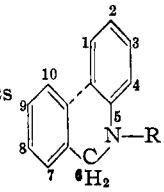
TABLE I

BASICALLY SUBSTITUTED 5,6-DIHYDROPHENANTHRIDINES



No.	R	Yield, %	M. p., °C.		Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	$-CH_2CH_2N(CH_3)_2$[a]	50	179	(Dimaleate)	$C_{25}H_{28}N_2O_8$	61.98	61.99	5.82	5.63	5.78	5.69
1	$-CH_2CH_2N(CH_3)_2$	50	183–184	(Dipicrate)	$C_{29}H_{26}N_8O_{14}$	49.02	49.01	3.68	3.66		
2	$-CH_2CH_2N(C_2H_5)_2$	55	158–159	(Dipicrate)	$C_{31}H_{30}N_8O_{14}$	50.41	50.29	4.09	4.04	15.16	14.96
3	$-CH_2CH_2NC_5H_{10}$	45	236–238	(Dihydrochloride)	$C_{20}H_{26}N_2Cl_2$[b]					7.66	7.62
3	$-CH_2CH_2NC_5H_{10}$	45	157–158	(Dimaleate)	$C_{28}H_{23}N_2O_8$	64.11	64.34	6.15	5.85	5.34	5.06
4	$-CH_2CH_2NC_4H_8O$	58	189–191	(Monohydrochloride)	$C_{19}H_{23}N_2OCl$	68.98	68.84	7.00	6.86	8.46	8.41
4	$-CH_2CH_2NC_4H_8O$	58	248	(Dihydrochloride)	$C_{19}H_{24}N_2OCl_2$[c]	62.13	61.98	6.59	6.77	7.63	7.62

[a] This compound has been reported by VIAUD, without any chemical data, *Prod. Pharmac.*, **2**, 53 (1947), to have no antihistaminic activity *in vitro* or *in vivo*. [b] Calcd.: Cl, 19.42. Found: Cl, 19.41. [c] Calcd.: Cl, 19.87. Found: Cl, 19.81.

replaced by a dialkylaminoalkyl group (see Table I).

5,6-Dihydrophenanthridine, the starting material, was prepared according to Ritchie[3] by reduction of phenanthridine with tin and concentrated hydrochloric acid and also (for the first time) by catalytic reduction using Raney nickel in dry ethanol. The latter method gave quantitative yields. 5,6-Dihydrophenanthridine as well as a number of substituted 5,6-dihydrophenanthridines were condensed with different substituted aminoethyl halides in the presence of sodamide using toluene as the solvent to give the desired compounds. The reaction mixtures were worked up according to the method previously described.[4]

The following four compounds (Table I) are reported at the present time. Compounds, 1, 3 and 4 have been tested in our Pharmacology Department (Dr. N. Ercoli, director) for their inhibitory action on contractions of the isolated guinea pig intestine induced by histamine. Compounds 1 and 4 were found to be completely inactive while compound 3 had very slight activity. (The doses required for inhibition were higher than 20 gamma/cc.)

Inspection of the generic structure of these compounds (Table I) reveals that they differ from the Antergan type only in the existence of the linkage represented by the dotted line. Whereas ring closures of this type can result in compounds of increased activity in the field of antispasmodics (*e. g.*, β-diethylaminoethyl diphenylacetate, Trasentine → β-diethylaminoethyl fluorene-9-carboxylate, Pavatrine[5]), it would seem that the same does *not* hold true in the case of antihistaminics. The loss of activity which occurs if the diphenylmethyl group of Benadryl is replaced by 9-fluorenyl[6] could be mentioned as an additional example.

The compounds, 1, 3 and 4 were also found to have no trypanocidal activity when tested in maximum tolerated dosage against *Trypanosoma equiperdum* in mice.

The author wishes to thank Dr. H. M. Wuest for his interest and encouragement.

(3) Ritchie, *J. Proc. Royal Soc. N. S. Wales*, **78**, 182 (1945).

