Medicinal Derivatives of *p*-Tertiarybutylbenzoic Acid^{*,†}

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Fifteen esters of *p*-tertiarybutylbenzoic acid with amino alcohols were synthesized, and their physical and chemical constants were determined. The rearrangement of the corresponding amide to β -ethylaminoethyl*p*-tertiarybutylbenzoate was shown to proceed with greater ease than the procedure previously described for similar amides obtained from secondary amino alcohols.

THERE have been several papers published from this College reporting derivatives of a substituted benzoic acid, namely, p-isopropyl benzoic acid, synthesized in the hope of producing useful medicinal or pharmaceutical products. Interest in a newly available derivative of benzoic acid can thus be readily understood.

p-Tertiarybutylbenzoic acid,¹ $C_{11}H_{14}O_2$, (mol. wt. 178.11) was apparently produced for the first time by Pahl (1) in 1884. It is a white, crystalline solid and has a reported low toxicity. Although this acid has been known for many years, no reports have been published on any of its derivatives which may have medicinal or pharmaceutical value.

The *p*-tertiarybutylbenzoic acid used in this investigation needed no additional purification before use. It was a colorless, crystalline solid with a melting point of $160-161^{\circ}$.

As one phase of this study, a series of esters of amino alcohols containing from one to five methylene groups in the alkyl portion of the molecule were synthesized. Pharmacological studies have been conducted on these compounds for use as local anesthetics and antispasmodics (9).

The Schotten-Baumann reaction was chosen as the most adaptable reaction for esterification of the amino alcohols. The preparation of the acid chloride was carried out by using a large excess of thionyl chloride. The thionyl chloride was purified by the procedure recommended by Fieser (2). Purification of the acid chloride by distillation had to be discontinued because of decomposition on heating to temperatures sufficient for distillation. Thus, it was felt that removal of the excess thionyl chloride by distillation was sufficient purification at this point of the synthesis.

The amino alcohols used in this study were obtained either commercially or by synthesis. The following were synthesized in this laboratory: diethylaminomethanol, diethylamino-*n*butanol, piperidinoethanol, morpholinoethanol, and 2-dibenzylaminoethanol.

EXPERIMENTAL

p-Tertiary-Butyl-Benzoyl Chloride.-One hundred grams (0.56 mole) of p-tertiarybutylbenzoic acid was refluxed for six hours with 150 Gm. (1.2 mole) of thionyl chloride. After the reaction was complete, a clear amber-colored liquid remained in the flask. The excess thionyl chloride was removed by distillation under reduced pressure, using a water aspirator at approximately 35 mm. The acid chloride boiled at 266-268° with decomposition. In order to establish definitely that *p*-tertiarybutylbenzoyl chloride had been synthesized, p-tertiarybutylbenzamide was prepared by adding 5 Gm. (0.025 mole) of acid chloride dropwise to 10 cc. of 28% ammonium hydroxide; the reaction was immediate and vigorous. The white, solid amide formed was filtered off and washed with water until no odor of ammonia remained; it was then crystallized from hot ethanol. The crystals were dried at 100° in an oven for two hours. The melting point was determined as $170-171^{\circ}$, a value corresponding to that reported by Kelbe and Pfeiffer (3).

Esters of p-Tertiarybutylbenzoic Acid.—All of the esters in this study, with the exception of 2-dibenzylaminoethyl - p - tertiarybutylbenzoate and methyl-p-tertiarybutylbenzoate, were prepared by methods which can be typified by the preparation of β -dimethylaminoethyl-p-tertiarybutylbenzoate. Thirty-six grams (0.41 mole) of *B*-dimethylaminoethyl alcohol was reacted with 79 Gm. (0.39 mole) of *p*-tertiarybutylbenzoyl chloride in the presence of 200 cc. of 10% aqueous sodium hydroxide solution. The reaction was immediate and external cooling was necessary; the solution was agitated by an electric stirrer. After the esterification was complete (approximately thirty minutes) the oily ester separated and was removed from the mixture. All excess alkali was removed by washing with water. The ester was dried over anhydrous sodium sulfate for twelve hours, and was then fractionated under reduced pressure. Physical constants of the esters are recorded in Table I.

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¹ This acid is currently being produced by the Shell Development Co, from petroleum raw products and is available in sufficient quantities for laboratory and commercial use.

