this anhydride from the acid and *N,N'*-dicyclohexylcarbodiimide gave a substance which analyzed correctly for *N,N'*-dicyclohexyl-*N*-ferrocenoylurea, m.p. 161°. Neutral, acidic, or weakly alkaline hydrogen peroxide caused oxidation of the iron in the acid chloride. Reaction of the chloride in pentane-pyridine with *t*-butyl hydroperoxide also resulted in oxidation of the iron.

EXPERIMENTAL[14]

Ferrocenoic acid, prepared by metallation and carbonation of ferrocene,[7,8] melted at 208–210° (*cf.* 208.5°,[15] 195–205°,[6] 225–230°[16]). Potentiometric titration in 95% aqueous acetone gave N.E. 232, Calcd. 230, with the equivalence point at *p*H reading 8.75 on a Beckman *p*H meter with glass and calomel electrodes. This *p*H reading was used when following the kinetics of solvolysis of ferrocenoyl chloride as described below.

Ferrocenoyl chloride. Ferrocenoic acid (2.3 g.) in 30 ml. of benzene was allowed to react with 2.5 g. of phosphorus pentachloride (nitrogen atmosphere) as described.[4] The residue, after removal of solvent and phosphorus oxychloride, was dissolved in pentane, washed with dilute base, water, then dried over anhydrous magnesium sulfate. Evaporation (cold) of the solvent gave a solid m.p. 46–47° which, after careful recrystallization from pentane, gave 1.2 g. of red crystals, m.p. 49°.

Anal. Calcd. for $C_{11}H_9ClFeO$: C, 53.69; H, 3.65; Fe, 22.70. Found: C, 53.79; H, 3.99; Fe, 22.73. The compound gave a strong Beilstein test. Its spectrum showed λ_{max} 458 mμ(ϵ = 200) and λ_{min} 398 mμ(ϵ = 120). Bands for the carbonyl (5.66μ), unsubstituted ferrocene ring[17] (6.94, 9.02, 10.00, 12.16μ) and a monosubstituted ferrocene ring[15] (10.69μ) were present. Concentrated aqueous ammonia converted the chloride to the amide, m.p. 167–168° (lit.[3] value, 167–169°).

The chloride (0.8 g.) was refluxed with an excess of sodium peroxide (0.5 g.) in 50 ml. of anhydrous ether (3 drops of water added) for 5 hr. After decomposing the excess of sodium peroxide by water under ice-cooling, enough ether was added to dissolve the insoluble part between the two layers. The ether layer was washed with water, dried, and the solvent evaporated. The yellow solid (0.5 g.) was recrystallized from pentane, m.p. 141–142°, and presumed to be *ferrocenoic anhydride.*

Anal. Calcd. for $C_{22}H_{18}O_3Fe_2$: C, 59.77; H, 4.10; Fe, 25.27. Found: C, 59.43; H, 4.41; Fe, 25.62. The infrared spectrum showed carbonyl (5.62, 5.80μ), and other bands at 6.89, 8.05, 9.02, 9.40, 9.58, 9.99, and 11.02μ.

N,N'-dicyclohexyl-N-ferrocenoylurea. Ferrocenoic acid (0.5 g.) and 0.5 g. of *N,N'*-dicyclohexylcarbodiimide in 20 ml. of tetrahydrofuran were allowed to stand (dry nitrogen atmosphere) at room temperature for 15 hr. The solvent was removed and the residue washed with ether and recrystallized twice from hexane, m.p. 161°.

Anal. Calcd. for $C_{24}H_{31}O_2N_2Fe$: C, 66.20; H, 7.18; N, 6.44; Fe, 12.85. Found: C, 65.87; H, 7.49; N, 6.58; Fe, 12.62.

Rate measurements. Acetone was carefully purified[18] and conductivity water was used. The solvent was prepared by diluting 50 ml. of water to 1 l. with acetone. For duplicate experiments, 0.852 g. of ferrocenoyl chloride was dissolved in 100 ml. of solvent and the solution divided between two stoppered flasks, maintained at 25.0 ± 0.1°. At convenient intervals, 5 ml. aliquots were withdrawn, quenched by running into 50 ml. of pure cold acetone, then titrated immediately with 0.0128*N* sodium hydroxide, using *p*H 8.75 on a Beckman instrument (*vide supra*) for the end point. The total titers (26.72, 26.85 ml.) were in good agreement with the calculated (26.8 ml.). Typical data are given in Table I.

