applied to a column of powdered sugar gave a principal dark pink colored zone. The center portion of the dark pink zone was eluted with chloroform and a red grease having a green metallic sheen remained after removing the solvent. Qualitative analysis of the product like this obtained from another experiment showed that it contained nitrogen; sulfur and halogen were absent. Treatment of the red grease in 95% ethyl alcohol with perchloric acid in the described fashion gave prodigiosin perchlorate, m.p. 224.5–226.0° (dec.).

Anal. Calcd. for $C_{20}H_{26}O_5N_3Cl$: Cl, 8.37. Found: 8.40.

The ultraviolet-visible absorption spectrum for the perchlorate is the same as that for authentic prodigiosin perchlorate.

Acknowledgment. We are grateful to Mrs. J. C. Kurtz, Mr. M. Bilitch, Dr. A. E. Blood, Mr. D. K. Fisher, Mr. J. Walter, and Dr. George C. Kleinspehn for assistance with certain phases of this investigation and to Mr. Martin Black of the Parke, Davis Co. for a supply of prodigiosin.

SANTA CLARA, CALIF.

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Unsymmetrically Substituted Piperazines. XII.[1] Benzhydrylpiperazines and Related Compounds with Spasmolytic and Anti-Fibrillatory Action[2]

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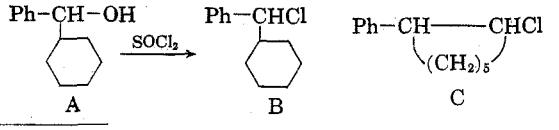
In a study of compounds showing activity against artificial fibrillation, a number of *o*-substituted benzhydrylpiperazines and related benzhydrylamines have been prepared.

In the course of work on piperazines having spasmolytic action, it was found that monoquaternary salts of *ortho*-substituted benzhydrylpiperazines[3] and of partially reduced benzhydrylpiperazines[4] had strong atropine-like action. A number of the ditertiary bases intermediate to these quaternary salts were also submitted to pharmacological screening. Some of these, especially those having *o*-alkyl substitution in the benzhydryl moiety, showed considerable activity in suppressing artificial fibrillation in experimental animals.[5]

In following up this lead we prepared the series of piperazine derivatives, data on which are presented in Table I. Since, *a priori*, it could not be assumed that the observed activity was dependent on a piperazine portion or indeed on any single feature of this type of substance, there were also prepared for comparison a number of benzhydrylamines, substituted ethylenediamines, *etc.* Many of these have already been reported from other sources but some appear to be new compounds. Their physical properties are shown in Table II and in the experimental part. The physiological studies showed that in fact the anti-fibrillatory action was not a function of the piperazine moiety although favorably influenced thereby. The critical requirements seem to be those of an antihistaminic. Activity is augmented, however, by *ortho*-substitution in the benzhydryl moiety.

The quaternary salts, data on which are presented in Table III, were largely prepared as spasmolytics. Compounds XXX, XXXIII, and XXXV have anti-cholinergic activities on isolated tissue of the same general order as atropine. Compounds XXVII–XXIX were tested for anthelmintic activity in mice against *Syphacia obvelata*;[6] of these the most active was XXVIII.

The quaternary salts XXX–XXXVI were prepared by quaternization of hexahydrobenzhydryl-*N'*-methylpiperazine[7] or of Compound III with the appropriate alkyl iodide, usually in acetone. The preparation of these ditertiary bases was initially rather troublesome, resulting in poor yields and leading to a search for an alternate route of synthesis.[4,8] Because of these poor yields and the apparent impurity of the bases as initially obtained, it was suspected that hexahydrobenzhydryl chloride might undergo a rearrangement either in formation from the carbinol, on refluxing with thionyl chloride, or in reaction with *N'*-alkyl piperazine in the sense:



(1) Paper XI in this series, M. Harfenist and E. Magnien, *J. Am. Chem. Soc.*, **80**, 6257 (1958).

