lizations from methanol gave 0.16 g. of hecogenin acetate, m.p. 245–247°, infrared spectrum identical to an authentic reference sample.

Correllogenin, 20α,22a,25L-spirost-5-en-3β-ol-12-one. The mother liquors from the ethyl acetate crystallization of gentrogenin acetate contained both correllogenin and gentrogenin acetates. Repeated crystallizations from ethyl acetate removed more gentrogenin acetate, leaving the soluble fractions enriched in correllogenin acetate. Chromatography on Florisil and silica gel was not particularly effective but gave a slight enrichment of correllogenin acetate in the more polar eluates. The residues from these treatments were crystallized repeatedly from ethyl acetate–methanol and finally methanol to give correllogenin acetate, needles from methanol, m.p. 213–214°, $[\alpha]_D^{25}$ −60°, infrared spectrum similar to gentrogenin acetate but showed typical 25L fingerprint bands[11a,b], 986 (s), 920 (s), 897 (w), and 852 (w) cm.$^{-1}$

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 73.90; H, 9.18.

Hydrolysis of the acetate gave correllogenin, m.p. 209–211°, $[\alpha]_D^{25}$ −69°.

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.14; H, 9.63.

Yamogenin from correllogenin. Wolff-Kishner reduction of correllogenin gave yamogenin, m.p. 187–189°, infrared spectrum identical to an authentic specimen.

Sisalagenin from correllogenin. Catalytic hydrogenation of correllogenin acetate followed by chromium trioxide oxidation in the same manner described for gentrogenin gave a product[20] which we believe is the recently isolated sisalagenin acetate,[12] m.p. 214–216°, $[\alpha]_D^{25}$ −12° (lit.[12] gives m.p. 228–232°, $[\alpha]_D^{22}$ −12°), infrared spectrum showed peaks at 1733 (s), 1712 (s), 1071 (s), 1037 (s), 987 (s), 919 (s), 899 (w), 849 (w) cm.$^{-1}$ which were in agreement with data of Callow and James.[12]

5,16-Pregnadien-3β-ol-12,20-dione 3-acetate (I). Eight g. of gentrogenin acetate was refluxed 5 hr. in 40 ml. of acetic anhydride to which was added 1.9 g. of pyridine hydrochloride. The crude pseudogentrogenin diacetate thus obtained was oxidized in our usual manner[13] and the oxidation intermediate treated with potassium hydroxide in *t*-butyl alcohol.[13] After the standard work-up, the product was acetylated and chromatographed on Florisil. Elution with benzene and chloroform followed by crystallization from ether gave 2.3 g. of I, m.p. 170–173°. The analytical sample after 3 ether crystallizations had m.p. 173–175°, $[\alpha]_D^{25}$ +57°, $\lambda_{max.}^{MeOH}$ 227.5 mμ, log ε 3.98; $\nu_{max.}^{CS_2}$ 1737, 1720, and 1684 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.35; H, 8.20.

Alkaline hydrolysis of I in *t*-butyl alcohol–potassium hydroxide gave 5,16-pregnadien-3β-ol-12,20-dione (II), needles from ethyl acetate, m.p. 198–202°, $[\alpha]_D^{25}$ +67.4°.

5-Pregnen-3β-ol-12,20-dione 3-acetate (III). Two-tenths g. of I was dissolved in 100 ml. of ethanol and catalytically hydrogenated in the presence of 0.4 g. of 10% palladium on barium sulfate at 3 atmospheres for 16 hr. After filtration and removal of the ethanol the residue was crystallized from methanol, long rods, m.p. 222–223°, $[\alpha]_D^{25}$ +90.4°, infrared spectrum shows absence of conjugated carbonyl, and presence of two strong carbonyl bands, 1735 cm.$^{-1}$ (acetate), 1710 cm.$^{-1}$ (C_{12} and C_{20} carbonyl).

