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SPIRO-PYRIMIDINES. I. CYCLOBUTANE-1,5-*spiro*-PYRIMIDINES.

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Introductory.

Since the discovery by Emil Fischer[1], in 1903, of the hypnotic properties of diethyl-barbituric acid (veronal, barbital), the barbituric acid derivatives have been a fruitful field for investigation. Most of this work is to be found in patent literature and deals principally with processes for the manufacture of 5,5-dialkyl-barbituric acids. Of the dialkyl derivatives which have found therapeutic application may be mentioned the diethyl-(veronal), dipropyl-(proponal), diallyl-(dial), and phenylethyl-(luminal) barbituric acids. The first of these has proved the most satisfactory for medicinal purposes. According to Fischer, the 5-mono-alkyl derivatives are physiologically inert, and the derivatives prepared by condensing diethyl-malonic ester with substituted ureas are either inert or toxic. Subsequent developments have therefore been mainly along the line of new and more or less indirect processes for preparing derivatives of the veronal type. Few, if any, of these methods, however, possess any real advantage over Fischer's[2] method of condensing the dialkyl-malonic ester with urea in the presence of absolute alcohol and sodium ethylate.

The malonic acid derivatives heretofore used in the preparation of hypnotics of the veronal type have been the esters, amides, chlorides and nitriles of dialkyl-malonic acids. These, by condensation with urea, or, in the case of the nitriles or amides, with phosgene, ethyl carbonate, etc., yield the pyrimidine nucleus with the desired substituent groups.

A new type of malonic acid derivatives with a cyclic structure has been studied quite extensively by Perkin and his co-workers. By condensing the sodium salt of ethyl malonate with dibromo-paraffins, Perkin obtained the esters of cyclopropane-,[3] cyclobutane-,[4] cyclopentane-,[5] cyclohexane-,[6] and cycloheptane-,[7] 1,1-dicarboxylic acids. In this reaction 2 products are formed; one in which one molecule of the dibromo-paraffin reacts with

[1] Fischer and von Mering, *Therap. Gegenw.*, **5**, 97–101 (1903).

[2] Fischer and Dilthey, *Ann.*, **335**, 334–68 (1904).

[3] Perkin, *Ber.*, **17**, 54–9(1884); *ibid.*, **18**, 1734–8 (1885); *J. Chem. Soc.*, **47**, 801–55 (1885).

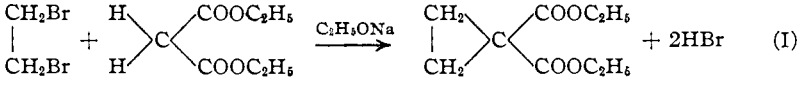
[4] Perkin *J. Chem. Soc.*, **51**, 1–28, 849–53 (1887); Colman and Perkin, *ibid.*, **51**, 228–48 (1887); Blackstock and Perkin, *Proc. Chem. Soc.*, **29**, 76–7 (1913).

[5] Colman and Perkin, *J. Chem. Soc.*, **53**, 185–202 (1888); Haworth and Perkin, *ibid.*, **65**, 86–105 (1894); Strauss, *Ber.*, **27**, 1228–30 (1894).

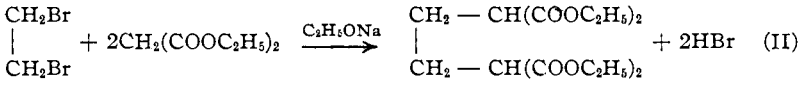
[6] Kipping and Perkin, *J. Chem. Soc.*, **57**, 304–23 (1890).