(2) The work reported here is part of a joint research carried out in cooperation with the Pharmacology Department of these laboratories.

(3) R. Baltzly, W. S. Ide, and E. Lorz, *J. Am. Chem. Soc.*, **77**, 4809 (1955).

(4) P. B. Russell and R. Baltzly, *J. Am. Chem. Soc.*, **77**, 629 (1955).

(5) C. H. Ellis, *Ann. N. Y. Acad. Sci.*, **64**, 552 (1956); C. H. Ellis and L. N. Sivertsen, *Arch. intern. pharmacodynamie*, **116**, 17 (1958).

(6) H. W. Brown, K. L. Hussey, K. F. Chan, M. Harfenist, R. V. Fanelli, and E. Magnien, in preparation.

(7) R. Baltzly, S. Dubreuil, W. S. Ide, and E. Lorz, *J. Org. Chem.*, **14**, 775 (1949).

(8) R. Baltzly, E. Lorz, P. B. Russell, and F. M Smith, *J. Am. Chem. Soc.*, **77**, 624 (1955).

TABLE I

N-SUBSTITUTED PIPERAZINES: R—N⟨⟩N—R′

Cpd. No.	R	R′	Empirical Formula of Salt	M.P., °C.	Analyses C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
I	$PhCH(CH_2)_3CH_3$	Me	$C_{16}H_{26}N_2 \cdot 2HCl$	248[a]	60.2	59.8	8.8	9.2
II	$PhCH(CH_2)_4CH_3$	Me[b]	$C_{17}H_{28}N_2 \cdot 2HCl$	252	61.3	61.3	9.0	9.0
III	$PhCHC_6H_{11}$	Et	$C_{19}H_{31}N_2 \cdot HCl$	266	63.5	63.6	9.0	8.8
IV	Ph_2CH	$CHMe_2$	$C_{20}H_{26}N_2 \cdot 2HCl$[c]	218	65.4	65.1	7.7	7.4
V	$MeO_2CCH_2CH_2$	Ph_2CH	$C_{21}H_{26}N_2O_2 \cdot 2HCl$	190–191	61.3	61.0	6.9	7.0
VI	p-$H_2NC_6H_4CO$	Me	$C_{12}H_{17}N_3O \cdot HCl$	238	56.5	56.8	7.0	7.1
VII	p-$H_2NC_6H_4CO$	$PhCH_2$	$C_{18}H_{21}N_3O \cdot 2HCl \cdot 2H_2O$	[d]	55.7	55.5	6.5	6.4
VIII	p-$H_2NC_6H_4CO$	Ph_2CH	$C_{24}H_{25}N_3O \cdot 2HCl \cdot 2H_2O$	[d]	62.3	62.2	6.3	6.7
IX	o-MeC_6H_4CHPh	COOEt	$C_{21}H_{26}N_2O_2 \cdot HCl$	206	67.3	66.7	7.3	7.0
X	o-MeC_6H_4CHPh	H	$C_{19}H_{22}N_2 \cdot HCl$	246	71.4	71.8	7.7	7.6
XI	m-MeC_6H_4CHPh	$CHMe_2$	$C_{21}H_{28}N_2 \cdot 2HCl$	226	66.1	66.0	7.9	8.4
XII	o-EtC_6H_4CHPh	Me	$C_{20}H_{26}N_2 \cdot 2HCl$	223–225	65.4	65.2	7.7	7.5
XIII	o-ClC_6H_4CHPh	$CHMe_2$	$C_{20}H_{25}ClN_2 \cdot HCl$	272	65.7	65.6	7.2	6.8
XIV	$(o\text{-}MeC_6H_4)_2CH$	Me	$C_{20}H_{26}N_2 \cdot 2HCl$	235[a]	65.4	65.2	7.7	7.8
XV	$(p\text{-}MeC_6H_4)_2CH$	Me	$C_{20}H_{26}N_2 \cdot HCl$	244–246[a]	72.6	72.2	8.2	8.1[e]
XVI	$(o\text{-}EtC_6H_4)_2CH$	Me	$C_{22}H_{30}N_2 \cdot 2HCl$	218	66.9	66.8	8.1	8.3
XVII	Ph_3C	Me	$C_{24}H_{26}N_2 \cdot HCl$	186–191[a]	Cl: Calcd. 9.4%. Found: 9.0			

