78.49 g. (0.31 mole) of α,α-diphenyl-N-isopropylacetamide and the mixture was heated under reflux with stirring for 3 hours. A solution of 44.7 g. (0.33 mole) of β-diethylaminoethyl chloride in 100 ml. of dry toluene was added slowly with stirring at reflux temperature and the heating was continued for 20 hours. The toluene solution was washed with water, and extracted with dilute hydrochloric acid. The aqueous solution was washed with toluene and made basic with sodium hydroxide. The free base was extracted with benzene which was washed with water, dried over sodium sulfate and the solvent distilled. A yellow oil remained which could not be crystallized.

The free base was dissolved in methyl ethyl ketone, acidified with a slight excess of ethanolic hydrogen chloride and evaporated. A gum was obtained which crystallized from dioxane giving white crystals, with the properties given in Table II.

Methobromide.—An aqueous solution of 10 g. of this hydrochloride was made basic with sodium hydroxide and extracted with benzene. A portion of the benzene was distilled to remove water and cooled. Then 30 g. of cold methyl bromide was added, the flask was stoppered, clamped and allowed to stand at room temperature for 3 days. Concentration of the solution caused an oil to separate which solidified on trituration with ether. It was recrystallized from ethyl acetate and a little ethanol giving crystals, m.p. 76–78°. Recrystallization of this material gave a different modification, m.p. 161–163°.

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

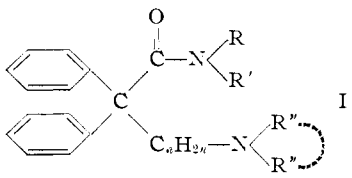
Antispasmodics. XII. α,α-Diphenyl-tertiaryamino-N,N-disubstituted Amides[1]

BY ROBERT BRUCE MOFFETT AND BROOKE D. ASPERGREN

RECEIVED MARCH 25, 1957

A series of α,α-diphenyl-γ-tertiaryamino-N,N-disubstituted amides (I, R and R′ = alkyl) have been prepared. In general they have been found to have little if any anticholinergic properties, but, like the monosubstituted amide series, the acid addition salts are oxytocics and/or diuretics.

Amides of the general type I (R and R′ = H), unsubstituted on the amide nitrogen, are well known as anticholinergics.[2]

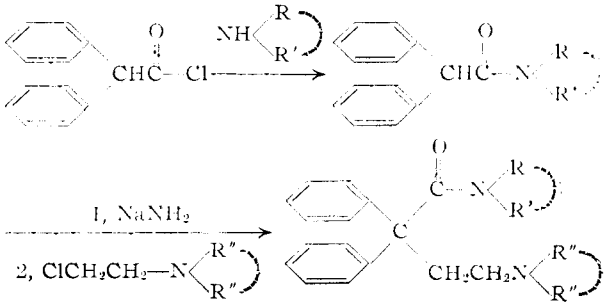


I

The preceding paper of this series[3] reported monosubstituted amides (I, R = H, R′ = alkyl). These were found to have little, if any, anticholinergic properties, but were powerful oxytocics and/or diuretics. It was therefore of interest to determine what type of activity would be shown by the disubstituted amides (I, R and R′ = alkyl). A very few of these disubstituted amides have been reported in the literature.[4–6] The first of these were reported in articles[4,5] dealing with antispasmodics but no pharmacology was given. Recently certain ones were reported to have high analgetic activity.[6]

A considerable number of these disubstituted amides have now been made and are listed in Table I. Like the monosubstituted amides[3] neither the hydrochlorides nor the methobromides had much antispasmodic activity in the Thiry-Vella dogs or gastric antisecretory activity in pyloric ligation rats but the hydrochlorides were generally oxytocics and/or diuretics.

