methanol containing sodium methoxide prepared from 0.92 g. (0.04 mole) of sodium, resulted in the formation of 0.8 g. of unsaponifiable oil (22% calculated as 1,1-diphenylethylene) and 2.7 g. (64%) of diphenylacetic acid, m. p. 143–146° (after saponification of the ester).

Diphenylacetic Acid from the Diethylaminoethyl Ester of α-Phenyltropic Acid.—A sodium methoxide solution prepared from 0.30 g. (0.013 mole) of sodium and 20 cc. of dry methanol was refluxed for twenty-six hours with 1.90 g. (0.005 mole) of the basic ester hydrochloride (V, R = C_2H_5). Working up the reaction mixture in the usual way gave 0.70 g. of diphenylacetic acid and 0.3 g. of a neutral oil which on saponification gave a further 0.22 g. of diphenylacetic acid. The total of 0.92 g. of acid obtained represents an 87% yield based on the ester hydrochloride.

Summary

1. α-Phenyltropic acid has been prepared in good yield by hydrolysis of α,α-diphenyl-β-propiolactone. A product reported by previous workers to be α-phenyltropic acid has been found to possess the isomeric α,β-diphenyllacetic acid structure.

2. The reaction with sodium methoxide of 2,2-diphenyl-3-bromo and chloropropanoic acids, α,α-diphenyl-β-propiolactone and a basic ester of α-phenyltropic acid, has in each case been found to lead to a mixture of diphenylacetic acid and its methyl ester. The mechanism of this cleavage reaction is discussed.

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE ABBOTT RESEARCH LABORATORIES]

Basic Esters and Amides of α-Substituted Diphenylacetic Acids

BY HAROLD E. ZAUGG AND BRUCE W. HORROM

In a routine search for compounds possessing therapeutic activity, primarily analgetic, a number of basic esters and amides derived from acids of type $(C_6H_5)_2RCCOOH$ were prepared.[1] Five carboxylic acids were employed in which R was varied as follows: CH_3, C_2H_5, $CH_2{=}CHCH_2$, $ClCH_2$, and $BrCH_2$. In addition, several basic amides of 2-phenylbutanoic acid, $C_6H_5CH(C_2H_5)$-COOH were prepared. Of these six acids the 2,2-diphenyl-3-chloropropanoic acid was the only one not previously reported in the literature. It was made by the condensation of benzene with chloropyruvic acid in the presence of concentrated sulfuric acid according to the procedure of Wegmann and Dahn[2] for the preparation of the corresponding bromo acid.

The basic esters and amides were prepared by the reaction of the carboxylic acid chlorides with amino alcohols and diamines, respectively, in ether solution. The only new amine used in this work seems to be β-dimethylaminoisopropylamine. It was obtained by the reductive amination, with ammonia, of dimethylaminoacetone.

In every case but one, the diamine employed in the preparation of the amides possessed one tertiary amino group. The exception, N,N'-dimethylethylenediamine, contained two secondary amino groups and as expected gave considerable amounts of the bis-amide on treatment with the acid chloride. Although the desired basic mono-amide still predominated in this case, the corresponding reaction with ethylenediamine itself produced only the bis-amide and none of the basic amide.

All the esters and amides are listed in the table. During the course of the present work the dimethylaminoethyl[3] and diethylaminoethyl[4] esters of 2,2-diphenylpropanoic acid were reported by other workers.

Pharmacology.—The increase of pain threshold produced in dogs as summarized in the table was determined by a modification of the method of Andrews and Workman.[5] The authors are indebted to Dr. R. K. Richards and Mr. K. E. Kueter of the Abbott Pharmacological Research Laboratories for these tests. The symbols express the increase of pain threshold according to the following scale: 0 = none; ± = doubtful; + <10%; ++ = 10–20%; +++ = 20–30%; ++++ = 30–40%. Doses one-fifth to one-tenth of the LD_{50} were injected subcutaneously in the dogs. The toxicities were determined intraperitoneally in mice. Since a limited number of mice were used these values can be in error by as much as ±50%.

