Anal. after drying to constant weight in high vacuum at 70°. Calcd. for $C_6H_6O_4$: C, 50.70; H, 4.22. Found: C, 51.95, 51.89. H, 6.06, 6.12. Molecular weight determinations could not be made because of the lack of solubility after drying.

Ethylene Maleate.—Thirty-two and five-tenths g. of maleic anhydride (0.33 mole) and 18.6 g. (0.30 mole) of glycol were heated at 195–200° for four hours, and then for some time at 210–215° under reduced pressure. The residue (40 g.) was separated from some insoluble material by solution in warm ethylene chloride and filtration. It was precipitated by cold ether. The product separated as an oil but solidified on standing at 5–10° for two hours. It was a white powder. Most of it melted between 88 and 95°. After drying *in vacuo* it had become insoluble in the common solvents including ethylene chloride and it did not melt below 250°.

Anal. after drying to constant weight in high vacuum at 70°. Calcd. for $C_6H_6O_4$: C, 50.70; H, 4.22. Found: C, 49.87, 49.70; H, 4.36, 4.28. Molecular weight determinations could not be made because of the lack of solubility after drying.

For his kind assistance in the analytical work we here express our thanks to Mr. Wendell H. Taylor.

Summary

The following esters have been prepared: ethylene malonate, ethylene succinate, trimethylene succinate, ethylene adipate, trimethylene adipate, hexamethylene succinate, hexamethylene adipate, ethylene sebacate, trimethylene sebacate, decamethylene succinate, hexamethylene sebacate, decamethylene adipate, decamethylene sebacate, ethylene maleate, ethylene fumarate, ethylene phthalate, trimethylene phthalate, hexamethylene phthalate and decamethylene phthalate. Their molecular weights have been determined. They are all highly polymeric. Their properties are described and their structures are discussed.

WILMINGTON, DELAWARE

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SHARP AND DOHME]

A NEW SERIES OF ANESTHETICS. ACYLANILINE DERIVATIVES

BY WALTER H. HARTUNG AND J. C. MUNCH

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While working in these Laboratories with *m*-aminobutyrophenone, it was found that this compound produced anesthesia in the lips and tongue. Examination revealed further that an aqueous solution of its hydrochloride also was anesthetic to the lips and tongue and when injected subcutaneously into animals. This fact was of sufficient interest to warrant investigation of other bases, and their salts, of the same general type as aminobutyrophenone. Accordingly, a series of acylanilines and acyltoluidines was prepared, a series of anesthetics to which no previous reference has been found.

Table I lists those compounds that have been prepared and established by analysis, for only the first two have been previously recorded; the table also includes preliminary data on the toxicity and anesthetic potency of the

hydrochlorides as compared to cocaine and novocaine. Other pharmacological studies will be published in an appropriate journal.

Higher homologs have been prepared, but because of the insolubility of their salts in water, due to hydrolysis, they have not been analyzed and, hence, are not included here.

TABLE I

COMPOUNDS AND ACTIVITIES

		M. L. D. of HCl salt mg./kg. subcut. to guinea pigs	Duration of anesthesia of 1 mg. applied to rabbit cornea, min.
1	*m*-Aminobutyrophenone	750	20
2	*o*-Aminobutyrophenone	Over 1000	25
3	*m*-Aminovalerophenone	Over 1000	25–90
4	(3-Amino-4-methyl-phenyl) ethyl ketone	Over 1000	3
5	(3-Amino-4-methyl-phenyl) propyl ketone	1000	7–14
6	(3-Amino-4-methylphenyl) *iso*propyl ketone	850	14
7	(3-Amino-4-methylphenyl) *n*-butyl ketone	1000	40
8	(3-Amino-4-methylphenyl) *iso*butyl ketone	500	45
9	Cocaine	60	30
10	Procaine	500	30

It is seen that in order to produce anesthesia at all, the alkyl portion of the ketone must be at least a propyl group, for the ethyl ketone derivative (No. 4) is practically inactive;[1] also, the *iso*propyl ketone (No. 6) is somewhat less active than the *n*-propyl compounds (Nos. 1 and 5). The toxicity is surprisingly low. While in the more highly anesthetic compounds the ratio of minimum effective dose to minimum lethal dose is quite high, yet it has been found that a solution of the salts injected subcutaneously into animals is quite irritating, probably because the salts of these aniline derivatives are so highly hydrolyzed in solution and free acid is formed.

Procedure

All of these compounds can be prepared easily, particularly the toluidine derivatives, according to the following scheme

$$ARCOR \xrightarrow{HNO_3} AR(NO_2)COR \xrightarrow{H_2} AR(NH_2)COR$$

The mixed arylalkyl ketones were prepared from the appropriate acid chloride and benzene or toluene by the Friedel–Crafts reaction. All the ketones used here are described in Beilstein.

