N-(Nicotinoylmethane)-*p*-chlorobenzamide.—This compound was prepared using a modified Schotten–Baumann reaction with saturated sodium bicarbonate solution as the alkalizing medium. Nicotinoylaminomethane dihydrochloride (0.418 g.) was dissolved in water and 0.350 g. of *p*-chlorobenzoyl chloride was added dropwise. The solution was kept alkaline with additions of sodium bicarbonate solution. The solid which separated was washed with 10 ml. of cold 7% hydrochloric acid. This solution was then made alkaline with cold 10% sodium hydroxide solution and extracted with three 10-ml. portions of chloroform. This was dried over anhydrous potassium carbonate, filtered and cooled. Dry hydrogen chloride was passed into the solution. The hygroscopic hydrochloride was filtered and washed with cold, saturated sodium bicarbonate solution. The free base was filtered off and recrystallized from 50% ethyl alcohol; white crystals, m. p. 152.0–152.5°.

Anal. Calcd. for $C_{14}H_{11}N_2O_2Cl$: C, 61.2; H, 4.0. Found: C, 61.4; H, 4.2.

Picolinoylaminomethane Dihydrochloride.—This was recrystallized from absolute ethyl alcohol by the addition of dry ether. The tan crystals were hygroscopic, exceedingly water soluble, and darkened in air; m. p. 178–180° (dec.); yield 60%.

Anal. Calcd. for $C_7H_{10}N_2OCl_2$: C, 40.2; H, 4.8. Found: C, 40.6; H, 5.1.

Isonicotinoylaminomethane Dihydrochloride.—The orange crystals were very hygroscopic, exceedingly water soluble and oxidized in air; m. p. 240–245° (dec.); yield 65%.

Anal. Calcd. for $C_7H_{10}N_2OCl_2$: C, 40.2; H, 4.8. Found: C, 40.4; H, 4.7.

β-(3-Pyridyl)-β-hydroxyethylamine Dihydrochloride.—Nicotinoylaminomethane dihydrochloride (5.50 g.) was reduced catalytically at atmospheric pressure and room temperature using 1.0 g. of palladium black[22] suspended in 100 ml. of water. The solution was acidified with 10 ml. of concentrated hydrochloric acid. The reaction ceased when one mole equivalent of hydrogen was absorbed. The palladium black was filtered off and the filtrate was concentrated under a nitrogen atmosphere in a vacuum concentrator. The residue was recrystallized from methyl alcohol; hygroscopic tan crystals, m. p. 189.5–191.0° (dec.); yield 95%.

Anal. Calcd. for $C_7H_{12}N_2OCl_2$: C, 39.8; H, 5.7. Found: C, 40.2; H, 5.9.

β-(2-Pyridyl)-β-hydroxyethylamine Dihydrochloride.—The gray crystals were very hygroscopic and oxidized in air; m. p. 198–204° (dec.).

Anal. Calcd. for $C_7H_{12}N_2OCl_2$: C, 39.8; H, 5.7. Found: C, 40.1; H, 5.7.

β-(4-Pyridyl)-β-hydroxyethylamine Dihydrochloride.—The gray crystals were hygroscopic and oxidized in air; m. p. 203–205° (dec.).

Anal. Calcd. for $C_7H_{12}N_2OCl_2$: C, 39.8; H, 5.7. Found: C, 40.1; H, 5.8.

β-(3-Pyridyl)-ethylamine Dihydrochloride.—The same procedure was followed as for the preparation of β-(3-pyridyl)-β-hydroxyethylamine dihydrochloride, except that 0.50 g. of platinum black[23] was used as catalyst. The reaction ceased when two mole equivalents of hydrogen were absorbed. The product was hygroscopic white salt which was recrystallized from absolute ethyl alcohol by the addition of ether. It agreed in properties with the compound described by Niemann and Hays[4]; yield 95%.

