characterization of two new crystalline compounds containing sulfur. Microanalytical data showed that one compound had the formula, $C_{20}H_{23}NO_7S$, and the other, $C_{19}H_{21}NO_7S$. They yielded erysovine ($C_{18}H_{21}NO_3$) and erysopine ($C_{17}H_{19}NO_3$), respectively, on hydrolysis. For correlation of names and to designate the sulfur atom present, they were named erysothiovine and erysothiopine. Since the hydrolytic reaction yielded one mole of sulfoacetic acid in each case, erysothiovine and erysothiopine are alkaloidal esters of sulfoacetic acid with erysovine and erysopine. Apparently, they are sulfonic esters.

Erysothiovine and erysothiopine are highly active for curare-like paralysis in frogs and they are three to four times more active than the corresponding alkaloids erysovine and erysopine.

RAHWAY, NEW JERSEY RECEIVED APRIL 15, 1944

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. VI

BY F. F. BLICKE AND R. F. FELDKAMP[1,2]

It has been well established, during the last ten years, that basic-alkyl esters of certain diaryl-, diaralkyl-, arylcycloalkyl- and arylalkyl-acetic acids are effective agents for relief of spasms of the gastrointestinal tract. Many of these esters also produce local anesthesia and mydriasis when applied to the cornea.

Since β-diethylaminoethyl diphenylacetate hydrochloride (Trasentin) is an effective spasmolytic, it was of interest to prepare other esters which contained two phenyl nuclei in the acyl radical. Obviously, esters of *p*-xenylacetic and of α-naphthylacetic acid represent such compounds. Esters of the former acid were described previously,[3] and this publication deals with esters of the latter type.

Incidentally, basic-alkyl esters of diphenylacetic acid which contain an *o,o'*-bridge, that is, esters of fluorene-9-carboxylic acid, have been shown to be active antispasmodics.[4]

Although α-naphthylacetic acid is analogous to diphenylacetic acid in that it contains two phenyl nuclei, it is unlike the latter inasmuch as it is a mono- instead of a disubstituted acid. Since the most active antispasmodics are esters of disubstituted acetic acids, and since β-diethyl-aminoethyl phenylpropylacetate has been shown to be a potent product,[5] we prepared also esters of α-naphthylalkylacetic acids in which the alkyl groups were represented by methyl and ethyl radicals. In addition, a few esters of α-naphthylphenylacetic acid were synthesized.

All esters were isolated in the form of crystalline hydrochlorides; attempts to obtain esters of α-naphthylpropyl- and α-naphthylbutylacetic acid as crystalline hydrochlorides were unsuccessful.

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by R. F. Feldkamp in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Frederick Stearns and Company Fellow.

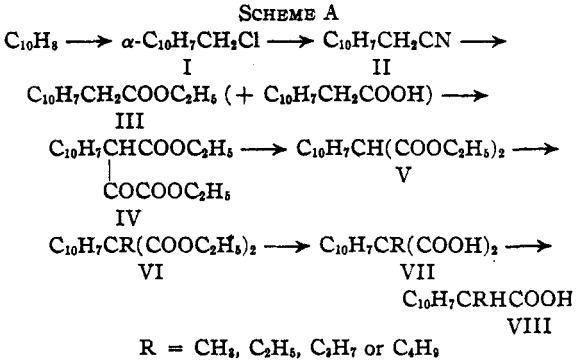
(3) Blicke and Grier, THIS JOURNAL, **65**, 1725 (1943).

(4) Burtner and Cusic, *ibid.*, **65**, 262 (1943); Lehmann and Knoefel, *J. Pharmacol. Exp. Therapy*, **74**, 274 (1942).

(5) Halpern, *Compt. rend. soc. biol.*, **126**, 678 (1937); *Arch. intern. pharmacodynamie*, **59**, 149 (1938).

The α-naphthylalkylacetic acids, required for the preparation of the esters, were synthesized according to schemes A and B. Only α-naphthylmethylacetic acid had been described hitherto. It was obtained by Tiffeneau and Daudel[6] by oxidation of α-naphthylmethylacetaldehyde.