[7] Haworth and Perkin, *ibid.*, **65**, 591–602 (1894).

one molecule of sodium malonic ester with ring closure to form a cycloparaffin-1,1-dicarboxylic ester, and another in which one molecule of dibromo-paraffin condenses with 2 molecules of sodium malonic ester to form a paraffin-$\alpha,\alpha,\omega,\omega$,-tetracarboxylic ester. Thus, from ethylene bromide and ethyl malonate are obtained cyclopropane-1,1-dicarboxylic ester and butane-1,1,4,4-tetracarboxylic ester, according to the following reactions,



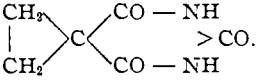
(I)



(II)

Franke and Hankam[1] claim to have made an 11-membered ring, hendecamethylene (cyclohendecane)-dicarboxylic ester by the same reaction.

The cycloparaffin-1,1-dicarboxylic esters, the formation of which is illustrated in Equation I above might be expected to condense with urea or substituted ureas to form a new type of barbituric acid derivatives in which the 5-carbon atom of barbituric acid enters into a cycloparaffin nucleus. In the case of cyclopropane-1,1-dicarboxylic ester (ethylene malonic ester), the product might be represented by the formula



Spiro Compounds.

Dicyclic structures such as the above, in which one carbon atom is common to 2 rings, were first designated by von Baeyer[2] "spirocyclanes." They may be conceived as 2 rings, the planes of which intersect at right angles. The term "spirane" was later proposed by Radulescu,[3] who worked out a system of nomenclature for such compounds. According to this system the substance represented by the above formula would be named cyclopropane-2,4,6-triketo-hexahydro-pyrimidine-1,5-spirane. The term "spirane" is objectionable in the case of heterocycles, in that the ending implies a hydrocarbon. There is at present considerable confusion as to the numbering of substituent groups. In some spiro compounds the 2 rings are numbered independently, in others continuously, and in still others in the manner of a figure 8. Patterson and Curran's[4] nomenclature is unsatisfactory in that the inclusion of substituent groups

[1] Franke and Hankam, *Monatsh.*, **31**, 177–89 (1910).

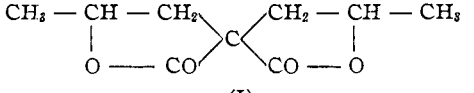
[2] von Baeyer, *Ber.*, **33**, 3771–5 (1900).

[3] Radulescu, *ibid.*, **44**, 1023–6 (1911).

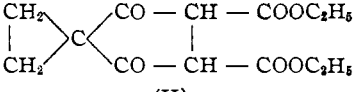
[4] Patterson and Curran, THIS JOURNAL, **39**, 1632 (1917).

is awkward.[1] We recommend that the 2 rings with their substituent groups be named separately in the customary way, and the term "*spiro*"[2] inserted between them, preceded by numbers locating the position of the central carbon with respect to each ring in the order named. Thus, cyclpropane-1,5-*spiro*-2,4,6-triketo-hexahydro-pyrimidine.

Spiro compounds have been known for some time, but comparatively few have been prepared. The first derivatives of this type to be studied were the double lactones of disubstituted malonic acids. Leuchs and Radulescu[3] showed that 2 types of spiro compounds may be prepared from malonic acid; a representative of the first being the dilactone of di-2-hydroxy-propylmalonic acid, and of the second type by the condensation product from cyclopropane-1,1-dicarboxylic ester and ethyl succinate. These are shown in Formulas I and II below.



(I).



(II).

Spiro compounds thus far described include both *spiro*-hydrocarbons (spiranes) and *spiro*-heterocycles where the hetero element is oxygen (lactones) or nitrogen (imides). The only *spiro*-ureides thus far described are the *spiro*-hydantoins to which the interesting substance caffolide[4] belongs.

Experimental.

