

water. The analytical data and melting points of the *N*-carboalkoxy derivatives are reported in Table II.

Condensation of Dichlorocarbonates with Procaine Hydrochloride.—The following example is illustrative of this reaction. A solution of 33.4 g. (0.122 mole) of procaine hydrochloride in 200 ml. of acetone and 25 ml. of water was stirred while 14.0 g. (0.61 mole) of pentamethylene dichlorocarbonate was added dropwise. The solution turned cloudy and crystallization was complete within 10 minutes after all of the dichlorocarbonate had been introduced. The reaction mixture was cooled, filtered and sucked as dry as possible. The white mass was dried in a vacuum oven at 65° (20 mm.) to give 42.5 g. (99%) of product. After crystallization from a mixture of alcohol and *n*-hexane, the compound melted at 175–177° dec.

The melting points, analytical data and crystallization solvents for the free bases, dihydrochlorides and other salts of the *N,N'*-disubstituted dicarbamates, which were all isolated in high yields, are given in Table III.

The free bases were obtained by carrying out the preceding type condensation in the presence of a slight excess of triethylamine. The latter was added dropwise, along with the dichlorocarbonate, to the aqueous acetone solution of procaine hydrochloride. The additions were controlled so that the dichlorocarbonate was in excess until near the end of the reaction. The acetone was evaporated by warming, and, after cooling the residue, the product was removed by filtration. Those bases which were liquids were isolated by extraction with *n*-butyl alcohol or chloroform.

The dioxalates, dipicrates, disalicylate and didilurate

were prepared by mixing hot, saturated alcohol solutions of the appropriate bases with hot, saturated alcohol solutions of the corresponding acids.

Hydrolysis of the Di- β -diethylaminoethyl Ester of *N,N'*-Di-(*p*-carboxyphenyl)-tetramethylene Diurethan.—Two grams of the ester dihydrochloride was refluxed with a solution of 15 ml. of concentrated hydrochloric acid in 100 ml. of water for two hours. The solid which had separated from solution was removed by filtration of the hot reaction mixture and dried; weight 1.2 g. The material was dissolved in 5% sodium hydroxide solution, the solution was filtered and the filtrate was acidified. The precipitate was collected, washed with water and dried; m.p. 300–301° dec. A mixed melting point determination with a sample of *N,N'*-di-(*p*-carboxyphenyl)-tetramethylene diurethan showed no depression.

Preparation of *N,N'*-Di-(*p*-carboxyphenyl)-tetramethylene Diurethan.—Twenty-seven and four-tenths grams (0.20 mole) of *p*-aminobenzoic acid was dissolved in 200 ml. of acetone and 21.5 g. (0.1 mole) of tetramethylene dichlorocarbonate was added dropwise with stirring. The reaction mixture was stirred for a further 10 minutes, allowed to cool and filtered. The product was washed several times with acetone and dried. There was obtained 39.0 g. (94%) of a light tan-colored solid which was purified further by dissolving it in dilute alkali, reprecipitating with acid and washing with hot methanol; m.p. 301–302° dec.

Anal. Calcd. for $C_{20}H_{20}O_8N_2$: C, 57.69; H, 4.84. Found: C, 57.51; H, 4.64.

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[CONTRIBUTION FROM THE WARNER INSTITUTE FOR THERAPEUTIC RESEARCH]

Antispasmodics. II. Studies on the Synthesis of 2-Diethylaminoethyl α -(2-Cycloalken-1-yl)-2-thienylacetates

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The 2-diethylaminoethyl esters (IV) of two α -(cycloalken-1-yl)-2-thienylacetic acids [I, R = 1-(2-C₅H₇) and 1-(2-C₆H₉)] have been synthesized both by condensation of the appropriately substituted 2-thienyl acetic acid with 2-diethylaminoethyl chloride and by transesterification of alkyl α -(2-cycloalken-1-yl)-2-thienylacetates (II) with 2-diethylaminoethanol. Alkylation of 2-thienylacetonitrile (V) with 2-cycloalken-1-yl halides in the presence of basic catalysts gave α -(2-cycloalken-1-yl)-2-thienylacetonitriles (VI) which could be saponified to either a mixture of the corresponding acid (I) and amide (VII) or to the acid alone. An alternative synthesis used in the preparation of one of the disubstituted acetic acids [I, R = 1-(2-C₆H₉)] involved the carbethoxylation of V to ethyl α -cyano-2-thienylacetate (VIII) and alkylation of VIII to ethyl α -cyano- α -(2-cyclohexen-1-yl)-2-thienylacetate (IX). Saponification of the cyanoacetate (IX) gave a mixture of the acid I and amide VII [both R = 1-(2-C₆H₉)]. Acid alcoholysis of the nitriles, VI, direct esterification of the acetic acids, I, and alkylation of ethyl 2-thienylacetate yielded alkyl α -(2-cycloalken-1-yl)-2-thienylacetates (II). The cyanoacetate, IX, was recovered unchanged from an attempted alcoholysis under conditions which converted the nitrile, VI, to the corresponding acetate (II).