Radicals	d_{2j}^{20}	72 ²⁰	B. P., °C. at 1 mm.	M. P., °C. (Corr.)	Molar Caled.	Refraction- Found	Vield, %
Diethvlaminomethvla				55 - 56			56.5
β-Diethylaminoethyl	0.9961	1.5040	153 - 154		83.02	87.48	91.4
β-Dimethylaminoethyl	0.9949	1.5050	143 - 144		73.73	74.32	64.7
γ -Diethylaminopropyl	0.9666	1.4970	157 - 158		87.66	88.14	74.5
β -Diethylaminopropyl	0.9776	1.5116	144-145		87.67	89.23	38
Diethylamino-n-butyl	0.9891	1.5082	$142 - 143^{d}$		92.23	91.87	89
1-Diethylamino-4-pentyl	0.9965	1.5093	170-171		96.96	95.61	41.5
Piperidinoethyl	1.0180	1.5149	158 - 160		85.67	85.67	79.4
Morpholinoethyl	1.0667	1.5210	167 - 168		82.78	83.08	61
2-Dibenzylaminoethyl	1.0409	1.5508	255 (dec.)		123.4	122.8	73
β -Ethylaminoethyl	1.0417	1.5240	158 - 160		73.59	73.16	76
N-methyl-diethylamino-bis	1.0681	1.5339	273 (dec.)		127.65	127.90	50
N-n-Butyl-diethylamino-bis	1.0440	1.5221	190 (dec.)		141.70	142.81	61.2
N-phenyl-diethylamino-bis ^b				104 - 105		• • • •	12.5
Methyl ^c	1.0113	1.5102	105106*		56.03	56.83	95

TABLE I.--ESTERS OF *p*-TERTIARYBUTYLBENZOIC ACID

^a Nitrogen determination, % (Kjeldahl): Calcd., 5.31. Found, 5.61.
^b Nitrogen determination, % (Kjeldahl): Calcd., 2.78. Found, 2.82.
^c Ester value: Calcd., 192.1. Found, 192.4.

^d At 3 mm. pressure. ^e At 2 mm. pressure.

Methyl-p-tertiarybutylbenzoate was prepared by the conventional method of esterification between an alcohol and acid, using sulfuric acid as a catalyst. 2-Dibenzylaminoethyl-p-tertiarybutylbenzoate was prepared by dissolving 25 Gm. (0.11 mole) of 2-dibenzylaminoethanol in 175 cc. of pyridine, adding 20 Gm. (0.11 mole) of p-tertiarybutylbenzoyl chloride, and stirring with an electric stirrer until solution was effected. The mixture was then refluxed for five hours and was poured into 1 L. of water. This aqueous mixture was extracted with 200 cc. of diethyl ether. After separation the ethereal solution was treated with 100 cc. of 10% hydrochloric acid, separated, and shaken with 50 cc. of 5% sodium carbonate solution. The ether was evaporated, and the ester was fractionated under reduced pressure. Physical constants are shown in Table I.

Amino Alcohols.-Diethylaminomethyl alcohol was prepared by the method of Henry (4). Diethylamino-n-butyl alcohol was synthesized by the procedure of Starr and Hixon (5) in which tetramethylene chlorohydrin was first prepared from tetrahydrofuran. The chlorohydrin was then condensed with diethylamine. Piperidinoethyl alcohol and morpholinoethyl alcohol were prepared by

Equimolar quantities of the similar methods. amine and ethylene chlorohydrin were refluxed for two hours on a steam bath. The mixture was contained in a two-necked flask and the ethylene chlorohydrin was added to 300 cc. of 30% aqueous sodium hydroxide solution and stirred vigorously with an electric stirrer. The amino alcohol, which separated as an oily layer, was extracted from the aqueous mixture with 200 cc. of diethyl ether. The ether was evaporated and the alcohol was fractionated under reduced pressure. The 2-dibenzylaminoethyl alcohol was synthesized by the method of Gump and Nikawitz (6).

Salts of the Esters .- The hydrochlorides were prepared by passing dry hydrogen chloride into the respective esters, using diethyl ether as a solvent. The resulting solid hydrochlorides were purified by crystallization from ethanol. The per cent of chlorine in each compound was determined gravimetrically by the silver method and was compared to the theoretical value (Table II). The oxalates and the maleate were formed by adding ethereal solutions of the esters to saturated solutions of the respective acids in diethyl ether. The solids were crystallized from hot ethanol.

