I. A. Kaye and I. C. Kogon, THIS JOURNAL, **73**, 5891 (1951).

TABLE I

SECONDARY AND TERTIARY AMINES, RR'N—CHR'$C_6H_5$

| R | R' | R'' | Procedure | B.p., °C. | Mm. | M.p., °C.[a] | Yield,[a] % | Formula | Nitrogen analyses, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|
| $C_6H_5$– | $-C_6H_5$ | H | H | 128 | 0.05 | 53–54.5 | 87 | $C_{19}H_{17}N$ | 5.40 | 5.48 |
| | | | | | | 191–192[b,c] | | $C_{19}H_{17}N\cdot HCl$ | 4.73 | 4.76 |
| $C_5H_4N$–[d] | $-C_6H_5$ | H | A(B)(F) | 130–132 | .04 | 101–102[e] | 53(82)(58) | $C_{18}H_{16}N_2\cdot C_6H_3N_3O_7$ | 59.02[h] | 58.90[h] |
| | | | | | | 183–184[f,g] | | | 4.25[i] | 3.91[i] |
| $C_5H_4N$–[d] | $-C_6H_4Cl(4)$ | H | B | 140–146 | .02 | 98.5–99[j] | 78 | $C_{18}H_{15}N_2Cl$ | 9.51 | 9.40 |
| $C_5H_4N$–[d] | $-C_6H_4(OCH_3)(4)$ | H | B | | | 103.5–104.5[k] | 58 | $C_{19}H_{18}N_2O$ | 9.66 | 9.45 |
| $C_5H_4N$–[d] | $-C_4H_3O$[l] | H | B | 132–135 | .05 | 126–127.5[f,m] | 45 | $C_{16}H_{14}N_2O\cdot C_6H_3N_3O_7$ | 14.61 | 15.25 |
| $C_5H_4N$–[d] | $-C_4H_3S$[n] | H | B | 140–144 | .13 | 97–98[j] | 64 | $C_{16}H_{14}N_2S$ | 10.53 | 10.41 |
| | | | | | | | | | 12.05[o] | 12.09[o] |
| $C_4H_3N_2$–[p] | $-C_6H_5$ | H | A | | | 138–139[e] | 20 | $C_{17}H_{16}N_3\cdot C_6H_3N_3O_7$[q] | 56.33[h] | 56.25[h] |
| | | | | | | | | | 3.70[i] | 4.18[i] |
| $C_4H_2NS$–[r] | $-C_6H_5$ | H | C | | | 169.5–171[j] | 99 | $C_{16}H_{14}N_2S$ | 10.53 | 10.41 |
| $C_{10}H_6N$–[s] | $-C_6H_5$ | H | A | | | 111.5–112[j] | 35 | $C_{23}H_{20}N_2$ | 8.64 | 8.43 |
| $C_6H_5$– | $-C_6H_5$ | $-(CH_2)_2N(CH_3)_2$ | D | 155–160 | .04 | 191–192[t] | 25 | $C_{23}H_{26}N\cdot H_2C_2O_4$ | 6.67 | 6.80 |
| $C_5H_4N$–[d] | $-C_6H_5$ | $-(CH_2)_2N(CH_3)_2$ | C | 144 | .03 | 160.5–161[t,j] | 92 | $C_{22}H_{26}N_2\cdot H_2C_2O_4$ | 9.97 | 9.70 |
| | | | E | | | 160–161.5[b,u] | 91 | $C_{22}H_{25}N_2\cdot 2HCl$ | 10.38 | 10.60 |
| $C_5H_4N$–[d] | $-C_6H_4Cl(4)$ | $-(CH_2)_2N(CH_3)_2$ | C | 155–160 | .02 | 164.5–165[j,t,v] | 96 | $C_{22}H_{24}N_2Cl$ | 11.48 | 11.25 |
| $C_5H_4N$–[d] | $-C_6H_4(OCH_3)(4)$ | $-(CH_2)_2N(CH_3)_2$ | C | 158–165 | .04 | 141.5–142[t,j] | 79 | $C_{23}H_{27}N_2O\cdot H_2C_2O_4$ | 9.33 | 9.29 |
| $C_5H_4N$–[d] | $-C_4H_3O$[l] | $-(CH_2)_2N(CH_3)_2$ | C | 137–144 | .04 | 140–141[t,m] | 85 | $C_{20}H_{23}N_2O\cdot H_2C_2O_4$ | 10.23 | 10.35 |
| $C_5H_4N$–[d] | $-C_4H_3S$[n] | $-(CH_2)_2N(CH_3)_2$[w] | C | 155–156 | .05 | 96–97[j] | 89 | $C_{20}H_{23}N_2S$ | 12.46 | 12.43 |
| $C_4H_3N_2$–[p] | $-C_6H_5$ | $-(CH_2)_2N(CH_3)_2$ | C | 151 | .04 | 152–153.5[b,x] | 93 | $C_{21}H_{24}N_4\cdot 2HCl$ | 13.83 | 13.43 |
| $C_4H_2NS$–[r] | $-C_6H_5$ | $-(CH_2)_2N(CH_3)_2$ | C | 163–167 | .07 | 178–179[t,j] | 82 | $C_{20}H_{23}N_2S\cdot H_2C_2O_4$ | 9.85 | 9.53 |
| | | | | | | | | $C_{20}H_{23}N_2S$ | 12.45 | 12.22 |
| $C_{10}H_6N$–[s] | $-C_6H_5$ | $-(CH_2)_2N(CH_3)_2$ | C | 192 | .04 | 192–193[b] | 82 | $C_{27}H_{29}N_3\cdot 2HCl$ | 8.97 | 9.08 |