The discovery of the clinically useful spasmolytic properties of 2-diethylaminoethyl α -(2-cyclopenten-1-yl)-2-thienylacetate hydrochloride^{1,2} [IV, R = 1-(2-C₅H₇)] and its 2-cyclohexen-1-yl homolog [IV, R = 1-(2-C₆H₉)] led to a study, the results of which are presented in this communication, of shorter and potentially more convenient methods of synthesis of the esters, IV, than that originally described.¹

Esters of commercially available aminoalcohols may be synthesized by a number of general reactions,³ each having its own peculiar advantages. The method of choice in any one instance is likely,

(1) F. Leonard, *THIS JOURNAL*, **74**, 2915 (1952).

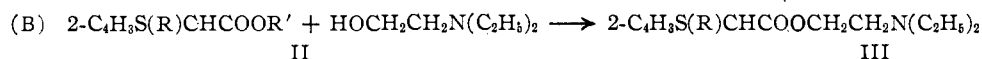
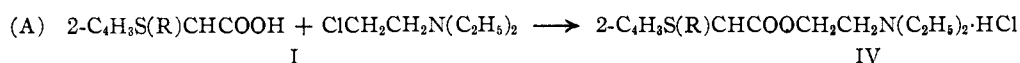
(2) Neotropine Hydrochloride Warner, U. S. Patent 2,561,385, July 24, 1951.

(3) See Antispasmodics by R. R. Burtner in "Medicinal Chemistry," Vol. I, C. M. Suter, Editor, John Wiley and Sons, Inc., New York, N. Y., 1951, and Histamine Antagonists, Review No. 3, pp. 22, by F. Leonard and C. P. Huttner, National Research Council, Washington, D. C., 1950.

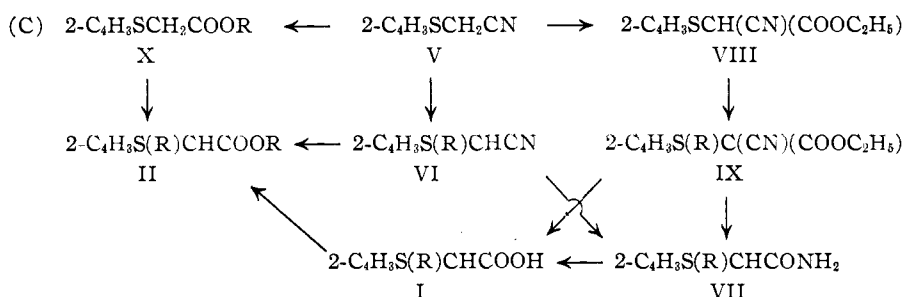
however, to depend primarily on the availability of the starting materials. This investigation on the synthesis of new intermediates for the synthesis of the esters, IV, was predicated on the ultimate condensation of 2-diethylaminoethyl chloride with a disubstituted acetic acid (I) or the transesterification of a lower alkyl disubstituted acetate (II) with 2-diethylaminoethanol.

Since acetic acids and acetic acid esters have been obtained by solvolysis of acetonitriles and cyanoacetates, the synthesis was undertaken of properly substituted acetonitriles (VI) and cyanoacetates (IX) which would be expected to yield, when hydrolyzed or alcoholized, the acids (I) and esters (II) required for the preparation of the basic-alkyl esters (IV).

The first attempt to prepare an α -(2-cycloalken-1-yl)-2-thienylacetonitrile (VI) by the alkylation of 2-thienylacetonitrile (V) in the presence of lithium amide failed, probably because V decom-



posed when refluxed in toluene with the basic catalyst. The preparation of the nitriles, VI, was found to proceed satisfactorily, however, when sodamide was substituted for lithium amide and all the reagents combined at low temperatures.



For example, when a suspension of sodamide in toluene was treated stepwise at -35° with 2-thienylacetonitrile and 2-cyclohexen-1-yl bromide, the mixture let slowly warm to room temperature and finally warmed at $60-70^\circ$ for several hours a 33% yield of α -(2-cyclohexen-1-yl)-2-thienylacetonitrile [VI, R = 1-(2-C₆H₉)] was obtained. In later experiments 50-55% yields of the nitriles, VI, [R = 1-(2-C₅H₇), 1-(2-C₆H₉)] were consistently obtained when the temperature was maintained at -10° during the first and second phases of the reaction, at $60-70^\circ$ during the third and an atmosphere of nitrogen maintained throughout (method A). Using this modification of our original procedure, lithium amide, likewise, catalyzed the alkylation but in lower yield.

Alkylation of V was found to proceed in 41% yield when the nitrile was simply stirred and heated at $50-60^\circ$ for five hours with 2-cyclohexen-1-yl bromide in 1,4-dioxane in the presence of sodium methoxide (method B) but when the same reaction was attempted under forcing conditions to eliminate methanol, none of the expected product was obtained.