SCHEME A



The conversion of naphthalene, by chloromethylation, into α-naphthylmethyl chloride (I), and of the latter into α-naphthylmethyl cyanide (II), requires no comments. When the cyanide was boiled with alcohol and sulfuric acid, ethyl α-naphthylacetate (III) was obtained; enough α-naphthylacetic acid for our purpose was also formed as a by-product so that it was not necessary to prepare this acid by a separate process. The acetate (III) reacted with ethyl oxalate and sodium ethylate to yield ethyl ethoxalyl-α-naphthylacetate (IV), and expulsion of carbon monoxide from the latter yielded diethyl α-naphthylmalonate (V). Alkyl groups were introduced in the usual manner to form diethyl α-naphthylalkylmalonates (VI). Hydrolysis of the esters, and partial decarboxylation of the acids yielded successively compounds of types VII and VIII.

The procedure indicated by scheme B was employed for the preparation of α-naphthylphenylacetic acid; we found that α-naphthylpropyl- and α-naphthylbutylacetic acid also can be synthesized satisfactorily by this method.

(6) Tiffeneau and Daudel, *Compt. rend.*, **147**, 679 (1908).

SCHEME B

$$C_{10}H_8 \longrightarrow \underset{\text{IX}}{\alpha\text{-}C_{10}H_7COCOOC_2H_5} \longrightarrow C_{10}H_7COCOOH \longrightarrow \underset{\text{X}}{C_{10}H_7CR(OH)COOH} \longrightarrow \underset{\text{XI}}{C_{10}H_7CRHCOOH} \quad \underset{\text{XII}}{}$$

R = C_6H_5, C_3H_7 or C_4H_9

Ethyl α-naphthylglyoxylate (IX) was prepared from naphthalene, ethyl oxalyl chloride and aluminum chloride. α-Naphthylglyoxylic acid (X), obtained by hydrolysis of the ester, was allowed to react with the required Grignard reagent with the formation of $C_{10}H_7CR(OMgBr)$-COOMgBr. Treatment of the latter with acid yielded the disubstituted hydroxyacetic acid (XI) which was reduced to the acetic acid (XII) by the use of red phosphorus and iodine.

Rousset[7] obtained ethyl α-naphthylglyoxylate (IX), and also some ethyl β-naphthylglyoxylate, from the interaction of naphthalene, ethyl oxalyl chloride and aluminum chloride with carbon disulfide as a solvent. When we used his procedure, the yield of the mixture of the two esters was only 19%. By the use of tetrachloroethane instead of carbon disulfide, and a few other changes, the yield of the ester mixture was increased to 69%. The esters were separated by the use of picric acid, a procedure which had been applied by Rousset. Upon hydrolysis of ethyl α-naphthylglyoxylate we obtained α-naphthylglyoxylic acid but the properties of this acid did not correspond to those mentioned by Rousset or by Darapsky.[8] When ethyl β-naphthylglyoxylate was hydrolyzed, we found that the β-naphthylglyoxylic acid possessed properties different from those reported by Popovici[9] who stated that she obtained this acid by oxidation of methyl β-naphthyl ketone.

Beckmann and Paul[10] obtained α-naphthylphenylglycolic acid (α-naphthylphenylhydroxyacetic acid; XI, R = C_6H_5) from the disodium derivative of phenyl α-naphthyl ketone and carbon dioxide. Later, McKenzie and Tattersall[11] prepared it from ethyl phenylglyoxylate and α-naphthylmagnesium bromide in 61% yield. When we synthesized the acid from ethyl α-naphthylglyoxylate and phenylmagnesium bromide, the yield was unsatisfactory. However, when phenylmagnesium bromide was allowed to react with α-naphthylglyoxylic acid, we obtained α-naphthylphenylglycolic acid in 76% yield. This procedure, the interaction of a Grignard reagent with the glyoxylic acid instead of the glyoxylate, had been shown previously by McKenzie and Ritchie[12] to be a practical one for the synthesis of phenylethylglycolic acid.

Our esters, in the form of their water-soluble hydrochlorides, were examined pharmacologically by Dr. C. W. Geiter and Dr. A. M. Lands in the Frederick Stearns and Company laboratories. All of them produced relaxation of the untreated, isolated intestine. The maximum effective dilution for the least active products, the morpholinoalkyl esters, ranged from 1:100,000 to 1:400,000. Several esters, among them β-diethylaminoethyl α-naphthylethylacetate, β-piperidinoethyl α-naphthylethylacetate and γ-diethylaminopropyl α-naphthylphenylacetate produced relaxation in dilutions of 1:1,000,000 to 1:2,000,000.