In cases where $-C_nH_{2n}-$ (I) was $-CH_2CH(CH_3)-$ or $-CH_2CH_2CH_2-$ the dimethylamides (no. 15–18 in the table) were prepared from the corresponding acid chloride by a procedure essentially like procedure A described in the preceding paper[3] using dimethylamine in place of monomethylamine. When C_nH_{2n} = $-CH_2CH_2-$ or with large or hindered secondary amines pyrrolidones[7,8] were the chief products. Where $-C_nH_{2n}-$ was $-CH_2CH_2-$ the disubstituted amides were prepared by the method



This method is illustrated by an example in the Experimental part and the physical properties of the amides are listed in Table II (no. 1–14).

Acknowledgments.—The authors are indebted to Dr. P. H. Seay, Mr. Wm. Veldkamp, Mr. O. F. Swoap, Mr. B. E. Graham and associates of our Department of Pharmacology for the pharmacological data. The authors also wish to express their appreciation to Dr. R. V. Heinzelman of our Department of Chemistry for guidance in this work.

Experimental

α,α-Diphenyl-γ-(2,2-dimethyl-1-pyrrolidyl)-N,N-dimethylbutyramide.—A mixture of 54 g. (0.226 mole) of diphenyl-

(1) Presented in part before the Division of Medicinal Chemistry, A.C.S., at Miami, Florida, April, 1957, Abstracts, p. 19-N.

(2) R. B. Moffett and B. D. Aspergren, THIS JOURNAL, **79**, 4451 (1957), and references given therein.

(3) R. B. Moffett, B. D. Aspergren and M. E. Speeter, *ibid.*, **79**, 4457 (1957).

(4) M. Bockmühl and G. Ehrhart, German Patent 731,560 (1943).

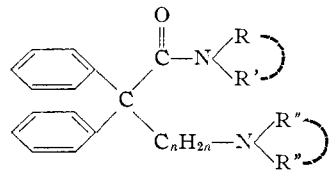
(5) L. C. Cheney, W. B. Wheatley, M. E. Speeter, W. M. Byrd, W. E. Fitzgibbon, W. F. Minor and S. B. Binkley, *J. Org. Chem.*, **17**, 770 (1952).

(6) P. Janssen, THIS JOURNAL, **78**, 3862 (1956).

(7) J. H. Gardner, N. R. Easton and J. R. Stevens, *ibid.*, **70**, 2960 (1948).

(8) R. L. Clarke, A. Mooradian, P. Lucas and T. J. Slanson, *ibid.*, **71**, 2821 (1949).