In the presence of the potassium hydroxide-dibutylacetal complex⁴ alkylation of 2-thienylacetonitrile (V) with 2-cyclohexen-1-yl bromide in excess dibutylacetal gave the disubstituted nitrile, VI, [R = 1-(2-C₆H₉)] in 53% yield (method C). The recovery of dibutylacetal, however, was unsatisfactory and when recovered acetal was used in the alkylation, the yield dropped to 23%.

Saponification (24 hours) of α -(2-cyclohexen-1-yl)-2-thienylacetonitrile with 16% aqueous alcoholic potassium hydroxide gave a mixture of α -(2-cyclohexen-1-yl)-2-thienylacetic acid [I, R = 1-(2-C₆H₉)] and α -(2-cyclohexen-1-yl)-2-thienylacetamide [VII, R = 1-(2-C₆H₉)]. When the nitriles (VI) were refluxed for 48 hours with 30% aqueous alcoholic potassium hydroxide, no amide was detected in the mixture and the desired acids were

obtained in 70-80% yields. Concentrated hydrochloric acid or diluted sulfuric acid in concentrations up to 40% at reflux temperature were without effect on the nitriles while boiling 60% sulfuric acid gave a carbonized product from which neither the starting nitrile nor the expected hydrolysis products could be isolated.

The alternative synthesis of the acids I which had as its key intermediate the substituted cyanoacetate (IX) proved to be less satisfactory than the synthesis described above.

Ethyl α -cyano- α -(2-cyclohexen-1-yl)-2-thienylacetate [IX, R = 1-(2-C₆H₉)] was prepared by carbethoxylation of 2-thienylacetonitrile (V) with diethyl carbonate under forcing conditions in the presence of sodium methoxide and alkylation, without isolation of the intermediate ethyl α -cyano-2-thienylacetate (VIII), with 2-cyclohexen-1-yl bromide. The disubstituted cyanoacetate was also obtained from a sample of VIII which had been isolated and characterized.

Saponification of ethyl α -cyano- α -(2-cyclohexen-1-yl)-2-thienylacetate (IX) proceeded much more slowly than saponification of the corresponding acetonitrile (VI). After 48 hours of reflux with 30% aqueous alcoholic potassium hydroxide, IX was converted to the corresponding crude acid (I) and relatively pure amide (VII) in yields of 39 and 52%, respectively. Boiling sulfuric acid in concentrations up to 40% was without effect while constant boiling hydrobromic and 60 or 80% sulfuric acids carbonized IX. Attempted acid alcoholysis of ethyl α -cyano- α -(2-cyclohexen-1-yl)-2-thienylacetate with 40% ethanolic sulfuric acid resulted merely in recovery of the starting material.

The alkyl esters, II, were obtained in a number of ways: (1) by direct esterification of the acids I in the usual manner (method D) in the presence of sulfuric acid with a large excess of ethanol or in ethylene dichloride solution (method E) with a 50% excess of methanol in the presence of methane sulfonic acid; (2) by alkylation of ethyl 2-thienylacetate (X) in dibutylacetal solution (method F) in the presence of the potassium hydroxide-dibutylacetal complex⁴; and (3) by acid-catalyzed alcoholysis of the nitriles VI with 40% ethanolic sulfuric acid (method G).

The acids, I, when refluxed with 2-diethylaminoethyl chloride in isopropyl alcohol for 18 to 20 hours gave the ester hydrochlorides, IV, in 50-60% yield after recrystallization.⁵ An alternative procedure (method H) which was found satisfactory was to

(4) C. Weizmann, E. Bergmann and M. Sulzberger, *THIS JOURNAL*, **70**, 1189 (1948); *J. Org. Chem.*, **15**, 918 (1950).

(5) For details see ref. 2. It is not necessary to reflux the reaction mixture for 48 hours as originally reported; the shorter period of reflux gave equally good yields.

stir and reflux for six hours an ethyl acetate solution of the acids, I, with 2-diethylaminoethyl chloride in the presence of potassium carbonate. The reaction products obtained as the free bases, were washed with water, dried and converted to the ester hydrochlorides simply on treatment with the theoretical amount of gaseous hydrogen chloride. Recrystallization afforded the pure ester hydrochlorides in yields of 75–79%.

Ester interchange experiments with the esters (II) and 2-diethylaminoethanol in xylene solution in the presence of catalytic amounts of sodium 2-diethylaminoethoxide gave the free basic esters (III). These esters (III) were obtained as pale yellow oils after fractionation *in vacuo* and were converted to hydrochlorides on treatment with alcoholic hydrochloric acid.

