TABLE I

PHENYL ESTERS

Acid	Formula	M.p., °C.	Solvent of cryst.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Benzoic	$C_{13}H_{10}O_2$	70–71					
Diglycolic	$C_{16}H_{14}O_5$	73–75	Heptane–toluene	67.12	67.45	4.93	4.91
Levulinic	$C_{11}H_{12}O_3$	32	Methanol–water	68.73	68.92	6.30	6.46
Maleic[a]	$C_{16}H_{12}O_4$	71–72	Heptane–toluene	71.63	72.01	4.51	4.72
Methacrylic[b]	$C_9H_{10}O_2$	17					
Phthalic[a,c]	$C_{20}H_{14}O_4$	73–74	Toluene–acetone				
Salicylic	$C_{13}H_{10}O_3$	42–43	Methanol				
Stearic[d]	$C_{24}H_{40}O_2$	51–52	Toluene				

[a] The anhydride was used as the starting material. [b] This agreed in b.p. and n_D with the lit. values,[2] and crystallized easily in the ice-box. [c] E. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 291. [d] *Ibid.*, p. 287.

acetic anhydride[3] which is not, however, readily accessible.

Phenyl esters of most carboxylic acids can be prepared easily and in good yields simply by heating the free acids with phenol in the presence of polyphosphoric acid on the steam-bath. In all cases tried the phenyl esters were easily separated from unreacted starting materials through their insolubility in dilute aqueous alkali. All solid phenyl esters crystallized beautifully, and we are tempted to suggest them as derivatives for the characterization of acids.

Experimental

Table I lists the esters prepared.

In a representative experiment, 50 g. of salicylic acid, 150 g. of phenol and 100 g. of polyphosphoric acid (Victor Chemical Co.) were stirred and heated on the steam-bath for 24 hours. The cooled mixture was diluted with water, extracted with toluene; and the toluene solution was extracted with aqueous sodium bicarbonate solution from which 14 g. of unreacted salicylic acid was recovered on acidification. The toluene solution was washed, stripped *in vacuo* and the residue distilled to yield unreacted phenol and 53 g. (95% based on unrecovered salicylic acid) of phenyl salicylate, b.p. 108–110° at 0.4 mm., which crystallized in the receiver. There was no flask residue. One crystallization from methanol yielded 49 g. of pure product melting at 42–43°.

Substantial quantities of polyphosphoric acid are desirable. In the preparation of diphenyl phthalate, phenolphthalein also was formed, and during the separations of phenyl levulinate and phenyl methacrylate, the aqueous alkali extracted products other than only starting materials. The yields (based on unrecovered organic acid) of phenyl levulinate and phenyl methacrylate were 35 and 55%, respectively, and in the other preparations yields ranged from 85 to 98%.

(3) (a) E. J. Bourne, M. Stacey, J. C. Tatlow and J. M. Tedder, *J. Chem. Soc.*, 2976 (1949); (b) A. H. Ahlbrecht and D. W. Codding, THIS JOURNAL, **75**, 984 (1953).

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Preparation of 1-Methyl-4-phenyl-4-(aminomethyl)- and 1-Methyl-4-phenyl-4-(methylaminomethyl)-piperidine

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When 1-methyl-4-phenyl-4-cyanopiperidine was heated with sodium and ethanol, Bergel, *et al.*,[1] obtained 1-methyl-4-phenylpiperidine. Provinciala[2] stated that sodium and ethanol, at 0°, reduced the 4-cyano to the corresponding 4-aminomethyl derivative which was claimed to be an active analgesic; a hydrochloride was obtained which melted at 190–192°. Kwartler and Lucas[3] prepared the 4-aminomethyl compound in 66.7% yield by hydrogenation of the 4-cyano derivative, in the presence of Raney nickel and ammonia, under 500 pounds pressure. According to them,[3a] the compound has negative analgesic activity; their dihydrochloride melted at 287–288°.

We found also that when 1-methyl-4-phenyl-4-cyanopiperidine was heated with sodium and ethanol, the cyano radical was replaced by hydrogen. The hydrochloride of the 1-methyl-4-phenylpiperidine obtained melted at 191–193°.[4] However, reduction with lithium aluminum hydride yielded the 4-aminomethyl compound in 83% yield; the dihydrochloride melted at 291–292°.

Formylation of the 4-aminomethyl derivative with chloral[5] produced the N-formyl derivative which was reduced with lithium aluminum hydride to the 4-methylaminomethyl compound.

Tested for analgesic activity in the Parke, Davis and Company laboratories under the direction of Dr. C. V. Winder, both the 4-aminomethyl and the 4-methylaminomethyl compound were found to be inactive as analgesics at the aspirin dose level.