[a] Melts with decomposition. [b] The monomethiodide melts at 119°. *Anal.* Calcd. for $C_{18}H_{31}IN_2$: C, 53.7; H, 7.7. Found: C, 53.7; H, 7.9. [c] The monohydro-iodide has been reported.[3] [d] Foams above 100°, unmelted at 250°. [e] Cl: Calcd. 10.7%. Found: 10.6.

TABLE II

BENZHYDRYLAMINES RELATED TO THE PIPERAZINES OF TABLE I. $PhCHR \cdot NR_2'$

Cpd. No.	R	NR_2'	Empirical Formula of Salt	M.P., °C.	Analyses C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
XVIII	o-ClC_6H_4	NHMe	$C_{14}H_{14}ClN \cdot HCl$	214.5–215	62.7	62.6	5.9	5.9
XIX	o-ClC_6H_4	NMe_2	$C_{15}H_{16}ClN \cdot HCl$	233–233.5	63.9	63.6	6.1	6.1
XX	o-ClC_6H_4	NC_5H_{10}[a]	$C_{18}H_{20}ClN \cdot HCl$	240–241	67.1	67.0	6.5	6.7
XXI	o-MeC_6H_4	NC_5H_{10}[a]	$C_{19}H_{23}N \cdot HCl$	265–266	75.6	75.7	8.0	7.8
XXII	o-MeC_6H_4	NC_4H_8O[b]	$C_{18}H_{21}NO \cdot HCl$	256 (dec.)	71.3	71.4	7.2	7.0
XXIII	o-ClC_6H_4	$NH(CH_2)_2NMe_2$	$C_{17}H_{21}ClN_2 \cdot 2HCl$	183–185	56.4	56.4	6.4	6.4
XXIV	o-MeC_6H_4	$NH(CH_2)_2NMe_2$	$C_{18}H_{24}N_2 \cdot 2HCl$	199–200	63.4	63.4	7.7	7.7
XXV	Ph	$NH(CH_2)_3NMe_2$	$C_{18}H_{24}N_2 \cdot 2HCl$	206–207	63.4	63.0	7.7	7.8
XXVI	Ph	$NH(CH_2)_2NC_4H_8O$[b]	$C_{19}H_{24}N_2O \cdot 2HCl$	243–244	61.8	61.8	7.1	7.3

[a] Piperidino. [b] Morpholino.

TABLE III

BENZHYDRYL AND HEXAHYDROBENZHYDRYLPIPERAZINE QUATERNARY HALIDES: PhCHRN⟨⟩N$^+$(R′)(R″) X$^-$

Cpd. No.	R	R′	R″	M.P., °C.[a]	Empirical Formula	Analyses C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
XXVII	Ph	Me	n-C_7H_{15}	183	$C_{25}H_{37}BrN_2$	67.4	67.4	8.4	8.1
XXVIII	p-ClC_6H_4	Me	n-C_7H_{15}	198	$C_{25}H_{36}BrClN_2$	62.6	63.0	7.6	7.4
XXIX	p-ClC_6H_4	Me	n-$C_{12}H_{25}$	156	$C_{30}H_{46}BrClN_2$	65.5	65.7	8.4	8.4
XXX	C_6H_{11}	Me	Me	214–215	$C_{19}H_{31}IN_2$	55.1	54.8	7.5	7.7
XXXI	C_6H_{11}	Me	Et	173–174	$C_{20}H_{33}IN_2$	56.1	56.1	7.8	7.7
XXXII	C_6H_{11}	Me	n-C_3H_7	182	$C_{21}H_{35}IN_2$	57.0	56.7	8.0	7.9
XXXIII	C_6H_{11}	Me	i-C_3H_7	194	$C_{21}H_{35}IN_2$	57.0	57.1	8.0	8.3
XXXIV	C_6H_{11}	Me	n-C_4H_9	108–110	$C_{22}H_{37}IN_2$	57.9	58.3	8.2	8.6
XXXV	C_6H_{11}	Et	Et	195	$C_{21}H_{35}IN_2$	57.0	57.1	8.0	7.6
XXXVI	C_6H_{11}	Et	i-C_3H_7	216	$C_{22}H_{37}IN_2$	57.9	57.5	8.2	8.5

