treated with Norite, filtered and allowed to cool. The product which separated was purified by crystallization from glacial acetic acid; colorless prisms, m. p. 165°.

Anal. Calcd. for $C_8H_5Br_2NO$: N, 4.81; Br, 54.95. Found: N, 4.86, 5.18; Br, 55.14.

Isatin-β-phenylhydrazone from V.—A solution of 5 g. of phenylhydrazine in 5 cc. of glacial acetic acid was added to a solution of 1.5 g. of V in 25 cc. of ethyl alcohol and the mixture heated at reflux temperature for one hour. The product, which separated on cooling, was crystallized from ethyl alcohol; yellow needles, m. p. 210°. A mixture with an authentic sample of isatin-β-phenylhydrazone exhibited the same m. p.

3,3-Diphenyloxindole from V.—To a solution of 1.5 g. of V in 20 cc. of dry benzene, 3 g. of anhydrous aluminum chloride was added in small portions. The mixture was heated for two hours at 60° and the benzene then removed under reduced pressure. Ice and then water were added, the solid residue collected and crystallized from benzene; colorless needles, m. p. 225–226°. Mixed with an authentic sample of 3,3-diphenyl-oxindole prepared similarly from 3,3-dichloroöxindole and benzene the m. p. was unchanged.

3,3,5-Tribromoöxindole (VI).—A solution of 8 g. (0.05 mole) of bromine in 100 cc. of anhydrous carbon tetrachloride was added slowly to a boiling mixture of 5.3 g. (0.025 mole) of 5-bromoöxindole and 300 cc. of anhydrous carbon tetrachloride. Heating was continued until there was no further evolution of hydrogen bromide. The resulting solution was concentrated and the product purified by crystallization from carbon tetrachloride or glacial acetic acid; colorless prisms. When heated in the usual way in a capillary tube the substance does not melt but begins to darken at about 190° and gradually decomposes by 250–260°. However, if the capillary tube is introduced into the heating bath at 235° or above the substance melts with decomposition.

Anal. Calcd. for $C_8H_4Br_3NO$: Br, 64.84; N, 3.78. Found: Br, 64.82; N, 3.70.

5-Bromoisatin-β-phenylhydrazone from VI.—A mixture of 1.5 g. of VI, 3 g. of phenylhydrazine and 20 cc. of ethyl alcohol was heated at reflux temperature for one hour. The product, which separated on cooling, was crystallized from ethyl alcohol; orange yellow needles, m. p. 271–272° alone and when mixed with an authentic sample of 5-bromoisatin-β-phenylhydrazone.

3,3,5,7-Tetrabromoöxindole (VII).—A solution of 6.4 g. (0.04 mole) of bromine in 100 cc. of anhydrous carbon tetrachloride was added slowly to a boiling solution of 5.82 g. (0.02 mole) of 5,7-dibromoöxindole in 400 cc. of anhydrous carbon tetrachloride. Heating was continued until there was no further evolution of hydrogen bromide. The resulting solution was concentrated and the product which separated on cooling purified by crystallization from glacial acetic acid; nearly colorless prisms, darkening at about 235° and melting at 250° (dec.).

Anal. Calcd. for $C_8H_3Br_4NO$: Br, 71.27; N, 3.12. Found: Br, 71.31; N, 3.00, 3.01.

5,7-Dibromoisatin-β-phenylhydrazone from VII.—A mixture of 0.6 g. of VII with 30 cc. of ethyl alcohol and 2 g. of phenylhydrazine was heated at reflux temperature for one hour. The product which separated was purified by crystallization from glacial acetic acid; m. p. 301–302° alone and when mixed with an authentic sample of 5,7-dibromoisatin-β-phenylhydrazone.

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Summary

1. The monobromoöxindole and the tribromoöxindole of Baeyer and Knop have been shown to be 5-bromoöxindole and 3,5,7-tribromoöxindole, respectively.

2. Bromination of oxindole in aqueous solution yields 5-bromoöxindole, 5,7-dibromoöxindole and 3,5,7-tribromoöxindole, respectively, as one, two and three molecular proportions of bromine are employed.

3. Bromination of oxindole and of nuclear substituted oxindole derivatives in anhydrous carbon tetrachloride yields the corresponding 3,3-dibromo derivatives.

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[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

The Synthesis of Some N-Methylbenzylamines and Derivatives

BY NORMAN H. CROMWELL AND HERMAN HOEKSEMA[1]

In a previous communication[2] directions for preparing N-methylbenzylamine in excellent yields were described. It was of interest to prepare certain N-methylbenzylamines containing hydroxy and methoxy groups on the benzene ring from the corresponding aldehydes. These secondary amines were desired for the preparation of various derivatives of possible pharmacological value.