Experimental⁶

α -(2-Cycloalken-1-yl)-2-thienylacetonitriles (VI). Method A.—A solution of 24.6 g. (0.2 mole) of 2-thienylacetonitrile in 100 ml. of dry toluene was added during one-half an hour with constant stirring at a temperature of -35 to -30° , to a suspension of 8.6 g. (0.22 mole) of pure sodamide in 150 ml. of dry toluene. The mixture was stirred for five minutes and then treated dropwise during one hour (temp. -35 to -30°) with 32.2 g. (0.2 mole) of 2-cyclohexen-1-yl bromide dissolved in 100 ml. of dry toluene. After the addition of the bromide had been completed, the mixture was stirred for 15 minutes at -35 to -30° , let warm to -5° where a copious solution of ammonia occurred. After one-half an hour at -5° the mixture was allowed to warm to room temperature where after 1.25 hours evolution of ammonia ceased. Water was added to the mixture, the toluene layer separated and washed until neutral. Fractionation of the toluene solution gave a heavy yellow oil which distilled at 147 – 150° (6.5 mm.), n_D^{20} 1.5569; yield 13.5 g. (33.3%). Refractionation gave 10.0 g. of pure α -(2-cyclohexen-1-yl)-2-thienylacetonitrile, b.p. 132 – 135° (4 mm.) and n_D^{20} 1.5557.

Anal. Calcd. for $C_{12}H_{12}NS$: C, 70.90; H, 6.44; N, 6.89. Found: C, 70.88; H, 6.66; N, 7.03.

When the reaction was run in an atmosphere of nitrogen, the temperature kept at -10° during the addition of both 2-thienylacetonitrile and 2-cyclohexen-1-yl bromide to the sodamide suspension, the reaction mixture stirred at 10° for 15 minutes after complete mixing of the reagents, let warm to room temperature, stirred at room temperature for one hour and let stand overnight, there was obtained a 55.6% yield of α -(2-cyclohexen-1-yl)-2-thienylacetonitrile, b.p. 110 – 124° (1 mm.); n_D^{20} 1.5580.

The alkylation of 2-thienylacetonitrile with 2-cyclopenten-1-yl chloride by the modified procedure described above gave α -(2-cyclopenten-1-yl)-2-thienylacetonitrile in 60% yield; b.p. 121 – 125° (1.5 mm.). A sample redistilled for analysis boiled at 113 – 117° (1.0 mm.); n_D^{20} 1.5530.

Anal. Calcd. for $C_{11}H_{11}NS$: C, 69.80; H, 5.86; N, 7.40. Found: C, 69.69; H, 6.17; N, 7.52.

Alkylation of the nitrile in the presence of lithium amide with 2-cyclopenten-1-yl chloride was found to proceed in 30–40% yield when metalation of the nitrile was carried out at 25° , alkylation at 0° and the mixture heated at 50 – 60° for two hours.

Method B.—A solution of 24.6 g. (0.2 mole) of 2-thienylacetonitrile, 11.9 g. (0.22 mole) of pure sodium methoxide in 400 ml. of dry dioxane was refluxed for five minutes, cooled to 50° and treated during one hour at 50 – 60° with 35.6 g. (0.22 mole) of 2-cyclohexen-1-yl bromide dissolved in 100 ml. of dry dioxane. The mixture was heated at 50 – 60° for five hours and let stand overnight. The solvent was removed *in vacuo*, and the residue dissolved in a mixture of water and toluene. The toluene layer was washed to neutrality, concentrated *in vacuo* and the residual oil distilled. The fraction distilling from 153 – 171° (6 mm.), n_D^{20} 1.5574–1.5584, was collected to give 16.9 g. (41.6% yield) of crude α -(2-cyclohexen-1-yl)-2-thienylacetonitrile.

Method C.—A mixture of 16.5 g. (0.25 mole) of 85% potassium hydroxide and 100 ml. of dibutylacetal was heated to 150° with vigorous stirring. At 115° potassium hydroxide dissolved to form the potassium hydroxide–dibutylacetal complex. On cooling to 0° the complex separated as a finely divided powder. A mixture of 30.7 g. (0.25 mole) of 2-thienylacetonitrile and 40.2 g. (0.25 mole) of 2-cyclohexen-1-yl bromide was added at once to the suspension of the complex at 0° . The temperature was allowed to rise to 15° , heated at 60° for three hours, cooled and treated with water. The organic layer was washed until neutral and dried over calcium chloride. Fractionation at 1.5 mm. gave 27.2 g. (53.6%) of α -(2-cyclohexen-1-yl)-2-thienylacetonitrile distilling at 139 – 150° (1.5 mm.); n_D^{20} 1.5560.

α -(2-Cycloalken-1-yl)-2-thienylacetic Acids (I).—A mixture of 29.1 g. (0.143 mole) of α -(2-cyclohexen-1-yl)-2-thienylacetonitrile, 16.0 g. (0.243 mole) of 85% potassium hydroxide, 16 ml. of water and 64 ml. of 95% ethanol (alkali concentration approximately 16% by weight) was refluxed for 24 hours and concentrated *in vacuo*. Water was added to the residue and the mixture extracted with ether. The aqueous layer (A) was separated from the ethereal layer (B), extracted with ether and, in the presence of ether, acidified with concentrated hydrochloric acid. The ethereal layer (C) was separated from the acidic aqueous phase, washed with water and dried with anhydrous magnesium sulfate. Upon evaporation of the ether, there was obtained 16.1 g. (51%) of α -(2-cyclohexen-1-yl)-2-thienylacetic acid, m.p. 98 – 100° . The ethereal layer (B) was combined with the ether extract of (A). When the combined ethereal extracts were washed, a neutral solid precipitated. Evaporation of ether from the suspension left a cotton-like yellow solid; yield 15.4 g., m.p., 145 – 147° . After two recrystallizations from ethylene dichloride, the α -(2-cyclohexen-1-yl)-2-thienylacetamide melted at 164 – 167° .

