

crepancy is of course due to his using a slightly lower value of  $\alpha_0$ .

It may be pointed out that our  $P_{2\mu}$  values calculated from the different equations, (1), (7), (9) or (10), the last being not included in the table, show excellent agreement among themselves. Equation (7), (9) or (10) though essentially the same equation, does not, however, give exactly identical values because of statistical treatment of data to obtain the limiting slopes.

Smith has obtained agreement in such cases where  $\epsilon_1 \neq n_1^2$  by applying a number of simplified equations. It can be shown easily by an analysis of the above data on *A*, *B* and *C* that the agreement is fortuitous. For example, we cannot neglect *B* for aniline in dioxane because *B* is about 4.7% of  $P_2$  and so, if we neglect *B* and put the atomic polarization,  $P_A = 0.05R$  the errors cancel each other.

In another case, he makes the simplification

$$P_{2\mu} = \frac{3M_2\psi_1}{(\epsilon_1 + 2)(n_1^2 + 2)} \left[ \frac{\partial(\epsilon - n^2)}{\partial w_2} \right], \quad (12)$$

and obtains fairly good agreement. Comparing this with our complete equation (equ. 7) it is seen that he is neglecting *B* and to compensate for that he is increasing the *A* term by dividing by  $(\epsilon_1 + 2)(n_1^2 + 2)$  instead of with  $(\epsilon_1 + 2)^2$  and is decreasing the *C* term by the same procedure which also increases  $P_{2\mu}$  to a smaller extent. It just happens that in this case these two increments nearly cancel the error made by neglecting *B*.

#### Question of Solution Density Measurements.

The attractive feature of the Guggenheim-Smith equation, however, could be retained without perceptibly sacrificing accuracy. This can be done by neglecting  $\beta_0/d_1$ , in comparison to unity in the *B*-term in equation (7). In such a case no solution density measurements are required and the equation takes the form

$$P_{2\mu} \approx \frac{3M_2(\epsilon_1 - n_1^2)}{d_1(\epsilon_1 + 2)(n_1^2 + 2)} + \frac{3M_2\alpha_0}{d_1(\epsilon_1 + 2)^2} - \frac{3M_2\gamma_0}{d_1(n_1^2 + 2)^2} \quad (13)$$

The error by such approximation would hardly exceed 1% under very unfavorable conditions and would usually be less than 0.2 unit of orientation polarization even in solvents like dioxane. At any event this simplified *B*-term can be calculated for any solvent and the effect of neglecting  $\beta_0$  can be easily judged because  $\beta_0$  generally lies between  $-0.3$  to  $+0.3$ . In case it seems rather risky to neglect  $\beta_0$ , it is safe to take density measurement correct to only 1% for one solution and calculate  $(d - d_1)/w_2$  and use the same value for  $\beta_0$ . The error would be hardly appreciable.

**Conclusions.**—From the above discussion it is now possible to conclude that for calculations of  $\propto p_2$  it is best to directly employ equation (1) as suggested by Palit and Banerjee,<sup>4</sup> the value of  $(\partial p/\partial w_2)_0$  being obtained by least square analysis by expressing  $p$  in the form,  $p = p_1 + bw_2 + cw_2^2$ .

For obtaining  $P_{2\mu}$  by simultaneous measurement of dielectric constant, refractive index and density it is advisable to use the complete equation in either of the forms of equation (6) or equation (7)

or equation (10), the first one being a little simpler in computation. In case it is intended to avoid solution density measurements, equation (13) should be used, which would usually give results within a few tenths of a unit. However, if great precision is aimed at without series of solution density measurements, it is advisable to take one solution of concentration nearabout the mean of the whole range studied and to measure its density correct to only 1% and therefrom to calculate  $(d - d_1)/w_2$  which is used as  $\beta_0$  in equation (7). The difference in the calculated  $P_{2\mu}$  would be hardly perceptible. Another method of making a fairly good estimate of  $\beta_0$  from refractive measurements alone would be to use equation (4),  $\propto p_2$  being known from bond refraction tables; by the same principle, if  $\beta_0$  is determined in one solvent it is possible to calculate its value in other solvents by using this equation.

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## 2-Methyl-2-monoalkylaminopropyl Aromatic Heterocyclic Carboxylates<sup>1</sup>

BY J. STANTON PIERCE AND HENRY A. RUTTER, JR.

RECEIVED APRIL 16, 1952

Esters of 2-amino-2-monoalkylamino-1-propanols with alkoxybenzoic acids,<sup>2</sup> alkoxyinnamic acids, hydrocinnamic acids, alkoxyhydrocinnamic acids<sup>3</sup> and *p*-aminobenzoic acids<sup>4</sup> have been prepared for use as local anesthetics. Since several thiophene, furan and pyridine analogs of some benzene-containing local anesthetics have been found to have some activity,<sup>5</sup> it seemed advisable to prepare a few esters of 2-methyl-2-monoalkylamino-1-propanols with furoic acid, nicotinic acid and 2-thiophenecarboxylic acid.