The most active compound proved to be the dimethylaminoethyl amide of 2,2-diphenyl-3-chloropropanoic acid. It induced the Straub phenomenon (tail erection) in mice, a characteristic of many narcotic drugs. However, it also produced considerable irritation at the site of subcutaneous injection, and by oral or intravenous administration it showed only a low order of activity. The same amide of the corresponding bromo acid suffered from the same defects. The values indicated in the table for the increase of pain threshold, therefore, do not reflect the true analgesic activities of these compounds. Some other property, possibly irritation, undoubtedly is responsible for the relatively high order of observed activity.

Several of these compounds were tested for

(1) For a discussion of the antispasmodic activity of certain derivatives of diphenylacetic acid, see Raymond, *J. Am. Pharm. Assoc.*, **32**, 249 (1943).

(2) Wegmann and Dahn, *Helv. Chim. Acta*, **29**, 415 (1946).

(3) Larsen, Ruddy, Elpern and MacMullen, THIS JOURNAL, **71**, 532 (1949).

(4) British Patent Spec. 33,582, Dec. 19, 1947.

(5) Andrews and Workman, *J. Pharmacol.*, **78**, 99 (1941).

TABLE I

BASIC ESTERS AND AMIDES, $(C_6H_5)_2RCCOR'$

R	R'	Yield,[a] %	M. p.,[b] °C.	Formula	Nitrogen, % Calcd.	Found	LD_{50} mg./kg.	Increase of pain threshold
CH_3	$-OCH_2CH_2N(CH_3)_2\cdot HCl$[c]	63	174-176	$C_{19}H_{24}ClNO_2$	4.20	4.23[e]	250	++
CH_3	$-OCH_2CH_2N(C_2H_5)_2\cdot HCl$[d]	50[d]	161-162	$C_{21}H_{28}ClNO_2$	3.87	3.88[e]	150	++
CH_3	$-OCH_2CH_2N(n\text{-}C_4H_9)_2$	33	183-185 (0.6 mm.)[f]	$C_{25}H_{35}NO_2$	3.67	3.76		
CH_3	$-OCH_2CH_2CH_2N(C_2H_5)_2\cdot HCl$	56	101-105[g]	$C_{22}H_{30}ClNO_2$	3.73	3.84	125	0
CH_3	$-OCH_2CH_2NC_4H_8O\cdot HCl$[h]	50	135-137	$C_{21}H_{28}ClNO_3$	3.73	3.53[h]	400	0
CH_3	$-OCH(CH_3)CH_2N(C_2H_5)_2\cdot HCl$	39	119-121	$C_{22}H_{30}ClNO_2$	3.73	3.71[i]	250	0
CH_3	$-OCH(CH_3)CH_2N(CH_3)_2\cdot HCl$	54	151-153	$C_{20}H_{26}ClNO_2$	4.03	4.09[j]	175	0
CH_3	$-NHCH_2CH_2N(CH_3)_2\cdot HCl$	24	183-185	$C_{19}H_{25}ClN_2O$	8.42	8.55[k]	30	0
CH_3	$-NHCH_2CH_2N(C_2H_5)_2\cdot HCl$	49	179-181	$C_{21}H_{29}ClN_2O$	7.76	7.75	150	+
CH_3	$-NHCH_2CH_2CH_2N(CH_3)_2\cdot HCl$	37	158-160	$C_{20}H_{27}ClN_2O$	8.08	8.25	175	0
C_2H_5	$-NHCH_2CH_2N(CH_3)_2$	92	78-79	$C_{20}H_{26}N_2O$	9.02	8.90	150	0
C_2H_5	$-NHCH_2CH_2N(C_2H_5)_2\cdot HCl$	85	141-142	$C_{22}H_{31}ClN_2O$	7.47	7.61	175	0
C_2H_5	$-NHCH(CH_3)CH_2N(CH_3)_2\cdot HCl$	68	156-157	$C_{21}H_{29}ClN_2O$	7.76	7.71	175	+
C_2H_5	$-NHCH_2C(CH_3)_2N(CH_3)_2\cdot HCl$	70	120-122	$C_{23}H_{31}ClN_2O$	7.47	7.25	175	0
C_2H_5	$-NC_4H_8N-CH_3$[z]	89	105-106	$C_{21}H_{26}N_2O$	8.69	8.91	150	0
$CH_2{=}CHCH_2-$	$-NHCH_2CH_2N(CH_3)_2$	74	58-60	$C_{21}H_{28}N_2O$	8.69	8.79	250	0
$CH_2{=}CHCH_2-$	$-NHCH_2CH_2N(C_2H_5)_2\cdot H_2C_2O_4$[l]	28	159-160	$C_{28}H_{32}N_2O_5$	6.36	6.43	>500[w]	0[w]
