The boric acid was administered by incorporating it in the diet, a commercial chick starting mash, in the amounts shown in Table I. The birds were given the drug-containing diet immediately after inoculation and were permitted to feed *ad libitum* throughout the period of the test. The trophozoite-infected birds were continued on the drug-diet for 5 days. The chicks receiving the sporozoite inoculation were fed the drug-diet for 3 days and were then transferred to the regular untreated stock diet for an additional 6 days.

At the end of the respective test period, thin blood smears were prepared, stained with Giemsa, and the effect of the therapy was judged by determining the number of parasitized cells among 10,000 erythrocytes. In each experiment a group of untreated birds and at least one group treated with a drug of known antimalarial activity served as controls.

The results of the experiments on trophozoite- and sporozoite-induced avian malaria are given in Table I. Whereas quinine, atabrine and sulfadiazine can be used interchangeably as suppressives for the trophozoite infections, only sulfadiazine has prophylactic activity against *P. gallinaceum*. It is apparent that boric acid at relatively high concentrations in the diet had a marked suppressive effect on both *P. cathemerium* and *P. gallinaceum* infections. Boric acid at high doses also showed definite prophylactic activity against *P. gallinaceum* infections.

Thus boric acid, unlike quinine and atabrine, possesses both suppressive and prophylactic activity. It should be noted, however, that the amounts of boric acid required to produce an effect on avian malaria closely approach toxic levels.

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Antifibrillating Action of N-Methyl-Dibenzyl-Amine and Some of Its Derivatives.

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Quinidine is the best known among the drugs effective against cardiac fibrillation induced by electrical stimulation or other agents. Other drugs have been reported, some with chemical structure resembling that of quinidine, and others entirely different, which also show some antifibrillating action.

We have found that α-fagarine, (an alkaloid isolated by Stuckert[1] from *Fagara coco* (collected by Gill Engler) exerts an antifibrillating effect as potent as, or more potent than, quinidine itself. It counteracts the influence of several fibrillating agents (faradic currents,[2,3] coronary occlusion[4]) and causes recovery of the sinus rhythm in cases of accidental or spontaneous auricular fibrillation[5] in animal experimentation or in man.[6,7]

Deulofeu and Labriola[6] have established that α-fagarine is a tertiary base to which the following tentative formula can be assigned:

[1] Stuckert, G., *Investigaciones de laboratorio de Quimica Biológica*, Córdoba, Vol. I, 1933; Vol. II, 1938.

[2] Moisset de Espanés, E., *Rev. Soc. Arg. Biol.*, 1937, **13**, 112; *C. R. Soc. Biol.*, 1938, **127**, 118.

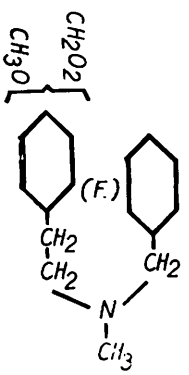
[3] Martínez, C., *Medicina* (Buenos Aires), 1944, **4**, 109.

[4] Moisset de Espanés, E., *Rev. Soc. Arg. Biol.*, 1937, **13**, 116; *C. R. Soc. Biol.*, 1938, **127**, 233.

[5] Moisset de Espanés, E., *Amér. Clín.*, 1945, **8**, 41; Moisset de Espanés, E., y Moyano Navarro, B., *Rev. Soc. Arg. Biol.*, 1936, **12**, 137; *C. R. Soc. Biol.*, 1938, **127**, 510.

[6] Deulofeu, V., Labriola, R., Orías, O., Moisset de Espanés, E., y Taquini, A., *Science*, 1945, **102**, 69; *Ciencia e Investigación*, 1945, **1**, 527.

[7] Taquini, A., *Rev. Arg. Cardiol.*, 1945, **12**, 83.