This compound also was obtained when the above procedure was followed using 4.2 g. of β-(3-pyridyl)-β-hydroxyethylamine dihydrochloride. The reaction ceased when one mole equivalent of hydrogen was absorbed; yield 95%.

N-β-(3-Pyridyl)-ethyl-*p*-chlorobenzamide Monohydrate.—This compound was prepared by a typical Schotten–Baumann reaction using β-(3-pyridyl)-ethylamine dihydrochloride and *p*-chlorobenzoyl chloride with 10% sodium hydroxide solution as the alkalizing medium. It was dissolved in 5% hydrochloric acid and filtered. The solution was then made alkaline with 10% sodium hydroxide solution. It was recrystallized from 60% ethyl alcohol; white crystals, m. p. 173–175° (dec.).

Anal. Calcd. for $C_{14}H_{15}N_2O_2Cl$: C, 60.3; H, 5.4. Found: C, 60.4; H, 5.4.

β-(2-Pyridyl)-ethylamine Dihydrochloride.—This compound agreed in properties with the compound described by Walter, Hunt and Fosbinder.[3]

β-(4-Pyridyl)-ethylamine Dihydrochloride.—This compound agreed in properties with the compound described by Walter, Hunt and Fosbinder.[3]

The microanalyses were performed by Mr. Saul Gottlieb of these laboratories.

(22) Purchased from the American Platinum Works, Newark, N. J.

Summary

β-(2-, 3- and 4-pyridyl)-β-hydroxyethylamine dihydrochlorides and the corresponding ketones have been described. A new method of synthesis for compounds of these types is reported.

(23) "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley & Sons, Inc., New York, N. Y., p. 463.

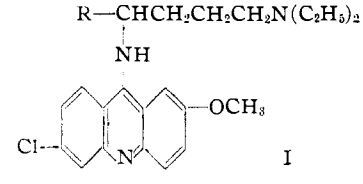
NEW YORK, N. Y. RECEIVED APRIL 7, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Synthesis of Quinacrine Analogs Having Aromatic Groups in the Side Chain[1]

BY DAVID S. BRESLOW, HOWARD G. WALKER, ROBERT S. YOST AND CHARLES R. HAUSER

Quinacrine (I, R = CH_3) and its analogs in which R in the α-position is varied are prepared generally by coupling the appropriate diamine, $RCH(NH_2)CH_2CH_2CH_2N(C_2H_5)_2$, with 2-methoxy-6,9-dichloroacridine. The synthesis of a series of these analogs in which R is an aliphatic group higher than methyl was described recently.[2]



I

In the present investigation analogs in which R is benzyl, phenyl and certain substituted phenyl groups have been synthesized. The diamines were prepared by reduction[2] of the oximes of the

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Duke University.

(2) Breslow, Yost, Walker and Hauser, THIS JOURNAL, **66**, 1921 (1944).

corresponding amino ketones, $RCOCH_2CH_2CH_2N(C_2H_5)_2$. The latter were synthesized either by alkylation of the appropriate β-keto ester with β-diethylaminoethyl chloride followed by acidic hydrolysis[2] or by the reaction of the appropriate aromatic aldehyde with γ-diethylaminopropylmagnesium chloride followed by oxidation of the resulting alcohol. These two methods are represented by the following transformations.

$$RCOCH(Na)CO_2C_2H_5 + ClCH_2CH_2N(C_2H_5)_2 \xrightarrow{CH_2CH_2N(C_2H_5)_2} RCOCHCO_2C_2H_5 \xrightarrow[H_2SO_4]{CrO_3} RCOCH_2CH_2CH_2N(C_2H_5)_2$$

$$RCHO + ClMgCH_2CH_2CH_2N(C_2H_5)_2 \longrightarrow RCH(OH)CH_2CH_2CH_2N(C_2H_5)_2 \xrightarrow[H_2SO_4]{CrO_3} RCOCH_2CH_2CH_2N(C_2H_5)_2$$