(4) Huttrer, Djerassi, Beears, Mayer and Scholz, THIS JOURNAL, **68**, 1999 (1946).

(5) Burtner and Cusic, *ibid.*, **65**, 262, 1582 (1943).

(6) Rieveschl, A. A. A. S. Symposium on Histamine Antagonists, Gibson Island, Md., 1945.

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Some Reactions of the Trifluoromethyl Group in the Benzotrifluoride Series. I. Hydrolysis

BY GENE M. LE FAVE[1]

The inertness of the trifluoromethyl (CF_3–) group in benzotrifluoride and many of its derivatives is well-known.[2] However, it has also been observed that concentrated hydrobromic acid,[3] sodium hydroxide,[4] and 60–80% sulfuric acid[5,6] can bring about the hydrolysis of this group in benzotrifluoride or certain of its derivatives.

While attempting to sulfonate benzotrifluoride with concentrated sulfuric acid, hydrolysis occurred resulting in excellent yields of benzoic acid rather than the expected *m*-sulfonic acid of benzotrifluoride. In order to ascertain the applicability of this reaction, the substituted benzoic acids listed in Table I were prepared from the corresponding benzotrifluorides by treatment with approximately 100% sulfuric acid followed by hydrolysis of the reaction product.

(1) J. I. Holcomb Research Fellow, 1948–1950.

(2) See, for example, Swarts, *Bull. acad. roy. med. Belg.*, **8**, 343 (1922).

(3) Swarts, *ibid.*, **6**, 389 (1920).

(4) Jones, THIS JOURNAL, **69**, 2346 (1947).

(5) McBee and Frederick, *ibid.*, **71**, 1490 (1949).

(6) E. Wertyporoch, *Ann.*, **493**, 1536 (1932).

TABLE I

PHYSICAL AND ANALYTICAL DATA FOR SUBSTITUTED BENZOIC ACIDS

R	M. p., °C.[a]	Yield, %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
H-	120–121	94.0	68.85	68.65	4.90	4.88
p-Chloro-	237–238	93.9	53.79	53.66	3.19	3.41
m-Chloro-	154–156	95.6	53.79	53.70	3.19	3.29
o-Chloro-	140–141	95.0	53.79	53.73	3.19	3.32
m-Nitro-	139–140	70.6	50.33	50.39	3.01	3.23
m-Amino-	173–174	72.2	61.32	61.41	5.15	5.01
m-Hydroxy-	Ca. 200	79.2	60.81	60.69	4.03	3.81
2-Chloro-5-nitro-	165–166	83.0	41.52	41.71	1.99	2.11
3-Nitro-4-chloro-	180–182	87.3	41.52	41.80	1.99	2.17

[a] All melting points are uncorrected.

Trifluoromethylaryls.—With the exception of *m*-hydroxybenzotrifluoride, all trifluoromethylaryls were obtained through the courtesy of the Hooker Electrochemical Company and were used without further purification. The *m*-hydroxybenzotrifluoride was easily prepared by conversion of *m*-aminobenzotrifluoride through the diazonium transformation.

Hydrolysis of Benzotrifluoride.—A mixture of 36.5 g. (0.25 mole) of benzotrifluoride and 28 g. of 100% sulfuric acid was heated cautiously until the evolution of hydrogen fluoride began as could be detected by its etching of the glass walls of the reaction vessel. The heat source then was withdrawn and reapplied intermittently until the benzotrifluoride layer disappeared. After the evolution of hydrogen fluoride had ceased, the reaction mixture was poured, with stirring, into 1 l. of ice-water, the resultant precipitate sucked dry, and finally washed thoroughly with cold water. The crude product was purified through its sodium salt using Norit, and the free acid was recrystallized from hot water.[7] This procedure is typical for the series investigated.