2-Methyl-2-monoalkylaminopropyl furoates were prepared by condensing the alkanolamines with furoyl chloride, with no solvent, and were isolated as the hydrochlorides. The corresponding 2-thiophenecarboxylate hydrochlorides were formed from the alkanolamine hydrochlorides with 2-thiophenecarboxyl chloride, with no solvent. 2-Methyl-2-*n*-anilaminopropyl nicotinate was prepared by the reaction, in chloroform solution, of nicotiny chloride hydrochloride and the alkanolamine hydrochloride.

(1) Acknowledgment is made to Dr. E. Emmet Reid, Research Adviser to the Chemistry Department of the University of Richmond, for his advice in this work.

(2) J. S. Pierce, J. M. Salsbury, W. W. Haden and L. H. Willis, *THIS JOURNAL*, **64**, 2884 (1942).

(3) J. S. Pierce, R. D. Gano and J. M. Lukeman, *ibid.*, **70**, 255 (1948).

(4) S. D. Goldberg and W. F. Whitmore, *ibid.*, **59**, 2280 (1937).

(5) (a) W. Steinkopf and W. Ohse, *C. A.*, **18**, 2158 (1924); *Ann.*, **437**, 14 (1924); (b) Henry Gilman and R. M. Pickens, *THIS JOURNAL*, **47**, 245 (1925); (c) P. G. Menshakov, *C. A.*, **33**, 6442 (1939); *Bull. biol. med. exper. U.S.S.R.*, **4**, 269 (1937); (d) G. A. Levy and H. B. Nisbet, *J. Chem. Soc.*, 1053 (1938); (e) R. R. Renshaw and P. F. Dreisbach, *U. S. Patent* 2,189,404 (1940); (f) R. R. Renshaw and P. F. Dreisbach, *U. S. Patent* 2,194,567 (1940); (g) R. R. Renshaw and P. F. Dreisbach, *U. S. Patent* 2,199,839 (1940); (h) F. F. Blicke and E. L. Jenner, *THIS JOURNAL*, **64**, 1721 (1942); (i) M. C. Chiang and W. H. Hartung, *J. Org. Chem.*, **10**, 26 (1945); (j) A. L. Mndzhoyan, *C. A.*, **41**, 2033 (1947); *J. Gen. Chem. (U.S.S.R.)*, **16**, 751 (1946); (k) E. Campaigne and W. M. LeSuer, *THIS JOURNAL*, **70**, 3498 (1948).

TABLE I

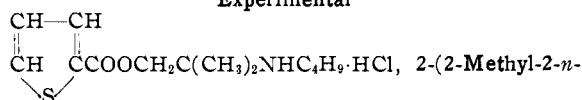
2-METHYL-2-MONOALKYLAMINOPROPYL FURGOATE AND 2-THIOPHENECARBOXYLATE HYDROCHLORIDES<sup>a</sup> RCOOCH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>-NHR'-HCl

R	R'	M.p., °C. (uncor.)	Formula	Chlorine, %	
				Calcd.	Found <sup>b</sup>
2-Furan	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	184-185	C <sub>12</sub> H <sub>20</sub> O <sub>3</sub> NCl	13.54	13.32
2-Furan	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	146-147	C <sub>13</sub> H <sub>22</sub> O <sub>3</sub> NCl	12.86	12.58
2-Furan	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	144-145	C <sub>14</sub> H <sub>24</sub> O <sub>3</sub> NCl	12.24	12.12
2-Thiophene	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	165-166	C <sub>12</sub> H <sub>20</sub> O <sub>2</sub> NCIS	12.76	12.87
2-Thiophene	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	175-176	C <sub>13</sub> H <sub>22</sub> O <sub>2</sub> NCIS	12.15	12.25
2-Thiophene	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	130-131	C <sub>14</sub> H <sub>24</sub> O <sub>2</sub> NCIS	11.59	11.54

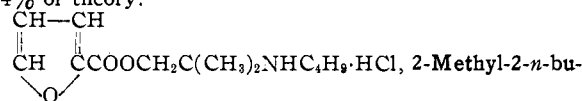
<sup>a</sup> These compounds will be tested for anesthetic activity by Dr. H. B. Haag of the Medical College of Virginia and the results reported elsewhere. <sup>b</sup> Analyses by R. L. Kersey.

ride and was isolated as the disulfate. Each of the 2-methyl-2-monoalkylaminopropyl aromatic carboxylates, in the process of purification, was converted into the free base, dissolved in isopropyl ether and precipitated as the salt by the addition of hydrogen chloride or concentrated sulfuric acid.