[a] Analyses and melting points were performed on salts which had been dried at *ca.* 0.1 mm. and at *ca.* 30–40° under the melting points. When a product was distilled, the yield given is based on the weight of distillate. When solid, yield calculation is based on the weight of the once-recrystallized material. [b] Hydrochloride. [c] Recrystallized from methanol–ether. [d] 2-Pyridyl. [e] Recrystallized from methanol. [f] Picrate. [g] Recrystallized from acetone–ethanol. [h] Carbon analysis. [i] Hydrogen analysis. [j] Recrystallized from isopropyl alcohol. [k] Recrystallized from isopropyl ether. The picrate melted at 150.5–151.5°. [l] 2-Furyl. [m] Recrystallized from ethanol. [n] 2-Thienyl. [o] Sulfur analysis. [p] 2-Pyrimidyl. [q] The picrate melted at 148.5–149.5° after recrystallization from ethanol. [r] 2-Thiazolyl. [s] 2-Lepidyl. [t] Oxalate. [u] Recrystallized from isopropyl acetate. [v] *Anal.* (on the oxalate, dried at 0.1 mm. and 120°). Calcd. for $C_{22}H_{24}N_2\cdot H_2C_2O_4$: N, 9.22; Cl, 7.77. Found: N, 8.97; Cl, 7.65. The air-dried oxalate contained water of hydration. *Anal.* Calcd. for $C_{22}H_{24}N_2\cdot H_2C_2O_4\cdot 4H_2O$: $H_2O$, 13.63. Found: $H_2O$, 13.48. After drying in a vacuum desiccator over concd. sulfuric acid, some of the water of hydration was apparently lost. *Anal.* Calcd. for $C_{22}H_{24}N_2\cdot H_2C_2O_4\cdot 2H_2O$: N, 8.54. Found: N, 8.66. [w] The oxalate, recrystallized from ethanol–isopropyl acetate, melted at 135–136°. [x] The methiodide melted at 174.8–175.2°.

ml. The warm solution of this compound was used without further purification. The product was obtained in 75% yield by this procedure and in 82% yield when the distilled Schiff base was used.

**Tertiary Amines [I (A-E)G, I AH, I AI and I AJ]. Method C.**—Method A was followed except for the fact that dimethylaminoethyl chloride hydrochloride and lithium amide were each added in 20% excess. Since it was later found unnecessary to perform this reaction in two steps (*i.e.*, to add the dimethylaminoethyl chloride hydrochloride to the lithiated heterocyclic amine),[24] in some reactions a mixture of all three reactants in benzene was refluxed (*cf.* Method D).