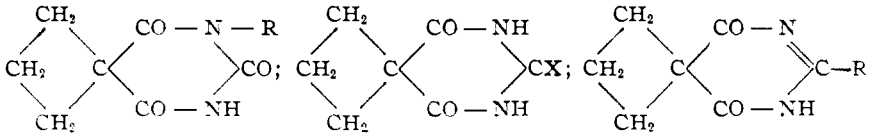
The present paper describes the preparation of a series of derivatives of a *spiro*-pyrimidine in which the 2 nuclei are the well-known cyclobutane and barbituric acid. The starting point for these syntheses was Perkin's trimethylene-malonic ester (ethyl cyclobutane-1,1-dicarboxylate) prepared from sodium malonic ester and 1,3-dibromopropane. From this the ureides were prepared by condensation with substituted ureas by the method Fischer employed in his synthesis of veronal. The urea derivatives used comprise 3 types—(1) N-substituted ureas, in which the substituent is an alkyl, aryl or amino group, (2) C-substituted ureas where the substituent is a sulfur (thio-urea) or imino group (guanidine, dicyanodiamide) and (3) amidines. Three types of products were thus obtained,

[1] In a personal communication, Dr. Patterson suggests for the first derivative described on a subsequent page the name spiro [1-cyclobutane-5'-2,4,6(1,3.5)-pyrimidinetrione], in conformity to the system used in the Decennial Index of *Chemical Abstracts*.

[2] It is recommended that *spiro* be written in italics to conform with such terms as *cis*, *trans*, *syn*, *anti*, etc.

[3] Leuchs and Radulescu, *Ber.*, **45**, 189–201 (1912).

[4] Bilz, *ibid.*, **43**, 1589–1600 (1910).



(I). (II). (III).

Preparation of Cyclobutane-1,1-Dicarboxylic Ester.

A considerable quantity of this ester was required for the work. The starting point was the commercial trimethylene glycol which was purified by redistillation *in vacuo*. This was converted into 1,3-dibromopropane by boiling with sulfuric and hydrobromic acids, according to the method of Kamm and Marvel.[1] A yield of 90% or better was easily obtained. The dibromopropane was then condensed with the sodium salt of ethyl malonate. In the first few runs the method of Perkin was followed. The best yield obtained by Perkin was 27%. By the following modification of Perkin's method we succeeded in increasing the yield to 42%.

To a solution of 23 g. of sodium in absolute alcohol 80 g. of ethyl malonate was added. This mixture was added from a dropping funnel to 105 g. of 1,3-dibromopropane and 50 cc. of absolute alcohol contained in a flask provided with a condenser and a mechanical stirring device. The flask was kept immersed in a bath maintained at 78°. The addition of the alcoholic sodium malonic ester required 1.5 hours during which time the contents of the flask were stirred continuously. Heating and stirring were continued for 2 hours, at the end of which time the mixture was neutral to litmus. The condenser was then set for downward distillation and most of the alcohol distilled off with continuous stirring. Water was added to the residue to dissolve the remaining alcohol and the sodium bromide that had crystallized out. This caused the separation of a yellow oil which was collected in a separatory funnel. The aqueous layer was shaken several times with ether and the ethereal extract added to the oil. The ether containing the oil was again washed with water and finally dried over calcium chloride. The weight of the crude oil after evaporation of the ether was 96 g. It was distilled from a distilling flask provided with an efficient fractionating column. The portion collected between 97 and 110° (mostly 102–105°) at 10 mm. pressure was nearly pure ethyl cyclobutane-1,1-dicarboxylate. Forty-three g. was obtained, corresponding to a 42% yield. The high boiling viscous residue in the flask consisted principally of pentane-1,1,5,5-tetracarboxylic ester. Perkin states that his product had a slight odor of camphor. Ours had not the slightest suggestion of camphor, but rather a pleasant fruity odor much resembling that of ethyl diethylmalonate. The cyclobutane-1,1-dicarboxylic ester obtained as above was used without further purification for the preparation of the *spiro*-ureides.