The possibility of preparing easily a series of bases derived from methyl-dibenzyl-amine, which has a chemical structure greatly resembling that of the possible structure of α-fagarine, and the hope of finding new antifibrillating substances which, because of efficiency or facility of preparation, would offer advantages, induced us to assay them pharmacologically. Methyl-dibenzyl-amine, which also exerts some antifibrillating effect, as shown by Martinez,[3] was taken as standard to compare the activity of its derivatives.

So far we have studied the following bases, arranged according to the increasing complexity of the substituents attached to the aromatic nuclei: (1) N-methyl-dibenzyl-amine; (2) N-methyl-o-anisyl-p-anisyl-amine; (3) N-methyl-di(o-anisyl)-amine; (4) N-methyl-di-(3,4-dimethoxy-benzyl)-amine; (5) N-methyl-di-(2,3-dimethoxy-benzyl) - amine; (6) N-methyl-di-(p-anisyl)-amine; (7) N-methyl - benzyl - piperonyl - amine; (8) N-methyl-di-(piperonyl)-amine; (9) N-methyl-p-anisyl-piperonyl-amine. The following bases were also studied: (10) N-ethyl-dibenzyl-amine; (11) N-methyl-benzyl-anisidine; (12) N-methyl-benzyl-phenethyl-amine. We shall refer to the above mentioned bases by the number preceding each. (Fig. 1).

All the bases were prepared under the direction of Doctors V. Deulofeu and R. Labriola in the Laboratory of Organic Chemistry in the Facultad de Ciencias Exactas, Fisicas y Naturales de Buenos Aires. Some are already known and the others were obtained by classical methods. The description of the new bases will be given elsewhere.

Rabbits weighing from 1200 to 1800 g were anesthetized with 0.6 g of dial per kg of body weight, half of that dosage being injected intravenously and the other half intraperitoneally. The heart was exposed, with the pleural sacs left untouched, and the thresholds to obtain both auricular and ventricular fibrillation with faradic current were determined. Control experiments showed that such thresholds do not show appreciable variations within the 2 or 3 hours following the beginning of anesthesia.

Two, 7, 17, and 32 minutes after intravenous injection of the substance to be tested, the threshold was again determined, and the maximal variation was taken as indicative of the activity of the drug for comparative purposes.

Table I summarizes the results obtained. The activity of each drug is expressed according to the percentage of threshold increase found after injection. Each figure is the average of the values found in the different animals injected with the same drug. The relative value represents the ratio of the activity of the investigated substance to that of the same dose of the standard substance (methyl-dibenzyl-amine), to which was assigned an activity value of 100. The opponent action of both quinidine and α-fagarine against auricular and ventricular fibrillation was also determined for comparative purposes.

The results show that methyl-dibenzyl-amine exerts antifibrillatory action and that its potency is about the same on auricular and ventricular fibrillation (Table I). The addition of either methoxylic or dioxymethylenic groups to the aromatic nuclei of methyl-dibenzyl-amine, obviously modified its effect. In some cases it decreased (bases 4 and 5) and in some others it increased (bases 3 and 9) but the change did not affect to the same extent the auricular and ventricular effects. All the bases to which only methoxylic groups were added (bases 2, 3, 4, 5, and 6) showed increased activity against ventricular fibrillation, whereas those to which only dioxymethylenic groups were added, (bases 7 and 8), showed increased activity against auricular fibrillation as compared with that of the original nucleus. Bases either having no such groups (bases 1, 10, 11, and 12) or hav-