When dimethylaminoisopropyl chloride hydrochloride was substituted for dimethylaminoethyl chloride hydrochloride, an 84% yield of product was obtained from 2-benzohydrylaminopyridine, b.p. 152–155° (0.03 mm.), and an 88% yield from 2-benzohydrylaminolepidine, b.p. 179° (0.04 mm.). Neither product,[12] nor their hydrochlorides or methiodides, gave a satisfactory analysis. From the analytical results, the methyl iodide compounds appeared to be predominantly monomethiodides. Since repeat analyses on the purified products indicated an increase in iodine, but decrease in nitrogen content, it would seem that dimethiodide formation occurred during the purification.

The pyridine methiodide melted at 139.5°, then solidified and remelted at 235–236°.

*Anal.* Calcd. for $C_{23}H_{27}N_3\cdot CH_3I$: N, 8.62; I, 26.04. Found: N, 8.39; I, 27.00 (repeat on product recrystallized from ethanol–isopropyl acetate: I, 27.70 and 27.61).

The lepidine methiodide melted at 155.5–156.5°.

*Anal.* Calcd. for $C_{28}H_{31}N_3\cdot CH_3I$: N, 7.62; I, 23.05. Found: N, 7.18; I, 24.60 (repeat on product washed repeatedly with hot isopropyl acetate: N, 7.10; I, 25.81 and 25.90).

**N,N-Dimethyl-N'-benzohydryl-N'-phenylethylenediamine. Method D.**—A mixture of 32.8 g. (0.2 mole) of N,N-dimethyl-N'-phenylethylenediamine,[5] 48.6 g. (0.22 mole) of benzohydryl chloride and 11.6 g. (0.48 mole) of lithium amide[25a] in 200 ml. of benzene was refluxed 24 hours. The lithium chloride was separated by filtration and washed with benzene. After the filtrate had been stripped of solvents, the oil which remained was distilled *in vacuo*. The red, viscous liquid, which was collected at 155–160° (0.04 mm.), weighed 24.0 g. A white precipitate, weighing 6.0 g. and melting at 210–211° (*sym*-tetraphenylethane is reported as melting at 209–210.5°[27]) was removed after suspending the distillate in isopropyl alcohol. The oxalate was prepared by adding ethereal oxalic acid to the isopropanolic solution of the base. The salt weighed 21 g. (25%), m.p. 191–192°, after washing with isopropyl acetate and drying at 110° and 0.1 mm.

N,N-Dimethyl-N'-(2-pyridyl)-ethylenediamine (III)[5,25b] and some substituted benzohydryl chlorides[26] (4-chloro-, 4-methoxy, 4,4'-dichloro- and 4,4'-dimethoxy-) were treated in a similar fashion except that, instead of isolating the base by distillation, each reaction mixture was extracted several times with dilute hydrochloric acid. The aqueous extracts were combined, made alkaline and extracted with ether. Ethereal picric acid was added to the combined ether extracts which had previously been dried over potassium carbonate. Each reaction yielded the same picrate which melted at 200–201° after one recrystallization from methyl ethyl ketone. Mixed with the picrate of III, m.p. 201–202°, there was no depression in melting point.

*Anal.* Calcd. for $C_9H_{15}N_3\cdot 2C_6H_3N_3O_7$: N, 20.22. Found: N, 20.05.

**N,N-Dimethyl-N'-benzohydryl-N'-(2-pyridyl)-ethylenediamine Dihydrochloride. Method E.**—Lithium chloride was separated by filtration from a mixture of 26.0 g. (0.1 mole) of 2-benzohydrylaminopyridine, 12.2 g. (0.12 mole)

(25) Samples were generously donated by (a) Metalloy Corp. and (b) Monsanto Chemical Co.

(26) These compounds were prepared by Messrs. W. J. Burlant and H. C. Klein by modifying the methods described in the literature [*cf.* K. E. Hamlin, A. W. Weston, F. E. Fischer and R. J. Michaels, Jr., THIS JOURNAL, **71**, 2731 (1949)]. A description of this work will appear at a later date.

of dimethylaminoethyl chloride hydrochloride, 5.6 g. (0.24 mole) of lithium amide and 100 ml. of dry benzene which had been refluxed for 7 hours. Ethereal hydrogen chloride was added until no precipitate appeared on further addition. The salt, after filtration and washing with ether, was dissolved in about 100 ml. of water and the aqueous layer made alkaline and extracted several times with ether. To the combined ether extracts, dried over anhydrous potassium carbonate, was added ethereal hydrogen chloride to maximum precipitation. The hydrochloride was separated, washed with ether and dried *in vacuo* over concentrated sulfuric acid. The salt weighed 37.3 g. (91%) and melted at 155–160°. After three recrystallizations from isopropyl acetate, the melting point remained constant at 160–161.5°.