Method of Condensation.—The condensations with urea derivatives were performed in a small autoclave at a temperature of 105 to 108°. The reaction mixture, consisting of the ester, an excess of the urea, and 3 times the molecular equivalent of sodium dissolved in a minimum amount of absolute alcohol, was placed in a cork-stoppered bottle in the autoclave. A layer of absolute alcohol in the bottom of the autoclave equalized

[1] Kamm and Marvel, THIS JOURNAL, 42, 307 (1920).

the pressure and thus precluded all danger of bursting the bottle. It is essential to have the alcohol as nearly absolute as possible. A few tenths of a per cent. of water greatly reduces the yield of the condensation product. After heating in the autoclave 4 to 6 hours and cooling, the contents of the bottle, unless otherwise stated, were transferred to an evaporating dish and the greater part of the alcohol evaporated by blowing a current of air over the surface. In most cases hydrochloric acid was then added to liberate the condensation product from its sodium salt. A large excess of acid is undesirable since it tends to hydrolyze the ureide. Acid was therefore added until the mixture had a distinctly sour taste, whereupon the ureide separated usually in the form of crystals. These were filtered with suction, washed with cold water and recrystallized once or twice from hot water or alcohol.

The highest yields obtained were with guanidine which gave 90%, and with urea, which gave 71%. Nitrogen substituted ureas usually gave a much smaller yield. It would appear that the secondary amino group is less reactive under the conditions of these experiments than the primary amino group. In practically every case the reaction mixture had a strong odor of ammonia and the insoluble residue contained sodium carbonate, indicating destruction of the urea, hence an excess of 30 to 50% over the molecular proportion was used.

Type I.

Cyclobutane-1,5-*spiro*-2,4,6-triketo-hexahydro-pyrimidine (Trimethylene Barbituric Acid).—Three and forty-five hundredths g. of sodium was dissolved in 85 cc. of absolute alcohol (99.7%) under a reflux condenser. Ten g. of ethyl cyclobutane-1,1-dicarboxylate and 5 g. of urea were then added and the mixture heated in the autoclave at 105 to 108° for 5.5 hours. The sodium salt of the condensation product separated as a white slimy mass. The mixture was neutralized to litmus, and during evaporation on the steam-bath more acid was added from time to time to maintain neutrality as the sodium salt dissolved. After most of the alcohol had been removed, 50 cc. of water was added and the mixture warmed until the reddish color changed to yellow. On cooling, the product separated out in white, lustrous, scaly crystals. The yield was 5.7 g. or 71%. After recrystallizing from hot water the product was snow white and melted at 258°.[1] It is readily soluble in hot water, alcohol and acetone, much less soluble in cold water. It has a bitter taste much resembling that of veronal. Nitrogen determinations[2] gave the following figures:

Analyses.—Subs., 0.2, 0.2: NH_3, 23.53, 23.58 cc. 0.1 *N*. Calc. for $C_7H_8N_2O_3$: N, 16.67. Found: 16.50, 16.47.

Cyclobutane - 1,5 - *spiro* - 1 - methyl - 2,4,6 - triketo - hexahydropyrimidine.—To 3.5 g. of sodium dissolved in 55 cc. of absolute alcohol, 7 g. of the ester and 6 g. of methylurea nitrate were added. The mixture was heated in the autoclave at 105° for 4 hours. The insoluble portion, consisting mainly of sodium carbonate, was filtered off and acidified but it yielded none of the condensation product. The alcoholic filtrate

[1] Melting points reported in this paper were determined by means of short thermometers completely immersed, hence are "corrected."

[2] Nitrogen determinations were made by Mr. F. L. Zindler, of the Analytical Department, using the Kjeldahl-Gunning method.

was evaporated at room temperature, the residue taken up with water and acidified. White crystals consisting of flat plates separated. The yield was 2 g. or 31%. After recrystallization from hot water they showed a melting point of 170°. The substance is soluble in alcohol and in hot water. It has a disagreeable and somewhat bitter taste.

Analyses.—Subs., 0.2, 0.2: NH_3, 22.0 cc., 22.2 cc. 0.1 *N*. Calc. for $C_8H_{10}N_2O_3$: N, 15.38. Found: 15.41, 15.55.

