and a precipitate of the amine hydrochloride immediately formed which, after a single recrystallization in water, melted with decomposition at 227°. *Anal.* Calcd. for $C_{12}H_{11}NCl$: C, 60.02; H, 4.62. Found: C, 59.89, 60.03; H, 4.83, 4.94.

The total crude 3-chloro-3-aminobiphenyl was added to a solution of 500 ml. of sulfuric acid in 1000 ml. of water. After the mixture was cooled to 5°, a solution of sodium nitrite in water was added (temperature maintained at 5–10°) until a positive test with potassium iodide–starch paper was obtained. The diazotization reaction proceeded very slowly, probably due to the insolubility of the amine sulfate. A solution of 125 g. (0.75 mole) of potassium iodide in a minimum of water was added and the mixture was allowed to warm to room temperature and stand for eight hours. The organic layer which had settled to the bottom was extracted with ether, washed with sodium thiosulfate solution and dried over anhydrous magnesium sulfate. Distillation of this solution under reduced pressure yielded crude 3-chloro-3-iodobiphenyl boiling at 160–170° (1.0 mm.). This material was further purified by dissolution in 30–60° petroleum ether, passing through a column of activated alumina and redistilling; yield 74 g. (50% from 3-chloro-3-nitrobiphenyl). *Anal.* Calcd. for $C_{12}H_8ICl$: C, 45.82; H, 2.56. Found: C, 46.11; H, 2.70.

COLLEGE PARK, MARYLAND RECEIVED DECEMBER 6, 1950

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Chemistry of the Benzylpyridines. II. Nuclear Substituted 2-Benzylpyridines[1]

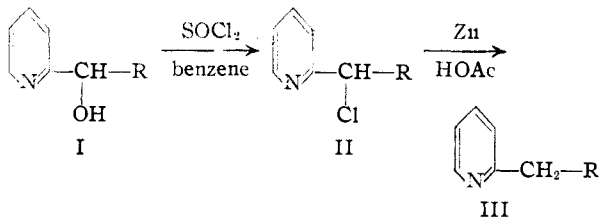
BY NATHAN SPERBER, DOMENICK PAPA, ERWIN SCHWENK AND MARGARET SHERLOCK

A series of nuclear substituted 2-benzylpyridines has been prepared by the conversion of the appropriately substituted phenyl-2-pyridylcarbinols to the corresponding chlorides, followed by reductive dehalogenation with zinc and acetic acid. A substantial improvement in the synthesis of the phenyl-2-pyridylcarbinols also is described.

As part of an extensive research program on the preparation of histamine antagonists, nuclear substituted 2-benzylpyridines were required as intermediates. Although three methods have been described for the preparation of 2- and 4-benzylpyridine, the nuclear substituted compounds, except in isolated cases,[2] are not known. Chichibabin[3] obtained a mixture of 2- and 4-benzylpyridines by the reaction of pyridine, benzyl chloride and a copper catalyst. The 2- and 4-isomers were separated by fractional crystallization of the picrates, which when decomposed yielded the pure, free bases. Separation of the isomers has been effected by fractional distillation of the crude mixture of isomers, thus eliminating the tedious picrate purification step.[4] 4-Benzylpyridine also has been obtained as a by-product of the reaction of pyridine and benzylmagnesium chloride.[5]

Recently an elegant synthesis of 2- and 4-benzylpyridines has been described.[6] Phenylacetonitrile is alkylated with 2- or 4-chloropyridine and the intermediate phenyl-2- or phenyl-4-pyridylacetonitrile is hydrolyzed and decarboxylated with sulfuric acid. This method is well suited for the preparation of substituted 2- and 4-benzylpyridines, provided the requisite substituted phenylacetonitriles are accessible.[7]

However, it appeared to us that a more direct synthesis of substituted 2-benzylpyridines could be effected by the conversion of the previously described aryl-2-pyridylcarbinols[8] in accordance with the equation



R = phenyl or substituted phenyl

This approach to the substituted 2-benzylpyridines seemed attractive in view of a substantial improvement in the synthesis of the intermediate carbinols and the availability of substituted benzaldehydes. In place of 2-pyridylmagnesium bromide,[9] it was found that the reaction of 2-pyridyllithium with aromatic aldehydes gave 70–90% yields of the carbinols I. These yields are in sharp contrast with those obtained by other methods.[8] The conversion of the carbinols to the corresponding 2-benzylpyridines proceeded in good yields by treatment of I with thionyl chloride in benzene,[10] followed by reductive dehalogenation of the chloride II, with zinc and acetic acid.[11,12] The *o*- and *p*-hydroxy-2-

(1) This is part of a paper presented before the Division of Medicinal Chemistry of the American Chemical Society, Chicago, April, 1948.