The preparation of I BG was attempted in a similar manner from 2-(4-methoxybenzohydryl)-aminopyridine and dimethylaminoethyl chloride hydrochloride. However, instead of adding ethereal hydrogen chloride, the benzene filtrate was saturated with dry hydrogen chloride gas. The product, subsequently isolated as the dipicrate, weighed 25 g. and melted at 200–201° after recrystallization from methyl ethyl ketone. It showed no depression in melting point when mixed with an authentic sample of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine dipicrate. In the same way, from II AG and dimethylaminoisopropyl chloride, there was obtained 29 g. of a dipicrate[12] which melted at 209–210° after two recrystallizations from water. The oxalate of this product melted at 170–171° after recrystallization from ethanol. There was no depression in melting point on admixture with a sample[12] prepared from 2-aminopyridine and dimethylaminoisopropyl chloride hydrochloride (Method A).

*Anal.* Calcd. for $C_{10}H_{17}N_3 \cdot 2H_2C_2O_4$: N, 11.70. Found: N, 11.53.

From 2-benzohydrylaminopyrimidine and dimethylaminoisopropyl chloride hydrochloride, by the same procedure, there was collected 16.5 g. of a dipicrate,[12] m.p. 191–192° after three recrystallizations from ethanol.

*Anal.* Calcd. for $C_9H_{16}N_4 \cdot 2C_6H_3N_3O_7$: N, 21.94. Found: N, 22.39.

**Displacement of the Benzohydryl Group from N,N-Dimethyl-N′-benzohydryl-N′-(2-pyridyl)-ethylenediamine.**—A solution of 10 g. of I AG in 50 ml. of absolute ethanol was saturated with dry hydrogen chloride gas. On concentrating to about 25 ml. and chilling in an ice-bath, there appeared a white, crystalline precipitate of N,N-dimethyl-N′-(2-pyridyl)-ethylenediamine dihydrochloride. This weighed 4.8 g. and melted at 221–223°[27] after washing with hot isopropyl acetate. The filtrate was evaporated to dryness. The residue was suspended in isopropyl alcohol, the mixture filtered and the insoluble *sym*-tetraphenylethane washed with the same solvent. The hydrocarbon weighed 2.0 g. after air-drying and melted at 209–210°.[7]

When a solution of I AG dihydrochloride in anhydrous ethanol was refluxed for 24 hours and then concentrated to about one-half of its original volume, no precipitate appeared. It was evaporated to dryness and the residue recrystallized from isopropyl acetate. The crystalline precipitate melted at 158–160° and showed no depression in melting point when admixed with the dihydrochloride of I AG.

**2-Benzohydrylaminopyridine from 2-Aminopyridine and Benzohydryl Chloride. Method F.**[11b]—A solution of 18.8 g. (0.2 mole) of 2-aminopyridine and 20.3 g. (0.1 mole) of benzohydryl chloride in 100 ml. of benzene was refluxed 24 hours. After removal of both the precipitated 2-aminopyridine hydrochloride and the solvent, the residue was crystallized from hexane. The crude product weighed 15.2 g. (58%), m.p. 84–92°. After one recrystallization from isopropyl alcohol, the melting point rose to 101–102° and remained constant on admixture with product obtained by Method A.

**Benzohydryl Isothiocyanate.**—The method described in "Organic Syntheses"[28] for the preparation of methyl isothiocyanate was employed. From 165.0 g. (0.9 mole) of benzohydrylamine,[29] there was obtained 174 g. (86%) of a deep blue liquid which was collected at 165–167° (9 mm.). The product crystallized on standing. Recrystallization of a sample to constant melting point from aqueous methanol yielded a colorless product, m.p. 56.5–57.5°.[30,31]

*Anal.* Calcd. for $C_{14}H_{11}NS$: N, 6.22. Found: N, 6.40.

