[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Dialkylaminoalkyl Esters of Trisubstituted Acetic Acids

BY A. A. LARSEN, A. WAYNE RUDDY, B. ELPERN AND MILDRED MACMULLIN

In connection with studies directed toward the synthesis of compounds possessing antispasmodic activity a series of dialkylaminoalkyl esters of 2,2-diphenylalkanoic acids, 2,2-diphenyl-4-pentenoic acid and 2-cyclohexyl-2-phenylbutanoic acid was prepared. The 2,2-diphenylalkanoic acids were prepared by the following sequence of reactions.

$$C_6H_5CH_2CN \longrightarrow C_6H_5CHBrCN \longrightarrow$$
$$(C_6H_5)_2CHCN \longrightarrow (C_6H_5)_2CRCN \longrightarrow (C_6H_5)_2CRCO_2H$$

Diphenylacetonitrile was obtained in about 80% yield from phenylacetonitrile. Subsequent alkylation with sodamide gave upward of 80% of the tertiary nitriles. Hydrolysis of these nitriles was best accomplished by refluxing with 70% sulfuric acid for about sixty hours.[1] Increased concentrations of sulfuric acid led to the formation of water soluble products, probably sulfonated material. Use of less concentrated acid and shorter periods of heating gave an increased amount of the corresponding amides. Wieland and Dorrer[2] employed 75% sulfuric acid for the hydrolysis of 2,2-diphenylpropanenitrile; however, their period of heating was short and the principal product isolated was the amide. Hydrolysis with alkali and water or alcohols was attended with little success, resulting in low yields of the amides. Hydrolysis of the nitriles in a sealed tube with hydrochloric and sulfuric acids gave the desired product, but was less convenient than the method employed.

2-Cyclohexyl-2-phenylbutanoic acid was readily obtained by alkylation of cyclohexylphenylacetonitrile followed by hydrolysis of the tertiary nitrile to the acid. 2,2-Diphenyl-4-pentenoic acid was prepared from allyl diphenylacetate by rearrangement with sodamide.[3] The unsaturated acid obtained in this manner had the same melting ing point as that reported by Ramart,[4] which was prepared by allylation of benzyl diphenylacetate followed by hydrolysis to the acid.

The various acids were converted to the corresponding acyl chlorides upon treatment with thionyl chloride and then allowed to react with an excess of the appropriate amino alcohol to give the desired esters (Table I).

Experimental

Preparation of the 2,2-Diphenylalkanoic Acids.—The general procedure employed here is suitably illustrated by the preparation of 2,2-diphenylbutanoic acid.

A well-stirred mixture of 193 g. (1 mole) of diphenylacetonitrile[5] and 48 g. (1.2 moles) of sodamide in 600 ml. of dry benzene was refluxed for two hours. The deep red-colored mixture was cooled to 60° and 312 g. (2 moles) of ethyl iodide was added as rapidly as possible. The reaction mixture was then refluxed for several hours. Upon working up there was obtained 196 g. (88%) of 2,2-diphenylbutanenitrile, b. p. 145–147° (0.3 mm.), $n^{25}D$ 1.5660.

A mixture of 111 g. (0.5 mole) of the above nitrile and 686 g. of 70% (d. 1.61) sulfuric acid was heated with stirring at 150° until a test portion remained clear when diluted with water and made alkaline. The reaction mixture was cooled to 100° and poured onto ice and water with vigorous stirring. The solid material was filtered off by means of a large fluted filter paper and washed repeatedly with water to leave a practically colorless product. The crude acid was taken up in 2% sodium hydroxide, filtered and slowly reprecipitated with dilute sulfuric acid. The white 2,2-diphenylbutanoic acid after drying weighed 86 g. (71%) and melted from 170–173°. A small portion when recrystallized from benzene melted at 174–175°.[6]

In a similar manner, 2,2-diphenylpropanenitrile[2] (95% yield, b. p. 127–130° (1.5 mm.), $n^{25}D$ 1.5713), 2,2-diphenylpropanoic acid[2,4] (66% yield, m. p. 173–175°), 2,2-diphenylpentanenitrile[5] (81% yield, b. p. 126–130° (0.2 mm.), $n^{25}D$ 1.5634), and 2,2-diphenylpentanoic acid[7] (56% yield, m. p. 156–157°) were also prepared.

2-Cyclohexyl-2-phenylbutanoic Acid.—Cyclohexylphenylacetonitrile[8] was alkylated with ethyl bromide and sodamide in the same manner as that employed for the alkylation of diphenylacetonitrile to give 2-cyclohexyl-2-phenylbutanenitrile (94%), b. p. 120–126° (1 mm.), $n^{25}D$ 1.5264.

Anal. Calcd. for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.47; H, 9.44; N, 6.20.

After this nitrile was refluxed with 70% sulfuric acid the reaction mixture was poured onto ice and water, the layers separated and the acid extracted with dilute alkali. Upon acidification the alkali extracts gave the desired acid which when recrystallized from dilute methanol melted at 121–123° (64% based on unrecovered nitrile).