Anal. Calcd. for $C_{12}H_{12}NOS$: C, 65.11; H, 6.83; N, 6.33. Found: C, 65.39; H, 6.92; N, 6.23.

The amide (8.4 g.), on boiling with 16.4% aqueous alcoholic potassium hydroxide for 24 hours, gave a mixture of 3.4 g. of recovered amide, m.p. 151 – 155° , and 3.2 g. of the corresponding acid, m.p. 104 – 107° .

When 20.3 g. (0.1 mole) of α -(2-cyclohexen-1-yl)-2-thienylacetonitrile was refluxed for 48 hours with approximately 30% by weight aqueous alcoholic potassium hydroxide solution (16.8 g., 0.255 mole of 85% potassium hydroxide dissolved in a mixture of water and 16.8 ml. of 95% ethanol), the mixture cooled, diluted with 75 ml. of water, and extracted with ether, no amide was obtained upon evaporation of the ethereal extract. The alkaline aqueous alcoholic layer was acidified to pH 4 with 12 *N* sulfuric acid in the presence of 50 ml. of toluene. The toluene layer was separated and the acidic phase extracted with toluene. The combined organic layers were washed until neutral with water and evaporated *in vacuo* to an oily residue which crystallized on standing; yield 17.1 g. (80.7%) of α -(2-cyclohexen-1-yl)-2-thienylacetic acid, m.p. 99 – 101° .

α -(2-Cyclopenten-1-yl)-2-thienylacetonitrile may be saponified in the same manner as its 2-cyclohexen-1-yl homolog in yields of 70–80%.

Both acids were esterified with 2-diethylaminoethyl chloride without further purification.

Ethyl α -Cyano-2-thienylacetate (VIII).—A mixture of commercial sodium methoxide (45.3 g., 0.84 mole), 100 g. (0.82 mole) of 2-thienylacetonitrile and 575 ml. of dry diethyl carbonate was stirred and heated in a three-necked flask provided with stirrer, thermometer and 12" Vigreux column. Distillate was collected over the temperature range 81 – 123° during a period of 2.25 hours, the reaction mixture cooled, poured into water and neutralized with 50% acetic acid. The organic layer was separated, combined with the ether extract of the aqueous layer and dried over anhydrous potassium carbonate. Fractionation gave 98 g. (61.2%) of a yellow oil which distilled at 126 – 130° (4 mm.); n_D^{20} 1.5182. This substance stains the skin green.

Anal. Calcd. for $C_9H_9O_2NS$: C, 55.38; H, 4.65; N, 7.18. Found: C, 55.64; H, 4.52; N, 7.19.

Ethyl α -Cyano- α -(2-cyclohexen-1-yl)-2-thienylacetate (IX).—A solution of 19.7 g. (0.16 mole) of 2-thienylacetonitrile and 8.74 g. (0.16 mole) of commercial sodium methoxide in 130 ml. of dry diethyl carbonate was stirred and heated and a distillate, a mixture of methanol and ethanol, collected over a period of three hours. When the distillate

(6) All melting points and boiling points are uncorrected.

vapor temperature reached 120°, heating was stopped, the reaction mixture cooled to 60°, treated during one-half an hour with a solution of 25.8 g. (0.16 mole) of 2-cyclohexen-1-yl bromide in 40 ml. of diethyl carbonate and heated at 60–65° for one hour after all of the bromide had been added to the reaction mixture. Water was added to the cool mixture, the organic layer separated, washed with saturated sodium chloride solution and dried over anhydrous potassium carbonate. The drying agent was filtered off and the filtrate fractionated to yield diethyl carbonate and a heavy yellow oil which distilled at 120–138° (0.15–0.20 mm.), n_D^{20} 1.5347; yield 27.9 g. Two redistillations gave analytically pure ester which boiled at 122.5–123° (0.03 mm.), n_D^{20} 1.5348.

Anal. Calcd. for $C_{15}H_{17}NO_2S$: C, 65.41; H, 6.22. Found: C, 65.22; H, 5.88.

The same ester was obtained in 67% yield by alkylation of ethyl α -cyano-2-thienylacetate (28 g., 0.145 mole) with 2-cyclohexen-1-yl bromide (28.5 g., 0.16 mole) in absolute ethanol solution (150 ml.) in the presence of sodium ethoxide (prepared from 3.62 g., 0.16 g. atom of sodium).