The nitro compounds were obtained by adding the ketones slowly to cold agitated fuming nitric acid in the ratio of 75 cc. of acid to a tenth mole of ketone, the temperature being kept below $+10°$. Fuming nitric acid was found most satisfactory in nitrating butyrophenone; it was also discovered that if most of the fumes were first removed by bubbling air through the acid, the nitration of butyrophenone went more smoothly

[1] This compound produces no anesthesia when injected subcutaneously in dogs.

and to greater extent. Hence for all subsequent nitrations fuming acid from which most of the fumes had been expelled was used. After complete addition of the ketone the mixture was allowed to stand in the ice-bath for another minute and then poured into excess ice water. In cases where the resulting nitro ketone was a solid, it was filtered off, washed and recrystallized from an appropriate medium; when liquid, it was quickly drawn off in a separatory funnel, washed with bicarbonate solution to remove adhering acid, dried and distilled. The yields varied from 60 to 80%.

The position taken by the entering nitro group was proved by oxidation to the aromatic acid, which was then identified.

The reduction proceeded very smoothly by dissolving the nitro ketone in an equal weight of acetic acid, adding an equal weight of mossy tin, warming and slowly adding sufficient concentrated hydrochloric acid to dissolve all of the metal. The amine was isolated by adding excess alkali, extracting with ether, drying and distilling. The yield of the amine was from 60 to 80% based on the nitro compound.

The hydrochloride salts were prepared by adding to an ethereal solution of the free base an absolute alcoholic solution of hydrogen chloride. The salt usually came down immediately and could be recrystallized from a concentrated solution in absolute alcohol; the mother liquors, however, retained the greater part of the salt in solution; it could be forced out by dilution with ether.

Experimental

***m*-Aminobutyrophenone and *o*-aminobutyrophenone,** with their corresponding intermediates, have been described by Morgan and Hickenbottom.[2]

Table II contains a tabular summary of the data concerning the other intermediate nitro compounds, and in some cases their semicarbazones.

TABLE II

NITRO COMPOUNDS

Ketone	Recryst. from	M. p. or b. p., °C.
m-Nitrovalerophenone	Liquid	145–150 (3 mm.)
(3-Nitro-4-methylphenyl) ethyl[a]	Dil. alc.	51
(3-Nitro-4-methylphenyl) propyl	Toluene	77.5
(3-Nitro-4-methylphenyl) *iso*propyl	Ligroin	41.0
(3-Nitro-4-methylphenyl) *n*-butyl	Ligroin	48.0
(3-Nitro-4-methylphenyl) *iso*butyl	Ligroin	54.5

The nitro ketones were oxidized with dilute nitric acid and in each case gave *m*-nitrobenzoic acid or the *p*-methyl-*m*-nitrobenzoic acid.

[a] This compound is described in Beilstein, 4th ed., Vol. VII, p. 318.

[2] Morgan and Hickenbottom, *J. Chem. Soc.*, 119, 1879 (1921).

TABLE II (*Concluded*)

Nitrogen analyses (Kjeldahl) Formula	Calcd., %	Found, %	M. p., °C.	Semicarbazone Formula	Nitrogen analyses[a] Calcd., %	Found, %
$C_{11}H_{13}O_3N$	6.76	6.48 6.55 6.80	...	.....	...	...
.....	..	....	...	.....	...	...
$C_{11}H_{13}O_3N$	6.76	6.51 6.92	215–216	$C_{12}H_{16}O_3N_4$	10.60	10.14 11.06
$C_{11}H_{13}O_3N$	6.76	6.74 6.87	...	.....	...	...
$C_{12}H_{15}O_3N$	6.34	6.16 6.36	210	$C_{13}H_{18}O_3N_4$	10.07	10.08
$C_{12}H_{15}O_3N$	6.34	6.32 6.18	214	$C_{13}H_{18}O_3N_4$	10.07	10.24

[a] The available nitrogen was determined according to the method of Rimini (*Z. anal. Chem.*, **47**, 645 (1908)).

Table III gives in tabular form the data for the amino compounds and those derivatives that have been prepared.

TABLE III

DATA ON AMINO COMPOUNDS

Ketone, ( ) = (3-amino-4-methylphenyl)	Free base B. p., °C.	Free base M. p., °C.	Acetamino deriv. M. p., °C.	Hydrochloride M. p., °C.
1 *m*-Aminovalerophenone	160–163 (3 mm.)	Liquid	[a]	155.5–156.0[b]
2 ( ) ethyl	190–195 (20 mm.)	85.5–86.0[c]	131.5[c,d]	204 (dec.)
3 ( ) propyl	150–165 (3 mm.)	69.0[c]	130.5	168
4 ( ) *iso*propyl	150–153 (3 mm.)	Liquid	...	167.5[e]
5 ( ) *n*-butyl	170–185 (3 mm.)	61.0[f]	93–94[g]	91.5–93.0[h]
6 ( ) *iso*butyl	165–170 (3 mm.)	Liquid	117.5[g]	142.5[i]