TABLE I



No. of base	$-N\begin{matrix}R\\R'\end{matrix}$	$-C_nH_{2n}-N\begin{matrix}R''\\R''\end{matrix}$	Salt	Toxicity LD_{50} (mg./kg.)[a]	Oxytocic activity at 1 mg./kg.[b]	Diuretic activity at 10 mg./kg.[c]
1	$-N(CH_3)_2$	$-CH_2CH_2-N(CH_3)_2$	HCl	100	Inactive	Excellent
1	$-N(CH_3)_2$	$-CH_2CH_2-N(CH_3)_2$	CH_3Br	65	Inactive	Inactive
2	$-N(CH_3)_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	HCl	65	Pronounced	Excellent
2	$-N(CH_3)_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	CH_3Br	77	Inactive	Inactive
3	$-N(CH_3)_2$	$-CH_2CH_2-N[CH(CH_3)_2]_2$	HCl	65	Pronounced	Good
3	$-N(CH_3)_2$	$-CH_2CH_2-N[CH(CH_3)_2]_2$	CH_3Br	200	Inactive	Inactive
4	$-N(CH_3)_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2$	HCl	65	Slight	Inactive
4	$-N(CH_3)_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2$	CH_3Br	65	Inactive	Inactive
5	$-N(CH_3)_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	HCl	65	Pronounced	Excellent
5	$-N(CH_3)_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	CH_3Br		Inactive	Inactive
5	$-N(CH_3)_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH_2CH_2$	→O·HBr	200	Inactive	Fair
6	$-N(CH_3)_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH(CH_3)CH_2$	HCl	65		Fair
6	$-N(CH_3)_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH(CH_3)CH_2$	CH_3Br		Inactive	
7	$-N(CH_3)_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	Base[d]	200	Inactive	Slight
7	$-N(CH_3)_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	CH_3Br	65	Inactive	Inactive
8	$-N(CH_3)_2$	$-CH_2CH_2-N(CH_2)_3C(CH_2)_4CH_2$	HBr[e,f]	65	Slight	Inactive
8	$-N(CH_3)_2$	$-CH_2CH_2-N(CH_2)_3C(CH_2)_4CH_2$	CH_3Br[f]	167		
9	$-N(CH_2CH_3)_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	HCl[3]		Slight	Good
9	$-N(CH_2CH_3)_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	CH_3Br			
10	$-N[CH(CH_3)_2]_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	HCl	20	Slight	Good
10	$-N[CH(CH_3)_2]_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	$CH_3Br\cdot H_2O$		Slight	Inactive
11	$-N[CH(CH_3)_2]_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH(CH_3)CH_2$	HCl			Inactive
11	$-N[CH(CH_3)_2]_2$	$-CH_2CH_2-NC(CH_3)_2CH_2CH(CH_3)CH_2$	CH_3Br			
12	$-NCH_2CH_2CH_2CH_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	HCl	65	Moderate	Excellent
12	$-NCH_2CH_2CH_2CH_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	CH_3Br		Inactive	
13	$-NCH_2CH_2CH_2CH_2CH_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	HCl	65	Moderate	Inactive
13	$-NCH_2CH_2CH_2CH_2CH_2$	$-CH_2CH_2-N(CH_2CH_3)_2$	CH_3Br	167	Inactive	Inactive
14	$-NCH_2CH_2CH_2CH_2CH_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	Base[d]	167	Inactive	Inactive
14	$-NCH_2CH_2CH_2CH_2CH_2$	$-CH_2CH_2-NCH_2CH_2CH_2CH_2CH_2$	CH_3Br	77	Inactive	Inactive
15	$-N(CH_3)_2$	(*dl*)$-CH_2CH(CH_3)N(CH_3)_2$	HCl	65	Slight	Excellent
15	$-N(CH_3)_2$	(*dl*)$-CH_2CH(CH_3)N(CH_3)_2$	$CH_3Br\cdot H_2O$		Slight	
15	$-N(CH_3)_2$	(*dl*)$-CH_2CH(CH_3)N(CH_3)_2$	→O·HBr	233	Slight	Good
16	$-N(CH_3)_2$	(*d*)$-CH_2CH(CH_3)N(CH_3)_2$	HCl			Excellent
16	$-N(CH_3)_2$	(*d*)$-CH_2CH(CH_3)N(CH_3)_2$	CH_3Br			
17	$-N(CH_3)_2$	(*l*)$-CH_2CH(CH_3)N(CH_3)_2$	HCl			Excellent
17	$-N(CH_3)_2$	(*l*)$-CH_2CH(CH_3)N(CH_3)_2$	CH_3Br	65	Inactive	Inactive
18	$-N(CH_3)_2$	$-CH_2CH_2CH_2-N(CH_2CH_3)_2$	HCl	65	Slight	Inactive
18	$-N(CH_3)_2$	$-CH_2CH_2CH_2-N(CH_2CH_3)_2$	CH_3Br	30	Inactive	Inactive

[a] Administered to mice intraperitoneally. The values are approximations with an accuracy of about +100% to −50%. [b] Tested by intravenous administration in cats by a modification of the method of M. L. Clary, A. Cameron and B. N. Cramer, *Proc. Soc. Exp. Biol. Med.*, **77**, 778 (1951). [c] Administered orally to rats. [d] Previously reported.[5] This base was dissolved in dilute acid for testing. [e] Isolated as a solvate containing one molecule of acetone. [f] Preparation previously reported, R. B. Moffett, THIS JOURNAL, **79**, 4457 (1957).