Allopregnane-3β-ol-12,20-dione 3-acetate (IV). One-tenth g. of I in 47 ml. of ether containing 3 ml. of glacial acetic acid was catalytically hydrogenated in the presence of 0.1 g. of platinum oxide at 3 atmospheres pressure for 16 hr. After the usual work-up, the residual glass was oxidized in chromium trioxide–pyridine.[21] Dilution with water, and ether extraction gave a crude product which was taken up in a small volume of methylene chloride to which was added a large volume of ether. The solution was concentrated on the steam bath. On standing, 30 mg. of crystalline product was obtained, m.p. 190–192° with infrared spectrum identical to an authentic specimen of IV from hecogenin.[13]

Allopregnane-3,12,20-trione (V). Two-tenths g. of II were reduced and oxidized as described under IV. The crude product was chromatographed on Florisil and the benzene and chloroform eluates were combined and triturated with ether. The ether-insoluble residue was crystallized from ethyl acetate as irregular plates, m.p. 210–212° (lit.[9a] gives m.p. 207–208°), infrared spectrum identical with that of an authentic specimen derived from hecogenin.

Acknowledgment. We wish to thank R. F. Mininger for optical rotation data and K. Zbinden for C and H analyses. The infrared spectra were obtained by C. S. Fenske under the supervision of C. R. Eddy.

PHILADELPHIA 18, PENNSYLVANIA

(20) We were unable to obtain enough pure correllogenin acetate to purify adequately the reduction product or obtain analytical data.

(21) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

[CONTRIBUTION FROM THE DEPARTMENT OF PATHOLOGY, GEORGETOWN UNIVERSITY MEDICAL CENTER]

Hypotensive Agents. VI.[1] Substituted 3-Azabicyclo[3.2.1]octane Derivatives[2]

LEONARD M. RICE AND CHARLES H. GROGAN

Received July 18, 1956

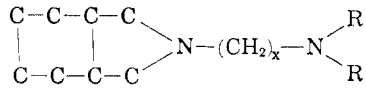
A series of unsymmetrical α,ω-bis-tertiary amines has been prepared in which 3-azabicyclo[3.2.1]octane is employed as one of the bridgehead substituents. The acid addition and bis-quaternary salts of these bases have been prepared and screened for pharmacological activity. These bases were prepared by reaction of d- or dl-camphoric anhydride and the dialkylaminoalkylamines followed by reduction of the resulting imides. Several members of these series were potent hypotensive agents in mammals and were effective when administered orally.

As part of a continuing search for hypotensive agents, many series of symmetrically and unsymmetrically substituted α,ω-bisamines and their acid addition and quaternary salts have been prepared Among the most active of these substances were members in several series in which various modifi-

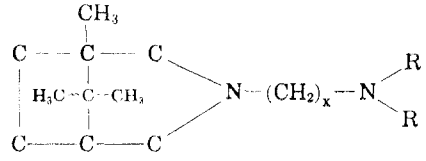
(1) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, **77**, 616 (1955).

(2) Supported by a research grant from the Geschickter Fund for Medical Research, Inc.

cations of the isoindole nucleus were employed as one or both of the bridgehead substituents, I.[1,3] In exploring the effects of modifying the heretocyclic nucleus employed as one or both of the terminal substituents, both symmetrically and unsymmetrically substituted series employing the 1,8,8-trimethyl-3-azabicyclo[3.2.1]octane nucleus, II, have been synthesized.