[a] Most of these compounds melt with decomposition.

Such a rearrangement would be conceivable wherever a reaction passed through a carbonium ion intermediate. The chloride C would, of course, be much less reactive than B.

While the existence of such rearrangements cannot be excluded completely, attempts to demonstrate them have been unsuccessful. Refluxing hexahydrobenzylhydryl chloride with two equivalents of methylpiperazine for 24 hours (presumptive temperature *ca.* 140°) resulted in yields of water-insoluble base as high as 75%. This basic material was subjected to exhaustive chromatography in pentane on alumina and two fractions apparently different chromatographically were isolated. Both gave monohydrochlorides from water melting around 250° alone and mixed. Both gave quaternary salts (XXX, XXXI, and XXXIII) not clearly distinguishable (since these salts melt with decomposition). Finally, the infrared spectra of the monohydrochlorides were indistinguishable from each other.

Most of the compounds of Tables I and II were also prepared by conventional methods. Referring to Table I, Compounds I–IV, IX, and XI–XVII were prepared by reaction of the appropriate halide, RCl with the N′-R′ substituted piperazines. The preparations of XV and XVII were run with equivalent amounts of the two reagents in acetonitrile as solvent at reflux.[9] The other compounds were obtained from reactions with two equivalents of the piperazine without solvent on the steam bath.[7] The preparations of I and II required around two days heating. The benzhydryl halides needed only 4–8 hours for substantially complete reaction. Preparation of XVII had been attempted previously[10] and the base had presumably been obtained but decomposed during extraction with acid (as the dihydrochloride). The monohydrochloride now reported is somewhat unstable in aqueous solution at room temperature and breaks down rapidly on the steam bath with formation of triphenylcarbinol.

Compound V was formed by action of methylacrylate on *N*-benzhydrylpiperazine.[11]

Compound X was obtained by alkaline hydrolysis of IX followed by neutralization of the base, *N*-*o*-methylbenzylhydrylpiperazine. For the preparation of VI–VIII, *p*-nitrobenzoyl chloride was treated with *N*-methyl- *N*-benzyl- and *N*-benzhydryl-piperazines respectively and the resultant *p*-nitrobenzoyl derivatives were reduced with Adams' Catalyst in methanol containing hydrogen chloride.[12]

Of the compounds of Table II, all but XVIII and XIX were prepared by reaction of the appropriate benzhydryl chloride with two or more equivalents of piperidine, morpholine, or the corresponding *N*′-tertiary amino alkylenediamine. Compound XVIII was prepared in 35–40% yield by addition of phenylmagnesium bromide to *o*-chlorobenzalmethylamine. The secondary base was converted to Compound XIX by the Clarke-Eschweiler methylation. The hydrochlorides of these two amines both crystallized as hydrates. Removal of water before analysis required drying in high vacuum (60–70° at 1 μ pressure).

Several previously unreported compounds belonging to the α,α-diphenylpyridine-4-methanol and piperidine-4-methanol series are also described in the experimental section. One of these, 1-methyl-α,α-bis-*o*-tolylpiperidine-4-methanol differed significantly from its diphenyl analog in being quite resistant to dehydration. This may be due to hindrance that prevents coplanarity in the carbonium ion stage, which is generally involved in dehydration under acid conditions.