$CH_2{=}CHCH_2-$	$-NC_4H_8N-CH_3$[z]	73	98-99	$C_{23}H_{26}N_2O$	8.37	8.40[m]	125	0
$CH_2{=}CHCH_2-$	$-NHCH(CH_3)CH_2N(CH_3)_2$	66	153-155 (0.2 mm.)[x]	$C_{22}H_{28}N_2O$	8.33	8.35	175	0
$ClCH_2$	$-OCH_2CH_2N(CH_3)_2\cdot HCl$	88	158-159	$C_{19}H_{24}Cl_2NO_2$	3.80	4.09[n]	350	±
$ClCH_2$	$-OCH_2CH_2N(C_2H_5)_2\cdot HCl$	90	107-109	$C_{21}H_{27}Cl_2NO_2$	3.53	3.72[o]	250	+++
$ClCH_2$	$-NHCH_2CH_2N(CH_3)_2$	91	123-124	$C_{19}H_{23}ClN_2O$	8.46	8.30	225	++++
$ClCH_2$	$-NHCH_2CH_2N(CH_3)_2\cdot HCl$	82	175-176	$C_{19}H_{24}Cl_2N_2O$	7.62	7.71		
$ClCH_2$	$-NHCH_2CH_2N(C_2H_5)_2\cdot HCl$	71	176-177	$C_{21}H_{28}Cl_2N_2O$	7.08	6.82	200	+++
$ClCH_2$	$-NHCH_2CH_2CH_2N(C_2H_5)_2$	91	67-68	$C_{22}H_{29}ClN_2O$	7.52	7.57	125	0
$ClCH_2$	$-NHCH(CH_3)CH_2N(CH_3)_2$	90	102-103	$C_{20}H_{25}ClN_2O$	8.12	8.02	250	0
$ClCH_2$	$-NHCH(CH_3)(CH_2)_2N(C_2H_5)_2\cdot HCl$	64	140-141	$C_{24}H_{34}Cl_2N_2O$	6.40	6.25	75	0
$ClCH_2$	$-NHCH_2C(CH_3)_2N(CH_3)_2$	78	96-97	$C_{21}H_{27}ClN_2O$	7.80	7.95	200	0
$ClCH_2$	$-N(CH_3)CH_2CH_2NHCH_3\cdot HCl$	55	203-204	$C_{19}H_{24}Cl_2N_2O$	7.63	7.44	275	++
$ClCH_2$	$-NC_4H_8N-CH_3$[z]	85	138-139	$C_{20}H_{23}ClN_2O$	8.17	8.03	30	++
$ClCH_2$	$-NH\text{-}4\text{-}cyclohexyl\text{-}N(C_2H_5)_2\cdot HCl$[p]	85	204-207	$C_{25}H_{34}Cl_2N_2O$	6.23	6.35	125	0
$BrCH_2$	$-OCH_2CH_2N(CH_3)_2\cdot HCl$	45	126-128	$C_{19}H_{23}BrClNO_2$	3.39	3.35[q]	350	0
$BrCH_2$	$-OCH_2CH_2N(C_2H_5)_2\cdot HCl$	61	131-132	$C_{21}H_{27}BrClNO_2$	3.17	3.19	250	0
$BrCH_2$	$-OCH_2CH_2CH_2N(C_2H_5)_2\cdot HCl$	55	155-156	$C_{22}H_{29}BrClNO_2$	3.07	3.07[r]	150	0
$BrCH_2$	$-OCH_2CH_2NC_4H_8O\cdot HCl$[v]	41	173-174	$C_{21}H_{25}BrClNO_3$	3.08	2.96[s]	150	++
$BrCH_2$	$-NHCH_2CH_2N(CH_3)_2$	92	124-125	$C_{19}H_{23}BrN_2O$	7.46	7.32	200	++++
$BrCH_2$	$-NHCH_2CH_2N(C_2H_5)_2\cdot HCl$	68	150-151	$C_{21}H_{28}BrCl_2NO$	6.37	6.24	300	+++
$BrCH_2$	$-NHCH_2CH_2CH_2N(CH_3)_2$	68	121-122	$C_{20}H_{25}BrN_2O$	7.19	7.09	250	++
$BrCH_2$	$-NHCH_2CH_2CH_2N(C_2H_5)_2$	83	80-81	$C_{22}H_{29}BrN_2O$	6.71	6.62	125	++
$BrCH_2$	$-NHCH_2CH_2CH_2N(n\text{-}C_5H_{11})_2$	65	86-87	$C_{28}H_{41}BrN_2O$	5.58	5.61	175	0
$BrCH_2$	$-NHCH(CH_3)(CH_2)_2N(C_2H_5)_2\cdot HCl$	85	147-148	$C_{24}H_{34}BrClN_2O$	5.81	5.62	125	0
$BrCH_2$	$-NC_4H_8N-C_2H_5$[z]	78	140-141	$C_{21}H_{25}BrN_2O$	6.97	6.64	175	0
$BrCH_2$	$-NH\text{-}4\text{-}cyclohexyl\text{-}N(C_2H_5)_2\cdot HCl$[p]	36	155-160	$C_{25}H_{34}BrClN_2O$	5.67	5.49	125	+++
$C_6H_5CH(C_2H_5)CONHCH_2CH_2N(CH_3)_2\cdot HCl$		28	193-194	$C_{14}H_{23}ClN_2O$	10.33	10.35[t]	500	++
$C_6H_5CH(C_2H_5)CONHCH_2CH_2N(C_2H_5)_2$		90	140-142 (0.2 mm.)[u]	$C_{16}H_{26}N_2O$	10.68	10.56	200	0
$C_6H_5CH(C_2H_5)CONC_4H_8N-CH_3\cdot HCl$[z]		64	237-238	$C_{15}H_{23}ClN_2O$	9.90	9.95	275	0
$C_6H_5CH(C_2H_5)CONH\text{-}4\text{-}cyclohexyl\text{-}N(C_2H_5)_2$[p]		56	170-174 (0.1 mm.)[v]	$C_{20}H_{32}N_2O$	8.85	8.73	175	±