TABLE II	-SALTS (OF ESTERS	OF <i>p</i> -TERTIARYBUTYLBENZOIC ACI	D

	M. P.¢	Nitrog	en.a %	Chlori	ne,b %	Yield,
Radicals	°C.	Caled.	Found	Calcd.	Found	%
β -Diethylaminoethyl HCl	154 - 155	4.47	4.42	11.31	11.35	66
β-Dimethylaminoethyl HCl	183–184	4.91	5.01	12.41	12.47	73.4
γ -Diethylaminopropyl HCl	188-189	4.27	3.91	10.82	10.77	59.4
β-Diethylaminopropyl HCl	1 79–18 0	4.27	4.24	10.82	10.87	72.4
Diethylamino-n-butyl HCl	79–98	4.10	3.90	10.39	10.34	80
1-Diethylamino-4-pentyl Oxalate	127 - 129	3.14	3.16			78
Piperidinoethyl HCl	193–194	4.29	4.17	10.88	11.20	71
Morpholinoethyl HCl	195-196	4.27	4.15	10.82	11.13	70
2-Dibenzylaminoethyl HCl	181-182	3.19	3.09	8.07	7.91	62.5
β-Ethylaminoethyl HCl	178–179	4.89	4.81	12.42	12.03	41.5
N-methyl-diethylamino-bis maleate	168169	2.52	2.53			79.4
N-n-butyl-diethylamino-bis oxalate	121 - 122	2.45	2.51			25.2

By the semimicro Kjeldahl method. By the gravimetric method.

Corrected melting points.

Rearrangement of N- β -Hydroxyethyl-p-Tertiarybutylbenzamide to β -Ethylaminoethyl-p-tertiarybutylbenzoate .-- It has been shown by Hancock and Cope (7) that an amide is formed when secondary amino alcohols are used in the Schotten-Baumann reaction. This fact was confirmed by Reasenberg and Goldberg (8) and was found to hold true in this instance:

$$(C_{4}H_{9})C_{6}H_{4}COCl + HOCH_{2}CH_{2}NH(C_{2}H_{5})$$

$$\longrightarrow (C_{4}H_{9})-C_{6}H_{4}CON(C_{2}H_{5})-CH_{2}CH_{2}OH$$

$$\stackrel{heat}{\longrightarrow} (C_{4}H_{9})-C_{6}H_{4}COOCH_{2}CH_{2}NH-(C_{2}H_{5})$$

After the reaction in which the amide was formed, the tertiary nitrogen was shown to be neutral when it failed to react with strong mineral and organic acids to form salts.

In order to effect rearrangement of the amide to the amine by the method of Hancock and Cope (7), the amide was treated with concentrated hydrochloric acid and heated for five minutes; it was then poured into water and the excess acid was neutralized with ammonium hydroxide. After this treatment, an oil separated from the mixture and was isolated. The oil readily formed both an oxalate and a hydrochloride.

In an attempt to purify the amide by vacuum distillation, it was found that complete conversion to the amine took place, confirmed by the melting point. Therefore heat alone is sufficient to rearrange the molecule, and no strong mineral acid is required.

SUMMARY AND CONCLUSIONS

A number of esters of *p*-tertiarybutylbenzoic acid have been synthesized. With the exception of methyl-p-tertiarybutylbenzoate, all of the esters contained an amino alcohol as a component part of the molecule. All liquid esters were converted to solids by formation of the respective hydrochloride, oxalate, or maleate.

The following physical and chemical constants were determined for the compounds: boiling point, specific gravity, refractive index, and molar refraction for the liquids; melting point, nitrogen determination, and chloride determination for the solids.

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Solution Time of Hypodermic Tablets*

By E. L. WALTERS, G. L. CHRISTENSON, and H. R. KREIDER, Jr.

An apparatus for determining dissolution rates of soluble tablets is described. The importance of control of agitation in dissolution rate determination is shown. The instrument described can be closely controlled in this factor, and dissolution rate results achieved with it are more accurate and reproducible than those obtainable when operator judgment governs inversion rate.

TUMEROUS papers have appeared in the literature reporting different methods of determining the disintegration time of compressed tablets, sugar coated tablets, and enteric coated tablets. Pieces of apparatus have been described which can be used for this purpose (1-4), as well as for many others.

A large-scale study has been carried out by a Subcommittee of the Combined Contact Committee of the A. D. M. A. and A. PH. M. A. and, the Stoll-Gershberg apparatus has now been selected as the official U.S.P. method. This study included only compressed tablets which disintegrate in the presence of water or artificial gastric juice and yield granules of the original mixture, before compression, sufficiently small to pass through a No. 10 screen. It is ob-

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