Cyclobutane - 1,5 - *spiro* - 1 - ethyl - 2,4,6 - triketo - hexahydro - pyrimidine.—Eight g. of the ester and 4.5 g. of ethylurea were added to a solution of 2.8 g. of sodium in 50 cc. of absolute alcohol. The mixture was heated for 4 hours at 105°. The insoluble product was filtered off and the filtrate which still had the odor of the ester was again heated at 105° for 1 hour. The filtrate on evaporation at room temperature gave a separation of oil, which, however, did not have the odor of the ester, and from which no crystals could be obtained. The aqueous extract on acidifying gave 3 g. of white, scaly crystals, or 37%. The substance is soluble in hot water and alcohol, and has the same taste as the methyl derivative. It melts at 135°.

Analyses.—Subs., 0.1445, 0.206: NH_3, 13.89 cc., 20.78 cc. 0.1 *N*. Calc. for $C_9H_{12}N_2O_3$: N, 14.28. Found: 14.12, 14.43.

Cyclobutane - 1,5 - *spiro* - 1 - phenyl - 2,4,6 - triketo - hexahydro - pyrimidine.—The reaction mixture, consisting of 3.5 g. of sodium in 65 cc. of absolute alcohol, 10 g. of ester and 9 g. of phenylurea, was heated for 4 hours at 105°. The product was filtered and the filtrate heated again for one hour at 105°. The sodium salt of the ureide was readily soluble in alcohol. The alcoholic solution was acidified and the precipitate which immediately formed was filtered off. Evaporation of the mother liquor gave a further portion. The product was washed with cold water and recrystallized from hot alcohol. It consisted of very fine-hair-like needles, A 1% solution in hot alcohol on cooling gave a felt-like mass of crystals which could be inverted without loss of mother liquor. It is moderately soluble in hot alcohol, difficultly soluble in boiling water, and melts at 225°. It is practically tasteless. The yield was 3.5 g. or 28%.

Analyses.—Subs., 0.2, 0.2: NH_3, 16.47 cc., 16.40 cc. 0.1 *N*. Calc. for $C_{13}H_{12}N_2O_3$: N, 11.47. Found: 11.53, 11.48.

Cyclobutane - 1,5 - *spiro* - 1 - benzyl - 2,4,6 - triketo - hexahydro - pyrimidine.—A mixture of 2.5 g. of sodium dissolved in 45 cc. of absolute alcohol, 7.2 g. of ester and 7 g. of benzylurea was heated for 4 hours at 105°. The sodium salt of the product remained in the alcoholic solution. The mixture was acidified and the precipitated ureide filtered off. Evaporation of the mother liquor gave a further portion. The product was washed with cold water and recrystallized from hot alcohol. It consisted of white needles, soluble in hot alcohol, sparingly soluble in hot water, and melting at 131°. It has a bitter taste. The yield was 5 g. or 39%.

Analyses.—Subs., 0.2, 0.2: NH_3, 16.1 cc., 16.3 cc. 0.1 *N*. Calc. for $C_{14}H_{14}N_2O_3$: N, 10.85. Found: 11.22, 11.41.

Cyclobutane - 1,5 - *spiro* - 1 - amino - 2,4,6 - triketo - hexahydro - pyrimidine.—A mixture consisting of 5 g. of sodium in 127 cc. of absolute alcohol, 10 g. of ester and 8 g. of semicarbazine hydrochloride, was heated for 5 hours at 105–108°. The product was neutralized with hydrochloric acid and evaporated to a paste. Sufficient cold water was added to dissolve the sodium chloride, and the residue after filtration was recrystallized from water. The yield was 2 g. of white, scaly crystals. About 3.5 g. of semicarbazine hydrochloride was recovered from the mother liquor, showing that the reaction was far from complete under the conditions of the experiment. The substance dissolves in acids, from which solution it is precipitated as a fine, crystalline powder by ammonia. It is practically tasteless. The substance melts sharply at 262° with sudden evolution of gas, but the melt remains colorless. This behavior suggests the possibility that the condensation may have taken place between the ester and the 2

adjacent nitrogen atoms of the semicarbazine, forming a 5-membered ring with a side chain of —$CONH_2$, which on melting would lose water and leave a CN group.