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00; neut. equiv., 246. Found: C, 77.94; H, 9.10; neut. equiv., 246.

When this acid was refluxed for two hours with excess thionyl chloride there was obtained a 90% yield of 2-cyclohexyl-2-phenylbutanoyl chloride, b. p. 119–120° (1 mm.), $n^{25}D$ 1.5418.

Anal. Calcd. for $C_{16}H_{21}ClO$: Cl, 13.39. Found: Cl, 13.28.

2,2-Diphenyl-4-pentenoic Acid.[4]—A mixture of 10 g. (0.04 mole) of allyl diphenylacetate and 1.5 g. (0.04 mole) of sodamide in 75 ml. of dry benzene was refluxed for thirty hours. After the reaction mixture was diluted with water, extracted with benzene, and the alkaline layer acidified, an oil separated out which soon solidified. The crude acid weighed 7.7 g. and melted from 120–130°. After two recrystallizations from methanol it melted at 142–143°.

Anal. Calcd. for $C_{17}H_{16}O_2$: neut. equiv., 252. Found: neut. equiv., 249.

Preparation of the Basic Esters.—The same general procedure outlined below was used to prepare all the esters listed in Table I except that the acid chloride from 2-cyclohexyl-2-phenylbutanoic acid was prepared in one lot and distilled before using. Yields of the basic esters varied from 40–70%.

(1) Bockmühl and Ehrhart, U. S. Patent 2,230,774 (Feb. 4, 1941).

(2) Wieland and Dorrer, *Ber.*, **63B**, 407 (1930).

(3) Hauser and Hudson, "The Acetoacetic Ester Condensation," "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1942, p. 272.

(4) Ramart, *Compt. rend.*, **178**, 396 (1924).

(5) Schultz, Robb and Sprague, THIS JOURNAL, **69**, 2454 (1947).

(6) Klingemann, *Ann.*, **275**, 85 (1893).

(7) Danilov, *J. Russ. Phys.-Chem. Soc.*, **52**, 369 (1920); *C. A.*, **18**, 1484 (1924).

(8) Hancock and Cope, "Organic Syntheses," **25**, 25 (1945).

TABLE I

BASIC ESTER HYDROCHLORIDES $R{-}C(C_6H_5)(R'){-}CO_2R''{\cdot}HCl$

R	R'	R''	M. p., °C.[a]	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found
$-CH_3$	$-C_6H_5$	$-CH_2CH_2N(CH_3)_2$	178–180	$C_{19}H_{23}NO_2{\cdot}HCl$	68.36	68.48	7.24	7.15	10.63	10.42
$-C_2H_5$	$-C_6H_5$	$-CH_2CH_2N(CH_3)_2$[b]	164–165	$C_{20}H_{25}NO_2{\cdot}HCl$	69.05	69.16	7.53	7.45	10.19	10.21
$-C_2H_5$	$-C_6H_5$	$-CH_2CH_2N(C_2H_5)_2$	124–126	$C_{22}H_{29}NO_2{\cdot}HCl$	70.29	70.43	8.05	8.09	9.43	9.46
$-C_2H_5$	$-C_6H_5$	$-CH_2CH_2NC_5H_{10}$	146–147	$C_{23}H_{29}NO_2{\cdot}HCl$	71.23	71.25	7.77	7.89	9.14	8.92
$-C_2H_5$	$-C_6H_5$	$-CH_2CH_2CH_2N(C_2H_5)_2$	152–153	$C_{23}H_{31}NO_2{\cdot}HCl$	70.83	71.13	8.27	8.16	9.09	9.21
$-C_2H_5$	$-C_6H_5$	$-CH_2CH_2CH_2NC_5H_{10}$	143–144	$C_{24}H_{31}NO_2{\cdot}HCl$	71.70	71.98	8.02	8.12	8.82	9.00
$-C_2H_5$	$-C_6H_5$	$-CH(CH_3)CH_2N(CH_3)_2$	165–166	$C_{21}H_{27}NO_2{\cdot}HCl$	69.70	69.97	7.80	7.96	9.79	9.53
$-C_2H_5$	$-C_6H_5$	$-CH(CH_3)CH_2N(C_2H_5)_2$	117–118	$C_{23}H_{31}NO_2{\cdot}HCl$	70.83	70.81	8.27	8.16	9.09	8.96
$-C_2H_5$	$-C_5H_5$	$-CH(CH_3)CH_2NC_5H_{10}$[c]	218–219	$C_{24}H_{31}NO_2{\cdot}HCl$	71.70	71.53	8.02	8.04	8.82	8.83
$-C_2H_5$	$-C_6H_{11}$	$-CH_2CH_2N(CH_3)_2$	170–171	$C_{20}H_{31}NO_2{\cdot}HCl$	67.87	67.65	9.11	9.00	10.02	10.09
$-C_2H_5$	$-C_6H_{11}$	$-CH_2CH_2N(C_2H_5)_2$	185–186	$C_{22}H_{35}NO_2{\cdot}HCl$	69.17	69.27	9.50	9.67	9.28	9.23
$-C_2H_5$	$-C_6H_{11}$	$-CH_2CH_2NC_5H_{10}$	158–159	$C_{23}H_{35}NO_2{\cdot}HCl$	70.11	70.29	9.21	9.18	9.00	8.95
$-CH_2CH_2CH_3$	$-C_6H_5$	$-CH_2CH_2N(CH_3)_2$	176–177	$C_{21}H_{27}NO_2{\cdot}HCl$	69.70	69.85	7.80	7.64	9.79	9.73
$-CH_2CH{=}CH_2$	$-C_6H_5$	$-CH_2CH_2N(CH_3)_2$[d]	147–148	$C_{21}H_{25}NO_2{\cdot}HCl$	70.08	70.05	7.28	7.64	9.85	10.02