Experimental Part

Ethyl α-Naphthylacetate (III).—α-Naphthylmethyl chloride[13] was converted into α-naphthylmethyl cyanide (II)[13a] by the use of potassium cyanide in 82% yield. To a mixture of 100 g. of the cyanide and 225 g. of absolute alcohol there was added, carefully, 225 g. of concd. sulfuric acid. The material was heated on a steam-bath for twelve hours, poured into 1000 cc. of cold water, and the product extracted with ether. The extract was shaken with water, and then with dilute sodium carbonate solution. Upon acidification of the alkaline layer, 15 g. of α-naphthylacetic acid precipitated; m. p. 131–132° after recrystallization from dilute acetic acid. The ether layer was dried with magnesium sulfate, the solvent removed and the residue fractionated. The ester boiled at 180–181° (15 mm.)[14]; yield 87 g. (67%).

Diethyl α-Naphthylmalonate (V).—A solution of sodium ethylate, prepared from 11.5 g. of sodium and 250 cc. of absolute alcohol in a liter, 3-necked flask fitted with a stirrer and reflux condenser, was stirred and 73 g. of pure diethyl oxalate added, followed by 112 g. of ethyl α-naphthylacetate. The mixture was heated until it just began to reflux, and the heating was then discontinued. After about fifteen minutes the mixture solidified. It was removed from the flask with the aid of ether, filtered, and the product (158 g.) washed with ether. The material was mixed with 700 cc. of water whereupon most of it dissolved; 200 cc. of ether was added, and then just enough 50% sulfuric acid (about 60 cc.) to make the aqueous layer acidic to litmus. The mixture was stirred, the ether layer removed, and the aqueous layer extracted with ether. The combined ether solutions were dried with magnesium sulfate. The ether was removed in a Claisen flask, and 20 g. of powdered glass was added to the residue, ethyl oxalyl-α-naphthylacetate (IV). The latter was heated in a bath under 15 mm. pressure until the bath temperature reached 175°. This temperature was maintained for about an hour. At the end of this time no more carbon monoxide was evolved. The malonate boiled at 178–182° (2–3 mm.); yield 104 g. (69%); m. p. 62°[15] after recrystallization from petroleum ether (60–70°).

Diethyl α-Naphthylalkylmalonates (VI). Diethyl α-Naphthylethylmalonate.—The general procedure employed is illustrated in the case of diethyl α-naphthylethylmalonate. Three and forty-five hundredths grams (0.15 mole) of sodium was converted into very fine pellets under xylene, the xylene replaced by 100 cc. of dry benzene, the mixture refluxed, and 42.8 g. (0.15 mole) of diethyl α-naphthylmalonate, dissolved in 100 cc. of benzene, added over a two-hour period. After the mixture had been refluxed for four hours, the sodium derivative had formed as a cake in the flask; 46.8 g. (0.30 mole) of ethyl iodide was added, and the material was refluxed for about forty-eight hours. After the addition of 15 cc. of alcohol to destroy any traces of sodium, 200 cc. of ether and enough water (100–

(7) Rousset, *Bull. soc. chim.*, [3] **17**, 301 (1897).

(8) Darapsky, *J. prakt. Chem.*, **46**, 302 (1936).

(9) Popovici, *Compt. rend.*, **191**, 210 (1930); *C. A.* **24**,, 5301 (1930).

(10) Beckmann and Paul, *Ann.*, **266**, 12 (1891).

(11) McKenzie and Tattersall, *J. Chem. Soc.*, **127**, 2522 (1925).

(12) McKenzie and Ritchie, *Ber.*, **70**, 33 (1937).

(13) (a) Cambron, *Can. J. Research*, **17B**, 10 (1939); (b) Grummitt and Buck, THIS JOURNAL, **65**, 295 (1943).

(14) Cambron (ref. 13a) reported 160–164° (6–7 mm.).

(15) This product had been obtained by Wislicenus, Butterfass and Koken (*Ann.*, **436**, 81 (1924)) by a less satisfactory procedure. They reported the melting point to be 59–60°.

150 cc.) to dissolve the sodium iodide were added. The benzene–ether layer was separated, and washed with sodium thiosulfate solution. The solvents were removed on a steam-bath, and the residue distilled. The oily distillate was mixed with an equal volume of petroleum ether (30–40°), and the mixture cooled and rubbed, whereupon the ester was obtained in crystalline form.