Experimental

1-Methyl-4-phenyl-4-(aminomethyl)-piperidine.—1-Methyl-4-phenyl-4-cyanopiperidine (20.0 g.), dissolved in 50 cc. of ether, was reduced by adding the solution to 3.0 g. of lithium aluminum hydride, dissolved in 150 cc. of ether, in the usual manner. After the addition of 6 cc. of water, the mixture was filtered. From the filtrate there was obtained 16.6 g. (83%) of the desired product; b.p. 109–112° (1 mm.).[6]

The dihydrochloride precipitated when an ethereal solution of the base was treated with hydrogen chloride; m.p. 291–292° (dec.) after recrystallization from methanol.[7]

Anal. Calcd. for $C_{13}H_{22}N_2Cl_2$: N, 10.11; Cl, 25.63. Found: N, 10.37; Cl, 25.70.

(1) F. Bergel, J. W. Haworth, A. L. Morrison and H. Rinkerknecht, *J. Chem. Soc.*, 261 (1944).

(2) C. Provinciala, *Boll. chim. farm.*, **85**, 228 (1946); *C. A.*, **41**, 1328 (1947).

(3) (a) C. E. Kwartler and P. Lucas, THIS JOURNAL, **69**, 2582 (1947); (b) U. S. Patent 2,538,107; *C. A.*, **45**, 6664 (1951).

(4) O. Eisleb (*Ber.*, **74**, 1433 (1941)), who decarboxylated 1-methyl-4-phenylpiperidine-4-carboxylic acid, stated that the hydrochloride melted at 196–197°.

(5) F. F. Blicke and C. J. Lu, THIS JOURNAL, **74**, 3933 (1952).

(6) Ref. 3, b.p. 170–172° (12.5 mm.).

(7) Ref. 3, m.p. 287–288°.

1-Methyl-4-phenyl-4-(formamidomethyl)-piperidine.—Chloral (4.5 g.) was added slowly to 6.1 g. of the 4-aminomethyl compound with occasional cooling. After 12 hours at room temperature, the solid product was recrystallized from benzene; m.p. 108.5–110°; yield 4.4 g. (63.8%).

The dihydrochloride was recrystallized from ethanol; m.p. 276–277° (dec.).

Anal. Calcd. for $C_{14}H_{22}ON_2Cl_2$: N, 9.18; Cl, 23.23. Found: N, 9.22; Cl, 23.50.

1-Methyl-4-phenyl-4-(methylaminomethyl)-piperidine.—The formyl derivative (5.0 g.) was added in small portions to a stirred solution of 1.0 g. of lithium aluminum hydride in 50 cc. of ether. After the mixture had been stirred and refluxed for 4 hours, it was cooled, 2 cc. of water was added, dropwise, and the mixture filtered. The product obtained from the filtrate boiled at 117–119° (1.5 mm.); yield 3.8 g. (81%).

The dihydrochloride was recrystallized from ethanol; m.p. 256–257° (dec.).

Anal. Calcd. for $C_{14}H_{24}N_2Cl_2$: N, 9.62; Cl, 24.35. Found: N, 9.37; Cl, 24.68.

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Preparation of Cycloöctanone

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It was found that cycloöctanone can be obtained quite readily, in relatively large amounts, from the dimethyl ester of azelaic acid. This method is especially advantageous since azelaic acid has become a cheap commercial chemical.

The cyclization of the ester was attempted by Dieckmann[1] but he obtained only a resinous mass. By the use of sodium hydride[2] and high dilution technique, we converted dimethyl azelate into 2-carbomethoxycycloöctanone in 47.5% yield. Simultaneous hydrolysis and decarboxylation of the β-keto ester yielded cycloöctanone.[3]

Cycloöctanone was prepared also by a second procedure in which cycloheptanone cyanohydrin[4] was reduced with lithium aluminum hydride to 1-(aminomethyl)-cycloheptanol and the latter compound was then treated with nitrous acid.

Experimental

Dimethyl Azelate.—A practical grade of azelaic acid[5] was recrystallized from benzene with the use of Norite. After a second recrystallization from benzene, the acid melted at 94–97° and was sufficiently pure for the preparation of the ester.

A mixture of 752.8 g. of azelaic acid, 3.2 liters of methanol and 128 g. of concd. sulfuric acid was refluxed for 48 hours and then most of the solvent was removed under reduced pressure, the residue was poured into ice-water, the product extracted with ether, the ether solution shaken first with a saturated bicarbonate solution and then with water. The solution was dried with magnesium sulfate, the solvent removed and the ester distilled, yield 695.0 g. (80%), b.p. 145–153° (12 mm.).

2-Carbomethoxycycloöctanone.—To the middle neck of a 3-necked, 5-liter flask there was attached a jacketed 4" condenser. The upper end of the condenser was fitted with a ball joint lubricated with glycerol to which a short tube was attached. A Hershberg stirrer passed through the joint and the condenser into the flask. A piece of rubber tubing connected to the top of the short tube made a seal between the tube and the shaft of the stirrer. To the other necks of the flasks a nitrogen inlet tube and a dilution apparatus[6] were attached.