Attempted Hydrolyses of Ethyl α -Cyano- α -(2-cyclohexen-1-yl)-2-thienylacetate (1) with 30% Aqueous Alcoholic Potassium Hydroxide.—A mixture of 7.36 g. (0.0267 mole) of ethyl α -cyano- α -(2-cyclohexen-1-yl)-2-thienylacetate, 6 g. of potassium hydroxide, 6 ml. of water and 6 ml. of 95% ethanol was refluxed for 48 hours. The dark brown reaction mixture was cooled and diluted with water. The white solid which precipitated was filtered, washed with water and dried; yield 3.1 g., m.p. 175–176° (Fraction A). The filtrate was acidified to pH 7.5 and extracted with toluene. Upon removal of the toluene an oily residue was obtained, weight 0.43 g. (fraction B). The aqueous layer was acidified further to pH 4.0 with 12 N sulfuric acid in the presence of toluene. Evaporation of the toluene gave a sirupy residue, yield 2.34 g., which slowly crystallized under petroleum ether (fraction C). Fraction A, after two recrystallizations from a benzene–petroleum ether mixture, melted at 168.5–170° and produced no melting point depression when mixed with a sample of α -(2-cyclohexen-1-yl)-2-thienylacetamide obtained from the saponification of α -(2-cyclohexen-1-yl)-2-thienylacetoneitrile. Fraction C melted at 101–104° in agreement with the known melting point of α -(2-cyclohexen-1-yl)-2-thienylacetic acid.

(2) **With 40% Sulfuric Acid.**—10 g. (0.0364 mole) of the cyanoacetate was refluxed for 48 hours with 100 ml. of 40% by weight sulfuric acid. The mixture gradually blackened. At the end of the reflux period, the mixture was cooled, extracted with ether and the ether extracts shaken with 10% sodium carbonate solution. The carbonate layer was acidified in the presence of ether, the ethereal solution washed to neutrality and dried. Evaporation of the ether left no residue.

(3) **With 60 and 80% Sulfuric Acid.**—Ten-gram portions of the cyanoacetate were set up for reflux with 60 and 80% (by weight) sulfuric acid. With 80% sulfuric acid, the reaction mixture foamed out of the condenser shortly after heat had been applied to the system. The odor of sulfur dioxide was noticed. Reflux was possible for 48 hours with 60% sulfuric acid but carbonization took place. Nothing could be isolated from the reaction mass.

(4) **With 48% Hydrobromic Acid.**—A 5-g. sample of the cyanoacetate was refluxed with 17 ml. of 48% hydrobromic acid. After four hours a black tar formed which was insoluble in sodium hydroxide. The preparation was discarded.

Attempted Alcoholysis of Ethyl α -Cyano- α -(2-cyclohexen-1-yl)-2-thienylacetate.—A mixture of 5 g. of the cyanoacetate, 10.4 ml. of concentrated sulfuric acid and 36 ml. of 95% ethanol was refluxed for 48 hours, cooled and poured into ice-water and the mixture extracted with toluene. The toluene layer was washed neutral and fractionated to yield 0.96 g. of unreacted cyanoacetate, b.p. 100–155° (0.04 mm.), n_D^{20} 1.5347 and 0.72 g. of a product, b.p. 115–120° (0.04 mm.), n_D^{20} 1.5377, which probably was contaminated cyanoacetate. It should be noted that if partial alcoholysis had occurred the refractive index would have dropped since n_D^{20} of the corresponding malonate is 1.5239.²

Alkyl α -(2-Cycloalken-1-yl)-2-thienylacetates (II). Method D.—A mixture of 22.2 g. (0.1 mole) of crude α -(2-cyclohexen-1-yl)-2-thienylacetic acid, 70 ml. of 95% ethanol and 15.7 ml. of concentrated sulfuric acid was refluxed

for 24 hours, cooled and poured into water. The organic layer was separated and the aqueous layer extracted with ether. The combined organic phases were washed neutral with 2% sodium carbonate solution and water and dried over anhydrous potassium carbonate. After removal of the ether the residual oil was fractionated at 5 mm. Ethyl α -(2-cyclohexen-1-yl)-2-thienylacetate distilled over the temperature range 134–150°; n_D^{20} 1.5299. Redistillation gave a product which distilled at 144–146° (5–6 mm.); n_D^{20} 1.5300.

Anal. Calcd. for $C_{14}H_{18}O_2S$: C, 67.17; H, 7.25. Found: C, 67.00; H, 7.03.

Method E.—A mixture of 70.5 g. (0.34 mole) of crude α -(2-cyclopenten-1-yl)-2-thienylacetic acid, 16.3 g. (0.51 mole) of methanol, 68 ml. of ethylene dichloride and 1.63 g. (0.017 mole) of methane sulfonic acid was refluxed for 24 hours.⁷ Water (7.3 ml.) was separated, the organic layer washed three times with 30-ml. portions of 10% sodium carbonate, once with 50 ml. of water and dried over anhydrous potassium carbonate. Distillation gave 50.6 g. (67%) of methyl α -(2-cyclopenten-1-yl)-2-thienylacetate, b.p. 119.5–120.5° (2 mm.), n_D^{20} 1.5344. On redistillation the ester distilled at 119–120° (2 mm.) and had n_D^{20} 1.5340.