[a] The acetyl derivative of *m*-aminovalerophenone was not analyzed as such; however, with permanganate it was oxidized to an acid which melted at 237°, identified as *m*-acetaminobenzoic acid. [b] This salt is purified with difficulty. It hydrolyzed almost completely in water and was best recrystallized from anhydrous *iso*propyl alcohol. [c] Recrystallized from toluene. [d] Formed a semicarbazone (not analyzed) which melted with decomposition at 203.5°. [e] Prepared by adding an absolute alcoholic solution of hydrogen chloride to an absolute ethereal solution of the free base. The salt could be recrystallized from anhydrous *iso*propyl alcohol or from toluene. [f] Recrystallized from ligroin. [g] Recrystallized from benzene–ligroin mixture (1:2). [h] Recrystallized from xylene. The salt is not so well defined as its lower homologs. Chlorine and nitrogen determinations were unsatisfactory. It did not dissolve completely in water without further addition of acid. [i] Dissolves in water with slight turbidity.

NITROGEN ANALYSES (KJELDAHL) OF FREE BASE AND ACETAMINO DERIVATIVE

	Free base Formula	Calcd., %	Found, %	Acetamino derivative Formula	Calcd., %	Found, %
1	$C_{11}H_{15}ON$	..	..	.....	..	..
2	$C_{10}H_{13}ON$	8.59	8.75	$C_{12}H_{15}O_2N$	6.83	6.58
3	$C_{11}H_{15}ON$	7.90	7.90	$C_{13}H_{17}O_2N$	6.39	6.53 6.41
4	$C_{11}H_{15}ON$	7.90	7.78 7.77	.....	..	..
5	$C_{12}H_{17}ON$	7.33	7.31 6.91	$C_{14}H_{19}O_2N$	6.00	5.83
6	$C_{12}H_{17}ON$	7.33	7.24 7.42	$C_{14}H_{19}O_2N$	6.00	5.87

TABLE III (*Concluded*)

ANALYSES OF HYDROCHLORIDE

	Formula	Chlorine (as AgCl) Calcd., %	Chlorine (as AgCl) Found, %	Nitrogen (Kjeldahl) Calcd., %	Nitrogen (Kjeldahl) Found, %
1	$C_{11}H_{15}ON\cdot HCl$	16.60	16.15 16.20	6.57	6.71
2	$C_{10}H_{13}ON\cdot HCl$	17.76	17.43 17.42	7.01	6.73 6.72
3	$C_{11}H_{15}ON\cdot HCl$	16.60	16.63 16.67	..	..
4	$C_{11}H_{15}ON\cdot HCl$	16.60	16.55 16.37	..	..
5	$C_{12}H_{17}ON\cdot HCl$	...	[a]	..	..
6	$C_{12}H_{17}ON\cdot HCl$	15.58	15.05 15.37	..	..

[a] Chlorine and nitrogen determinations were unsatisfactory.

Summary

1. Acylanilines and acyltoluidines have anesthetic properties, particularly their hydrochlorides, if there is at least a butyrophenone skeleton.

2. Data concerning eight such compounds are given.

3. Six of the eight amines are new and are described together with their intermediates and, in some cases, their derivatives.

BALTIMORE, MARYLAND

[CONTRIBUTION FROM THE INSECTICIDE DIVISION, BUREAU OF CHEMISTRY AND SOILS]

ROTENONE. I. REDUCTION PRODUCTS OF ROTENONE

BY F. B. LAFORGE AND L. E. SMITH

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Rotenone, the active insecticidal principle of *Derris elliptica*, has been the subject of numerous investigations in recent years.[1] As it is perhaps natural to expect in the case of such a complicated compound, the published chemical articles contain numerous errors, corrections and retractions. It is indeed only in the past year that the empirical formula of rotenone has been established with certainty.

A large share of what is known of the chemistry of the compound has been contributed by the Japanese. Nagai[2] seems to have been the first to isolate it in a pure state. He gave it its present name and showed that it contained a keto group. Ishikawa[3] found that the compound was optically active, and Kariyone[4] showed the presence of methoxyl and an unsaturated bond, and obtained tubaic acid of the formula $C_{12}H_{12}O_4$

[1] The Insecticide Division of the Bureau of Chemistry and Soils has collected and abstracted over 250 articles on *Derris*, and a publication entitled "A Bibliography of *Derris* (*Deguelia*) Species Used as Insecticides," by Dr. R. C. Roark, will be issued shortly in multigraphed form.

[2] Nagai, *J. Tokyo Chem. Soc.*, **23**, 740 (1902).

[3] Ishikawa, *Tokyo Medical J.*, 31, No. 4 (1917).

[4] Kariyone and Atsumi, *J. Pharm. Soc.* (Japan), No. 491, 10 (1923); Kariyone, Kimura and Kondo, *ibid.*, No. 514, 1049 (1924); Kariyone and Kondo, *ibid.*, No. 518, 376 (1925).