This tertiary carbinol was prepared in very poor yield by the addition of *o*-tolylmagnesium bromide to ethyl 1-methylisonipecotate. The bulk of the product appeared to be the ketone 1-methyl-4-*o*-methylbenzoylpiperidine.[13]

EXPERIMENTAL

The compounds of Tables I–III were isolated, in general, by previously described techniques: The choice of mono- or dihydrochlorides for the piperazines of Table I was largely a matter of convenience. A considerable number of the monohydrochlorides of benzhydrylpiperazines can be crystallized from water and solutions of such salts have a *p*H in the range 5–5.5. The dihydrochlorides are perhaps more readily crystallized from alcohol-ether mixtures than the monohydrochlorides.

Hexahydrobenzhydryl chloride.[14] One-tenth mole (19.1 g.) of hexahydrobenzhydrol was dissolved in 100 cc. of toluene in a flask with reflux condenser. To this was added 10 cc. (16 g.) of thionyl chloride. After an initial rapid evolution of gas had subsided, the solution was refluxed for 1 hr. After standing overnight the volatile material was removed on a steam bath at water pump vacuum. The residual oil was distilled at 1 mm. pressure. There was obtained 16 g. (a 75% yield) of colorless oil boiling at 99.5–102°.

Anal. Calcd. for $C_{13}H_{17}Cl$: C, 74.8%; H, 8.2%. Found: C, 75.0; H, 8.3.

This material therefore contained no significant amount of unsaturated hydrocarbon, though a small amount could have escaped during the preparation.

(9) This technique, which was originated by Dr. M. Harfenist, is convenient in cases wherein the monohydrochloride of the product crystallizes readily. As might be expected, the first half of the reaction proceeds rapidly, whereas the second half is slow being dependent on gradual release of secondary piperazine nitrogen from an unfavorable equilibrium.

(10) L. P. Albro, R. Baltzly, and A. P. Phillips, *J. Org. Chem.*, **14**, 771 (1949).

(11) K. E. Hamlin, A. W. Weston, F. W. Fischer, and R. J. Michaels, Jr., *J. Am. Chem. Soc.*, **71**, 2731 (1949).

(12) The reductions of the precursors of VII and VIII were stopped when 3 equivalents of hydrogen had been absorbed to avoid debenzylation.

(13) Similar predominance of ketone over tertiary carbinol from the reaction of Grignard reagents with γ-ω tertiary-amino esters has been reported from other sources: Brit. Patent, **614,567**, U.S. Patent, **2,649,444**.

(14) P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **75**, 587 (1927).

N-Hexahydrobenzhydryl-N'-ethylpiperazine (III). Eight and three-tenths g. (0.04 mole) of the above halide was added to 9.1 g. (0.08 mole) of *N*-ethylpiperazine and the solution was heated at gentle reflux for 96 hr. The reaction mixture was partitioned between ether and water and the ethereal layer was washed with water until the washings were neutral. The ethereal layer was then shaken with *N* hydrochloric acid and the base was liberated from the aqueous layer. The base was taken into ether, dried over potassium carbonate, and acidified with excess alcoholic hydrogen chloride.

N-Hexahydrobenzhydryl-N',N'-diethylpiperazinium iodide (XXXV). One and six-tenths g. (6 mmole) of base liberated from the above hydrochloride was dissolved in 10 cc. of acetone. To it was added 2 g. of ethyl iodide and the covered flask was placed beside a steam bath (T. *ca.* 40°). After standing 1 day, 1.3 g. of solid, m.p. 194–195° had separated.