TABLE I

DIETHYL α-NAPHTHYLALKYLMALONATES, α-$C_{10}H_7CR(COOC_2H_5)_2$

R	% Yield Oil	% Yield Crystals	M. p., °C.	B. p., °C.	Recrystallized from
CH_3	76.8	75.6	46–47	170–171 (2–3 mm.)	Pet. ether
C_2H_5	79.5	59	48–49	171–174 (3 mm.)	(30–40°)
C_3H_7	62.6	40	51–52	182–184 (4 mm.)	Dil. alcohol
C_4H_9	55.6	22	53–54	185–188 (4 mm.)	Dil. alcohol

R	Formula	Analyses, %[a] Calcd. C	Calcd. H	Found C	Found H
CH_3	$C_{18}H_{20}O_4$	72.03	6.71	69.80[b]	6.83
C_2H_5	$C_{19}H_{22}O_4$	72.59	7.05	71.84	7.26
C_3H_7	$C_{20}H_{24}O_4$	73.20	7.32	72.77	7.54
C_4H_9	$C_{21}H_{26}O_4$	73.70	7.65	73.24	7.82

[a] The analyses were made with the crystalline esters. It seems from the analytical data that the esters, in spite of their fairly sharp melting and boiling points, were not quite pure. Since the melting points of the esters were not raised by several recrystallizations, it did not seem justifiable to lose valuable material in further attempts at purification, especially since the purity was entirely satisfactory for subsequent procedures. [b] We believe that this low value is due to an error in analysis. Unfortunately, circumstances did not permit us to make another analysis.

α-Naphthylalkylacetic Acids (VIII). α-Naphthylmethylacetic Acid.—The general procedure is illustrated in the case of α-naphthylmethylacetic acid. Twenty-nine grams (0.0965 mole) of diethyl α-naphthylmethylmalonate, dissolved in 75 cc. of alcohol, and 20 g. of potassium hydroxide, dissolved in the least possible amount of water, were refluxed for five hours. During this time the potassium salt of the malonic acid precipitated. The alcohol was removed under reduced pressure, the residue dissolved in 100 cc. of water, the solution cooled, and neutralized with hydrochloric acid. The α-naphthylmethylmalonic acid (VII, R = CH_3), which precipitated as an oil, began to lose carbon dioxide spontaneously with the formation of the crystalline α-naphthylmethylacetic acid (VIII, R = CH_3). The latter was filtered, dried, and then heated in a flask at 180° for two hours in order to make certain that decarboxylation was completed.[16] The acetic acid was dissolved in 100 cc. of 10% sodium carbonate solution, heated with Norite for two hours, filtered, the filtrate shaken with ether to remove traces of impurities, the ether layer removed, and the aqueous layer heated to remove all of the ether. After acidification, the precipitated acid was recrystallized from dilute alcohol; yield 17.5 g. (91%).

TABLE II

α-NAPHTHYLALKYLACETIC ACIDS

The methyl derivative was recrystallized from dilute alcohol, the ethyl derivative from petroleum ether (90–100°), and the butyl derivative from petroleum ether (30–40°).

α-$C_{10}H_7CHRCOOH$

	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	148–149[a]	$C_{13}H_{12}O_2$	78.00	77.70	6.04	6.16
C_2H_5	86– 87	$C_{14}H_{14}O_2$	78.49	78.49	6.58	6.74
C_3H_7	Oil[b]	$C_{15}H_{16}O_2$	78.91	78.74	7.06	7.16
C_4H_9	64– 65[c]	$C_{16}H_{18}O_2$	79.31	79.03	7.48	7.52

[a] Tiffeneau and Daudel (*Compt. rend.*, **147**, 679 (1908)) found 145°. [b] B. p. 190° (4 mm.). [c] B. p. 183° (3 mm.).

(16) This operation may not be necessary since there was no evidence that any carbon dioxide was evolved.