The N-methylbenzalimines were obtained in good yields from the reactions of aqueous methylamine with salicylaldehyde, *p*-hydroxybenzaldehyde, *o*-methoxybenzaldehyde, and anisaldehyde. These imines were readily reduced, catalytically, to the secondary amines, (V), (VII), (VIII) and (XI) in good yields. The purification of the free base of (V) was difficult because of the relative ease with which this compound lost methylamine and gave, apparently, a phenol–formaldehyde type of condensation product. Heating the free base of (VII) also caused self-condensation with loss of methylamine and formation of a resin. The lability of these C–N bonds will be discussed in a future communication.

The N-benzoyl derivatives of the free base of (V), (VIII) and (XI) were obtained in excellent yields. It had been hoped that the *p*-aminobenzenesulfonamides of the *s*-amines might be prepared. Although (XI) gave a good yield of N-(*p*-acetylaminobenzene-sulfonyl)-N-methyl-*p*-methoxybenzylamine (XIV), it was not possible to hydrolyze this product in the usual way to the sulfanilamido derivative.

(1) Part of the experimental work described was done under a Parke, Davis and Company Research Fellowship, 1943–1944.

(2) Cromwell, Babson and Harris, THIS JOURNAL, **65**, 313 (1943).

TABLE I

PHYSICAL AND ANALYTICAL DATA

N-methyl benzalimines	No.	M. p. or b. p., °C. (mm.)	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
o-Hydroxy[a]	I	145 (20)	88			
p-Hydroxy	II	180	76	C_8H_9NO	10.36	10.15
o-Methoxy	III	134 (20)	82	$C_9H_{11}NO$	9.39	9.35
p-Methoxy[b]	IV	134 (26)	76			
N-methyl benzylamines						
o-Hydroxy						
Hydrochloride[c]	V	146	75	$C_8H_{12}NOCl$	Cl, 20.55	20.49
N-Benzoyl[d]	VI	129	90	$C_{15}H_{15}NO_2$	5.79	5.79
p-Hydroxy						
Hydrochloride	VII	183	87	$C_8H_{12}NOCl$	8.07	7.98
o-Methoxy[e]	VIII	128 (35)	80			
Hydrochloride	IX	124	95	$C_8H_{14}NOCl$	7.47	7.63
N-Benzoyl	X	83	91	$C_{16}H_{17}NO_2$	5.48	5.32
p-Methoxy[f]	XI	137 (30)	90			
Hydrochloride[f]	XII	176	96	$C_9H_{14}NOCl$	7.47	7.34
N-Benzoyl	XIII	58	90	$C_{16}H_{17}NO_2$	5.48	5.40
N-(*p*-Acetylaminobenzenesulfonyl)	XIV	170	64	$C_{17}H_{20}N_2SO_4$	8.03	7.80
Benzylacetones						
α,β-Di-(*o*-hydroxy-N-methylbenzylamino)	XV	163	20	$C_{26}H_{30}N_2O_3$	6.68	6.53
α,β-Di-(*o*-methoxy-N-methylbenzylamino)	XVI	114	80	$C_{28}H_{34}N_2O_3$	6.28	6.10
α,β-Di-(*p*-methoxy-N-methylbenzylamino)	XVII	103	75	$C_{28}H_{34}N_2O_3$	6.28	6.09
α-Bromo-β-(*p*-methoxy-N-methylbenzylamino)	XVIII	99	50	$C_{19}H_{22}NO_2Br$	3.72	3.49
α-(*p*-Methoxy-N-methylbenzylamino)-β-(N-8-amino-6-methoxyquinoline)[g]	XIX	173	90	$C_{29}H_{31}N_3O_3$		
Benzylacetophenones						
α-Bromo-β-(*p*-methoxy-N-methylbenzylamino)	XX	103	83	$C_{24}H_{24}NO_2Br$	3.18	3.13
α-Morpholino-β-(*o*-methoxy-N-methylbenzylamino)	XXI	174	10	$C_{28}H_{32}N_2O_3$	6.30	6.39
α-(*p*-Methoxy-N-methylbenzylamino)-benzalacetophenone	XXII	82	90	$C_{24}H_{24}N_2O_2$	3.92	3.72

[a] Dennstedt and Zimmermann, *Ber.*, 21, 1553 (1888). [b] Kindler and Kording, *Ann.*, **431**, 225 (1923). [c] Zemplén and Kunz, *Ber.*, **55**, 986 (1922), report this compound, m. p. 130°. [d] Calcd.: C, 74.67, H, 6.27. Found: C, 74.78, H, 6.31. [e] Wojahn and Erdelmeier, *Arch. Pharm.*, **280**, 223 (1942); Holly and Cope, THIS JOURNAL, **66**, 1879 (1944). [f] Tiffeneau, *Bull soc. chim.*, [4] **9**, 826 (1911). [g] Calcd.: C, 74.17; H, 6.65. Found: C, 74.01; H, 6.72.