[a] Based on crude carboxylic acid chloride. [b] Uncorrected. [c] Calcd.: C, 68.35; H, 7.25. Found: C, 68.51; H, 7.13. [d] Prepared in a 75% yield by refluxing the carboxylic acid with an equivalent amount of β-diethylaminoethyl chloride in isopropanol. [e] Calcd.: C, 69.69; H, 7.80. Found: C, 69.94; H, 7.87. [f] B. p. of the free base, $n^{24}D$ 1.5208, *Anal.* Calcd.: C, 78.69; H, 9.25. Found: C, 78.56; H, 9.02. [g] Product could not be obtained entirely pure, *Anal.* Calcd.: C, 70.29; H, 8.04. Found: C, 69.48; H, 7.76. [h] Calcd.: C, 67.10; H, 6.97. Found: C, 67.46; H, 6.96. [i] Calcd.: C, 70.29; H, 8.04. Found: C, 70.36; H, 7.75. [j] Calcd.: C, 69.05; H, 7.53. Found: C, 69.04; H, 7.27. [k] Calcd.: C, 68.55; H, 7.57. Found: C, 68.65; H, 7.52. [l] Isolated as the bioxalate. [m] Calcd.: C, 79.00; H, 7.83. Found: C, 78.70; H, 7.70. [n] Calcd.: C, 61.95; H, 6.28. Found: C, 62.18; H, 6.07. [o] Calcd.: C, 63.63; H, 6.87. Found: C, 64.10; H, 7.08. [p] Probably consists of a mixture of the two *cis-trans* isomers. [q] Calcd.: C, 55.28; H, 5.62. Found: C, 55.48; H, 5.44. [r] Calcd.: C, 58.09; H, 6.41. Found: C, 57.86; H, 6.27. [s] Calcd.: C, 55.46; H, 5.54. Found: C, 55.72; H, 5.71. [t] Calcd.: C, 62.08; H, 8.56. Found: C, 61.89; H, 8.21. [u] B. p. of the free base, $n^{25}D$ 1.5150. [v] B. p. of free base. [w] Oral toxicity in mice. No analgesia in dogs at 50 mg./kg. orally. [x] B. p. of the free base, $n^{25}D$ 1.5540. [y] NC_4H_4O = morpholino-. [z] $NC_4H_8NCH_3$=N-methylpiperazino-.