Ethyl α-Naphthylglyoxylate (IX) and Ethyl β-Naphthylglyoxylate.—Seventy-six grams (0.59 mole) of naphthalene was dissolved in 500 cc. of dry tetrachloroethane, 89.5 g. (0.65 mole) of ethyl oxalyl chloride added, and the mixture poured into a 3-liter, 3-necked flask fitted with a mercury-sealed stirrer and a reflux condenser.[17] One neck of the flask was connected with a 500-cc. Erlenmeyer flask by means of a piece of wide rubber tubing abut eight inches long. The Erlenmeyer flask was supported by a ring stand, neck down, and 95 g. (0.71 mole) of aluminum chloride, which had been placed in the flask, was added to the reaction mixture in portions during a two-hour period. This was effected with the aid of two pinch clamps which had been attached to the rubber tubing a few centimeters apart. The mixture was cooled with ice during the addition and finally stirred for twelve hours at ordinary temperature. The material was poured onto ice, the organic layer separated, washed thoroughly with water, then with dilute sodium carbonate solution, and finally with water. The tetrachloroethane was removed at 50° under reduced pressure, and the residue distilled; b. p. 164–168° (3 mm.).[18] The pale yellow oil, which is a mixture of ethyl α-naphthyl- and ethyl β-naphthylglyoxylate, weighed 93 g. (69%).

In order to isolate the α-naphthyl ester, 50 g. of the oil was dissolved in 86 cc. of absolute alcohol, and 50 g. of picric acid added. The mixture was heated until a clear yellow solution was obtained. The latter was cooled, the crystalline precipitate filtered, and washed with cold alcohol. The filtrate was treated in the manner described below. The picric acid compound weighed 90 g. and melted at 76°. The latter was suspended in 1000 cc. of water, and 10% sodium carbonate solution added until the mixture was slightly alkaline to litmus. The oily ethyl α-naphthylglyoxylate which separated was extracted with four 40-cc. portions of carbon tetrachloride. The combined extracts were shaken with water until free from picric acid. The solvent was removed by distillation, and the residue fractionated; b. p. 167° (3 mm.)[19]; yield 38 g. (46%).

The alcohol was removed from the filtrate by distillation, and the oily residue treated with sodium carbonate solution. Subsequent operations were the same as those described above. The ethyl β-naphthylglyoxylate boiled at 161–165° (2–3 mm.).[20]

α-Naphthylglyoxylic Acid (X).—A mixture of 51 g. of ethyl α-naphthylglyoxylate, 400 cc. of 10% sodium carbonate solution and 100 cc. of alcohol was refluxed for twelve hours. The mixture was poured into an evaporating dish, heated on a steam-bath, and the alcohol and water removed in a stream of air. The solid residue was dissolved in 400 cc. of water, 100 cc. of ether added, the mixture stirred and made just acidic to litmus with hydrochloric acid. The ether layer was separated, the aqueous layer extracted with ether, the combined ether solutions dried with magnesium sulfate, and the solvent removed. The oily residue was heated in a flask on a steam-bath under reduced pressure for some time in order to remove all of the water. When the oil was cooled, it solidified; yield 43 g. (96%); it was recrystallized three times from xylene; m. p. 112–113°.[21]

Anal. Calcd. for $C_{12}H_8O_3$: C, 72.00; H, 4.03. Found: C, 71.88; H, 4.16.

β-Naphthylglyoxylic Acid.—A mixture of 56.5 g.[22] of ethyl β-naphthylglyoxylate, 340 cc. of 10% sodium car-

(17) Adickes, Brunnert and Lücher, *J. prakt. Chem.*, **130**, 168 (1931). Kindler, Metzendorf and Dschi-yin-Kwok, *Ber.*, **76**, 308 (1943).

(18) Rousset (ref. 7) found 200–210° (10 mm.).

(19) Rousset (ref. 7) found 213–215° (23 mm.).

(20) The reported boiling point (ref. 7) is 212–215° (20 mm.).

(21) Rousset (ref. 7) stated that he obtained red-brown crystals from benzene which effervesce in air. When heated they became brown at 95° and melted at 100°. Material which had been dried in a vacuum desiccator melted at 107–108° with decomposition. Darapsky (ref. 8) found 105°.

(22) This material represented combined batches of the β-naphthyl ester which had been obtained from a number of experiments.

TABLE III

HYDROCHLORIDES OF BASIC-ALKYL ESTERS OF α-NAPHTHYLACETIC AND SUBSTITUTED α-NAPHTHYLACETIC ACIDS

Compound 1 was recrystallized from a mixture of alcohol and ethyl acetate; compounds 2 and 6 from a mixture of alcohol and ether; compounds 4, 5, 8, 9, 12 and 13 from ethyl acetate; compounds 3, 7, 10, 11, 14 and 16 from a mixture of isopropyl alcohol and isopropyl ether; compound 15 is hygroscopic, and was merely washed with absolute ether.