The α,β-diaminobenzylacetones, (XV), (XVI) and (XVII), were prepared by treating the free base of (V) with α-bromobenzalacetone, and (VIII) and (XI), respectively, with α,β-dibromobenzylacetone. It was not possible to prepare the corresponding secondary alcohol from (XVI) by reduction with aluminum isopropoxide, nor with sodium and alcohol. The carbonyl groups in these α,β-diamino ketones appear to resist some of the usual carbonyl reactions.[3]

The orange-red α-(*p*-methoxy-N-methylbenzylamino)-benzalacetophenone (XXII) was obtained in good yield from the α-bromo-β-aminobenzylacetophenone (XX). The mixed diaminobenzylacetone, (XIX) was prepared by treating the α - bromo - β - (*p* - methoxy - N - methylbenzylamino)-benzylacetone (XVIII) with 6-methoxy-8-aminoquinoline in the usual way.[3]

A very low yield of the mixed diaminobenzylacetophenone (XXI) resulted when α-bromo-β-morpholinobenzylacetophenone reacted with (VIII). It has been pointed out previously that low yields are to be expected from such reactions when open chain secondary amines are used.

(3) Cromwell and Hoeksema, THIS JOURNAL, **67**, 124 (1945).

Experimental[5]

N-Methylbenzalimines.—The imines (I), (III) and (IV) were prepared from the corresponding aldehydes and 33% aqueous methylamine according to the directions previously described for N-methylbenzylimine.[2] The imine (II) was prepared by dissolving 50 g. of *p*-hydroxybenzaldehyde in 50 ml. of hot absolute alcohol, and adding rapidly 54 ml. of 33% aqueous methylamine at about 40°. The solution was cooled in an ice-bath for two hours to deposit a white crystalline product, which was filtered and washed with cold 40% alcohol and water, m. p. 178–180°.

N-Methylbenzylamines.—The imines (I), (II), (III) and (IV) were reduced catalytically according to the previously described method[2] to the *s*-amines. Evaporation of the solvent *in vacuo* from the reduction of (I) left a yellow oil which solidified on cooling. Attempts to recrystallize or vacuum distill this product resulted in self-condensation with the loss of methylamine and the formation of a resin. The *s*-amines (VIII) and (XI) were obtained by evaporation of the reduction mixtures and vacuum distillation of

(4) Cromwell, Caughlan and Gilbert, *ibid.*, **66**, 402 (1944).

(5) Micro-Kjeldahl analyses for nitrogen are by Margaret M. Ledyard of the Parke, Davis and Company Research Laboratories, Detroit, Michigan.

the residual oils. The hydrochlorides (V), (VII), (IX) and (XII) were prepared by passing dry hydrogen chloride gas into dry ether solutions of the *s*-amines. These products were recrystallized from 95% alcohol–ether mixtures as colorless products. (V) and (VII) were stable to ten minutes boiling in water solutions, but the free bases gave off methylamine and formed a resin under these conditions.

N-Methyl-N-benzoylbenzylamines.—The N-benzoyl derivatives (VI), (X) and (XIII) were obtained in 90% yields or better, by adding one equivalent of benzoyl chloride to a cold, dry ether solution of two equivalents of the secondary amine. The amine hydrochlorides were filtered off and the ether solutions shaken with sodium bicarbonate solutions, dried, and evaporated to give the colorless products. (VI) was recrystallized from 50% alcohol and water solutions, (X) from benzene and petroleum ether solutions, and (XIII) from dry ether, petroleum ether solutions.

N-(*p*-Acetylaminobenzenesulfonyl)-N-methyl-*p*-methoxybenzylamine (XIV).—To a solution of 10.0 g. (0.066 mole) of (XI) in 60 ml. of pyridine was added 15.1 g. (0.075 mole) of *p*-acetylaminobenzenesulfonyl chloride in small portions in thirty minutes. The dark brown solution was allowed to stand at room temperature for twelve hours and then heated on the steam-bath for thirty minutes. The solution was cooled and slowly poured with stirring into 600 ml. of water. The yellow solid precipitate was collected on the filter and washed several times with water and dried. Recrystallization from boiling 95% alcohol gave colorless needles.