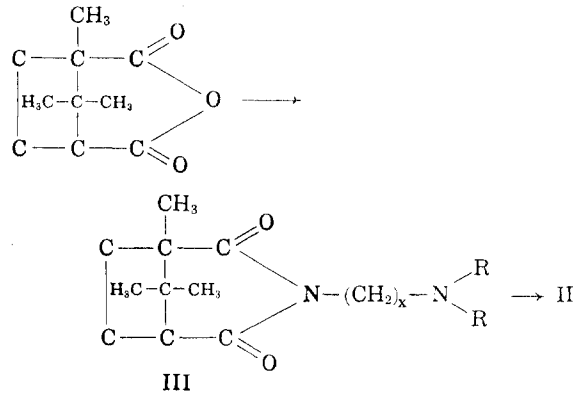
I



II

These compounds were prepared by reacting d- or dl-camphoric anhydride with suitable dialkylaminoalkylamines to obtain the camphorimides, III. Camphorimides in which the N-substituent was dimethylaminoethyl and diethylaminoethyl have been reported by Kurodo and Nishimune[4] and Faust.[5] These imides yielded the base from which the unsymmetrically substituted salts were derived. By reaction with an alkyl amine, such as methyl amine, followed by reduction, a base was obtained which when quaternized with an α,ω-bishalide yielded symmetrically substituted salts.

The reaction was carried out by mixing the anhydride and the appropriate amine in equimolecular amounts and gently heating the partly reacted mass until a clear reaction mixture was obtained. The resulting mixture consisting of camphoramic acid and imide (the latter formed by the heat generated and applied in the reaction) was heated to a temperature of 180° and maintained at that temperature for several hours. Any unreacted camphoramic acid was thus dehydrated and cyclized to the imide by this process.



III

After allowing the reaction mixture to cool, the material was vacuum distilled and the desired camphorimides were collected in excellent yields in a high state of purity. The imides are tabulated in Table I together with their refractive indices and other pertinent data.

It can be seen that compounds 3 and 4 bear the same substituent on the nitrogen. These two compounds were prepared from d- and dl-camphoric anhydride, respectively, in order to ascertain if one would show an appreciable difference in hypotensive response. In the listed series of compounds it can be seen that the methylene bridging chain between the two nitrogens has from two to five carbon atoms, while the alkyl group attached to the ω-nitrogen has from one to four carbons, or is part of a heterocyclic base such as pyrrolidine or morpholine. The dialkylaminoalkyl camphorimides thus obtained were converted into suitable derivatives, the hydrochlorides and methiodides. The methiodides formed readily and were generally nice crystalline compounds. In Table II are listed the hydrochlorides and methiodides of these compounds.

(3) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, **75**, 4911 (1953).

(4) S. Kurodo and K. Nishimune, *J. Pharm. Soc. Japan*, 64, 160 (1944).

(5) E. S. Faust, U.S. Pat., **1,406,547** (1922).

TABLE I

N-DIALKYLAMINOALKYL CAMPHORIMIDES

N Substitution	Formula	B.P., °C.	Mm.	n_D^{25}	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1. Dimethylaminoethyl[a,b]	$C_{14}H_{24}N_2O_2$	106–108	0.5	1.4895	66.64	66.59	9.59	9.59	11.10	11.45
2. Diethylaminoethyl[a,b]	$C_{16}H_{28}N_2O_2$	114–120	0.2	1.4877	68.54	68.76	10.07	10.38	9.99	10.17
3. Dimethylaminopropyl[b]	$C_{15}H_{26}N_2O_2$	114–119	0.2	1.4893	67.63	67.46	9.84	9.58	10.52	10.31
4. Dimethylaminopropyl[c]	$C_{15}H_{26}N_2O_2$	112–116	0.1	1.4893	67.63	67.38	9.84	9.82	10.52	10.51
5. Diethylaminopropyl[b]	$C_{17}H_{30}N_2O_2$	132–138	0.2	1.4886	69.35	69.65	10.27	10.24	9.52	9.62
6. Diethylaminobutyl[b]	$C_{18}H_{32}N_2O$	137–145	0.4	1.4874	70.09	70.15	10.46	10.58	9.08	8.86
7. Diethylaminoamyl[b]	$C_{19}H_{34}N_2O_2$	157–167	0.4	1.4863	70.76	70.96	10.63	10.66	8.69	8.81
8. Dibutylaminopropyl[b]	$C_{21}H_{38}N_2O_2$	150–155	0.2	1.4880	71.95	72.09	10.93	10.97	7.99	7.88
9. Morpholinoethyl[b]	$C_{16}H_{26}N_2O_3$	138–148	0.3	47–48[d]	65.28	65.57	8.90	9.11	9.52	9.33
10. Pyrrolidinoethyl[b]	$C_{16}H_{26}N_2O_2$	112–115	0.1	1.5028	69.03	69.23	10.06	10.06	9.41	9.40

[a] References (4) and (5). [b] d-Camphoric anhydride as starting material. [c] dl-Camphoric anhydride as starting material. [d] Melting point.