N-Hexahydrobenzhydryl-N'-methylpiperazine. Ten g. (0.048 mole) of hexahydrobenzhydryl chloride was added to 20 g. (0.2 mole) of *N*-methylpiperazine in a round-bottomed flask. The solution was heated under reflux for 23.5 hr. and worked up as described for the *N'*-ethyl derivative. The base was distilled at 1 mm., 9.8 g. (75% of the calculated yield). The monohydrochloride can be crystallized from concentrated aqueous solution or from isopropyl alcohol. It darkens on heating above 240° and melts with decomposition about 255°.

N-(4,4'-Dimethylbenzhydryl)-N'-methylpiperazine (XV). Nine g. (0.039 mole) of 4,4'-dimethylbenzhydryl chloride and 4.3 g. (0.043 mole) of *N*-methylpiperazine were dissolved in 100 cc. of distilled acetonitrile. The solution was refluxed for 24 hr. and then placed in the refrigerator. The crystals that separated were filtered off and washed with acetonitrile until colorless. They weighed 8.4 g. (65%) and melted at 245–250° dec. After recrystallization from absolute ethanol the hydrochloride melted at 244–246° dec.

N-Diphenylacetylpyrrolidine. Ten g. of pyrrolidine was added to 12.5 g. of diphenylacetylchloride in 50 cc. of acetone. After the initial vigorous reaction had subsided, the mixture was refluxed 1 hr., cooled, and diluted with water. The precipitated amide was washed with water and recrystallized from ether-methanol mixture, m.p., 162–163°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.5; H, 7.2. Found: C, 81.6; H, 7.3.

N-[β,β-Diphenylethyl] pyrrolidine. The above amide (7.9 g.) was added to a suspension of 1.5 g. of lithium aluminum hydride in 200 cc. of ether. After refluxing for 5 hr., 5 cc. of water was admitted slowly. The ethereal solution was decanted from the precipitated inorganic matter and the latter was further washed with ether. The ethereal solution was extracted with dilute hydrochloric acid and the base was liberated from the aqueous layer. The base was taken into ether, dried over potassium carbonate, and converted to the hydrochloride with alcoholic hydrogen chloride solution. The hydrochloride was recrystallized from acetone-ether mixture and then melted at 174–175°.

Anal. Calcd. for $C_{18}H_{21}N.HCl$: C, 75.4; H, 7.7. Found: C, 75.3; H, 7.6.

N-(β,β-Diphenylethyl)-N'-methylpiperazine. *N*-Diphenylacetyl-*N'*-methylpiperazine[15] (8.8 g.) reduced with lithium aluminum hydride (2.5 g.) as described for the above pyrrolidine derivative, afforded *N*-diphenylethyl-*N'*-methylpiperazine. The dihydrochloride darkens above 250° and melts with decomposition at 256–257°.

Anal. Calcd. for $C_{19}H_{26}Cl_2N_2$: C, 64.7; H, 7.4. Found: C, 64.7; H, 7.3.

α,α-Diphenylpyridine-4-methanol methiodide. Thirteen g. of diphenyl-4-pyridylcarbinol[16] was dissolved in 150 cc. of methanol and 7 cc. of methyl iodide was added. The solution was refluxed 22 hr. After evaporation to small volume and addition of ether, the quaternary salt separated. It melted at 234–235° after recrystallization from methanol-ether mixture.

Anal. Calcd. for $C_{19}H_{18}INO$: C, 56.6; H, 4.5. Found: C, 56.7; H, 4.8.

α,α-Diphenyl-1-carbomethoxyethylpiperidine-4-methanol. Fourteen g. of α,α-diphenylpiperidine-4-methanol[16] was mixed with 20 cc. of methyl acrylate in 25 cc. of benzene and kept at 45–50° for 24 hr. It was then refluxed 5 hr. and evaporated *in vacuo* to small volume. On addition of hexane, cooling and scratching, crystals separated, m.p. 65–70°. Recrystallization from benzene-hexane raised the m.p. to 93–94°.