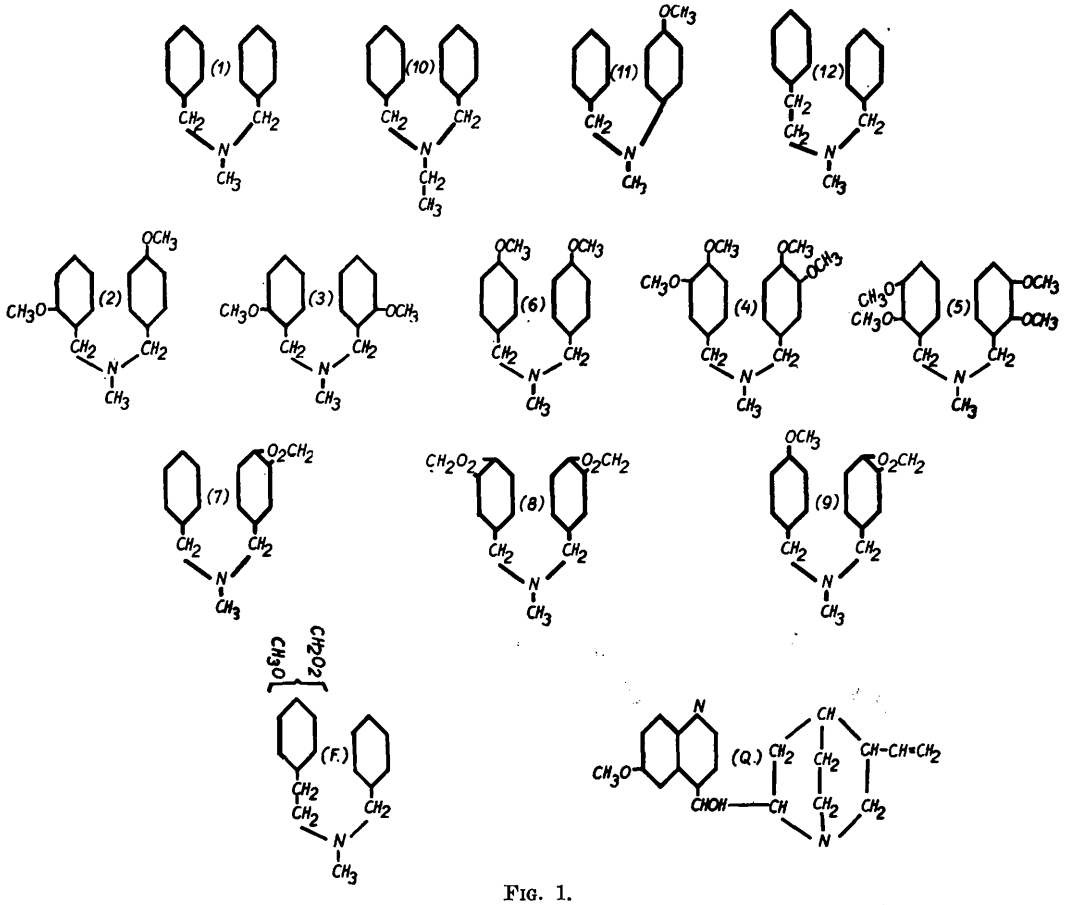


FIG. 1.

(1) N-methyl-dibenzyl-amine; (2) N-methyl-o-anisyl-p-anisyl-amine; (3) N-methyl-di(o-anisyl)-amine; (4) N-methyl-di-(3,4-dimethoxy-benzyl)-amine; (5) N-methyl-di-(2,3-dimethoxy-benzyl)-amine; (6) N-methyl-di-(p-anisyl)-amine; (7) N-methyl-benzyl-piperonyl-amine; (8) N-methyl-di-(piperonyl)-amine; (9) N-methyl-p-anisyl-piperonyl-amine; (10) N-ethyl-dibenzyl-amine; (11) N-methyl-benzyl-anisidine; (12) N-methyl-benzyl-phenetyl-amine.

ing both (one of each) (base 9) showed practically the same degree of activity against both auricular and ventricular fibrillation.

Ethyl-dibenzyl-amine (base 10) also was of interest because substances mentioned in the literature as having antifibrillatory activity have ethyl groups attached to nitrogen. In our substance the substitution of the ethyl for the methyl group rather reduced the activity of the standard substance.

Methyl-benzyl-phenetyl-amine (base 12) with a chemical structure even more closely resembling the proposed structure for α-fagarine than methyl-dibenzyl-amine, our standard substance, showed a somewhat higher activity than the latter.