TABLE II

DERIVATIVES OF COMPOUNDS IN TABLE I

Hydrochloride				Methiodide			
		Ionic Chlorine				Ionic Iodine	
Formula	M.p., °C.	Calcd.	Found	Formula	M.p., °C.	Calcd.	Found
1. $C_{14}H_{25}ClN_2O_2$	218.5–219.5	12.28	12.42	$C_{15}H_{27}IN_2O_2$	271–272	32.19	32.41
2. $C_{16}H_{29}ClN_2O$[2]	138.5–139.5[a]	11.19	11.45	$C_{17}H_{31}IN_2O_2$	—	—	—
3. $C_{15}H_{27}ClN_2O$[2]	182–183.5	11.71	11.47	$C_{16}H_{29}IN_2O_2$	283–284	31.08	31.02
4. $C_{15}H_{27}ClN_2O_2$	184–185	11.71	11.87	$C_{16}H_{29}IN_2O_2$	283–284	31.08	31.06
5. $C_{17}H_{31}ClN_2O_2$	139.5–140.5	10.72	11.04	$C_{18}H_{33}IN_2O_2$	177–178	29.08	29.00
6. $C_{18}H_{33}ClN_2O_2$	142–143	10.28	10.16	$C_{19}H_{35}IN_2O_2$	179–180	28.18	27.98
7. $C_{19}H_{35}ClN_2O_2$	162.5–163.5	9.88	9.59	$C_{20}H_{37}IN_2O_2$	162–163	27.33	27.08
8. $C_{21}H_{39}ClN_2O_2$	108–110	9.16	9.38	$C_{22}H_{41}IN_2O_2$	—	25.77	25.63
9. $C_{16}H_{27}ClN_2O_3$	212–213	10.72	10.63	$C_{17}H_{29}IN_2O_3$	252–254	29.09	29.08
10. $C_{16}H_{27}ClN_2O_2$	194–195	11.26	11.44	$C_{17}H_{29}IN_2O_2$	190–191	30.19	30.23

[a] M.p., reported 89–90°C. Reference (5).

The camphorimide bases were next reduced by means of lithium aluminum hydride in ether solution to yield the desired 3-azabicyclooctane bases (II). In all cases, the imides dissolved in anhydrous ether were added to a lithium aluminum hydride solution at such a rate as to just maintain reflux. During the addition of the imide the reaction mixture was stirred vigorously. The addition complex generally precipitated completely, coating the walls of the flask as a metallic-like product. On several occasions the addition product tended to form a hard metallic-like ball which was troublesome, as it would either break the stirrer or stop it. However, outside of these mechanical difficulties the addition proceeded smoothly. After stirring for an additional hour, the reaction mixture was decomposed by the slow dropwise addition of water until the ether ceased to reflux, and the addition complex had completely disappeared. After sufficient water had been added, it was sometimes necessary to continue the stirring for several hours in order to completely decompose the complex which was adhering to the sides of the reaction vessel. The N-dialkylaminoalkyl substituted-1,8,8-trimethyl-3-azabicyclo[3.2.1]-octanes thus prepared were isolated, Table III, as colorless oils by vacuum distillation in 50–65% yields. The products were stable on storage and some samples that have been kept for several years developed only a slight yellow coloration. The reaction was reasonably clean-cut, but judging from the distillation residue, considerable side reaction had occurred or partially reduced material remained. The refractive indices are lower in the bases than in the corresponding imides.