The Grignard type of reaction, which has previously been carried out by Marxer[3] with certain aromatic aldehydes, requires special conditions and, even then, the reaction has sometimes had to be repeated before satisfactory yields could be obtained. The yields and other data for the resulting amino alcohols are given in Table I. Although the reaction is applicable to various aromatic aldehydes, and also to certain ketones,[3] we obtained unsatisfactory results with an aliphatic aldehyde, propionaldehyde. Also, we obtained unsatisfactory results in an attempt to effect the analogous Grignard type of reaction with *p*-chlorobenzonitrile, although Marxer[3] has reported that the reaction can be effected with benzonitrile.

were slightly higher (50–57%) than those obtained by the alkylation method. When R is aliphatic, only the alkylation method appears to be applicable, but when R is aromatic, either method may generally be used, although the Grignard method is probably usually the more convenient. *p*-Dimethylaminobenzaldehyde gave a good yield of the amino alcohol in the Grignard reaction (see Table I) but, under the conditions employed, the oxidation gave no appreciable amount of the amino ketone.

In Table III are given the data for the oximes obtained from the amino ketones. It can be seen that, although certain of the ketones boiled over several degrees, they gave excellent yields of the oximes. We believe that the wide boiling ranges of the ketones, and also of the alcohols, are due to the low pressures at which they were distilled; in all cases investigated the boiling points were markedly affected by the rate of distillation. When the oximes were recrystallized from alcohol–water mixtures, no evidence of geometrical isomers was obtained. However, in one case, the *p*-chlorophenyl compound, two impure compounds were obtained on recrystallization from ligroin (70–90°)

TABLE I

$R—CH(OH)CH_2CH_2CH_2N(C_2H_5)_2$

R =	Yield, %	B. p., °C.	Mm.	Formula	Neutral equivalent Calcd.	Found
Phenyl	67	136–142	1	$C_{14}H_{23}ON$	221	221
p-Methoxyphenyl	64	159–165	1	$C_{15}H_{25}O_2N$	251	251
3,4-Methylenedioxyphenyl	72	170–175	1	$C_{15}H_{23}O_3N$	265	266
p-Chlorophenyl	59	148–158	1	$C_{14}H_{22}ONCl$	256	256
p-Dimethylaminophenyl	62	175–181	1	$C_{16}H_{28}ON_2$	264	259[a]

[a] Potentiometric titration. Compound would not give a sharp end-point with methyl red as indicator.

TABLE II

$R—COCH_2CH_2CH_2N(C_2H_5)_2$

R =	Method	Yield, %	B. p., °C.	Mm.	Formula	Neutral equivalent Calcd.	Found
Phenyl	Alkylation	44	118–124	1	$C_{14}H_{21}ON$	219	220
	Grignard	86					
p-Methoxyphenyl	Grignard	85	148–154	1	$C_{15}H_{23}O_2N$		
3,4-Methylenedioxyphenyl	Grignard	74	166–169	1	$C_{15}H_{21}O_3N$		
p-Chlorophenyl	Grignard	83	142–148	1	$C_{14}H_{20}ONCl$		
Benzyl	Alkylation	49	173–178	5	$C_{15}H_{23}ON$	233	237

In Table II are given the data for the amino ketones obtained by the alkylation and Grignard methods. In the alkylation method the yields are for the over-all, two-step reaction, since the intermediate β-keto esters were not isolated, but in the Grignard method the yields are for the oxidation of the intermediate amino alcohols (Table I); in the latter method the over-all yields but the mixture melted sharply after one recrystallization from alcohol–water.

In Table IV are given the data for the diamines obtained in excellent yields by catalytic reduction of the oximes with Raney nickel. This method of reduction was not attempted with the *p*-chlorophenyl compound because, as is well known, Raney nickel generally removes halogen from such compounds. Attempts were made to reduce the oxime with sodium in butanol[2] or with sodium

(3) Marxer, *Helv. Chim. Acta*, **24**, 209 (1941); *cf. C. A.*, **36**, 5134 (1942).