Furthermore, outside the methyl-dibenzyl-amine series, the aromatic base methyl-benzyl-anisidine was investigated, and showed a markedly weak potency against both auricular and ventricular fibrillation, indicating that the difference in chemical structure produced a difference in pharmacological properties.

Among the substances with higher potency than our standard substance, base 2 (methyl-o-anisyl-p-anisyl-amine) showed a very transient effect (it vanished in approximately 5 minutes) and base 3 (methyl-di(oanisyl)-amine) was highly toxic, producing an intense convulsive attack, more tonic than clonic, the intensity in proportion to the administered dose, appearing sometimes before

TABLE I.
Table Showing the Increase of Faradic Threshold to Fibrillation in Per cent of Initial Value and the Potency of Its Activity as Compared with That of Methyl-dibenzyl-amine at the Same Doses.

		Auricles			Ventricles		
Drug	Dose, mg/kg	No. of animals	% of fibrillation threshold increase (avg and P.E.)	Relative activity	No. of animals	% of fibrillation threshold increase (avg and P.E.)	Relative activity
1	1	24	18.3 ± 1.11	100	20	18.4 ± 1.01	100
	5	29	27.1 ± 2.15	100	20	32.8 ± 2.37	100
2	1	10	18.5 ± 6.65	101	10	25.7 ± 6.74	140
3	½	8	25.0 ± 6.13	137	8	34.6 ± 4.12	188
4	1	11	13.3 ± 1.23	73	11	16.1 ± 2.99	87
5	1	12	10.0 ± 5.81	55	12	14.4 ± 4.32	78
6	1	12	10.2 ± 3.24	56	11	29.4 ± 2.21	160
7	5	10	31.0 ± 4.07	114	10	18.8 ± 6.87	57
8	5	9	29.2 ± 1.98	108	10	12.4 ± 3.81	38
9	1	12	20.3 ± 2.36	111	12	23.3 ± 1.48	127
10	5	10	22.7 ± 1.67	84	10	23.9 ± 3.78	73
11	5	12	1.8 ± 3.84	7	11	5.2 ± 1.36	16
12	1	11	22.3 ± 2.06	122	11	21.6 ± 2.02	117
Q	1	17	21.8 ± 2.87	119	12	16.8 ± 2.60	91
F	1	21	24.8 ± 2.55	135	12	30.3 ± 2.12	165

the injection ended and ceasing under new doses of "dial."

Even though quinidine showed some higher activity against auricular fibrillation, its potency was of the same order as that of our standard substance; α-fagarine, on the other hand, being perhaps more effective against ventricular than against auricular fibrillation, showed, in general, a higher potency than methyl-dibenzyl-amine.

It seems necessary to emphasize that a strict ratio does not exist between the increase in potency as compared with the increase of the administered dose, as generally occurs in pharmacology. Also the relation dose/effect is different for each substance of the series; therefore, the relative activity may not be the same if doses other than those we have used are compared. Furthermore the toxicity of one substance as compared with the others does not necessarily parallel antifibrillating activity. More study will be needed to indicate which one is the most convenient from the practical point of view.

Summary. The antifibrillating activity of a series of tertiary bases with a carbon skeleton related to the possible chemical structure of α-fagarine has been assayed in rabbits. Eight of them were derivatives of methyl-dibenzyl-amine by addition of either methoxylic or dioxomethylenic groups to the aromatic nuclei; the others, also chemically related, were ethyl-dibenzyl-amine, methyl-benzyl-anisidine and methyl-benzyl-phenetyl-amine. Their effects were compared with those of quinidine and α-fagarine, tested under the same conditions.

All of them showed antifibrillating activity. The maximal effect, however, was given by α-fagarine. The addition of methoxylic and dioximethylenic groups modified the activity of methyl-dibenzyl-amine, the former enhancing the effect against fibrillation of the ventricles and the latter enhancing the effect against auricular fibrillation.