(2) F. Bryans and F. L. Pyman, *J. Chem. Soc.*, 549 (1929).

(3) A. E. Chichibabin, *Chem. Centr.*, [2] **72**, 127 (1901); [2] **87**, 146 (1916). Recent modifications of this procedure have been reported by: (a) F. B. La Forge, THIS JOURNAL, **50**, 2484 (1928); (b) K. E. Crook and S. M. McElvain, *ibid.*, **52**, 4006 (1930); (c) P. C. Teague, *ibid.*, **69**, 714 (1947).

(4) K. E. Crook, *ibid.*, **70**, 416 (1948).

(5) W. L. C. Veer and S. Goldschmidt, *Rec. trav. chim.*, **65**, 793 (1946).

(6) L. Panizzon, *Helv. Chim. Acta*, **27**, 1748 (1944).

(7) Further applications of this synthesis will be described in a forthcoming paper from our laboratories.

(8) (a) N. Sperber, D. Papa, E. Schwenk and M. Sherlock, THIS JOURNAL, **71**, 887 (1949); (b) C. H. Tilford, R. S. Shelton and M. C. Van Campen, Jr., *ibid.*, **70**, 4001 (1948).

(9) J. Overhoff and W. Proost, *Rec. trav. chim.*, **57**, 179 (1938).

(10) K. E. Hamlin, A. W. Weston, F. E. Fischer and R. J. Michaels, Jr., THIS JOURNAL, **71**, 2731 (1949), have prepared phenyl-2-pyridylmethyl chloride by the reaction of the carbinol with hydrogen chloride in an inert solvent.

(11) After this work was completed, R. Grewe, A. Mondon and E. Nolte, *Ann.*, **564**, 161 (1949), described the preparation of 1-(5,6,7,8-tetrahydroisoquinolyl)-phenylcarbinol which was subsequently reduced to the methane derivative with red phosphorus and hydriodic acid in a yield of 90%. The corresponding *p*-methoxy derivative was also obtained by conversion of the carbinol to the bromide with hydrogen bromide–acetic acid, followed by treatment with zinc.

(12) A. W. Ruddy and J. S. Buckley, Jr., THIS JOURNAL, **72**, 718 (1950), have prepared a series of 3-amino-1-phenylpropanes by converting the 1-propanols to the chlorides with thionyl chloride followed by dehalogenation with a palladium-on-charcoal catalyst.

TABLE I

COMPOUNDS OF FORMULA R—CH_2—R′

R	R′	Yield, %[a]	B.p., °C.	Mm.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
2-C_5H_4N	*p*-$CH_3C_6H_4$	82	117–122	2.0	$C_{13}H_{13}N$	85.21	85.32	7.15	7.24		
2-C_5H_4N	*p*-$CH_3OC_6H_4$	45	145–147	2.0	$C_{13}H_{13}NO$	78.36	78.06	6.57	6.34		
2-C_5H_4N	*o*-$CH_3OC_6H_4$[b]	85	134–138	1.5	$C_{13}H_{13}NO$	78.36	78.20	6.57	6.61		
2-C_5H_4N	*p*-HOC_6H_4	86	172–178[c]	0.5	$C_{12}H_{11}NO$					7.56	7.38
2-C_5H_4N	*o*-HOC_6H_4	65	133–139[d]	0.5	$C_{12}H_{11}NO$					7.56	7.31
2-C_5H_4N	*p*-*i*-$C_3H_7C_6H_4$	75	135–137	2.5	$C_{15}H_{17}N$	85.26	85.29	8.11	7.96		
2-C_5H_4N	*p*-ClC_6H_4	77	108–111	0.5	$C_{12}H_{10}NCl$					Cl, 17.43	17.27
2-C_5H_4N	*o*-ClC_6H_4	46	128–133	3.0	$C_{12}H_{10}NCl$					Cl, 17.43	17.21
2-C_5H_4N	3,4-$Cl_2C_6H_3$	69	142–148	2.0	$C_{12}H_9NCl_2$	60.52	60.48	3.81	4.08		
2-C_5H_4N	*p*-$(CH_3)_2NC_6H_4$	56	135–140	1.0	$C_{14}H_{16}N_2$					13.20	13.10
2-C_5H_4N	C_6H_{11}	57	95–96	2.5	$C_{12}H_{17}N$					8.00	8.17
2-C_5H_4N	2-C_5H_4N	71	102–106	0.5	$C_{11}H_{10}N_2$					16.46	15.79
3-CH_3-2-C_5H_3N	C_6H_5	71	101–106	0.5	$C_{13}H_{13}N$					7.64	7.68