antispasmodic activity. The most active, the diethylaminoethyl ester of 2,2-diphenylpropanoic acid, showed one-fifth to one-tenth the activity of atropine.

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Experimental

Diamines and Aminoalcohols.—N,N-Dimethylethylenediamine,[6] N,N′ - dimethylethylenediamine,[7] N - methylpiperazine[8] and N-ethylpiperazine[8] were prepared by published methods. All other diamines and aminoalcohols for which no procedure is given were obtained from commercial sources.

Dimethylaminoacetone.[9]—To a solution of 45 g. (1.0 mole) of dimethylamine in one liter of dry ether was added, rapidly with stirring at a temperature of 2–10°, a solution of 46.3 g. (0.5 mole) of monochloroacetone (Eastman Kodak Company) in 100 cc. of dry ether. The addition required fifteen minutes. The mixture was stirred at room temperature for seven hours and allowed to stand for three days. The precipitated dimethylamine hydrochloride was filtered, washed with dry ether and the combined filtrate and washings were dried over anhydrous magnesium sulfate. The ether was distilled from the filtered solution through a helix-packed column (10-inch) and the product was distilled *in vacuo* through the same column; yield 37.5 g. (74%) of a colorless liquid, b. p. 35–36° at 25 mm., $n^{20}D$ 1.4128 (lit.[9] $n^{20}D$ 1.4131; yield, 36% from bromoacetone).

β-Dimethylaminoisopropylamine.—A solution of 37.5 g. of dimethylaminoacetone in 100 cc. of dry methanol was treated with 40 cc. of liquid ammonia and hydrogenated with 4–6 g. of Raney nickel catalyst at a temperature of 80° and at 2000 pounds hydrogen pressure. Reduction seemed to be complete in an hour. The catalyst was removed by filtration and the filtrate was fractionated at atmospheric pressure through a 10-inch helix-packed column. There was obtained 15 g. of β-dimethylaminoisopropylamine. For analysis, this material was refractionated from a small amount of metallic sodium, b. p. 113°, $n^{25}D$ 1.4177.

Anal. Calcd. for $C_5H_{14}N_2$: N, 27.42. Found: N, 27.00.

Substituted Diphenylacetic Acids.—2,2-Diphenylpropanoic acid was prepared by both of two published methods.[10] 2,2-Diphenyl-3-bromopropanoic acid likewise was prepared by a known method.[2] Allyldiphenylacetic acid was obtained from the Research Laboratories of General Mills, Inc., and the 2-phenylbutanoic acid from a commercial source.