The azabicyclooctane bases were converted into suitable derivatives, hydrochlorides and mono- and dimethiodides. The hydrochlorides formed readily. In contrast to most other series, such as the dialkylaminoalkyl isoindoles, I, the monomethiodides of the azabicyclooctanes formed readily in most cases and in a high state of purity. This particularly was the case when the alkylene chain, between the nitrogens, was four carbons or less. In the isoindole series previously studied this was not generally the case, as the dimethiodide formed very easily. Quaternization of both nitrogens proceeded relatively easily, making isolation of pure monoquaternary salt difficult.

In the cases where the alkylene chain was two or three carbon atoms, the dimethonium salts of the azabicyclooctanes were not formed in appreciable amounts in the usual manner. For example, even on refluxing for several days with an excess of methyl iodide in methanol, there was obtained only a small amount of dimethiodide. This was very surprising, since N-methyl azabicyclooctane (N-methyl cam-

TABLE III

N-DIALKYLAMINOALKYL-1-METHYL-8,8-DIMETHYL-3-AZABICYCLO [3.2.1] OCTANES

N-Substitution	Formula	B.p., °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	n_D^{25}
1. Dimethylaminoethyl	$C_{14}H_{28}N_2$	64–66	0.4	74.94	75.05	12.58	12.44	12.49	12.79	1.4781
2. Diethylaminoethyl	$C_{16}H_{32}N_2$	70–74	0.1	76.12	76.28	12.78	12.86	11.10	11.28	1.4780
3. Dimethylaminopropyl	$C_{15}H_{30}N_2$	76–80	0.2	75.56	75.21	12.68	12.40	11.75	11.67	1.4772
4. Dimethylaminopropyl	$C_{15}H_{30}N_2$	70–72	0.1	75.56	75.30	12.68	12.30	11.75	11.54	1.4770
5. Diethylaminopropyl	$C_{17}H_{34}N_2$	81–89	0.05	76.62	76.63	12.86	12.73	10.51	10.44	1.4778
6. Diethylaminobutyl	$C_{18}H_{36}N_2$	96–100	0.1	77.07	77.06	12.94	12.92	9.99	9.67	1.4771
7. Diethylaminoamyl	$C_{19}H_{38}N_2$	100–105	0.1	77.48	77.63	13.01	13.10	9.51	9.36	1.4766
8. Dibutylaminopropyl	$C_{21}H_{42}N_2$	106–110	0.1	78.19	77.94	13.12	12.95	8.69	8.23	1.4756
9. Morpholinoethyl	$C_{16}H_{30}N_2O$	102–105	0.1	72.13	71.85	11.35	11.36	10.52	10.31	1.4954
10. Pyrrolidinoethyl	$C_{16}H_{30}N_2$	88–93	0.2	76.74	76.49	12.08	12.42	11.19	10.79	1.4950

phidine) quaternized without difficulty with methylene diiodide and ethylene dibromide to give a bis-quaternary salt. This had not been our experience with the N-methylated isoindole bases.[1] With the N-methyl isoindole bases, only one side of the bis-halide reacted and the product was a β- or γ-halogen alkyl isoindole monoquaternary salt. However, by heating the 3-dialkylaminoalkyl azabicyclooctane bases with an excess of methyl iodide in methanol in a bomb tube at 100°, bis-quaternary salts were readily formed in almost analytically pure state. Table IV shows a compilation of various salts, hydrochlorides, monomethiodides, and dimethiodides which were prepared from the unsymmetrical α,ω-azabicyclooctane bases.

num hydride reduction of N-methyl camphorimide which proceeded in the expected manner with good yield.

Table V shows several members of this type of compound in which the central methylene carbons number from one to six. As was pointed out earlier, it was surprising to have complete quaternization of the N-methyl base as compared to some other series. These symmetrical bis- compounds were quite toxic. Starting with compound number one which has a L.D. 50 in rats of approximately 100 mg./kg. by I.P. injection, there is a steady increase in toxicity to hexamethylene number six.