Analyses.—Subs., 0.2, 0.2: NH_3, 32.7 cc., 32.65 cc. 0.1 *N*. Calc. for $C_7H_9N_3O_3$: N, 22.95. Found: 22.91, 22.87.

Type II.

Cyclobutane - 1,5 - *spiro* - 2 - imino - 4,6 - diketo - hexahydro - pyrimidine.—Three and a half g. of sodium dissolved in 60 cc. of absolute alcohol, 10 g. of ester and 7.7 g. of guanidine carbonate were heated for 4 hours at 105°. The insoluble product was filtered from the alcoholic mother liquor, suspended in water and dissolved in dil. nitric acid. From the filtrate the free base was precipitated by ammonia. The original alcoholic mother liquor contained only a small amount of the product. The yield was 7.5 g. or 90%. The substance is insoluble in neutral solvents, but soluble in acids and alkalies. From alkaline solution it is precipitated by excess of acetic acid. It is tasteless, amorphous, and does not melt at 300°.

Analyses.—Subs., 0.2, 0.2: NH_3, 35.8 cc., 36.0 cc. 0.1 *N*. Calc. for $C_7H_9N_3O_2$: N, 25.15. Found: 25.07, 25.21.

Cyclobutane - 1,5 - *spiro* - 2 - cyamino - 4,6 - diketo - hexahydro - pyrimidine.—Three and a half g. of sodium in 85 cc. of absolute alcohol, 10 g. of ester and 6.3 g. of dicyano-diamide were heated for 5 hours at 105°. After neutralizing, the alcohol was evaporated at 40°, the residue taken up with water and the solution acidified. The product consisted of 2.8 g. of white, flat needles, soluble in hot water and alcohol. The substance has a slightly bitter taste, and does not melt at 300°.

Analyses.—Subs., 0.106, 0.184: NH_3, 21.94 cc., 37.40 cc. 0.1 *N*. Calc. for $C_8H_8N_4O_2$: N, 29.06. Found: 28.98, 29.28.

Cyclobutane - 1,5 - *spiro* - 2 - thio - 4,6 - diketo - hexahydro - pyrimidine.—This preparation was not entirely successful. When the ester was heated in the autoclave with sodium ethylate and thio-urea, the reaction mixture on being treated in the usual way gave only a gum which could not be induced to crystallize from any solvent. A second attempt produced the same result. In a third trial, a parallel run was made with ethyl diethylmalonate and thio-urea, and no difficulty was experienced in obtaining a fair yield of diethyl-thiobarbituric acid. Finally we succeeded in obtaining a small amount of the desired product by boiling a mixture of 3.5 g. of sodium in 65 cc. of absolute alcohol, 10 g. of the ester and 6.5 g. of thio-urea under a reflux condenser for 8 hours. The sodium salt of the thio derivative remained in the alcoholic mother liquor but on cooling separated in long, white needles. These were collected on a filter, dissolved in a small amount of water, and the solution acidified. The thio-ureide separated in lustrous, scaly crystals having a pale straw color. It is soluble in hot water and alcohol, and melts at about 240° to a red liquid. It has a slightly bitter taste. Analysis gave figures somewhat high for nitrogen and low for sulfur—close enough to the calculated amount for approximate identification, but otherwise unsatisfactory. Unfortunately, not enough of the substance was left for further purification. The insoluble portion of the reaction mixture gave the same gum referred to above.

Type III.