Anal. Calcd. for $C_{13}H_{16}O_2S$: C, 64.82; H, 6.35. Found: C, 64.55; H, 6.31.

Methyl α -(2-cyclohexen-1-yl)-2-thienylacetate was obtained in the same way from 31.9 g. (0.139 mole) of crude α -(2-cyclohexen-1-yl)-2-thienylacetic acid, 6.6 g. (8.25 ml., 0.157 mole) of methanol, 0.672 g. (0.46 ml., 0.007 mole) of methane sulfonic acid; yield 23.6 g. (71.8%); b.p. 150–160° (10 mm.); n_D^{20} 1.5396. The product was redistilled at 0.8 mm. (b.p. 116–117°) with no change in refractive index.

Anal. Calcd. for $C_{14}H_{18}O_2S$: C, 66.07; H, 6.83. Found: C, 65.90; H, 7.12.

Method F.—Potassium hydroxide (16.5 g., 85%, 0.25 mole) and dibutylacetal (180 ml.) were heated to 150° with vigorous stirring, then cooled to room temperature. A mixture of 42.5 g. (0.25 mole) of ethyl 2-thienylacetate and 40.2 g. (0.25 mole) of 2-cyclohexen-1-yl bromide was added rapidly to the cool suspension of the potassium hydroxide–dibutylacetal complex and the mixture heated at 90–95° for two hours. The reaction mixture was cooled, treated with 75 ml. of water and worked up in the usual way. Fractionation at 10 mm. gave 20.2 g. (47.5%) of unreacted ethyl 2-thienylacetate, b.p. 110–120°, and 13.3 g. (21.2%) of ethyl α -(2-cyclohexen-1-yl)-2-thienylacetate, b.p. 165–173°, n_D^{20} 1.5350.

Method G.—A mixture of 20.3 g. (0.1 mole) of α -(2-cyclopenten-1-yl)-2-thienylacetoneitrile, 135 ml. of 95% ethanol and 39 ml. of concentrated sulfuric acid was refluxed for 48 hours, cooled and poured into ice-water. The mixture was extracted with toluene, the extract washed neutral and concentrated *in vacuo*. Fractionation of the residual oil at 2 mm. gave ethyl α -(2-cyclopenten-1-yl)-2-thienylacetate, b.p. 117–140°; n_D^{20} 1.5265; yield 18.0 g. (70%). When redistilled the ester distilled at 89–92° (0.05–0.06 mm.); n_D^{20} 1.5264.

Anal. Calcd. for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.83. Found: C, 65.87; H, 7.26.

Ethyl α -(2-cyclohexen-1-yl)-2-thienylacetate was likewise prepared by refluxing 11.8 g. (0.058 mole) of α -(2-cyclohexen-1-yl)-2-thienylacetoneitrile with a solution of 21.6 ml. of concentrated sulfuric acid in 75 ml. of 95% ethanol; yield 4.5 g. (31%); b.p. 105–115° (0.03 mm.); n_D^{20} 1.5330.

2-Diethylaminoethyl α -(2-Cycloalkenyl)-2-thienylacetate Hydrochlorides (IV). Method H.—An ethyl acetate solution (595 ml.) of α -(2-cyclopenten-1-yl)-2-thienylacetic acid (181 g., 0.87 mole) was mixed with 118 g. (0.87 mole) of 2-diethylaminoethyl chloride and 132 g. (0.957 mole) of anhydrous potassium carbonate. The mixture was stirred and refluxed for seven hours, cooled and filtered by suction. The precipitate was washed with ethyl acetate, the washings combined with the original filtrate and the combined solutions refluxed with charcoal for one-half an hour. The charcoal was removed by suction filtration, the solution treated without cooling with a weighed amount of gaseous hydrogen chloride (based on titration of an aliquot of the solution in the presence of methyl red indicator) and the hot mixture set

(7) General procedure of R. O. Clinton and S. C. Laskowski, THIS JOURNAL, 70, 3135 (1948), for the preparation of methyl esters.

aside to crystallize. The crystalline cake was broken up, filtered and dried; yield 55.7 g. (89.2%), m.p. 128.0–129.5°. Recrystallized from a mixture of ethyl acetate and ethanol, the salt melted at 131.0–132.5°; yield 49.3 g. (79%).

In like manner there was obtained a 90.7% yield of 2-diethylaminoethyl α -(2-cyclohexen-1-yl)-2-thienylacetate hydrochloride, melting at 151.5–153°. Recrystallization from an ethyl acetate-ethanol mixture yielded a product which melted at 152.0 to 153.5°; yield 80% based on starting materials.

