and a droplet of sulfuric acid on the end of a glass rod. The difficultly soluble diketone dissolved immediately and new crystals appeared. The mixture was warmed to bring everything into solution and then cooled, allowed to crystallize, and filtered; yield 0.02 g. of nearly pure dimesityldimethylfuran of m. p. 134–140°; identified by recrystallization and mixed melting point.

Summary

The synthesis and preliminary study of *cis* and *trans* benzoyldimethylacrylic acids is reported. The inversion of the *trans* isomer to the *cis* under the influence of alkali is discussed.

Diaroyl-dimethylethylenes have been synthesized from dimethylfumaryl chloride.

The 1,6-addition of hydrogen to *cis* and *trans* di-trimethylbenzoyldimethylethylene is discussed.

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The Effect of Strong Ultraviolet Irradiation upon the Toxicity of Pure Nicotine

BY GLEN WAKEHAM AND CLARENCE B. JOHNSTON

Two years ago A. J. Pacini and Hugh McGuigan[1] reported that the toxic action of nicotine upon frogs was destroyed by ultraviolet irradiation. Some time later, George P. Tracy, working with the senior author of the present paper (G. W.), demonstrated that while the toxic effects of nicotine upon albino rats can be considerably diminished by ultraviolet irradiation they are by no means destroyed.[2] At the same time it was shown that irradiation beyond the optimum time of exposure will almost completely restore the original toxicity of the nicotine. The work recorded in the present paper is an attempt to ascertain whether any reasonable amount of ultraviolet irradiation will destroy the toxic effects of nicotine upon albino rats.

Experimental

The source of irradiation used was a carbon arc for which the makers claim an intensity in the ultraviolet region forty times that of the ordinary mercury vapor lamp. This claim was approximately verified. In the work earlier reported[2] an irradiation of seventy-five minutes was required, under the mercury vapor lamp, at a distance of ten centimeters, to produce the maximum detoxication. At a distance of fifteen centimeters from the carbon arc the maximum detoxication effects were obtained by irradiation periods of three or four minutes.

In the first series of experiments here recorded, pure, freshly redistilled nicotine was irradiated, in quartz-glass tubes, at a distance of fifteen centimeters from the arc, for periods of from one to sixty minutes. The layer of nicotine (water-clear) was about

(1) Pacini and McGuigan, *J. Pharmacol.*, **33**, 241 (1930).
(2) Wakeham and Tracy, *ibid.*, **44**, 295 (1932).

one millimeter deep. The maximum period of exposure (sixty minutes) was at least equivalent to fifteen hours of irradiation at a distance of ten centimeters from an ordinary mercury vapor lamp.

In the second series of experiments a one per cent. solution of nicotine was exposed in open petri dishes to the carbon arc at a distance of twenty-five centimeters. The layer

TABLE I

DATA OBTAINED WHEN PURE NICOTINE WAS IRRADIATED AND ADMINISTERED HYPODERMICALLY IN A ONE PER CENT. SOLUTION

Rats in group	Irradiation, minutes	Range of dosage in mg. per kg. of rat wt.	Number of rats killed	Number of rats surviving	Highest non-lethal dose	Lowest fatal dose
17	0	12.3–29.1	8	9	23.3	15.6
6	1	15.7–39.2	2	4	23.1	28.6
4	1½	14.7–33.6	2	2	28.9	32.0
6	2	18.0–35.7	2	4	31.9	31.2
8	3	14.7–40.7	4	4	26.3	28.4
5	4	25.0–32.4	2	3	30.8	25.4
11	5	16.7–43.5	5	6	40.0	31.0
7	10	19.2–35.1	3	4	25.3	24.6
5	20	18.6–30.0	3	2	20.6	19.0
6	60	19.1–22.0	2	4	21.0	20.5

TABLE II

DATA OBTAINED WHEN A ONE PER CENT. SOLUTION OF NICOTINE WAS IRRADIATED AND ADMINISTERED HYPODERMICALLY

Rats in group	Irradiation, minutes	Range of dosage in mg. per kg. of rat wt.	Number of rats killed	Number of rats surviving	Highest non-lethal dose	Lowest fatal dose
4	1	20.0–28.0	2	2	28.0	25.0
5	2	20.0–33.8	2	3	28.5	25.0
6	3	20.0–33.3	2	4	31.5	32.4
6	4	15.2–24.2	3	3	18.1	17.1
3	5	16.6–24.6	1	2	23.0	24.6
4	10	19.8–22.5	3	1	21.3	19.8
8	20	19.8–31.1	3	5	31.1	22.0
4	60	20.8–24.6	2	2	24.6	20.9

TABLE III

DATA OBTAINED WHEN RATS WERE REPEATEDLY INJECTED WITH "CRITICAL" DOSES OF NICOTINE, BOTH RAW AND IRRADIATED. DOSES ARE GIVEN IN MG. PER KG. OF RAT WEIGHT, INTERVAL IN DAYS. WEIGHTS OF RATS GIVEN IN GRAMS