**N-Benzohydrylthiourea.**—When a solution of 33.8 g. (0.15 mole) of benzohydryl isothiocyanate in 50 ml. of acetone and 50 ml. of concd. ammonia water was heated to reflux, an exothermic reaction occurred, depositing a bulky, white precipitate. After this had been moderated somewhat, the mixture was refluxed 30 minutes longer. Water was then added and the product separated and washed with water. The air-dried compound weighed 35.9 g. (99%) and melted at 183–185°. The analytical sample melted at 184–185° after three recrystallizations from isopropyl alcohol. The melting point has been reported as 189°.[31]

*Anal.* Calcd. for $C_{14}H_{14}N_2S$: N, 11.57. Found: N, 11.46.

**2-Benzohydrylaminothiazole. Method G.**—A solution of 9.7 g. (0.04 mole) of N-benzohydrylthiourea and 6.0 g. (0.048 mole) of dimethyl chloroacetal in 100 ml. of water acidified with 2 ml. of 2 *N* hydrochloric acid was heated on a steam-bath for 5 hours. A small amount of insoluble material was removed by filtering the hot solution and the filtrate made alkaline with sodium hydroxide solution. The curdy, white precipitate, which formed on chilling, was collected, washed with water and air-dried. The crude product weighed 10.5 g. (99%), m.p. 165–168°. After five recrystallizations from isopropyl alcohol, the melting point remained constant at 169.5–171°.

From 5.0 g. (0.05 mole) of 2-aminothiazole and 12.2 g. (0.06 mole) of benzohydryl chloride in 100 ml. of isopropyl alcohol (Method F), 1.3 g. (10%) of crude product was obtained. After two recrystallizations from isopropyl alcohol, the compound melted at 169–171° and showed no depression in melting point when admixed with a pure sample prepared by the previous procedure.

**Benzophenone Anil.**—A mixture of 182.2 g. (1.0 mole) of benzophenone and 107.1 g. (1.15 moles) of aniline was maintained at an internal temperature of 210–215° for 16 hours. (At the end of this time, the mixture of aniline and water, which had been collected in a moisture trap, was extracted with chloroform (to remove suspended aniline). The aqueous layer amounted to 17.5 ml.) The hot reaction mixture was dissolved in 300 ml. of isopropyl alcohol. After standing in an ice-bath for some time, the crystalline imine was separated and washed with cold isopropyl alcohol until the washings were colorless. The product weighed 246.8 g. (96%) after air-drying, m.p. 112–113°.[19]

**N-Benzohydrylaniline. Method H.**—A mixture of 231.5 g. (0.9 mole) of benzophenone anil, 9 g. of 10% palladium–charcoal and 300 ml. of thiophene-free benzene was hydrogenated at an initial pressure of 58 lb. The hydrogen uptake was complete in about 2 hours. The mixture was then filtered to recover the catalyst after which benzene was removed from the filtrate by distillation. The oil which remained was distilled *in vacuo*. The fraction collected at 128° (0.05 mm.) weighed 203.8 g. (87%) and was a viscous oil which crystallized on rubbing with hexane. The crystalline product, after washing with hexane, melted at 53–54.5°.[20]

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(27) F. C. Whitmore, H. S. Mosher, D. P. J. Goldsmith and A. W. Rytina, THIS JOURNAL, **67**, 393 (1945), report, as their only salt of this compound, the dihydrochloride, m.p. 223–224°. In ref. 5, two melting points (224 and 229°) are recorded for III·2HCl while in ref. 7 the melting point is given as 223–225°.

(28) M. L. Moore and F. S. Crossley in *Org. Syntheses*, **21**, 81 (1941).

(29) N-Benzohydryl formamide was prepared in a crude yield of 95% by the method of V. J. Webers and W. F. Bruce, THIS JOURNAL, **70**, 1422 (1948), using calcium chloride catalysis, as suggested in a footnote of a publication by J. F. Bunnett and J. L. Marks, *ibid.*, **71**, 1587 (1949). The formamide, without purification, was hydrolyzed to the amine by the method of Blicke and Tsao (ref. 9) in an over-all yield of 90%, b.p. 138–140° (3 mm.).

(30) J. von Braun and H. Deutsch, *Ber.*, **45**, 2188 (1912), obtained a very poor yield of product distilling at 250° (11 mm.) and melting at 58°. Their product was also colored.

(31) H. L. Wheeler, *Am. Chem. J.*, **26**, 353 (1901), reported a melting point of 61° and a boiling point of 222–225° (37–38 mm.) for benzohydryl isothiocyanate. No yield was given.