TABLE II

PHYSICAL PROPERTIES

(Table I) No. of base	Salt or base	Yield, %[a]	M.p., °C.	Crystallizing solvent	Empirical formula	Carbon Calcd.	Carbon Found[b]	Hydrogen Calcd.	Hydrogen Found[b]	Nitrogen Calcd.	Nitrogen Found[b]	Halogen Calcd.	Halogen Found[b]
1	Base	23	97–99	Hexane	$C_{20}H_{26}N_2O$	77.37	76.78	8.44	8.84	9.03	9.11	.....	.....
1	HCl	89	228–230	*i*-PrOH + Et_2O	$C_{20}H_{27}ClN_2O$	69.24	69.08	7.85	7.88	8.08	7.95	Cl, 10.22	Cl, 10.21
1	CH_3Br	69	225–227	*i*-PrOH + Et_2O	$C_{20}H_{29}BrN_2O$	62.22	62.18	7.21	7.04	6.91	6.64	Br, 19.71	Br, 19.41
2	HCl	46[c]	184–186	Me_2CO	$C_{22}H_{31}ClN_2O$	70.47	70.42	8.33	8.45	7.47	7.33	Cl, 9.46	Cl, 9.44
2	CH_3Br	82[d]	177–179	*i*-PrOH + Et_2O	$C_{22}H_{34}BrN_2O$	63.73	64.09	7.67	7.52	6.46	6.29	Br, 18.44	Br, 17.73
3	Base	..	74–76	Pentane	$C_{24}H_{34}N_2O$	78.72	79.09	9.36	9.26	7.65	7.75	.....	.....
3	HCl	64	205–207	EtOH + EtOAc	$C_{24}H_{35}ClN_2O$	71.52	71.56	8.75	8.62	6.95	7.09	Cl, 8.80	Cl, 8.84
3	CH_3Br	79	188–190	MeEtCO	$C_{25}H_{37}BrN_2O$	65.06	65.09	8.08	8.11	6.07	6.00	Br, 17.32	Br, 17.43
4	Base	66	142–144	*i*-PrOH	$C_{22}H_{28}N_2O$	78.53	78.63	8.39	8.10	8.33	8.17	.....	.....
4	HCl	63	197–199	EtOH + MeEtCO	$C_{22}H_{29}ClN_2O$	70.85	71.07	7.84	7.57	7.51	7.49	Cl, 9.51	Cl, 9.63
4	CH_3Br	80	190–192	EtOAc	$C_{23}H_{31}BrN_2O$	64.03	64.08	7.24	7.32	6.49	6.56	Br, 18.52	Br, 18.53
5	Base	52	110–112	Hexane	$C_{24}H_{32}N_2O$	79.07	79.04	8.85	8.96	7.68	7.71	.....	.....
5	HCl	..	205–207	EtOAc	$C_{24}H_{33}ClN_2O$	71.88	71.86	8.29	8.40	6.99	7.07	Cl, 8.84	Cl, 8.56
5	CH_3Br	77	200–202	*i*-PrOH + Et_2O	$C_{25}H_{35}BrN_2O \cdot H_2O$[e]	62.88	62.81	7.81	7.71	5.87	6.05	Br, 16.74	Br, 17.29
5	→ O·HBr	13	158–162	*i*-PrOH	$C_{24}H_{32}BrN_2O_2$	62.60	62.84	7.01	7.19	6.09	6.42	Br, 17.36	Br, 17.27
6	Base	46	102–104	Cyclohexane	$C_{25}H_{34}N_2O$	79.32	79.53	9.05	8.99	7.40	7.32	.....	.....
6	HCl	55	218–220	EtOH + EtOAc	$C_{25}H_{35}ClN_2O$	72.35	71.89	8.50	8.48	6.75	6.65	Cl, 8.54	Cl, 8.51
6	CH_3Br	86	195–197	MeEtCO	$C_{26}H_{37}Br_2N_2O$	65.95	65.75	7.88	7.84	5.92	5.67	Br, 16.88	Br, 16.83
7	CH_3Br[f]	93	205–207	MeEtCO	$C_{24}H_{33}BrN_2O$	64.71	64.66	7.47	7.35	6.29	6.13	Br, 17.94	Br, 17.70