After the whole apparatus had been filled with dry nitrogen, 60.0 g. (2.5 moles) of sodium hydride, 60 g. of 5-mm. glass beads and 2.5 liters of xylene[7] were placed in the flask. A very slow stream of nitrogen was passed through the apparatus throughout the experiment. The suspension was stirred rapidly and 2 cc. of absolute methanol was added. The flask was heated and as soon as the mixture refluxed vigorously, the addition of 216.0 g. (1 mole) of dimethyl azelate, dissolved in 1.8 liters of xylene, was begun. The addition was made at the rate of about nine drops per minute and required about nine days. After the addition had been completed, the mixture was refluxed for one hour, and then allowed to cool to room temperature. The nitrogen inlet tube was replaced by a dropping funnel, and 150.0 g. (2.5 moles) of acetic acid was added to the stirred solution at such a rate that the reaction mixture did not become warm. After the mixture had been stirred for one hour, 142 cc. of water was added slowly. A few crystals of sodium acetate were added to induce the precipitation of the sodium acetate in the mixture. The precipitate was filtered and washed with xylene. The xylene solution was washed with concd. sodium bicarbonate solution, dried over anhydrous magnesium sulfate and then fractionated through a 15-cm. Vigreux column. The product which boiled at 129–135° (17 mm.) weighed 87.0 g. (47.5%); about 90% of this material boiled at 130–133° (17 mm.).[8]

Cycloheptanone Cyanohydrin.—Cycloheptanone[9] (224.0 g., 2 moles) and 98.0 g. (2 moles) of sodium cyanide were placed in a 2-liter, 3-necked flask equipped with a thermometer, stirrer and a dropping funnel. The mixture was stirred, cooled to 0° and a mixture of 115 cc. of concd. sulfuric acid and 460 cc. of water was added dropwise, at such a rate that the temperature of the mixture could be maintained below 5° by the use of an ice–salt-bath. After the addition was completed, water was added to dissolve the inorganic salts, the product was extracted with ether, the extract was washed free from acid and then dried with anhydrous magnesium sulfate. The dried extract was used for the next experiment.[10]

1-(Aminomethyl)-cycloheptanol.—The ether solution of the cyanohydrin was added, dropwise, to a stirred mixture of 100 g. of lithium aluminum hydride and 1 liter of ether. After the mixture had been stirred and refluxed for 36 hours, 120 cc. of water was added dropwise. The mixture was stirred for one-half hour, filtered and the inorganic salts washed with ether. From the ether solution there was obtained 124 g. (44% based on cycloheptanone) of product; b.p. 125–129° (17 mm.).[11] The hydrochloride melted at 217–218° after recrystallization from isopropyl alcohol–ether.

Cycloöctanone. (A).—A mixture of 174.0 g. (0.95 mole) of 2-carbomethoxycycloöctanone and 120.0 g. (3 moles) of sodium hydroxide, dissolved in 2.28 liters of water, was

(1) W. Dieckmann, *Ann.*, **317**, 49 (1901).

(2) Used previously in the Dieckmann cyclization by N. Green and L. B. LaForge, THIS JOURNAL, **70**, 2287 (1948).

(3) The procedure used successfully for the preparation of suberone (cycloheptanone) (F. F. Blicke, N. J. Doorenbos and R. H. Cox, *ibid.*, **74**, 2924 (1952)) could not be utilized for cycloöctanone since suberone condensed with nitromethane to form 1-(nitromethyl)-cycloheptanol in only 3% yield.

(4) Cyclohexanone cyanohydrin has been reduced with lithium aluminum hydride by H. R. Nace and B. B. Smith, *ibid.*, **74**, 1861 (1952).

(5) Purchased from The Matheson Company.

(6) For a description see N. J. Leonard and R. C. Sentz, *ibid.*, **74**, 1708 (1952). To neck D of this apparatus we connected a drip-tip condenser to which a calcium chloride tube was attached and a 1-liter Hershberg dropping funnel was inserted into neck E.

(7) All of the xylene used had been distilled from sodium.

(8) V. Prelog, L. Ruzicka, P. Barman and L. Frenkiel, *Helv. Chim. Acta*, **31**, 92 (1948), found 120° (12 mm.).

(9) F. F. Blicke, N. J. Doorenbos and R. H. Cox, THIS JOURNAL, **74**, 2924 (1952).

(10) B. Tchoubar (*Compt. rend.*, **215**, 224 (1942)), reported that the cyanohydrin boils at 138–139° (15 mm.). We found that upon distillation, under these conditions, about one-half of the cyanohydrin decomposed into cycloheptanone.

(11) B. Tchoubar (*Bull. soc. chim. France*, 160 (1949)), obtained this product in 50% yield by reduction of the cyanohydrin with hydrogen in the presence of platinum oxide; b.p. 124° (15 mm.); hydrochloride, m.p. 223°. Previously, B. Tchoubar (ref. 10) reported the melting point of the hydrochloride to be 185°.