2,2-Diphenyl-3-bromopropanoyl Chloride.—A mixture of 30 g. of 2,2-diphenyl-3-bromopropanoic acid and 75 cc. of thionyl chloride was refluxed with stirring for four hours. The excess thionyl chloride was distilled from the mixture and the residue was taken up in 100 cc. of dry benzene which was then distilled from the product. Recrystallization of the solid residue from Skellysolve B gave 28 g. (88%). Another recrystallization for analysis gave m. p. 85.5–87°.

Anal. Calcd. for $C_{15}H_{12}BrClO$: C, 55.66; H, 3.73. Found: C, 56.05; H, 3.74.

2,2-Diphenyl-3-chloropropanoic Acid.—Monochloropyruvic acid was prepared in a 95% yield, m. p. 60–63°, by the action of sulfuryl chloride on freshly distilled pyruvic acid using the method of Garino and Muzio.[11] This material was used in the next step without further purification.

To a suspension of 110 g. of chloropyruvic acid, in one liter of concentrated sulfuric acid cooled in an ice-bath, was added dropwise with good stirring 252 g. of dry thiophene-free benzene. The temperature was kept between 5 and 10° during the addition, after which the mixture was stirred for four hours in the ice-bath. The reaction mixture was then poured on ice and diluted with a large volume of water. Separation of the product by filtration, washing and drying gave 151.5 g. (65%); m. p. 195–198°. Recrystallization by dissolving in one liter of hot 95% ethanol, filtering and adding one liter of hot water gave 145 g. of colorless needles, m. p. 201–203° (dec.).

Anal. Calcd. for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.03. Found: C, 69.14; H, 5.00.

A mixture of this chloro acid (m. p. 201–203°) with the corresponding bromo acid (m. p. 202–203°) melted at 190–200°.

2,2-Diphenyl-3-chloropropanoyl chloride was prepared in the same way as indicated above for the corresponding bromo acid chloride. The purest sample obtained melted at 79–80.5° but was apparently not quite analytically pure.

Anal. Calcd. for $C_{15}H_{12}Cl_2O$: C, 64.54; H, 4.33. Found: C, 65.34; H, 4.26.

2,2-Diphenylbutanoic Acid.—Since the present work was completed the preparation of this acid by sulfuric acid hydrolysis of 2,2-diphenylbutanenitrile has been reported.[3] In our hands direct hydrolysis resulted in poor yields, but treatment of the intermediate amide with butyl nitrite in acetic acid according to the procedure of Sperber, Papa and Schwenk[12] proved more successful.

A suspension of 44.2 g. (0.2 mole) of 2,2-diphenylbutanenitrile[3] in a mixture of 86.4 cc. of concentrated sulfuric acid, 41.2 cc. of glacial acetic acid and 6 cc. of water was heated with stirring at 135° for thirty minutes. The clear solution was poured into three liters of water and after standing for three or four hours the solid amide was separated by filtration. It weighed 44.0 g. (92%). Two recrystallizations of a sample from dilute methanol gave heavy prisms, m. p. 105–107°.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16. Found: C, 80.58; H, 7.32.

Treatment of the crude amide (m. p. 101–104°) in the same way as has been described by Sperber, *et al.*,[12] for the hydrolysis of tributylacetamide gave 2,2-diphenylbutanoic acid in an 88% yield (81% over-all yield from the nitrile), m. p. 172–174°.

Preparation of Basic Esters. Diethylaminoethyl Ester of 2,2-Diphenyl-3-bromopropanoic Acid.—To a solution of 5 g. (0.043 mole) of β-diethylaminoethanol in 15 cc. of dry ether was added a solution of 7 g. (0.021 mole) of crude 2,2-diphenyl-3-bromopropanoyl chloride in 40 cc. of dry ether. Both solutions were cooled in ice before mixing and the mixture was then allowed to stand in ice for one hour. After two days at room temperature, the mixture, containing a precipitated hydrochloride, was poured into excess dilute hydrochloric acid. The ether was separated and the acidic layer was made alkaline with excess 20% sodium hydroxide solution. The oil which separated was taken up in ether and washed well with water. After drying over anhydrous magnesium sulfate, the ethereal solution was filtered and treated with dry ethereal hydrogen chloride. The hydrochloride of the product precipitated as an oil which solidified slowly. Two recrystallizations, each time from 40–50 cc. of ethyl acetate, gave 5.8 g., m. p. 131–132°.