The compounds were screened for hypotensive activity in dogs by two methods: (a) cannulation of

TABLE IV

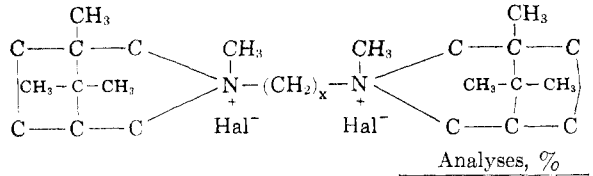
DERIVATIVES OF COMPOUNDS IN TABLE III

	HCL			Monomethiodide				Dimethiodide			
			Ionic Chloride				Ionic Iodine				Ionic Iodine
	Formula	M.p., °C.	Calcd.	Found	Formula	M.p., °C.	Calcd.	Found	Formula	M.p., °C.	Calcd.	Found
1.	$C_{14}H_{30}Cl_2N_2$	263–264	23.85	23.41	$C_{15}H_{31}IN_2$	241	34.65	34.46	$C_{16}H_{34}I_2N_2$	244–245	49.94	50.05
2.	$C_{16}H_{34}Cl_2N_2$	254.5–255.5	21.66	21.77	$C_{17}H_{35}IN_2$	193–194.5	32.18	31.87	$C_{18}H_{38}I_2N_2$	235–236	47.16	47.63
3.	$C_{15}H_{32}Cl_2N_2$	290–291	22.78	22.74	$C_{16}H_{33}IN_2$	237–238	33.37	33.90	$C_{17}H_{36}I_2N_2$	271–273	48.60	48.32
4.	$C_{15}H_{32}Cl_2N_2$	290–291	22.78	22.92	$C_{16}H_{33}IN_2$	237–238	33.37	33.75	$C_{17}H_{36}I_2N_2$	269–271	48.60	48.63
5.	$C_{17}H_{36}Cl_2N_2$	212–214	20.89	20.74	$C_{18}H_{37}IN_2$	196–198	31.07	31.13	$C_{19}H_{40}I_2N_2$	217–219	46.12	45.88
6.	$C_{18}H_{38}Cl_2N_2$	286–286	20.07	19.97	$C_{19}H_{39}IN_2$	172–173	30.04	30.43	$C_{20}H_{42}I_2N_2$	236–237	44.98	44.46
7.	$C_{19}H_{40}Cl_2N_2$	274–275	19.29	19.59	$C_{20}H_{41}IN_2$	—	—	—	$C_{21}H_{44}I_2N_2$	235–236	43.89	44.15
8.	$C_{21}H_{44}Cl_2N_2$	138–140	17.93	17.94	$C_{22}H_{45}IN_2$	—	—	—	$C_{23}H_{48}I_2N_2$	127–130	41.86	41.57
9.	$C_{16}H_{32}Cl_2N_2O$	263–264	20.90	20.72	$C_{17}H_{33}IN_2O$	205–207	31.07	30.94	$C_{18}H_{36}I_2N_2O$	226–228	46.13	45.96
10.	$C_{16}H_{32}Cl_2N_2$	263–265	21.93	22.10	$C_{17}H_{33}IN_2$	224–225	32.35	32.41	$C_{18}H_{36}I_2N_2$	250–251	47.51	47.85

In addition to the above compounds, a series of symmetrical α,ω-bis-azabicyclooctane alkane dimethonium salts were prepared. These were prepared by the reaction of 1,3,8,8-tetramethyl-3-azabicyclo[3.2.1]octane (N-methyl camphidine) with the appropriate α,ω-dihalogenated alkane in a suitable solvent, usually isopropanol, at 100°. The N-methyl camphidine needed for these reactions was conveniently prepared by the lithium alumi-