[a] All melting points are corrected. [b] The methiodide melted at 159–160°. *Anal.* Calcd. for $C_{21}H_{28}INO_2$: C, 55.63; H, 6.22; N, 3.09. Found: C, 55.61; H, 6.17; N, 2.90. [c] The methiodide melted at 211–213°. *Anal.* Calcd. for $C_{25}H_{34}INO_2$: C, 59.17; H, 6.75; N, 2.76. Found: C, 59.19; H, 6.75; N, 2.99. [d] *Anal.* Calcd. for $C_{21}H_{25}NO_2{\cdot}HCl$: bromine uptake, 1 mole. Found: bromine uptake, 0.98 mole.

A solution of 10 g. (0.04 mole) of 2,2-diphenylbutanoic acid in 25 ml. of thionyl chloride was refluxed for three hours. The solution was concentrated and then reconcentrated several times with benzene to remove the excess thionyl chloride. The residue was finally taken up in 40 ml. of dry benzene, decolorized with charcoal and refluxed for ten hours with 7.4 g. (0.08 mole) of dimethylaminoethanol. The reaction mixture was made alkaline with 10% sodium hydroxide, extracted with benzene and the benzene extracts washed well with water and finally concentrated at the water pump. The residue was taken up in dry ether and the hydrochloride of the basic ester precipitated with alcoholic hydrogen chloride. After washing with ether, the hydrochloride was recrystallized twice from ethyl acetate to give 8.3 g. (57%) of product, m. p. 164–165°.

Summary

A number of basically substituted esters of 2,2-diphenylalkanoic acids, 2,2-diphenyl-4-pentenoic acid and 2-cyclohexyl-2-phenylbutanoic acid have been prepared.

Procedures for the hydrolysis of certain tertiary nitriles to the corresponding acids have been investigated.

RENSSELAER, N. Y. RECEIVED AUGUST 20, 1948

[CONTRIBUTION FROM THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

A Synthesis of Adenine. The Incorporation of Isotopes of Nitrogen and Carbon[1]

BY LIEBE F. CAVALIERI, JOHN F. TINKER AND AARON BENDICH

The earlier procedure[2] used for the synthesis of adenine labeled with isotopic nitrogen in the 1 and 3 positions[3] suffered from the disadvantage that the yields in certain steps were variable. This procedure as well as others[4,5] has been re-investigated and the synthesis now developed (Fig. 1) provides uniformly reproducible and satisfactory yields. This synthesis has been used for the incorporation of isotopes of carbon and of nitrogen into adenine.

Formamidine hydrochloride was prepared in nearly quantitative yield according to the reactions shown in Fig. 1. It will be noted that the atom per cent. excess of N^{15} in the formamidine hydrochloride is one half of that in the ammonia used, and that the isotope is distributed equally between the two nitrogen atoms. The condensation of formamidine hydrochloride and phenylazomalononitrile, to give I was carried out in *n*-butanol in the presence of sodium butoxide. In our hands, the yield of I was consistently lower when the condensation was carried out in ethanol containing sodium ethoxide.[2]

The previously described catalytic hydrogenation of 4,6-diamino-5-phenylazopyrimidine (I) to 4,5,6-triaminopyrimidine (II)[2] was found to be sensitive to impurities and variable yields were obtained. Upon investigation of other methods it was found that reduction with zinc and water proceeded smoothly with crude I.

A two-step cyclization of 4,5,6-triaminopyrimidine (II) to adenine (IV) was accomplished by

(1) The authors gratefully acknowledge the assistance of the James Foundation of New York, Inc., the National Cancer Institute of the U. S. Public Health Service, the United States Office of Naval Research and the Barker Welfare Foundation.

(2) Baddiley, Lythgoe and Todd, *J. Chem. Soc.*, 387 (1943).

(3) Brown, Roll, Plentl and Cavalieri, *J. Biol. Chem.*, **172**, 469 (1948).

(4) Traube, *Ann.*, **331**, 64 (1904).

(5) Hoffer, "Jubilee of Emil Barell," 428 (1946); *C. A.*, **41**, 4108 (1947).