	R	M. p., °C.[a]	Formula	Chlorine, % Calcd.	Found
		$C_{10}H_7CH_2COOR\cdot HCl$			
1	$CH_2CH_2N(C_2H_5)_2$	128–130	$C_{18}H_{24}O_2NCl$	11.03	11.30
2	$CH_2CH_2NC_5H_{10}$[b]	122–124	$C_{19}H_{24}O_2NCl$	10.62	10.76
3	$CH_2CH_2NC_4H_8O$[c]	131–132	$C_{18}H_{22}O_3NCl$	10.58	10.59
4	$CH_2CH_2CH_2N(C_2H_5)_2$	110–111	$C_{19}H_{26}O_2NCl$	10.56	10.62
		$C_{10}H_7CH(CH_3)COOR\cdot HCl$			
5	$CH_2CH_2N(C_2H_5)_2$	98–100	$C_{19}H_{26}O_2NCl$	10.57	10.81
6	$CH_2CH_2NC_5H_{10}$	115–117	$C_{20}H_{26}O_2NCl$	10.21	10.32
7	$CH_2CH_2NC_4H_8O$	148–149	$C_{19}H_{24}O_3NCl$	10.13	10.22
8	$CH_2CH_2CH_2N(C_2H_5)_2$	90– 94	$C_{20}H_{28}O_2NCl$	10.15	10.32
		$C_{10}H_7CH(C_2H_5)COOR\cdot HCl$			
9	$CH_2CH_2N(C_2H_5)_2$	117–119	$C_{20}H_{28}O_2NCl$	10.14	10.41
10	$CH_2CH_2NC_5H_{10}$	139–140	$C_{21}H_{28}O_2NCl$	9.82	9.94
11	$CH_2CH_2NC_4H_8O$	167–168	$C_{20}H_{26}O_3NCl$	9.76	9.88
12	$CH_2CH_2CH_2N(C_2H_5)_2$	97– 98	$C_{21}H_{30}O_2NCl$	9.76	9.83
		$C_{10}H_7CH(C_6H_5)COOR\cdot HCl$			
13	$CH_2CH_2N(C_2H_5)_2$	124–126	$C_{24}H_{28}O_2NCl$	10.56	10.62
14	$CH_2CH_2NC_5H_{10}$	167–168	$C_{25}H_{28}O_2NCl$	8.66	8.73
15	$CH_2CH_2NC_4H_8O$	About 110	$C_{24}H_{26}O_3NCl$	8.63	8.67
16	$CH_2CH_2CH_2N(C_2H_5)_2$	About 107	$C_{25}H_{30}O_2NCl$	8.62	8.64

[a] In some cases the salts began to soften below the melting point. [b] NC_5H_{10} = piperidino. [c] NC_4H_8O = morpholino.

bonate and 85 cc. of alcohol was refluxed for three hours. The mixture was concentrated until a solid began to separate. The material was cooled, the precipitated sodium salt filtered, dissolved in 700 cc. of water, the solution treated with Norite on a steam-bath, and filtered. The yellow solution was acidified with dilute hydrochloric acid, the precipitated oily acid extracted with ether, the solution dried with magnesium sulfate, the ether removed, and the residual oil dried at 100° under reduced pressure. The product was dissolved in 100 cc. of hot xylene, the solution cooled, and the precipitated, yellow, crystalline acid recrystallized from xylene. The light yellow, water-insoluble compound weighed 20 g. and melted at 92–93°.[23] The melting point was not changed by four additional recrystallizations from xylene.

Anal. Calcd. for $C_{12}H_8O_3$: C, 72.00; H, 4.03. Found: C, 71.98; H, 4.14.

α-Naphthylphenylglycolic Acid (XI, R = C_6H_5).—Phenylmagnesium bromide was prepared from 47.1 g. (0.3 mole) of bromobenzene, 7.3 g. (0.3 mole) of magnesium and 150 cc. of dry ether in a 500-cc. flask fitted with a siphon to which a stopcock had been attached. The Grignard solution was added, dropwise, during the course of two hours to 20 g. (0.1 mole) of α-naphthylglyoxylic acid which had been dissolved in 150 cc. of ether and placed in a liter 3-necked flask, fitted with a stirrer and a condenser. During the addition, the mixture was cooled with a mixture of salt and ice, and stirred. The ether was decanted from the gummy precipitate and discarded; the latter was washed with ether. After treatment with ice and dilute sulfuric acid, the product was extracted with ether, the solution filtered, and the solvent removed. The oily residue was triturated with 10% sodium carbonate solution, the mixture filtered, and the filtrate extracted with ether to remove traces of impurities. The alkaline solution was acidified with dilute hydrochloric acid. The precipitated, crystalline acid weighed 25 g. It was recrystallized from dilute acetic acid. The acid, which contained solvent of crystallization,[24] does not melt sharply; it begins to soften about 90° and is completely melted at 147°. The product becomes green when moistened with concd. sulfuric acid.