9	HCl	..	172–174[g]	EtOAc	$C_{25}H_{35}ClN_2O$	72.35	72.22	8.50	8.40	6.75	6.89	Cl, 8.54	Cl, 8.62
9	CH_3Br	40	123–125	EtOAc	$C_{26}H_{37}BrN_2O$	65.95	66.09	7.88	7.89	5.92	5.61	Br, 16.88	Br, 16.81
10	Base	..	72–74	Pentane	$C_{26}H_{38}N_2O$	79.14	79.29	9.71	9.56	7.10	7.16	.....	.....
10	HCl	55	211–213	MeEtCO	$C_{26}H_{39}ClN_2O$	72.44	72.08	9.12	8.78	6.50	6.37	Cl, 8.23	Cl, 8.09
10	CH_3Br	81[h]	181–183	MeEtCO + Et_2O	$C_{27}H_{41}BrN_2O$	66.24	66.20	8.44	8.13	5.72	5.44	Br, 16.33	Br, 16.34
11	HCl	51[i]	228–230	EtOAc	$C_{29}H_{43}ClN_2O \cdot H_2O$[e]	71.21	71.38	9.27	9.08	5.73	5.72	Cl, 7.25	Cl, 7.33
11	CH_3Br	86[c]	226–228	MeEtCO	$C_{30}H_{45}BrN_2O$	68.03	68.21	8.56	8.65	5.29	5.30	Br, 15.09	Br, 14.95
12	HCl	..	212–214	MeEtCO	$C_{24}H_{33}ClN_2O$	71.88	72.17	8.30	8.06	6.99	6.95	Cl, 8.84	Cl, 8.49
12	CH_3Br	..	174–176	Benzene	$C_{25}H_{35}BrN_2O \cdot H_2O$[e]	62.88	62.97	7.81	7.59	5.87	5.75	Br, 16.74	Br, 16.66
13	HCl	56[j]	225–227	EtOH + MeEt + CO	$C_{25}H_{33}ClN_2O$	72.35	72.69	8.50	8.42	6.75	7.09	Cl, 8.54	Cl, 8.39
13	CH_3Br	75[d]	195–197	MeEtCO	$C_{26}H_{37}BrN_2O$	65.95	65.96	7.88	7.70	5.92	5.98	Br, 16.88	Br, 16.61
14	CH_3Br[e]	82	202–204	EtOH + EtOAc	$C_{27}H_{38}Br_2N_2O$	66.79	66.98	7.68	7.43	5.77	5.81	Br, 16.46	Br, 16.37
15	HCl	..	199–201	EtOAc	$C_{21}H_{29}ClN_2O$	69.88	69.56	8.10	8.16	7.76	8.10	Cl, 9.82	Cl, 9.91
15	CH_3Br	..	161–163	EtOAc	$C_{22}H_{31}BrN_2O \cdot H_2O$[d]	60.40	60.27	7.60	7.46	6.41	6.47	Br, 18.27	Br, 18.38
15	→ O·HBr	69[d]	116–119	*i*-PrOH + Et_2O	$C_{21}H_{29}BrN_2O_2$	59.85	56.66[k]	6.94	7.02	6.65	6.63	Br, 18.97	Br, 18.95
16	HCl	52[l]	192–194[m]	EtOH + EtOAc	$C_{21}H_{29}ClN_2O$	69.88	69.85	8.10	8.37	7.76	7.45	Cl, 9.82	Cl, 9.84
16	CH_3Br	49[l]	157–159[n]	EtOAc	$C_{22}H_{31}BrN_2O \cdot H_2O$[e]	60.40	59.80	7.60	8.17	6.41	6.57	Br, 18.27	Br, 18.35
17	HCl	58[l]	191–193[o]	EtOH + EtOAc	$C_{21}H_{29}ClN_2O$	69.88	69.79	8.10	8.24	7.76	7.58	Cl, 9.82	Cl, 9.83
17	CH_3Br	54[l]	155–157[p]	MeEtCO	$C_{22}H_{31}BrN_2O$[q]	63.00	63.26	7.45	7.11	6.68	6.75	Br, 19.06	Br, 19.23
18	HCl	65[l]	155–158	*i*-PrOH + Et_2O	$C_{23}H_{31}ClN_2O$	71.02	70.72	8.55	8.48	7.20	7.29	Cl, 9.12	Cl, 9.18
18	CH_3Br	73[d]	165–166	EtOH + EtOAc	$C_{24}H_{35}BrN_2O$	64.42	64.30	7.88	7.58	6.26	6.33	Br, 17.86	Br, 17.93