Cyclobutane - 1,5 - *spiro* - 2 - phenyl - 4,6 - diketo - tetrahydro - pyrimidine.—Three g. of sodium in 50 cc. of absolute alcohol, 6.4 g. of ester and 6.0 g. of benzamidine hydrochloride were heated for 4 hours at 100 to 105°. The reaction mixture was then concentrated, acidified, and further evaporated at room temperature to a pasty, yellow mass. This was filtered and washed with water. A bright yellow micro-crystalline product was obtained, amounting to 4.5 g. or 61%. It is easily soluble in alcohol and precipitated from alcoholic solution by dilution with water. It is practically tasteless and melts at 263°.

Analyses.—Subs., 0.2, 0.2: NH_3, 17.7 cc., 17.9 cc. 0.1 *N*. Calc. for $C_{13}H_{12}N_2O_2$: N, 12.28. Found: 12.39, 12.53.

Amide of Cyclobutane-1,1-dicarboxylic Acid.—Several of the veronal syntheses in the patent literature are based upon the condensation of diethylmalonyl amide with phosgene, ethyl carbonate, and oxalyl chloride. It was considered of interest, therefore, to prepare the corresponding amide of cyclobutane-1,1-dicarboxylic acid. Ethyl malonate reacts readily with aqueous ammonia. The monoalkyl malonic esters also react in like manner but less readily. The dialkyl malonic esters, on the other hand, do not react with aqueous, alcoholic, or even liquid ammonia. Fischer and Dilthey[1] explain this behavior on the ground that in the absence of a labile hydrogen the ester is unable to form an intermediate addition product with ammonia. The same reasoning would apply to cyclobutane-1,1-dicarboxylic ester where both the labile hydrogens of malonic ester have been replaced by the trimethylene group. Much to our surprise, however, the diamide was obtained without difficulty in a 40% yield. Five g. of the ester and 20 cc. of conc. ammonia were placed in a stoppered bottle for one week and occasionally shaken. After a few hours needle-shaped crystals appeared in the ammoniacal layer while the layer of ester gradually became white and pasty. At the end of a week the contents of the bottle were transferred to a beaker and heated on the steam-bath with enough water to dissolve the crystals and give a clear separation of the unchanged ester. The latter was removed by filtration and the aqueous solution evaporated to crystallization. The yield was 1.4 g. or 40%. The crystals melted at 278° before and after recrystallization. The nitrogen determinations gave results somewhat high, indicating a possible contamination with malonamide which, however, contains 27.45% nitrogen and melts at 170°.

Analyses.—Subs., 0.2, 0.2: NH_3. 29.0 cc., 29.4 cc. 0.1 *N*. Calc. for $C_6H_{10}N_2O_2$: N, 19.72. Found: 20.31, 20.59.

Summary.

1. In the preparation of cyclobutane-1,1-dicarboxylic ester the yield is considerably increased by adding the sodium malonic ester to the dibromoparaffin. By thus maintaining the latter in excess until the end of the reaction, the simultaneous formation of paraffin-tetracarboxylic ester is diminished. There is also less chance of removing hydrobromic acid from the dibromoparaffin.

2. Cyclobutane-1,1-dicarboxylic ester condenses with urea and substituted ureas in the same manner as do the dialkylmalonic esters, but yielding *spiro* compounds containing 1 carbon atom common to 2 rings.

3. Cyclobutane-1,5-*spiro*-barbituric acids resemble the corresponding diethyl-barbituric acids prepared by Fischer, in taste, solubility and solubility of their sodium salts. They differ from the latter, however, in crystalline form and in their higher melting points. They are isomeric with the corresponding monoallyl-barbituric acids, but have higher melting points and do not add bromine.

4. Condensations of cyclobutane-1,1-dicarboxylic ester with N-substituted ureas, C-substituted ureas and amidines yield 3 types of *spiro* pyrimidines, examples of which are described in this paper.

DETROIT, MICH.

[1] Fischer and Dilthey, *Ber.*, **35**, 844–56 (1902).