Rat no.	Rat wt.	Dose	Interval	Dose	Interval	Dose	Interval	Dose	Interval	Dose	Interval	Dose	
11	128	21.5	13	21.5	3	22.7	died						
4	152	21.4	3	21.8	died								
15c	140	28.5	3	26.7	died								
16c	160	25.0	18	23.1	3	26.3	died						
7	82	15.2	3	17.1	3	15.2	3	15.0	died				
6	88	22.7	3	22.7	3	20.6	3	22.2	died				
5	90	16.7	2	16.3	3	16.2	3	17.6	4	17.1	died		
2	116	17.2	2	19.4	died								
23	120	20.8	13	22.5	3	18.4	3	21.2	4	21.9	7	25.8	lived
13	120	16.6	8	14.9	7	17.9	died						
2a	112	17.8	8	16.1	3	19.2	4	22.2	lived				

of solution was never more than two millimeters deep. Both pure nicotine and the diluted nicotine turned to a deep, opaque brown color after long irradiation. This effect is commonly ascribed to oxidation, although quantitative determinations by means of silicotungstate precipitation do not reveal any appreciable decrease in the amount of nicotine present. It is suggested that the degree and intensity of irradiation used in these experiments greatly exceed what would be practicable in any commercial process for the treatment of tobacco.

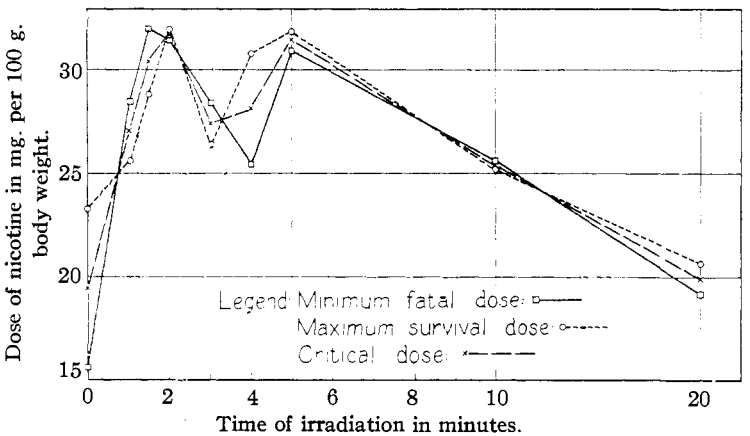

Fig. 1.—Irradiated pure nicotine.

In both series of experiments the nicotine, after irradiation, was injected beneath the loose belly-skin of the rat. The inferences recorded below are based upon what we venture to call the "critical dose," this being the mean of the highest dose which any rat

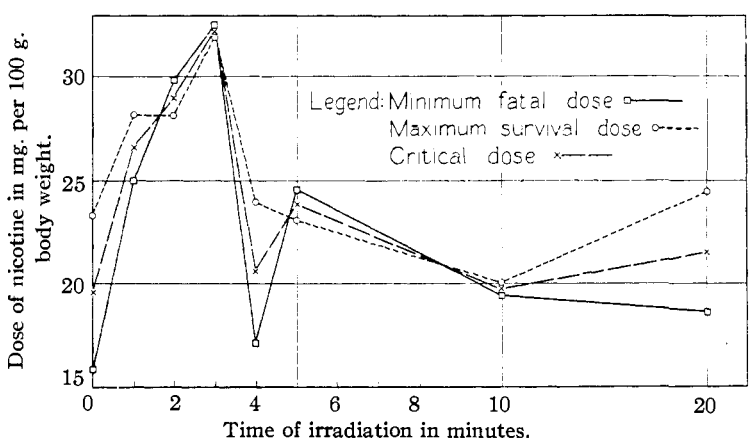

Fig. 2.—Irradiated 1% nicotine solution.

has survived and the lowest dose which has proved fatal. Individual idiosyncrasy is a very disturbing factor in quantitative animal toxicology. Two of the animals used in this work showed resistance to nicotine poisoning so far above the average that the data concerning them were rejected in making out the final diagrams. All doses are calcu-

lated in milligrams per kilogram of body weight. No rat was used twice in these experiments, save after an interval of several weeks. Table III presents data which seem to indicate that rats develop neither any marked tolerance nor increased sensitivity when subjected to "critical" doses at short intervals. Some rats succumbed to the second or third "critical" dose. Others maintained good health and gained rapidly in weight even when dosed to death's door every three or four days. Rat No. 23 survived six "critical" doses, and was pensioned.

Doses of nicotine far below the "critical" amount never fail to produce the violent, characteristic nicotine reaction, even when administered repeatedly at short intervals. Nicotine irradiated for certain periods is less toxic than the raw alkaloid, but is always highly poisonous.

Tables I and II give a condensed summary of the data obtained. Charts 1 and 2 are offered, with some hesitation, as the most nearly valid graphical interpretation which could be devised. They represent the general tendencies revealed by the data, although some minor discrepancies are apparent. In order to obtain parallel graphs for the three functions represented, a larger number of animals would have to be used. While it is suggestive that both charts show a second peak in the "detoxication" curve, this may not be significant. The data obtained for sixty-minute periods of irradiation are not included.

Results

It appears from this work that no reasonable amount of ultraviolet irradiation will destroy the toxicity of nicotine. The earlier observation[2] that the partial detoxication obtained by controlled irradiation is restored by over-irradiation, is confirmed.

Albino rats, when subjected to repeated heavy doses of nicotine, develop neither marked tolerance nor susceptibility.

Summary

Intense ultraviolet irradiation, even for long periods, does not destroy the toxicity of pure nicotine.

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