[a] Yields are based on a limited number of experiments and do not necessarily represent the maximum obtainable. [b] The intermediate *o*-methoxyphenyl-2-pyridylcarbinol was prepared by the reaction of picolinic acid and *o*-methoxybenzaldehyde in cymene; yield 27%; b.p. 140–143° (1 mm.), lit.[3b] b.p., 144–148° (0.3 mm.). The carbinol solidified upon standing, m.p. 81–81.5° after recrystallization from a mixture of benzene–petroleum ether. *Anal.* Calcd. for $C_{13}H_{13}NO_2$: N, 6.51. Found: N, 6.97. [c] M.p. 129.5–130.5°. [d] M.p. 98–99°.

benzylpyridines were prepared by refluxing the corresponding methoxy compounds with a mixture of hydrobromic–acetic acids.

Along with the substituted 2-benzylpyridines, we prepared 2-(cyclohexylmethyl)-pyridine and 1-(2-thienyl)-2-(2-pyridyl)-ethane, as well as the corresponding 5-chloro- derivative of the latter compound.[13] These three compounds were prepared by the condensation of the potassium salt of α-picoline and cyclohexyl bromide, 2-thenyl chloride[14] and 5-chloro-2-thenyl chloride,[15] respectively. An attempt to prepare 1-(5-bromo-2-thienyl)-2-(2-pyridyl)-ethane by the same procedure yielded tarry products. However, bromination of 1-(2-thienyl)-2-(2-pyridyl)-ethane in acetic acid gave a 60% yield of a bromo derivative which was assumed to be the 5-bromothienyl compound.[16]

Experimental[17]

The preparation of (3-methyl-2-pyridyl)-phenylcarbino illustrates the general procedure for securing substituted aryl-2-pyridylcarbinols: While a stream of dry nitrogen was passed through the apparatus, 500 ml. of anhydrous ether and 12 g. (1.74 moles) of lithium shot were placed in a two-liter, three-necked flask equipped with a condenser, dropping funnel, stirrer and thermometer. To the vigorously stirred mixture there was added 80.5 g. (0.87 mole) of *n*-butyl chloride[18] over a period of several hours. The cloudy solution was refluxed an additional 30 minutes, cooled in an acetone–Dry Ice-bath to −40°, and a solution of 116 g. (0.5 mole) of 3-methyl-2-bromopyridine[19] in 100 ml. of ether added. The brown reaction mixture was stirred for 15 minutes and 62 g. (0.59 mole) of benzaldehyde was added at a temperature of −30°. The temperature was then allowed to rise to −15°, and the mixture, after being stirred for 45 minutes, was poured on dilute hydrochloric acid and ice. The acid layer was separated, made alkaline with gaseous ammonia and the oily layer extracted with ether. The ether extracts were dried over sodium sulfate, filtered, and after removal of the ether, the residue was distilled; yield 92 g. (92.5%), b.p. 134–137° (1 mm.), m.p. 55.2–56.2°.

Anal. Calcd. for $C_{13}H_{13}NO$: N, 7.03. Found: N, 7.00.

With the exception of bis-(2-pyridyl)-methane and 2-(cyclohexylmethyl)-pyridine, the 2-benzylpyridines listed in Table I were prepared by the following general procedure.

2-Benzyl-3-methylpyridine.—To a stirred, cooled solution (5–10°) of 155 g. (0.78 mole) of (3-methyl-2-pyridyl)-phenylcarbinol in one liter of dry benzene, there was added 102 g. (0.86 mole) of purified thionyl chloride at such a rate that the temperature did not rise above 25°. Stirring was continued for an additional hour at room temperature. The reaction mixture was then cooled and made alkaline with 25% sodium hydroxide solution, the temperature being kept below 30°. The benzene layer was separated, washed with water, dried over sodium sulfate, filtered and concentrated *in vacuo*. The dark red residue was dissolved in 900 ml. of glacial acetic acid and to this solution was added, in portions, 110 g. of zinc dust. The reaction mixture was stirred and heated on a steam-bath for six hours. The zinc salts were filtered off, the acetic acid removed *in vacuo* on the steam-bath and the residue made basic with sodium hydroxide solution. The oil was extracted with ether, the ether layer dried over sodium sulfate, filtered, concentrated and the residue fractionated.