Boiling (XIV) with 4 *N* hydrochloric acid gave incomplete hydrolysis even after eight hours. Hydrolysis by boiling for thirty minutes 12 g. with a solution of 20 ml. of concd. hydrochloric acid and 60 ml. of absolute alcohol resulted in a very thick, clear, gummy product that refused to crystallize from various solvent mixtures. The product gave no color with ferric chloride solutions, was insoluble in dilute hydrochloric acid, in sodium hydroxide and in absolute alcohol.

Di-(N-methylbenzylamino)-benzylacetones.—The diamino ketone (XV) was prepared by heating to boiling a solution of 20 g. of α-bromobenzalacetone[6] in 30 ml. of absolute alcohol with 40 g. of crude *o*-hydroxy-N-methylbenzylamine. The dark solution was cooled in the ice-chest six hours. A white fluffy product resulted which was recrystallized first from chloroform and alcohol and then from chloroform and petroleum ether.

The diamino ketones (XVI) and (XVII) were both prepared from the dibromoketone. To suspensions of 10 g. (0.0327 mole) of α,β-dibromobenzylacetone[7] in 15 ml. of absolute alcohol was added 20.0 g. (0.133 mole) of (VIII) and (XI), respectively. The solutions evolved heat and all the dibromide dissolved. The red solutions were then heated in a water-bath for five minutes and allowed to cool to room temperature. On scratching the inside of the flasks both solutions set to solid masses. The products were filtered and washed with cold 90% alcohol, then water and again with cold 80% alcohol.

The reduction of the carbonyl group in (XVI) was attempted with aluminum isopropoxide in isopropyl alcohol in the usual way. All of the unchanged starting material was recovered. An attempted sodium and alcohol reduction of (XVI) resulted in decomposition of the starting material.

α-Bromo-β-(*p*-methoxy-N-methylbenzylamino)-benzylacetone (XVIII), was prepared by adding 13.4 g. of (XI) to a solution of 20 g. of α-bromobenzalacetone[6] in 20 ml. of petroleum ether (b. p. 50°) and 2.0 ml. of dry ether at room temperature. The solution evolved heat and an oil was precipitated which solidified on standing in the ice-chest twenty-four hours. The white product was filtered, washed as usual and dried.

α-(*p*-Methoxy-N-methylbenzylamino)-β-(N-8-amino-6-methoxyquinoline)-benzylacetone, (XIX).—To a suspension of 5.3 g. of (XVIII) in 17 ml. of absolute alcohol was added 4.9 g. of 6-methoxy-8-aminoquinoline and the reaction mixture boiled for two minutes to obtain complete solution. After standing in the ice-chest for two days the product was isolated and recrystallized from chloroform and 95% alcohol mixtures and dried under vacuum at 100° for one hour.

α-Morpholino-β-(*o*-methoxy-N-methylbenzylamino)-benzylacetophenone (XXI).—To a suspension of 6.5 g. of α-bromo-β-morpholinobenzylacetophenone[7] in 30 ml. of absolute alcohol was added 5.2 g. of (VIII). The reaction mixture was heated on the water-bath for a few minutes to dissolve all of the reactants. After standing in the ice-chest for twenty-four hours, the product was isolated and recrystallized once from benzene and petroleum ether, and once from chloroform and 95% alcohol, and dried *in vacuo* at 100° for two hours. From the red reaction mixture residue was also isolated 2.0 g. of α-morpholinobenzalacetophenone.[7]

α-Bromo-β-(*p*-methoxy-N-methylbenzylamino)-benzylacetophenone (XX), was prepared by adding 5.3 g. of (XI) to 10 g. of α-bromo-benzalacetophenone[8] dissolved in a mixture of 10 ml. of dry ether and 10 ml. of petroleum ether (b. p. 60–70°) at 0°. After four hours the product was filtered off and washed as usual.

α-(*p*-Methoxy-N-methylbenzylamino)-benzalacetophenone (XXII).—To a solution of 1.03 g. of sodium in 30 ml. of absolute alcohol was added 11.1 g. of (XX). The product was isolated as usual and recrystallized from 95% alcohol as orange-red plates.

Summary

1. A previously described[2] method has been applied to the preparation of *o*-hydroxy-, *p*-hydroxy-, *o*-methoxy- and *p*-methoxy-N-methylbenzylamines.

2. The reactions of these amines with various active halogen compounds such as benzoyl chloride, *p*-acetylaminobenzenesulfonyl chloride, and some bromo ketones have been carried out to give derivatives of possible pharmacological interest.

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(6) Cromwell and Cram, THIS JOURNAL, **65**, 305 (1943).

(7) Cromwell, *ibid.*, **62**, 3471 (1940).

(8) Cromwell, *ibid.*, **62**, 2899 (1940).