TABLE I

SOLVOLYSIS OF FERROCENOYL CHLORIDE IN 95% AQUEOUS ACETONE, 25.0°

t, Min.	Ml. of 0.0128*N* Base/5 Ml. Aliquot	$k_1 \times 10^{-5}$, sec.$^{-1}$
0[a]	4.12	...
28	7.27	8.88
42	8.86	9.31
67	10.92	8.87
90	12.48	8.59
126	15.05	8.85
252	20.35	8.39
end	26.72	...
	Av. $k_1 = 8.81 \pm 0.22 \times 10^{-5}$ sec.$^{-1}$	

[a] Zero time is taken as time first aliquot was removed.

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[14] Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Clark Microanalytical Laboratory, Urbana, Ill.

[15] K. L. Rinehart, Jr., K. L. Motz and S. Moon, *J. Am. Chem. Soc.*, **79**, 2749 (1957).

[16] V. Weinmayr, U. S. Patent **2,683,157** (1954).

[17] Ref. 12, p. 402.

[18] R. F. Hudson and J. E. Wardill, *J. Chem. Soc.*, 1729 (1950).

Benzhydryl Ethers of *N*-2-Hydroxyethyl-*O,N*-dialkylhydroxylamines

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The discovery that diphenhydramine, *N*-2-diphenylmethoxyethyl-*N,N*-dimethylamine hydrochloride, $(C_6H_5)_2CHO\text{-}CH_2CH_2N(CH_3)_2\cdot HCl$ is a useful antihistaminic drug with a high incidence of sedation in full therapeutic doses led to an extensive study of this amine and related compounds.[1]

Utilizing methods similar to those used in the synthesis of the corresponding amines,[1b,c] namely, the interaction of benzhydryl bromide and *N*-2-hydroxyethyl-*O,N*-dialkylhydroxylamines in presence of potassium carbonate according to the equation

$$(C_6H_5)_2CHBr + HOCH_2CH_2N(R)OR \xrightarrow{K_2CO_3} (C_6H_5)_2CHO\text{—}CH_2CH_2N(R)OR$$

two *N*-2-diphenylmethoxyethyl-*O,N*-dialkylhydroxylamines have been prepared.

Some of the pharmacological properties of the following compounds have been determined by Dr. C. A. Stone of the Merck Institute for Thera-

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[1] (a) American Medical Association, "New and Nonofficial Remedies," J. B. Lippincott Co., Philadelphia, 1956, p. 10. (b) G. Rieveschl, U. S. Patents **2,421,714**; **2,427,878**; Brit. Patent **743,495**. (c) J. B. Wright, H. G. Kolloff and J. H. Hunter, *J. Am. Chem. Soc.*, **70**, 3098 (1948).

peutic Research, West Point, Pa.: *N*-2-diphenylmethoxyethyl - *O,N* - dimethylhydroxylamine (I) and its iodomethylate (II) and the hydrochloride of *N* - 2 - diphenylmethoxyethyl - *O,N* - diethylhydroxylamine (III).

Administration of a dose of 100 mg. per kg. of I to monkeys intramuscularly, produced signs of restlessness, hyperactivity and piloerection. The signs were slow to appear. With intraperitoneal doses of 134 mg. per kg. of I the duration of hexobarbital-induced hypnosis in mice was increased 5.7 fold. Because of the magnitude of the dosage and the order of barbiturate potentiation induced by the compound, it seems more likely that the barbiturate potentiation may be due to the inhibition of the metabolic degradation of the hexobarbital.

Intravenous doses of 3.5 to 7.0 mg. per kg. of II produced weak atropinelike actions, antihistaminic and ganglionic blocking effects in the dog. Again, this compound is not particularly potent.

Compound III markedly prolonged the depressant effects of barbiturates in mice. The use of this agent with a barbiturate did not decrease the dose of barbiturate required to produce hypnosis, such as occurs with chlorpromazine.

EXPERIMENTAL[2]

N-2-hydroxyethyl-O,N-diethylhydroxylamine. To 42 g. (0.47 mole) *O,N*-diethylhydroxylamine in 30 ml. methanol was added a cold solution of 30 g. (0.68 mole) ethylene oxide in 90 ml. methanol. The mixture was refluxed for 7 hr. on a water bath with stirring (condenser temperature lower than 10°). During this time the reaction temperature rose to 65°. The reaction mixture was cooled, concentrated under reduced pressure, and the residue distilled; the fraction b.p. 85–90° (at 38 mm.) was collected; yield, 42 g. (66%). Upon redistillation, b.p. 65–66° (11 mm.). Jones and Burns[3] reported b.p. 63° (10 mm.)