2-(*p*-Hydroxybenzyl)-pyridine.—A solution of 32 g. of 2-(*p*-methoxybenzyl)-pyridine in 200 ml. of 48% hydrobromic acid and 50 ml. of glacial acetic acid was refluxed for 16 hours. The mixture was poured on ice, made alkaline with sodium hydroxide and extracted with ether. The alkaline layer was neutralized carefully with cold, dilute hydrochloric acid, the oil extracted with ether, the ether layer washed with water, dried and distilled.

Bis-(2-pyridyl)-acetonitrile.—To a stirred suspension of sodamide (17.5 g. of sodium) in 200 ml. of toluene at 80°, there was added 10.3 g. (0.25 mole) of acetonitrile. After the mixture had been stirred for 30 minutes, 79 g. (0.5 mole) of 2-bromopyridine was added slowly. The cloudy, brown mixture was refluxed for six hours, cooled and decomposed with water. The toluene layer was separated, washed with water, dried over anhydrous sodium sulfate and filtered. After the removal of the toluene, the residue, upon distillation, gave a forerun boiling at 120–180° (0.5 mm.). The substituted acetonitrile distilled as a dark red oil, b.p. 180–200° (0.5 mm.), yield 12.5 g. (25%), which solidified upon standing. After recrystallization from ethanol, the white solid melted at 138–139°.

Anal. Calcd. for $C_{12}H_9N_3$: N, 21.53. Found: N, 21.65.

Bis-(2-pyridyl)-methane was prepared essentially as described by Panizzon[6] for 2-benzylpyridine. In a 500-cc.,

(13) The procedure of F. W. Bergstrom, T. R. Norton and R. A. Seibert, *J. Org. Chem.*, **10**, 452 (1945), for the preparation of 2-(β-phenethyl)-pyridine was found to be satisfactory for the synthesis of these compounds.

(14) F. F. Blicke and F. Leonard, THIS JOURNAL, **68**, 1934 (1946).

(15) R. C. Clapp, J. H. Clark, J. R. Vaughan, J. P. English and G. W. Anderson, *ibid.*, **69**, 1549 (1947).

(16) See J. H. Ford, G. C. Prescott and D. R. Colingsworth, *ibid.*, **72**, 2109 (1950), for similar halogenations of thiophene compounds.

(17) All melting points are corrected.

(18) After this work had been completed, H. Gilman, *et al.*, *ibid.*, **71**, 1499 (1949), described the preparation of *n*-butyllithium from *n*-butyl bromide in yields of 75–90%. This modification has been used in subsequent experiments with excellent results.

(19) R. P. Mariella and V. Kvinge, *ibid.*, **70**, 3126 (1948).

three-necked flask equipped with a stirrer and a condenser connected to a trap containing an aqueous solution of barium hydroxide, a mixture of 100 g. of 80% sulfuric acid and 21 g. of bis-(2-pyridyl)-acetonitrile was heated at 125–130° with stirring for about two hours. At the end of this time no more carbon dioxide was evolved. The dark mixture was poured on ice, basified with gaseous ammonia, the oil extracted with ether, the ether layer dried, concentrated and the residue distilled.

2-(Cyclohexylmethyl)-pyridine.—To a solution of potassium amide prepared from 20 g. (0.51 mole) of potassium and 1,500 ml. of liquid ammonia, there was added slowly 46.5 g. (0.5 mole) of α-picoline. After ten minutes, 83.1 g. (0.51 mole) of cyclohexyl bromide was added as rapidly as possible, and stirring was continued until all of the ammonia had evaporated. The reaction mixture was decomposed with water, the oil extracted with ether, the ether extracts washed with water, dried over sodium sulfate, concentrated and the residue fractionated.

1-(2-Thienyl)-2-(2-pyridyl)-ethane was prepared according to the preceding experiment by condensing the potassium salt of α-picoline with 2-thenyl chloride in liquid ammonia; yield 56%, b.p. 106–110° (0.5 mm.).

Anal. Calcd. for $C_{11}H_{11}NS$: N, 7.40. Found: N, 7.31.

In a subsequent large-scale experiment a 35% yield of the desired product was obtained. Fractionation of the higher residue yielded 24% of di-(2-thenyl)-α-picoline as a viscous oil, b.p. 176–180° (1 mm.).

Anal. Calcd. for $C_{16}H_{15}NS_2$: N, 4.90. Found: N, 4.81.