TABLE III

$R—C(=NOH)CH_2CH_2CH_2N(C_2H_5)_2$

R =	Yield, %	M. p., °C.	B. p., °C.	Mm.	Formula	Neutral equivalent Calcd.	Found
Phenyl	80	65			$C_{14}H_{22}ON_2$	234	237
p-Methoxyphenyl	71	84.5–85.5			$C_{15}H_{24}O_2N_2$	264	267
3,4-Methylenedioxyphenyl	89	89.5–90.0	182–189	0.5	$C_{15}H_{22}O_3N_2$	278	280
p-Chlorophenyl	80	60–61			$C_{14}H_{21}ON_2Cl$	269	273
Benzyl	85		167–171	1	$C_{15}H_{24}ON_2$	249	254

TABLE IV

$R—CH(NH_2)CH_2CH_2CH_2N(C_2H_5)_2$

R =	Yield, %	B. p., °C.	Mm.	Derivative	M. p., °C.	Formula	N analyses,[a] % Calcd.	Found
Phenyl	84	146–150	5	Benzoate	101.5	$C_{21}H_{28}ON_2$	8.64	8.81
p-Methoxyphenyl	90	136–141	1	Picrate	177–178	$C_{21}H_{29}O_8N_5$	14.6	14.8
3,4-Methylenedioxyphenyl	79	146–153	0.5	Dipicrate	175–177	$C_{27}H_{30}O_{16}N_8$	15.5	15.3
Benzyl	61	130–133	1	Picrate	154–155	$C_{21}H_{29}O_7N_5$	15.1	15.5

[a] Analyses by Dr. T. S. Ma, Department of Chemistry, University of Chicago, Chicago, Illinois.

TABLE V

QUINACRINE ANALOGS (I)

R =	Yield, %	M. p., °C.	Formula	—Cl^- analyses,[a] %— Calcd.	Found
Phenyl	65	305–310	$C_{28}H_{32}ON_3Cl\cdot 2HCl\cdot H_2O$	12.82	12.92
p-Methoxyphenyl	64	350–352	$C_{29}H_{34}O_2N_3Cl\cdot 2HCl\cdot 2H_2O$	11.80	11.88
3,4-Methylenedioxyphenyl	55	360–365	$C_{29}H_{32}O_3N_3Cl\cdot 2HCl\cdot H_2O$	11.88	11.84
Benzyl	75	66–68	$C_{29}H_{34}ON_3Cl\cdot 2HCl\cdot 3H_2O$	11.76	11.70

[a] Macroanalyses by Mrs. Virginia Deal and Miss Mary K. Scholl.

amalgam in acetic acid and ethanol,[4] but no appreciable amount of the corresponding diamine was obtained. With sodium in butanol, the unsubstituted phenyl derivative was obtained in good yield. An attempt to convert the ketone directly to the diamine with ammonium formate[5] also failed.

In Table V are given the data for the quinacrine analogs obtained in the usual manner from the diamines and 2-methoxy-6,9-dichloroacridine in the presence of phenol. They were obtained in good yields as their dihydrochlorides, which were fine yellow powders containing varying amounts of water of crystallization. They melted over a range with decomposition, the phenyl compound being unusual in that it melted at about 180° and then resolidified, melting again above 300°.

The structures of the compounds obtained by the Grignard reaction were deduced from the method of preparation and from the fact that the oximes of the phenyl compound prepared by alkylation and by the Grignard reaction both melted at 65°, the mixed melting point showing no depression.

Experimental

Preparation and Purification of Materials.—Ethyl benzoylacetate (Eastman Kodak Co.) was dried over Drierite and used without distillation. Ethyl γ-phenylacetoacetate was prepared as previously described.[6]

The aldehydes used were all Eastman Kodak Co. best grade. The liquids were purified by extraction with sodium bicarbonate solution followed by water, drying over Drierite and distillation *in vacuo*. The solids were used without purification.