Anal. Calcd. for $C_{22}H_{27}NO_3$: C, 74.8; H, 7.7. Found: C, 74.6; H, 8.0.

α,α-Diphenyl-1-methylpiperidine-4-methanol methiodide. Methylation of the secondary base with excess methyl iodide and alkali afforded the quaternary iodide. It melted at 219–220° after recrystallization first from acetone and then from absolute ethanol. As first obtained it appeared to be a hemihydrate.

Anal. Calcd. for $C_{20}H_{26}INO$: C, 56.5; H, 6.2. Found: C, 56.5; H, 6.5.

α,α-Bis-o-tolyl-1-methylpiperidine-4-methanol and 1-methyl-4-o-methylbenzoylpiperidine. A solution of *o*-tolylmagnesium bromide was prepared from 3.7 g. of magnesium turnings and 28 g. of *o*-bromotoluene in anhydrous ether. To this was added over about 15 min. 8 g. of methyl *N*-methylisonipecotate. After 2 hr. reaction at room temperature and 1 at reflux, the reaction mixture was hydrolyzed with iced concentrated sodium hydroxide solution. After filtration from the sludge of magnesia and thorough washing of that with ether, the combined ethereal extracts were dried over potassium carbonate and acidified with ethanolic hydrogen chloride solution. There was obtained 15–17 g. of crude crystalline solid. From this, four crystallizations from alcohol-ether mixtures gave 3 g. of material melting at 183–185°.

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66.3; H, 8.0. Found: C, 66.1; H, 8.1.

Examination of the material in the mother liquors revealed the presence of a small amount of higher-melting material. After three crystallizations of the second crop obtained from the mother liquors, there was obtained 2 g. of material melting around 300°. The analytical sample melted at 300–302°.

Anal. Calcd. for $C_{21}H_{28}ClNO$: C, 73.0; H, 8.2. Found: C, 73.2; H, 8.2.

From the mother liquors of the above carbinol more material was obtained whose melting point could not be raised above 158°. The composition was that of the ketone hydrochloride. It is not known whether this material is isomeric with the ketone melting at 183–185° or whether a case of dimorphism has been encountered.

Whereas the diphenyl analog of the carbinol melting at 302° is quite readily dehydrated, this carbinol was recovered only slightly impure after 2 hr. refluxing with equal volumes of concentrated hydrochloric and acetic acids. With concentrated sulfuric acid (5 parts by wt.) on the steam bath it suffered extensive decomposition.

N-Benzhydryloxyethyl-N',N'-dimethyl piperazinium iodide. Five g. of benzhydryl chloride and 7.2 g. of *N*-methyl-*N'*-hydroxyethylpiperazine[17] were mixed in a little dry benzene and warmed on the steam bath for 3 days. The reaction mixture was partitioned between ether and water and the

(15) W. S. Ide, E. Lorz, and R. Baltzly, *J. Am. Chem. Soc.*, **77**, 3142 (1955).

(16) Purchased from the Reilly Tar and Chemical Co.

(17) W. S. Ide, E. Lorz, and R. Baltzly, *J. Am. Chem. Soc.*, **76**, 1122 (1954).

ethereal layer was washed with water, sodium carbonate solution, and again with water. The base in the ether layer was dried and converted to the hydrochloride which melts at 200°. The base was liberated from an aqueous solution of the hydrochloride and allowed to react with an excess of methyl iodide in ether. The quaternary salt melted at 181–182° as first obtained and at 182–185° after one crystallization from alcohol-ether mixture.

Anal. Calcd. for $C_{21}H_{29}IN_2O_2$: C, 55.8; H, 6.4. Found: C, 55.5; H, 6.6.