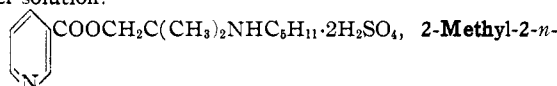
## Experimental



**butylaminopropyl) Thiophenecarboxylate Hydrochloride.**—To 13.1 g. (0.1 mole) of 2-methyl-2-*n*-butylamino-1-propanol was added 13.4 ml. (0.15 mole) of concentrated hydrochloric acid. The solution was evaporated to dryness in a vacuum. To the amino alcohol hydrochloride thus formed was added 14.6 g. (0.1 mole) of thiophenecarboxyl chloride.<sup>6</sup> The mixture was heated on an oil-bath at 100° for 15 minutes, at 130° for 15 minutes and at 150° for 15 minutes. The reaction mixture was taken up in 50 ml. of alcohol, the solution was poured into 100 ml. of *N* sodium hydroxide solution and the oil which separated was dissolved in isopropyl ether. The ethereal solution was saturated with dry hydrogen chloride. The solid formed was filtered with suction, washed with isopropyl ether and recrystallized to constant melting point from alcohol and isopropyl ether. The yield of purified 2-methyl-2-*n*-butylaminopropyl 2-thiophenecarboxylate hydrochloride was 7 g. or 24% of theory.



**tylaminopropyl Furoate Hydrochloride.**—Tenth molar quantities of 2-methyl-2-*n*-butylamino-1-propanol and furoyl chloride were heated, as above. The reaction product was dissolved in 50 ml. of ethanol and poured into 100 ml. of *N* sodium hydroxide solution. The free base separating was dissolved in isopropyl ether and precipitated as the crystalline hydrochloride by the addition of hydrogen chloride. 2-Methyl-2-*n*-butylaminopropyl furoate hydrochloride was obtained in 23% yield by washing with isopropyl ether and recrystallization from ethanol-isopropyl ether solution.



**amylaminopropyl Nicotinate Disulfate.**—Tenth molar quantities of 2-methyl-2-*n*-amylaminopropyl hydrochloride and nicotiny chloride were refluxed in 50 ml. of chloroform for approximately 18 hours. The reaction mixture was poured into hot water, the chloroform evaporated off and the 2-methyl-2-*n*-amylaminopropyl nicotinate set free as a dark oil by the addition of sodium hydroxide solution. The oil was dissolved in isopropyl ether and treated dropwise with concentrated sulfuric acid. The oil which precipitated was converted into a crystalline hygroscopic solid in a yield of 78% by trituration with anhydrous ether, suction

(6) Acknowledgment is made to Socony Vacuum Company for the 2-thiophene carboxylic acid used in the preparation of the acid chloride.

filtration and drying in a vacuum desiccator. On stirring the product with anhydrous acetone and suction filtration the product became less hygroscopic. Without further purification the product had a melting point of 135-142° and gave a sulfate analysis only 0.1% low in sulfur, the latter likely due to a balancing of errors. On three recrystallizations from absolute alcohol and anhydrous ether, the melting point was 153-153.5°. *Anal.* Calcd. for C<sub>15</sub>H<sub>21</sub>O<sub>2</sub>N<sub>2</sub>·2H<sub>2</sub>SO<sub>4</sub>: S, 13.93. Found: S, 14.05.

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Alkyl Half Esters of *cis*-3,6-Endomethylene- $\Delta^4$ -tetrahydrophthalic Acid

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Due to the continuing interest in alkyl chain length as a function of melting point, it was desirable to prepare the half esters of *cis*-3,6-endomethylene- $\Delta^4$ -tetrahydrophthalic acid and compare the melting points of these compounds with those of phthalic<sup>3</sup> and *cis*- $\Delta^4$ -tetrahydrophthalic acids<sup>4</sup> previously prepared.

This series of half esters melted with a more regular pattern in the compounds of alkyl chain length from methyl to octyl than the corresponding half esters of phthalic or tetrahydrophthalic acids. The series has a minimum at 34° for the octyl ester and then rises in a general pattern by small increments to 70° at the octadecyl half ester. In general it can be said that the melting points of these compounds are intermediate between the analogous compounds derived from phthalic or tetrahydrophthalic acids. The compounds prepared are listed in Table I.

## Experimental

**The Half Esters of Methyl through Amyl.**—A mixture of an excess of the appropriate water-free alcohol and the anhydride was refluxed three hours. After cooling the excess alcohol was removed from a steam-bath under reduced pressure. The oily residue generally solidified to a crystalline mass on cooling. Recrystallization was effected by alternately using petroleum ether and "heptane" until a constant melting product was obtained after vacuum drying.

**The Half Esters of Hexyl through Dodecyl.**—A mixture of 0.5 mole of the appropriate alcohol and 0.5 mole of the anhydride was slowly heated with stirring until the temperature rose to around 135°. At this point heating was

(1) Abstracted in part from the thesis submitted to Georgetown University in 1951, by Leonard M. Rice, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Professor Emeritus, Johns Hopkins University, Baltimore, Md.

(3) J. F. Goggins, Jr., and J. F. Copenhaver, *THIS JOURNAL*, **61**, 2909 (1939).

(4) White, Trigg, Sankins and E. E. Reid, private communication.