1-Diethylamino-3-chloropropane.—This compound was prepared by a modification of the method of Marxer.[3] Diethylamine (234 g., 3.2 moles) was added slowly to 252 g. (1.6 moles) of trimethylene chlorobromide[7] with stirring, the temperature being kept at 30°. The solution was stirred and heated at 35–40° for three hours (a copious precipitate of diethylamine hydrobromide forming) and allowed to stand overnight at room temperature. The salt was removed by extraction with two 75-ml. portions of cold water. The residual oil was added slowly to 1 liter of cold 2 *N* hydrochloric acid and the unreacted trimethylene chlorobromide was extracted with ether. The acid solution was made alkaline with excess potassium carbonate, the oil separated, the aqueous phase extracted with ether and the combined ether and oil dried over anhydrous potassium carbonate. The solvent was removed and the residue was distilled through a 15-cm. Widmer column surmounted by a total reflux, partial takeoff head; b. p., 68–70° at 20 mm.; yield, 166 g. (70%).

Preparation of Ketones by Alkylation and Cleavage.—The sodium derivative of ethyl benzoylacetate was alkylated with β-diethylaminoethyl chloride in benzene. The sodium derivative of ethyl γ-phenylacetoacetate was alkylated in dioxane. The alkylated β-keto esters were cleaved to the desired ketones by dilute sulfuric acid as previously described.[2]

Preparation of Alcohols by the Grignard Reaction. 4-Diethylamino-1-*p*-methoxyphenylbutanol-1.—A one-liter, three-necked flask was equipped with a mercury-sealed stirrer, reflux condenser, dropping funnel and nitrogen inlet tube. Magnesium turnings (7.6 g.) and Gilman's alloy[8] (2 g.) were placed in the flask and covered with 40

(4) Goldschmidt, *Ber.*, **19**, 3232 (1886).

(5) Ingersoll, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 503.

(6) Breslow, Baumgarten and Hauser, THIS JOURNAL, **66**, 1286 (1944).

(7) We are indebted to the Dow Chemical Company for a generous supply of trimethylene chlorobromide.

(8) A magnesium–copper alloy was obtained from Iowa State College through the courtesy of Dr. Henry Gilman.

ml. of dry ether. A crystal of iodine was added, followed by 1 ml. of ethyl bromide. As soon as the reaction had started, the stirrer was turned on, a slow stream of dry nitrogen was passed through the flask and 60 g. (0.4 mole) of 1-diethylamino-3-chloropropane, dissolved in 100 ml. of dry ether, was added over a period of ten minutes. Another ml. of ethyl bromide was added, the flask was heated in a water-bath kept at 45–50° for five minutes and then 27.2 g. (0.2 mole) of anisaldehyde, dissolved in 160 ml. of dry ether,[9] was added over a period of ninety minutes. The stirring, heating and nitrogen flow were continued during the addition and for twelve hours after the addition was complete. A white precipitate formed.[10] After standing overnight the reaction mixture was hydrolyzed by a solution of 75 g. of ammonium chloride in 200 ml. of water. The two layers were separated, the aqueous phase was extracted once with ether and the combined ether solutions were extracted with three 100-ml. portions of cold 2 *N* hydrochloric acid. The acid solutions were made alkaline with excess potassium carbonate and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, the ether distilled and the residue distilled through a 15-cm. Vigreux column, first at 20 mm. to recover the excess 1-diethylamino-3-chloropropane and then at 1 mm. The alcohols were obtained as pale yellow, viscous oils.

Oxidation of Alcohols to Ketones. 4-Diethylamino-1-*p*-methoxyphenylbutanone-1.—4-Diethylamino-1-*p*-methoxyphenylbutanol-1 (26.7 g., 0.11 mole) was dissolved in 125 ml. of glacial acetic acid contained in a 400-ml. beaker. The solution was heated to 60° on a steam-bath, the bath removed and a solution of chromic anhydride (prepared by dissolving 7.1 g. (0.071 mole) of the anhydride in 5 ml. of water and then adding 5 ml. of glacial acetic acid) was added with stirring at such a rate as to keep the temperature at 60–65°. The reaction mixture was heated for fifteen minutes on the steam-bath, chilled and poured into a cold solution of 150 g. of sodium hydroxide in 400 ml. of water. The ketone was immediately extracted with ether, since on standing chromium hydroxide precipitated. The ether solution was dried over anhydrous potassium carbonate, the ether distilled and the residue distilled through a 15-cm. Vigreux column.