[a] Unless otherwise noted the yields of the free bases are based on the diphenyl dialkylacetamide. The yields of the salts are based on the pure free bases. [b] Analyses and rotations are by Mr. William Struck and staff of our Analytical Chemistry Laboratory. Infrared spectra are by Dr. James L. Johnson and associates of our Department of Physics. [c] This yield is based on diphenyl-N,N-dimethylacetamide. The free basic amide was not isolated in pure form. [d] Yield based on pure hydrochloride. [e] The infrared spectrum[b] as well as the analysis indicates that this is a hydrate. [f] Prepared from the corresponding free base which has been previously reported.[5] [g] This salt has been reported by Bockmühl and Ehrhart[4] with m.p. 182–183°, but no analytical figures were given. It was prepared from diphenyl-N,N-diethylamide [N. Maxim, *Compt. rend.*, **182**, 1393 (1926); *Ann. chim.*, **9**, 55 (1928)]. [h] This compound was isolated as a hydrate, m.p. 129–132°. *Anal.* Calcd. for $C_{27}H_{41}BrN_2O \cdot H_2O$: N, 5.52; Br, 15.75. Found: N, 5.44; Br, 15.65. A sample was dried giving the properties listed in the table. The hydrate was used for pharmacological study. [i] The free base was not isolated. The hydrochloride crystallized from an aqueous acid solution on the addition of ether. [j] This yield is based on diphenylacetyl-1-piperidine.[5,9] The free basic amide was not isolated in pure form. [k] In spite of repeated attempts by two laboratories a satisfactory carbon analysis could not be obtained. The results ranged from 56.66 to 58.09. Good analyses for the other elements were obtained without difficulty. [l] Yield based on the α,α-diphenyl-γ or δ-*l*-aminovaleroyl chloride acid sulfate. The intermediate free basic amide was not isolated in pure form. [m] $[\alpha]^{23}D$ +59° (1% in CH_3OH). [n] $[\alpha]^{23}D$ +7° (1% in CH_3OH). [o] $[\alpha]^{23}D$ −63° (0.6% in CH_3OH). [p] $[\alpha]D$ −6° (1% in CH_3OH). [q] Isolated as a hydrate as shown by infrared[b] spectrum but after drying analyzed as anhydrous material.

N,N-dimethylacetamide,[5,9] 9.7 g. (0.25 mole) of sodium amide and 500 ml. of dry toluene was heated under reflux with stirring for 3 hours. To 44.8 g. (0.226 mole) of 2-(2,2-dimethyl-1-pyrrolidyl)-ethyl chloride hydrochloride[10] was added a slight excess of aqueous sodium hydroxide and the mixture was extracted with 300 ml. of toluene in several portions. The toluene solution was dried over potassium carbonate and slowly added to the above suspension of the sodium derivative. The mixture was heated under reflux with stirring for 2 hours, cooled, washed with water and extracted with dilute hydrochloric acid. The aqueous acid solution was made basic with dilute sodium hydroxide and the product was extracted with benzene. After removal of the solvent an oil was obtained which crystallized from pentane and was recrystallized from hexane giving white crystals having the properties given in Table II (no. 5, base).

Hydrochloride.—This was prepared by treating a sample of the free base in ethyl acetate with a slight excess of ethanolic hydrogen chloride. It was recrystallized from ethyl acetate, m.p. 206–207° (no. 5, HCl).