TABLE V

α,ω-BIS(1,8,8-TRIMETHYL-3-AZABICYCLO[3.2.1]-3-OCTYL)ALKANE METHONIUM IODIDES



			Analyses, %	
			Ionic	Iodine
X	Formula	B.P., °C.	Calcd.	Found
1.	$C_{23}H_{44}I_2N_2$	291–294	42.14	41.93
2.	$C_{24}H_{46}Br_2N_2$	200–202	30.59	30.43
3.	$C_{25}H_{48}I_2N_2$	233–235	40.26	40.25
4.	$C_{26}H_{50}I_2N_2$	253–254	39.38	39.52
5.	$C_{27}H_{52}I_2N_2$	255–256	38.55	38.68
6.	$C_{28}H_{54}I_2N_2$	230–231	37.89	37.82

the carotid artery while under Nembutal anesthesia; (b) femoral artery puncture in the intact animal. In the latter method the drugs were administered by I.M., I.V., and oral routes.

When screened in this manner the following information was obtained: The imides as their hydrochloride salts and their methonium salts were inactive. The azabicyclooctane bases as such were inactive as hypotensive agents when tested as their hydrochloride salts except at toxic levels. However, the mono- and bis- quaternary methonium salts were potent as hypotensive agents. In addition to the usual ganglionic blocking, we believe that there is a strong central component of action. In some cases, the hypotensive effect after oral administration or I.M. injection lasted for 26 hr. No difference was noted in response between the d- and dl- form when the ring had a dimethylaminopropyl side chain. In this series it was found that the optimum activity resided in compounds which had 2 to 3 carbons between the nitrogens.

EXPERIMENTAL

N-Methyl camphidine. In a 2-liter 3-necked flask fitted with a mercury sealed stirrer, dropping funnel, and a long condenser to which a calcium chloride tube was attached were placed 19 g. of lithium aluminum hydride and 1 l.

of absolute ether. After all the hydride had dissolved, a solution of 50 g. of N-methyl camphorimide in 500 ml. of absolute ether was added dropwise with rapid stirring. The rate of addition was adjusted so that the mixture refluxed gently. During the addition a fine suspension of the complex precipitated. After the addition was completed, the stirring was continued for several hours and the mixture allowed to stand overnight. The flask was cooled in an ice bath and, with vigorous stirring, the reaction mixture was decomposed by the dropwise addition of water. The addition of water was regulated so that reflux was just maintained and then 10 cc. in excess was added at the end. After decomposition, the mixture was stirred an additional hour and filtered with suction. The inorganic precipitate was well pressed and washed with three portions of ether. After drying over sodium sulfate, the ether was stripped and the residue distilled under reduced pressure. There was obtained 36 g. of material boiling at 99–102° at 38 mm. (68° at 10 mm.) n_D^{25} 1.4776.

Anal. Calcd. for $C_{11}H_{21}N$: C, 78.98; H, 12.65; N, 8.37. Found: C, 79.39; H, 12.52; N, 8.45.

The methiodide was prepared by heating with a slight excess of methyl iodide in a bomb tube at 100° for 8 hr. using methanol as a solvent. After recrystallization from methanol-ether the product melted over 300°.

Anal. Calcd. for $C_{12}H_{24}NI$: I, 41.04. Found: I, 40.65.

The hydrochloride was prepared in the usual way by means of alcoholic hydrogen chloride and melted at 226–227° after recrystallization from methanol-ether.

Anal. Calcd. for $C_{11}H_{22}NCl$: Cl, 17.42. Found: Cl, 17.54.

Dialkylaminoalkyl camphorimides. Into a flask fitted with a reflux condenser was placed 0.4 mole of camphoric anhydride. With cooling and intermittent shaking, 0.41 mole of the appropriate dialkylaminoalkylamine was added slowly. After the reaction had subsided, the reaction mixture was heated until a clear homogeneous melt was obtained and then maintained by means of an oil bath at 180° for 2 hr. The resulting crude product was fractionated in vacuum and the pure imide obtained as a colorless oil. (See Table I.)