Method I.—A mixture of 14.8 g. (0.127 mole) of 2-diethylaminoethanol, 25.0 g. (0.106 mole) of ethyl α -(2-cyclopenten-1-yl)-2-thienylacetate, 0.28 g. (0.012 mole) of sodium and 170 ml. of dry xylene in a 500-ml. flask equipped with a short fractionating column was slowly distilled during a period of six hours. A mixture of alcohol and xylene was collected first and then xylene (total volume of distillate 68 ml.). The cooled reaction mixture was washed neutral and concentrated *in vacuo* to a brown oil which distilled at 115–123° (0.001 mm.), n_D^{20} 1.5170; yield 20.1 g. The distillate was dissolved in 80 ml. of ethyl acetate and treated with 14.6 ml. of 4.47 *N* ethanolic hydrochloric acid. The

salt, 2-diethylaminoethyl α -(2-cyclopenten-1-yl)-2-thienylacetate hydrochloride was obtained in 42% yield (15 g.) and melted at 131–132.5° before crystallization, 134–135° after recrystallization from a mixture of ethyl acetate and ethanol.

From 25 g. (0.106 mole) of methyl α -(2-cyclohexen-1-yl)-2-thienylacetate and the same quantities of reagents used in the preparation of the 2-cyclopenten-1-yl ester described above, there was obtained 27.1 g. of 2-diethylaminoethyl α -(2-cyclohexen-1-yl)-2-thienylacetate, b.p. 135–145° (0.001 mm.), n_D^{20} 1.5222, which was converted to its hydrochloride with alcoholic hydrochloric acid; yield 26.5 g. (70%), m.p. 151–154°.

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The Preparation of Some Pyridazonyl Acids

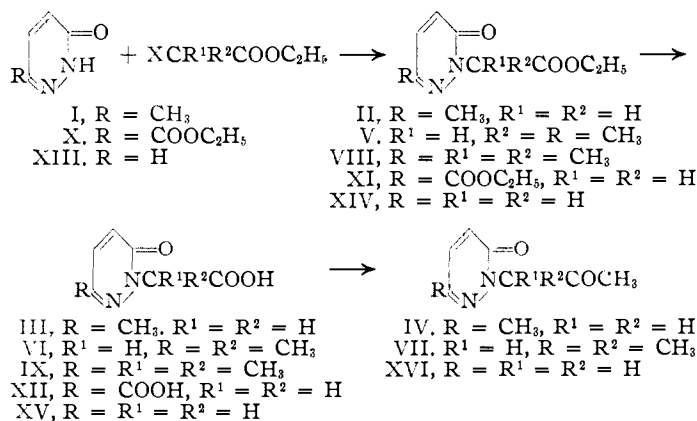
By JOHN A. KING AND FREEMAN H. McMILLAN

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6-Methyl-3-pyridazone has been alkylated in the 2-position with α -halo esters of acetic, propionic and isobutyric acids and both 6-carbomethoxy-3-pyridazone and 3-pyridazone have been similarly alkylated with haloacetic esters. All of the esters were hydrolyzed to the corresponding acids and three of these acids were converted to methyl ketone.

As a part of some exploratory work in the field of pyridazine chemistry we considered it desirable to study a series of 2-(3-pyridazonyl)-acetic acids and their derivatives, a description of the preparation of which forms the subject of the present paper.

6-Methyl-3-pyridazone (I) underwent ready alkylation on the nitrogen with ethyl bromoacetate in the presence of sodium ethoxide; the resultant ester (II) was hydrolyzed to the acid III, as well as ammonolyzed to the corresponding amide of III.



The diethyl amide of III was prepared by the alkylation of I with N,N-diethylchloroacetamide, while the anilide of III was prepared from III directly. As proof that alkylation of I had occurred on nitrogen instead of on oxygen the acid III was thermally decarboxylated to 2,6-dimethyl-3-pyridazone, identical with a sample prepared by meth-

ylation of I by the procedure of Homer¹ and co workers, who proved the structure of their material. The acid III, on treatment with acetic anhydride and pyridine gave a good yield of the acetone derivative IV.

Substitution of ethyl α -bromopropionate for ethyl α -bromoacetate in the alkylation of I furnished the corresponding propionic ester V; this was hydrolyzed to the acid VI which was converted, by acetic anhydride and pyridine, to the methyl ethyl ketone derivative VII. Similarly, ethyl α -bromoisobutyrate alkylated I to produce the tri-substituted acetic acid ester VIII. The ester group of VIII could be removed by hydrolysis to the acid IX, but the latter substance could not be converted to a ketone by acetic anhydride and pyridine, the acid being recovered unchanged.

The methyl group in I was oxidized to a carboxyl which was esterified to give X, by procedures essentially as described² in the literature. N-Methylation of X was easily accomplished and the resultant ester was hydrolyzed to 6-(2-methyl-3-pyridazonyl)-carboxylic acid. Alkylation of X with ethyl bromoacetate afforded the ester XI, which was hydrolyzed to the corresponding acid XIII.

Decarboxylation of the acid I, R = COOH, produced 3-pyridazone (XIII) which was similarly condensed with ethyl chloroacetate, giving the ester

(1) R. F. Homer, H. Gregory and L. F. Wiggins, *J. Chem. Soc.*, 2191 (1948).

(2) R. F. Homer, H. Gregory, W. G. Overend and L. F. Wiggins, *ibid.*, 2195 (1948).