α-Naphthylphenylacetic Acid (XII, R = C_6H_5).—When 21 g. of the glycolic acid was reduced with red phosphorus and iodine by the procedure described in "Organic Syntheses,"[25] 17.6 g. (89%) of the acetic acid was obtained after recrystallization from dilute acetic acid; m. p. 139–140°.[26]

α-Naphthylpropylglycolic and α-Naphthylpropylacetic Acid.—The glyoxylic acid was obtained in the manner described above from 36.9 g. of propyl bromide, 7.3 g. of magnesium, 150 cc. of ether and 20 g. of the keto acid. After two recrystallizations from benzene, the glycolic acid weighed 11 g. (58%); m. p. 139–140°. The acid turned orange when moistened with concd. sulfuric acid.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.68; H, 6.88.

Upon reduction of 11 g. of the glycolic acid, 8 g. (78%) of the acetic acid was obtained; b. p. 182–184° (3 mm.).

α-Naphthylbutylglycolic and α-Naphthylbutylacetic Acid.—From 41.1 g. of butyl bromide, 7.3 g. of magnesium, 150 cc. of ether and 20 g. of the keto acid there was produced 16.5 g. (64%) of the glycolic acid after two recrystallizations from benzene; m. p. 116–117°.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.03. Found: C, 74.18; H, 7.18.

From 15 g. of the glycolic acid, 1.5 g. of red phosphorus, 0.5 g. of iodine and 25 cc. of acetic acid there was obtained 11 g. (78%) of the acetic acid; b. p. 182–183°. After some time the distillate partially crystallized. The material was dissolved in 15 cc. of petroleum ether (30–

(23) According to Rousset (ref. 7) the acid is an oil. Popovici (ref. 9) stated that the acid melts at 171°.

(24) See McKenzie and Tattersall, ref. 11.

(25) "Organic Syntheses," Coll. Vol. 1, p. 224, 2nd ed.

(26) McKenzie and Tattersall (ref. 11) found 140–141°.

40°), and cooled with ice and salt. The crystals which precipitated melted at 62–63°.

Basic Esters.—A mixture of 0.015 mole of the acetic acid, 0.015 mole of the basic alkyl chloride[27] and 40 cc. of dry isopropyl alcohol[28] was refluxed for forty hours, the alcohol removed on a steam-bath in a current of air, and the residue washed repeatedly with absolute ether.

In order to obtain the β-morpholinoethyl esters, 0.02 mole of the acetic acid and 7 cc. of pure thionyl chloride were refluxed for two hours. The excess thionyl chloride was removed on a steam-bath under reduced pressure. In order to remove traces of thionyl chloride, 10 cc. of dry benzene was added, and then removed under diminished pressure; this process was repeated three times. The acetyl chloride was cooled with ice, and 2.98 g. (0.0275 mole) of β-morpholinoethyl alcohol, dissolved in 20 cc. of dry benzene added slowly while the mixture cooled in ice and was shaken. The latter was refluxed for two hours on a steam-bath, and the benzene removed under reduced pressure. The crystalline residue was triturated with 50 cc. of water which contained a few drops of hydrochloric acid. The mixture was extracted with ether, the aqueous layer separated, and made alkaline with sodium carbonate solution. The precipitated ester was extracted with ether, and the extract shaken with water to remove any traces of the alcohol. The extract was dried with magnesium sulfate, filtered and hydrogen chloride passed into it. The ester precipitated in crystalline form in about 60% yield.

(27) The melting point for β-piperidinoethyl chloride hydrochloride was reported to be 208° by Marckwald and Frobenius (*Ber.*, **34**, 3557 (1901)), as well as by Knorr, Hörlein and Roth (*ibid.*, **38**, 3138 (1905)). Dunlop (*J. Chem. Soc.*, **101**, 2202 (1912)) stated that the salt melts at 231°. Prepared by Dunlop's method, we found that the hydrochloride melts at 229–230° and that β-piperidinoethyl chloride boils at 69° (12 mm.).