1-(5-Chloro-2-thienyl)-2-(2-pyridyl)-ethane was prepared from the potassium salt of α-picoline and 5-chloro-2-thenyl chloride; yield 31%, b.p. 126–128° (0.5 mm.).

Anal. Calcd. for $C_{11}H_{10}NSCl$: Cl, 15.85. Found: Cl, 15.35.

1-(5-Bromo-2-thienyl)-2-(2-pyridyl)-ethane.—To a stirred, cooled solution (10°) of 9.4 g. of 1-(2-thienyl)-2-(2-pyridyl)-ethane in 25 ml. of glacial acetic acid, there was added slowly 3 ml. of bromine in 40 cc. of glacial acetic acid. The solution was made alkaline with gaseous ammonia, ether extracted, the ether layer dried, concentrated and the residue distilled; yield 60%, b.p. 129–133° (0.5 mm.).

Anal. Calcd. for $C_{11}H_{10}NSBr$: Br, 29.79. Found: Br, 29.58.

BLOOMFIELD, N. J. RECEIVED FEBRUARY 27, 1951

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS UNIVERSITY]

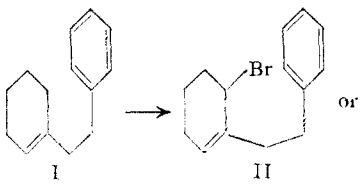
Reactions of N-Bromosuccinimide. II[1,2]

BY RODERICK A. BARNES AND GEOFFREY R. BUCKWALTER[3,4]

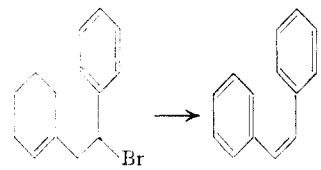
The reaction of N-bromosuccinimide with four hydrocarbons has been studied in order to gain some information concerning possible side reactions which may limit the use of this substance as a dehydrogenating agent. 1-(β-Phenylethyl)-1-cyclohexene was dehydrogenated to stilbene; no cyclization products were detected. Ionene was converted in a stepwise process to a bromide which rearranged with migration of a methyl group to produce 1,2,6-trimethylnaphthalene. Limonene could be converted to *p*-cymene and with more reagent the latter substance reacted to yield a bromide and a dimeric hydrocarbon.

Previous work[1] on the reaction of N-bromosuccinimide with hydrocarbons has illustrated the usefulness of this reagent in effecting the low temperature dehydrogenation of some hydroaromatic compounds. The main purpose of the present work was to investigate the reactions of some substances which might be expected to dehydrogenate with rearrangement or which are known to rearrange when the usual high temperature methods are employed.

In the reaction of 1-(β-phenylethyl)-1-cyclohexene (I) with N-bromosuccinimide some phenanthrene might be expected either by hydrogen bromide catalyzed cyclization[5] of the olefin (I) or by intramolecular reaction of bromide II or the free radical intermediate in formation of II.



I II



III IV

The isolation of stilbene (IV) as the major reaction product and the absence of any detectable amount of phenanthrene showed that in this case cyclization is not a factor which need be considered in interpreting the results of a dehydrogenation by N-bromosuccinimide.[6]

It is to be noted that the reaction with this cyclohexene derivative does not take the same course as with unsubstituted cyclohexene.[7] The explanation for the difference probably lies in the fact that bromide III is produced most rapidly from I and then with loss of hydrogen bromide 1-styryl-1-cyclohexene (V) is formed as the next intermediate.

V

(1) For the first paper see R. A. Barnes, THIS JOURNAL, **70**, 145 (1948).

(2) Presented at the Chicago Meeting of the A. C. S., Sept. 6, 1950.

(3) From the Ph.D. thesis of G. R. Buckwalter presented to the Graduate Faculty in October, 1950.

(4) du Pont Fellow in Chemistry, 1949–1950.

(5) It is known that acids such as aluminum chloride and sulfuric acid will cause cyclization of olefins analogous to I; see J. W. Cook, N. A. McGinnis and S. Mitchell, *J. Chem. Soc.*, 286 (1944), and R. A. Barnes and L. Gordon, THIS JOURNAL, **71**, 2644 (1949).

(6) Phenanthrene can be formed when dibenzyl is heated with platinum on charcoal at 300°: N. D. Zelinskii and I. N. Titz, *Ber.*, **62**, 2869 (1929); N. D. Zelinskii, I. N. Titz and M. V. Gaverdovskii, *ibid.*, **59**, 2596 (1926).

(7) Cyclohexene has been found to produce a mixture of *m*- and *p*-dibromobenzenes when treated with excess N-bromosuccinimide; ref. 1.