Using 80% sulfuric acid the starting material is recovered unchanged after refluxing for several hours, while with 20–30% fuming sulfuric acid small amounts of sulfones and sulfonic acids are formed. Prolonged or excessive heating gives rise to tars. Occasionally it is difficult to initiate the reaction. In these cases, the addition of small amounts of 20–30% oleum portionwise is effective. *m*-Nitrobenzotrifluoride in particular is subject to this difficulty and with it 15% oleum must be used for the reaction to take place.

Since 65% fuming sulfuric acid is required to effect satisfactory sulfonation of trifluoromethylaryls,[8] probably because of the strong inductive effect of the meta-directing CF_3– group, it is apparent that the rate of sulfonation is far slower than attack of the CF_3– group. This competitive situation accounts for the appearance of sulfur-containing by-products only at the higher concentrations of sulfur trioxide.

Acknowledgments.—The author expresses appreciation to Dr. K. M. Seymour and Mr. P. G. Scheurer for their helpful suggestions.

(7) Only traces of fluorine and no sulfur or chlorine could be detected by the usual qualitative tests.

(8) Zitscher, U. S. Patent 2,141,893 (Dec. 27, 1938).

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Steroidal Sapogenins. 174. 17-Hydroxy-20-ketopregnanes from Steroidal Sapogenins

BY RUSSELL E. MARKER[1]

In the synthesis of cortisone and its analogs the introduction of a hydroxyl group on the C-17 carbon of the pregnanes is quite complicated and involved leading to low yields. A new and very simple reaction has now been found in which this can be accomplished in high yield from naturally occurring steroidal sapogenins containing ketonic groups on C-12. As sapogenins occur widely distributed in nature, they now present a large potential source of material for this synthesis.

Treatment of the oxidation product of the diacetate of pseudobotogenin with a dilute methanolic solution of potassium carbonate gives an immediate precipitation of the acetate of 16-dehydropregnen-5-ol-3-dione-12,20 removing it from further action with the alkaline solution.[2] A small amount of a secondary product resulting from this reaction was further studied. It has now been found that this new material is the major product of the hydrolysis if alcoholic potassium hydroxide is employed instead of dilute methanolic potassium carbonate. In this case the product does not precipitate during the reaction. The same product was obtained when 16-dehydropregnen-5-ol-3-dione-12,20 acetate was treated with alcoholic potassium hydroxide. The new product analyzes for a pregnendioldione, containing two hydroxyl groups, only one of which acetylates with boiling acetic anhydride. It is recovered unchanged when shaken with hydrogen and palladium catalyst, showing that it does not contain the conjugated double bond system. These reactions indicate that the new hydroxyl group was introduced in the 17-position as a tertiary carbinol. A secondary hydroxyl group on C-16 would readily form an acetate under the conditions employed. Whether the formation of a 17-hydroxyl group in the conjugated ketone system by alkali is characteristic only of pregnenes containing a ketone group in the beta-position at C-12 has not been determined but present indications are that the addition of water to the 16-double bond is influenced by the presence of a C-12 ketone in the molecule. In the strong alkaline hydrolysis of the oxidation product, the first product formed is probably the expected 16-dehydropregnene which then hydrates under the influence of alkali to give the 17-hydroxy compound.

Because of the significance of this reaction in the preparation of cortisone or its analogs from steroidal sapogenins, it has been applied to kammogenin, another possible starting material for the antiarthritic hormone. This sapogenin is now known to occur in many plants and new sources for it and the other steroidal sapogenins will be reported at a later date.

Pseudokammogenin triacetate[3] was oxidized as described for pseudobotogenin diacetate.[2] Treatment of the oxidation product with alcoholic potassium hydroxide gave a diketopregnene containing three hydroxyl groups, only two of which are acetylatable. The product cannot be

(1) Present address: Hotel Geneve, Mexico City, Mexico.

(2) Marker, THIS JOURNAL, 71, 2656 (1949).

(3) Marker and Lopez, *ibid.*, 69, 2373, 2375 (1947).