Methobromide.—To a cold solution of 10 g. (0.0322 mole) of the free base in 100 ml. of methyl ethyl ketone was added a large excess of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature for 2 days. The crystals which separated had the properties given in Table II (no. 5, CH_3Br).

N-Oxide Hydrobromide.—A solution of 14.6 g. (0.04 mole) of the above free base and 10 ml. of 30% hydrogen peroxide in 150 ml. of methanol was allowed to stand at room temperature for 2 days. The excess hydrogen peroxide was decomposed by adding a small amount of a slurry of platinum-on-charcoal and shaking for 2 hours. The solution was filtered and distilled to dryness under reduced pressure below 30°. The resulting gummy free base failed to crystallize. It was dissolved in acetone and made acidic with a slight excess of 48% hydrobromic acid, and diluted with ether. On standing, the gummy hydrobromide partly crystallized. This was rubbed with ethyl acetate giving a solid product. This was recrystallized from isopropyl alcohol giving light tan crystals having the properties given in Table II (no. 5 → O·HBr).

α,α-Diphenylacetyl-1-pyrrolidine.—A mixture of 106.1 g. (0.5 mole) of diphenylacetic acid, 73 ml. of thionyl chloride and 100 ml. of benzene was heated under reflux with stirring for 1 hour. The solvent and excess thionyl chloride were removed by distillation under reduced pressure and the crude acid chloride was diluted with 300 ml. of benzene. To this was added slowly with stirring a solution of 85.4 g. (1.2 moles) of dry pyrrolidine in 200 ml. of benzene. After standing at room temperature overnight or heating under reflux for 1 hour, the solution was washed with water. The benzene solution was concentrated by distillation, treated with decolorizing charcoal, and cooled. It crystallized giving 111 g. (84%) of white crystals, m.p. 163–165°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.66; H, 8.01; N, 5.38.

Diphenyl-N,N-diisopropylacetamide.—By a similar procedure this was prepared from diisopropylamine. It was recrystallized from *n*-pentane giving a 60% yield of amide, m.p. 53–55°.

Anal. Calcd. for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.26; H, 8.59; N, 4.88.

KALAMAZOO, MICHIGAN

(9) V. G. Gokhale, N. L. Phalnikar and B. V. Bhide, *J. Univ. Bombay*, **16**, No. 5, 32–36 (1948); *C. A.*, **43**, 1144e (1949).

(10) R. B. Moffett, J. L. White, B. D. Aspergren and F. F. Visscher, THIS JOURNAL, **77**, 1565 (1955).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE A. M. TODD COMPANY]

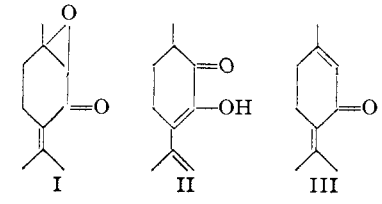
The Synthesis of Racemic Piperitenone Oxide and Diosphenolene

BY ROBERT H. REITSEMA[1]

RECEIVED OCTOBER 12, 1956

The enolic diketone, diosphenolene, separated from the oil of *Mentha rotundifolia* has been synthesized by three methods. Piperitenone has been converted to a monoepoxide and this with acid gave diosphenolene. Pulegone was a useful starting material for two other methods. The syntheses provide further evidence that the structure of diosphenolene is 3,8(9)-*p*-menthadiene-2-one as previously proposed.

Mentha rotundifolia is one of the more interesting mint species and its oil contains constituents which are quite different from most other mint oils. It has been shown that the major constituent is piperitenone oxide (1,2-epoxy-4(8)-*p*-menthene-3-one) (I).[2] Associated with this keto oxide in the oil and readily obtained from it in the laboratory is a new enolic ketone called diosphenolene for which the structure of 3-hydroxy-3,8(9)-*p*-menthadiene-2-one (II) was proposed.[2]



I II III

The evidence for the location of the double bond

(1) The Ohio Oil Company, Denver Research Center, Littleton, Colorado.

(2) R. H. Reitsema, THIS JOURNAL, **78**, 5022 (1956).