The hydrochlorides of the above imides were prepared in the usual way by means of alcoholic hydrogen chloride and recrystallized from methanol or isopropanol-ether mixtures.

The methiodides of the above imides were prepared by reaction with methyl iodide in absolute alcohol in the usual way and recrystallized from methanol or isopropanol-ether.

N-Dialkylaminoalkyl-1,8,8-trimethyl-3-azabicyclo-[3.2.1]*-octanes.* These were prepared in a manner analogous to that of the N-methyl camphidine base above. (See Table III.)

The dihydrochlorides and monomethiodides of the N-substituted camphidine bases above were prepared in the usual manner and recrystallized from methanol-ether.

The dimethiodides of these bases were obtained by heating the base in a bomb tube at 100° for 8 hr. with an excess of methyl iodide and were recrystallized from methanol.

α,ω-Bis(1,8,8-trimethyl-3-azabicyclo[3.2.1]-3-octyl)alkane dimethonium salts. (See Table V.)

To 0.06 mole of N-methyl camphidine dissolved in 20 ml. of isopropanol in a bomb tube was added 0.03 mole of the α,ω-dihalogenated alkane. The mixture was allowed to stand at room temperature for 1 hr. and then heated to 100° and maintained at this temperature for an additional 8 hr. The crude product was filtered, washed with alcohol-ether mixture, recrystallized from a mixture of methanol and ethanol, and dried.

WASHINGTON 7, D. C.

[CONTRIBUTION FROM U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, PUBLIC HEALTH SERVICE, THE ROBERT A. TAFT SANITARY ENGINEERING CENTER]

Structure of Dactylin

G. E. INGLETT[1]

Received July 26, 1956

Dactylin is shown to be isorhamnetin 3,4′-diglucoside, I.

A flavonoid glycoside, dactylin, was found to occur in pollens of timothy and orchard grass in 1931 by Moore and Moore.[2] This flavonoid glycoside has become of particular importance recently since it was shown by Johnson *et al.*[3] to possess allergenic activity. Whether this activity is associated with the pure dactylin or with impurities in the pigment remains to be established. However, the present studies are concerned only with the structure of dactylin.

Heyl[4] in 1919 isolated a quercetin glucoside as the least soluble flavonoid from ragweed pollen and isorhamnetin by hydrolysis of the more soluble fractions. Since this report, several investigators have reported the presence of flavonoids in pollens.[5–7] Kuhn and Löw[8] have isolated and characterized a flavonoid glycoside of *Crocus Sir John Bright* to be isorhamnetin 3,4′-diglucoside.

Dactylin was obtained as a light yellow solid from a 1955 crop of defatted timothy pollen by alcoholic extraction. It gave only one spot on chromatograms developed in three different solvent systems. Methoxyl content was 3.60%, and the dactylin aglycone, obtained by 2*N* sulfuric acid hydrolysis of dactylin, revealed 6.93% methoxyl content. Infrared spectra, ultraviolet spectra, and melting point data revealed the aglycone to be impure isorhamnetin. Acetylation of dactylin aglycone

(1) Present address, Box 345, Corn Products Refining Co., Argo, Ill.

(2) M. B. Moore and E. E. Moore, *J. Am. Chem. Soc.*, **53**, 2744 (1931).

(3) M. C. Johnson, S. F. Hampton, A. W. Schiele, S. Frankel, *J. Allergy*, **25**, 82 (1954).

(4) F. W. Heyl, *J. Am. Chem. Soc.*, **41**, 1285 (1919).

(5) F. A. Stevens, D. Moore, and H. Baer, *J. Allergy*, **22**, 165 (1951).

(6) M. S. El Ridi, L. A. Strait, and M. H. A. Wafa, *Arch. Biochem. and Biophys.*, **39**, 317 (1952).

(7) G. Tappi and E. Menziani, *Gazz. chim. ital.*, **85**, 703 (1955).

(8) R. Kuhn and I. Löw, *Ber.*, **77**, 196 (1944).