Preparation of Diamines.—The ketones were converted to oximes as described previously,[2] the oximes being recrystallized from dilute alcohol. They were then reduced catalytically.[2]

Preparation of Quinacrine Analogs.—The couplings were carried out essentially as described before.[2] In general the hydrochlorides obtained were much less soluble than those prepared previously, some of them being quite insoluble even in hot water.

(9) In other cases more ether was needed to completely dissolve the aldehyde.

(10) When a colored precipitate or solution was obtained, the yield of alcohol was almost invariably poor. However, we have been unable to discover why this should happen occasionally.

Summary

1. Quinacrine analogs (I) in which the group R in the α-position of the side chain is benzyl, phenyl, *p*-methoxyphenyl and 3,4-methylenedioxyphenyl have been synthesized.

2. 4-Diethylamino-1-*p*-dimethylaminophenylbutanol-1 and 4-diethylamino-1-*p*-chlorophenylbutanone-1 have been prepared.

DURHAM, N. C. RECEIVED APRIL 20, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SCHIEFFELIN & CO.]

Synthetic Estrogenic Compounds. II. Dialkyl Derivatives of 1,3-Di-(*p*-hydroxyphenyl)-propane

BY ALFRED H. STUART, ANTHONY J. SHUKIS AND RALPH C. TALLMAN

In the first paper of this series[1] we reported a number of compounds derived from 1,3-di-(*p*-hydroxyphenyl)-propane by substitution of an alkyl or aryl group in the propane chain. As a continuation of this study, relating structure to estrogenic activity, we have prepared several compounds in which the di-(*p*-hydroxyphenyl)-propane nucleus has been further modified by the introduction of alkyl groups on two of the carbon atoms of the propane chain, giving the two types of di-alkyl derivatives IV and VII. In this investigation the substituent groups have been limited to methyl, ethyl and *n*-propyl.

All of the six possible 1,3-di-alkyl compounds (IV) have been prepared, three of them only as mixtures of isomeric forms. Starting materials for this series were the 1,3-di-(*p*-methoxyphenyl)-ketones (I, R = CH_3, C_2H_5, C_3H_7) previously described.[1] These reacted smoothly with Grignard reagents in refluxing ether; the resulting carbinols were not isolated, but dehydrated on distillation. The position of the double bond thus introduced was dependent on the nature of the entering alkyl group. Using methylmagnesium iodide we obtained unsaturated compounds (II) which gave *p*-methoxyacetophenone and anisic acid on permanganate oxidation. Similar oxidation of the products from ethyl and propyl Grignard reagents, however, gave the original ketones (I), indicating a preponderance of the structure III.

Hydrogenation of these unsaturated compounds, followed by demethylation, gave the series of phenols IV. In the case of both the dimethyl and diethyl compounds only a single crystalline product was obtained. The phenol in which R_1 = CH_3 and R_2 = C_3H_7 was also obtained crystalline, but there was evidence of the presence of a second isomer in minor amounts. The remaining three derivatives were thick, clear resins. Preparation of the unsymmetrical compounds by alternating the order in which the alkyl groups were introduced had no appreciable effect on the physical or physiological properties of the products.

The α-alkyl-di-*p*-methoxychalcones described in the previous communication were used as starting materials for the synthesis of 1,2-dialkyl derivatives of 1,3-di-(*p*-hydroxyphenyl)-propane. Introduction of a second alkyl group was effected

(1) Stuart and Tallman, THIS JOURNAL, **65**, 1579 (1943).