N-2-diphenylmethoxyethyl-O,N-dimethylhydroxylamine (I). A mixture of 40 g. benzhydryl bromide[4] (0.16 mole), 18.7 g. *N*-2-hydroxyethyl-*O,N*-dimethylhydroxylamine[5] (0.18 mole), 24 g. finely powdered anhydrous potassium carbonate (0.18 mole), and 60 cc. dry toluene was heated with stirring on a water bath. If the evolution of carbon dioxide did not start immediately some drops of water were added. After 6 to 10 hr. the gas evolution ceased. The mixture was cooled and acidified with 100 cc. diluted hydrochloric acid. The aqueous layer was washed with ether and alkalinized with potassium hydroxide solution. An oil separated and was extracted with ether; upon evaporation of the dried extract 21.0 g. of crude I (48%) was left as a yellowish oil. Redistillation furnished 15.5 g. pure product, b.p. 138–141° (0.2 mm.).

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80. Found: C, 74.97; H, 7.66.

The *hydrochloride* was obtained with etheral hydrochloric acid as an oil which did not crystallize.

The *picrate* was prepared in isopropanol and crystallized in 93% yield as yellow prisms, m.p. 102–103°.

Anal. Calcd. for $C_{23}H_{24}N_4O_9$: C, 55.20; H, 4.83. Found: C, 55.43; H, 4.93.

The *iodomethylate* (II) was separated slowly from an ethereal solution of the base after treatment with excessive methyl iodide. Recrystallization from ethanol/ether furnished 80% yield of colorless needles, m.p. 112°.

Anal. Calcd. for $C_{18}H_{24}INO_2$: C, 52.31; H, 5.85. Found: C, 52.61; H, 5.72.

N-2-diphenylmethoxyethyl-O,N-diethylhydroxylamine was prepared as described above in 41% yield, b.p. 155–157° (0.65 mm.).

Anal. Calcd. for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42. Found: C, 76.41; H, 8.08.

The *hydrochloride* (III) was obtained with etheral hydrochloric acid and recrystallized from ethyl acetate/ether; m.p. 81–83°.

Anal. Calcd. for $C_{19}H_{26}ClNO_2$: C, 67.94; H, 7.83. Found: C, 68.25; H, 7.89.

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[2] Melting points and boiling points are uncorrected; microanalyses by Mrs. J. Jensen of this Laboratory.

[3] L. W. Jones and G. R. Burns, *J. Am. Chem. Soc.*, **47**, 2972 (1925).

[4] C. H. Courtot, Anales de Chemie, **5**, 80 (1916).

[5] R. T. Major and L. H. Petersen, *J. Org. Chem.*, **22**, 579 (1957).

Triphenylphosphoniumfluorenylide[1]

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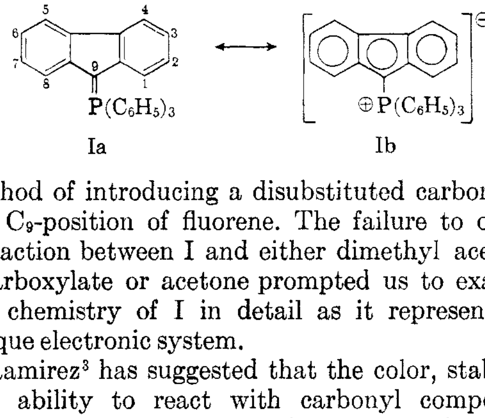
In connection with another problem the reaction of triphenylphosphoniumfluorenylide (I)[2] with symmetrical ketones was examined as a potential



Ia Ib

method of introducing a disubstituted carbon into the C_9-position of fluorene. The failure to obtain a reaction between I and either dimethyl acetonedicarboxylate or acetone prompted us to examine the chemistry of I in detail as it represented a unique electronic system.

Ramirez[3] has suggested that the color, stability, and ability to react with carbonyl compounds reflects the distribution of negative charge in phosphinemethylenes (II).[1] In agreement with this

$$(C_6H_5)_3\overset{+}{P}—\overset{-}{R}$$

IIa R = cyclopentadienyl
b CH_2
c CHC_6H_5
d $CHCOC_6H_5$
e $CHCOOC_2H_5$

postulate, he found that triphenylphosphoniumcyclopentadienylide (IIa), a stable and high melting solid, failed to react with aldehydes or

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[1] For nomenclature of these compounds see reference 10, footnote 1.

[2] L. A. Pinck and G. A. Hilbert, *J. Am. Chem. Soc.*, **69**, 723 (1947).

[3] F. Ramirez and S. Levy, *J. Am. Chem. Soc.*, **79**, 67 (1957).