Anal. Calcd. for $C_{21}H_{27}BrClNO_2$: C, 57.21; H, 6.16. Found: C, 57.26; H, 5.94.

With one exception the basic esters were all isolated as the hydrochlorides. The dibutylaminoethyl ester of 2,2-diphenylpropanoic acid was purified by distillation of the free base when it was found that a solid hydrochloride could not be prepared. In all reactions with both aminoalcohols and diamines crude acid chlorides were used. The carboxylic acids were treated with thionyl chloride in the usual manner and solvent and excess thionyl chloride were removed.

Preparation of Basic Amides.—The procedure used was the same as that described above for the preparation of the basic ester with replacement of the aminoalcohol by the appropriate diamine. Although not theoretically necessary it was found advantageous to maintain a one mole excess of diamine over the carboxylic acid chloride. The reaction mixture was allowed to stand at room tempera-

(6) Turner, THIS JOURNAL, **68**, 1607 (1946); U. S. Pat. 2,364,178.

(7) Boon, *J. Chem. Soc.*, 307 (1947).

(8) Hamlin, Weston, Fischer and Michaels, THIS JOURNAL, **71**, 2731 (1949).

(9) Compare Magee and Henze, *ibid.*, **60**, 2148 (1938); Stoermer and Dzimski, *Ber.*, **28**, 2223 (1895).

(10) Meerwein, *Ann.*, **396**, 257 (1913); Böttinger, *Ber.*, **14**, 1595 (1881).

(11) Garino and Muzio, *Gazz. chim. ital.*, **52**, II, 226 (1922).

(12) Sperber, Papa and Schwenk, THIS JOURNAL, **70**, 3091 (1948).

ture for an arbitrary period ranging from one to three days. If treatment of the aqueous acidic solution of the product with excess sodium hydroxide resulted in the precipitation of a solid free base, it was separated by filtration and recrystallized from an appropriate solvent (usually a Skellysolve or other hydrocarbon solvent). If, on the other hand, an oil was formed, it was taken up in ether and dried. If removal of the ether still did not yield a solid residue it was taken up in more dry ether and converted to the hydrochloride. The solvents used most frequently for recrystallizations of these hydrochlorides were isopropyl alcohol–acetone, ethyl acetate and the solvent pairs, methanol–ether and ethanol–ether. Two basic amides (see table) of 2-phenylbutanoic acid were purified by distillation *in vacuo*. The diethylaminoethylamide of allyl diphenylacetic acid was isolated as the acid oxalate, and the corresponding dimethylaminoisopropylamide by distillation.

Reaction of 2,2-Diphenyl-3-chloropropanoyl Chloride with N,N' - Dimethylethylenediamine.—The reaction carried out as described above gave, in addition to a 55% yield of the desired amide, a 28% yield of an acid-insoluble product which proved to be the bis-amide formed by reaction of the acid chloride with both secondary amino groups. Recrystallization from 70% acetic acid gave colorless leaflets, m. p. 210–211°.

Anal. Calcd. for $C_{34}H_{34}Cl_2N_2O_2$: C, 71.19; H, 5.97; N, 4.88. Found: C, 71.71; H, 6.11; N, 4.77.

Similar treatment of 2,2-diphenyl-3-chloropropanoyl chloride with ethylenediamine resulted in exclusive formation of the bis-amide in a nearly quantitative yield. It formed colorless needles from 60% acetic acid, m. p. 190–191°.

Anal. Calcd. for $C_{32}H_{30}Cl_2N_2O_2$: C, 70.45; H, 5.54; N, 5.13. Found: C, 70.41; H, 5.62; N, 5.12.