TUCKAHOE 7, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE]

Preparation of DL-*beta*-(2-Fluorenyl)alanine[1]

D. C. MORRISON

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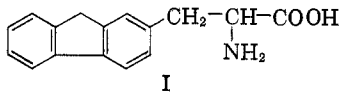
An amino acid derived from fluorene, DL-β-(2-fluorenyl)alanine, was synthesized from fluorene-2-carboxaldehyde or ethyl fluorene-2-carboxylate as starting materials. The physical and chemical properties were determined and the amino acid was characterized as its hydrochloride salt and as the *N*-benzenesulfonyl derivative.

The preparation of DL-β-(2-fluorenyl)alanine was undertaken for work involving cancer chemotherapy with 2-substituted fluorenes containing biologically important polar side chains. The compound was thought to be of interest due to the known carcinogenic activity of 2-fluorenylamines, and because of the desirability of obtaining amino acids derived from the fluorene ring system for growth and antagonism studies. The compound (I) may also be considered as an indenophenyl alanine.



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The amino acid was synthesized from fluorene-2-carboxaldehyde or from ethyl fluorene-2-carboxylate as starting materials. These substances were reduced with lithium aluminum hydride to the corresponding carbinol, which was transformed to the bromide with phosphorus tribromide. The carbinol and bromide have been previously prepared by another method,[2] but the hydride reduction seemed to be a simpler process. The bromide was used to alkylate the sodium derivative of diethyl acetamidomalonate, and the product was hydrolyzed and decarboxylated with difficulty by hydrochloric acid to the amino acid hydrochloride. The latter gave the desired compound when treated with ammonium hydroxide.

The amino acid is a high melting, very insoluble substance. The physical properties showed some resemblance to those of the corresponding 5-acenaphthenyl alanine,[3] but it was somewhat more stable than the latter, especially in hot alkaline media. The compound was characterized as the hydrochloride and as the *N*-benzenesulfonyl derivative.

EXPERIMENTAL

Melting points are uncorrected and were taken on a Fisher-Johns block.

2-Fluorenemethanol. A. From ethyl fluorene-2-carboxylate. The ethyl ester[4] of fluorene-2-carboxylic acid was employed due to its much greater solubility in solvents compared to the free acid.

A mixture of 8 g. of lithium aluminum hydride and 200 ml. of ether was refluxed for 1 hr. and cooled. To this was added slowly with stirring, a solution of 6.75 g. of the ethyl ester in 50 ml. of benzene. The liquid was then refluxed for 0.5 hr. and excess hydride decomposed with ethanol and dilute hydrochloric acid. The organic solvents were evaporated at room temperature and the aqueous-acid suspension filtered to yield the solid carbinol. Extraction of the latter with ether, and filtration, removed inorganic residues. The filtrate was diluted with petroleum ether and decolorized with Norit, and then filtered and evaporated. After recrystallization from dilute aqueous acetone, the material weighed 5.04 g. or 90.6%. On heating, it softened at about 120° and melted at 125–142° (lit. 131[2]). When the compound was recrystallized twice from ether-petroleum ether, it had m.p. 138–142°, and after 5 more recrystallizations, m.p. 140.5–142.5°. The melting point of the substance is sensitive to impurities but preparative methods and analysis of subsequent products would seem to confirm its identity.

B. From fluorene-2-aldehyde. The aldehyde was prepared by the method of Ayling, Hinkel, and Beynon.[5] Inorganic salts were removed from the product by extraction of the aldehyde with ether, filtration, and evaporation of the solvent.

A solution of 8 g. of lithium aluminum hydride in ether, prepared as above, was treated gradually with a solution of 6.9 g. of the aldehyde in 100 ml. of ether-benzene. A yellow-green color formed together with a light colored precipitate. The solution was refluxed 10 min. and then decomposed by ethanol and dilute hydrochloric acid. The organic solvents were removed at room temperature and the dilute acid suspension of the product was filtered. After washing and drying, the crude aldehyde weighed 6.87 g. or 98.5%. Without further purification, the cream-white solid had m.p. 126–130°. Both preparations of the carbinol gave the same bromide and subsequent derivatives.

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