(28) Method of Horenstein and Pählicke (*Ber.*, **71**, 1654 (1938)).

Summary

Basic esters of α-naphthylacetic, α-naphthylmethyl-, α-naphthylethyl- and α-naphthylphenylacetic acid have been prepared. All of the esters have been found to be antispasmodics, and some of them exhibit high activity.

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[CONTRIBUTION FROM THE KENT AND GEORGE HERBERT JONES CHEMICAL LABORATORIES, UNIVERSITY OF CHICAGO]

The Synthesis of DL-Threose. Preparation of DL-Tribenzoyl-erythrose

BY W. W. LAKE[1] WITH J. W. E. GLATTFELD

For a number of years these Laboratories have been engaged in the synthesis and characterization of the eleven C_4-saccharinic acids which are the theoretically possible products of the saccharinic acid rearrangement of the aldotetroses as defined in the third paper cited below.[2]

More recently, attempts have been made to synthesize the aldotetroses themselves. Some success has been achieved in the preparation of DL-erythrose[3] by the reduction of DL-erythronic lactone. The present paper reports the development of a method for the synthesis of DL-threose which is needed as the initial material in a proposed study of the saccharinic acid rearrangement of the tetroses.

DL-Threose.—DL-Threonic acid, synthesized by Braun[4] from glycerol dichlorohydrin and recently by Glattfeld and Rietz[5] from allyl alcohol, offered a starting material of the right configuration, which, if successfully reduced, would yield the desired DL-threose. It was thought that the reduction might be accomplished by the complete benzoylation of DL-threonic acid, conversion to the corresponding acid chloride, and reduction of the benzoyl acid chloride by a method similar to that employed by Glattfeld and Kribben[3] in the reduction of DL-triacetyl-erythronic acid. However, benzoylation of DL-threonic acid yielded DL-dibenzoyl-threonic lactone instead of the desired DL-tribenzoyl-threonic acid and indirect methods of obtaining the completely benzoylated acid were thus shown to be necessary.

During the progress of this work, Hurd and Sowden[6] published a satisfactory method for the preparation of fully acetylated aldonic acids by the action of nitrous anhydride in glacial acetic acid on the amides of fully acetylated aldonic acids. About the same time, Robbins and Upson[7] showed that the amides of fully acetylated aldonic acids could be prepared in good yield by direct acetylation of aldonic amides. Glattfeld and Macmillan[8] have shown that the amides of aldonic acids may be conveniently prepared in good yield by the action of liquid ammonia on the corresponding acid lactones. A combination of procedures similar to these seemed, therefore, to offer a promising method for the preparation of fully benzoylated DL-threonic acid from DL-threonic lactone.

It was found that DL-threonic lactone could be readily obtained in good yield by thermal decomposition, at reduced pressure, of the potassium salt of DL-*threo*-2,3-dihydroxy-4-chloro-butanoic acid which is an intermediate in the synthesis of DL-threonic acid by the methods of both Braun[4] and Glattfeld and Rietz.[5] The solid potassium salt of DL-*threo*-2,3-dihydroxy-4-chlorobutanoic acid was prepared in practically quanti-

(1) This article is condensed from a dissertation presented by W. W. Lake in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Chicago, 1941. Much of the experimental work was carried out in the laboratories of the Texas College of Mines and Metallurgy.

(2) Glattfeld and co-workers, THIS JOURNAL, **42**, 2314 (1920); **43**, 2675 (1921); **47**, 1742 (1925); **49**, 2309 (1927); **53**, 3164 (1931); **55**, 1114 (1933); **55**, 3663 (1933); **60**, 415 (1938).

(3) Glattfeld and Kribben, *ibid.*, **61**, 1720 (1939).

(4) Braun, *ibid.*, **52**, 3167 (1930); **52**, 3176 (1930).

(5) Glattfeld and Rietz, *ibid.*, **62**, 974 (1940).

(6) Hurd and Sowden, *ibid.*, **60**, 235 (1938).

(7) Robbins and Upson, *ibid.*, **60**, 1788 (1938).

(8) Glattfeld and Macmillan, *ibid.*, **56**, 2481 (1934).