Summary

The synthesis of a number of basic esters and amides of carboxylic acids of type, $(C_6H_5)_2$-RCCOOH, where R = CH_3, C_2H_5, CH_2=$CHCH_2$, $ClCH_2$ and $BrCH_2$, and of the acid, $C_6H_5CH(C_2H_5)COOH$, is reported. The results of tests for analgesic activity in these compounds are summarized.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF TEXAS]

The Nitrogen Compounds in Petroleum Distillates. XXVII. Isolation and Identification of 2,3-Dimethyl-6-isopropyl-pyridine from California Petroleum

BY H. L. LOCHTE, A. D. BARTON,[1,2] STILES M. ROBERTS[3] AND J. R. BAILEY[4]

The bases used in the present study were recovered from the hydrochlorides found in the chloroform layers after the "cumulative" extraction[5] of an aqueous solution of the hydrochlorides of petroleum bases boiling in the range 175–235°. When these bases were subjected to a procedure which involved fractionation by sulfurous acid, fractional distillation and fractional methiodide formation, the methiodide of a $C_{10}H_{15}N$ base was isolated and analyzed. The base was liberated by thermal decomposition of the purified methiodide and again subjected to fractional distillation.

The structure of the base was established through the following reactions: (1) Oxidation of the base by permanganate yielded 2,5-pyridinedicarboxylic acid under conditions such that it probably was formed by decarboxylation of 2,3,6-pyridinetricarboxylic acid produced originally since this is the only pyridinetricarboxylic acid which yields 2,5-pyridinedicarboxylic acid on decarboxylation; oxalic acid was also isolated, thus confirming the presence of two adjacent unsubstituted positions in the pyridine nucleus. (2) Condensation with phthalic anhydride yielded a phthalone which indicated the presence of a methyl group in one of the alpha positions. (3) On ozonolysis the base yielded isobutyramide; this indicated the presence of an isopropyl group in the other alpha position, since the carbon and nitrogen atoms of the carboxamide group must have come from the alpha carbon and nitrogen atom of the pyridine ring.[6] (4) To determine the relative positions of the three substituents, the α-methyl group was removed by condensation with benzaldehyde followed by ozonolysis of the 2-stilbazone derivative formed to give the corresponding 2-pyridinecarboxylic acid which was then decarboxylated. When the resulting demethylated base was oxidized with permanganate, 2,5-pyridinedicarboxylic acid was formed, thus showing that the demethylated base was 3-methyl-6-isopropylpyridine and that the base isolated from petroleum was 2,3-dimethyl-6-isopropylpyridine.

Isolation of the $C_{10}H_{15}N$ Base.—The material for this investigation consisted of 750 ml. of bases boiling in the range 192–230° which had been isolated[7] from the hydrochlorides in the chloroform layers after the extraction of an aqueous solution of the hydrochlorides of petroleum bases[8] boiling in the range 170–235°. The material was

(1) Abstracted from theses submitted by Stiles M. Roberts (1939) and A. D. Barton (1949) in partial fulfillment of requirements for the degree of Doctor of Philosophy.

(2) du Pont Fellow, 1947–1948; McArdle Memorial Laboratory, Medical School, University of Wisconsin, Madison, Wis.

(3) Central Research Laboratory, General Aniline and Film Corporation, Easton, Penna.

(4) Isolation and preliminary study of this base was carried out by Stiles M. Roberts before the death of Professor Bailey.

(5) This method of fractionating petroleum bases was developed in this Laboratory by Perrin and Bailey, THIS JOURNAL, **55**, 4136 (1933).

(6) Shive, Roberts, Mahan and Bailey, *ibid.*, **64**, 909 (1942); Lochte, Crouch and Thomas, *ibid.*, **64**, 2753 (1942); Shive, Ballweber and Ackermann, *ibid.*, **68**, 2144 (1946).

(7) Meadows, Ph.D. Dissertation, University of Texas, 1937.

(8) These bases comprised part of a large quantity of bases which were generously donated to this Laboratory by the Union Oil Company of California.