[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Quaternary Carbon Compounds. I. Trialkylacetic Acids as Antispasmodic Agents[1]

BY NATHAN SPERBER, DOMENICK PAPA AND ERWIN SCHWENK

In a series of investigations on the pharmacological action of trialkylacetamides (I)[2] and trialkylethylamines (II),[3] it was shown that appreciable

$RR'R''CCONH_2$ (I) $\qquad RR'R''C—CH_2NH_2$ (II)

antispasmodic activity is exhibited by those compounds wherein R, R′ and R″ are three, four or five carbon alkyl groups and total 12–17 carbon atoms. In contrast, trialkylacetamides having 7–11 carbon atoms show only weak antispasmodic activity.[4] However, the latter substances are potent soporifics, a type of action not shown by the higher homologous compounds even in large doses.

In view of the accessibility of the trialkylacetamides, it was of interest to establish whether comparable antispasmodic activity would be exhibited by trialkylacetic acids with the requisite number of carbon atoms. A survey of the literature disclosed that, although methods for securing trialkylacetic acids[5] were known, none of them were apparently applicable to the synthesis of those acids wherein the three alkyl groups were of relatively equal size and each alkyl group contained three to five carbon atoms.[6] Haller and Bauer[7] prepared trisubstituted acetic acids containing two lower alkyl groups by cleavage of aryl *t*-alkyl ketones to the corresponding acetamides, the latter being hydrolyzed to the acids with either nitrosyl sulfate or sodium nitrite in hydrochloric acid. However, the hydrolysis procedure, although applicable to lower members of the series, failed with amides of higher molecular weight.

Trialkylacetic acids have also been prepared by the carbonation of *t*-alkylmagnesium chlorides.[8] However, difficulty has been encountered in the preparation of Grignard reagents with high molecular weight tertiary alkyl halides.[9]

Notwithstanding the apparent limitations in the hydrolysis of highly hindered trialkylacetamides, a reinvestigation of the published methods was undertaken since the appropriately substituted acetamides (Table II) are readily available in good yields from the corresponding trialkylacetonitriles[10] (Table I) by hydrolysis with 80% sulfuric acid.[2a]

It was established early in this investigation that the trialkylacetamides (I) are resistant to hydrolysis with the standard hydrolytic agents. The agents studied were boiling 50% sulfuric acid, concentrated hydrochloric acid, phosphoric acid, a mixture of acetic and sulfuric acids and alkali in aqueous solution or in organic solvents.

The action of sodium nitrite and sulfuric acid on acetamides[11] is particularly well adapted to the hydrolysis of trialkylacetamides wherein at least one or more lower alkyl groups are present. However, tributylacetamide, which served as a model for comparing the various hydrolytic methods, was recovered unchanged under these conditions. When tributylacetamide in acetic acid was treated with an excess of butyl nitrite and gaseous hydrochloric acid, tributylacetic acid was obtained in 80–90% yield.[12] The hydrolysis reaction was accompanied by the evolution of heat and nitrogen. The hydrolysis proceeded with equal ease and in somewhat better yield when dioxane was used as solvent. Ether and benzene were also satisfactory solvents, and, on the basis of these results, it appears that any relatively inert organic solvent can be used.

Several new trialkylacetic acids, Table III, wherein R, R′ and R″ total ten or more carbon atoms were secured by this method. The antispasmodic activity of the compounds was determined on isolated rabbit intestinal muscle by measuring the relaxation produced by the test compound against barium chloride and Doryl induced spasms. In general, the structural requirements for antispasmodic activity observed for the trialkylacetamides and trialkylethylamines are approximately the same for the trialkylacetic acids.

(1) Presented in abstract before the Division of Medicinal Chemistry at the Chicago Meeting of the American Chemical Society, April 20, 1948.

(2) (a) Junkmann and Allardt, U. S. Patent 2,186,976, Jan. 16, 1940; (b) Junkmann, *Arch. fur Exper. Path. Pharm.*, **185**, 552 (1937).

(3) Allardt and Junkmann, U. S. Patent 2,361,524, Oct. 31, 1944.

(4) Fromherz, *Arch. f. Exp. Pathologie und Pharm.*, **173**, 78 (1933); also 2b.

(5) Interest in trisubstituted acetic acids has been stimulated recently by the possible relationship of these acids to phthioic acid, isolated by Anderson and co-workers (Anderson, *et al.*, *J. Biol. Chem.*, **114**, 467 (1936)) from the lipoids of tubercle bacilli. Stenhagen and Stallberg (*ibid.*, **139**, 345 (1941)) have concluded from physical measurements and X-ray data that phthioic acid may be a trialkylacetic acid containing one lower and two long chain alkyl groups. Robinson (*J. Chem. Soc.*, 389 (1945)) prepared several acids having the configuration postulated by Stenhagen and Stallberg for phthioic acid and none were found to conform in physical characteristics to phthioic acid.

(6) In a recent publication, Cason (THIS JOURNAL, **69**, 1548 (1947)) has described the synthesis of α-ethyl-α-butylpelargonic acid by the reaction of dibutylcadmium on γ-carbmethoxy-γ-ethyl-γ-butylbutyryl chloride followed by a Clemmensen reduction.

(7) Haller and Bauer, *Ann. chim.*, [9] **1**, 5 (1914); *Compt. rend.*, **148**, 130 (1909); *ibid.*, **149**, 5 (1909); compare Carter and Slater, *J. Chem. Soc.*, 130 (1946); Buu-Hoi and Cagniant, *Rec. trav. chim.*, **65**, 246 (1946).

(8) Whitmore and Badertscher, THIS JOURNAL, **55**, 1559 (1933); see ref. 19.

(9) Compare Birch and Robinson, *J. Chem. Soc.*, 488 (1942).

(10) Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932).

(11) Bouveault, *Bull. soc. chim.*, [3] **9**, 368 (1892); compare Sudborough, *J. Chem. Soc.*, **67**, 601 (1895).

(12) Tributylacetamide was hydrolyzed to the corresponding acid by nitrous anhydride in glacial acetic acid. Compare Hurd and Sowden, THIS JOURNAL, **60**, 235 (1938).

TABLE I

TRISUBSTITUTED ACETONITRILES, RR'R"C—CN

R	R'	R"	B. p. °C.	Mm.	Yield, %	Empirical formula	Analyses, % nitrogen Calculated	Found
n-C_3H_7	*n*-C_3H_7	*n*-C_3H_7	70	2	76	$C_{11}H_{21}N$	8.09	8.05
n-C_4H_9	*n*-C_4H_9	*n*-C_4H_9	126–128	4.6	80	$C_{14}H_{27}N$[a]	6.70	6.86
n-C_4H_9	*n*-C_5H_{11}	*n*-C_5H_{11}	131–132	3.5	40	$C_{16}H_{31}N$	5.90	5.84
n-C_5H_{11}	*n*-C_5H_{11}	*n*-C_5H_{11}	163–163.5	10	57	$C_{17}H_{33}N$	5.57	5.71
CH_3	*n*-C_7H_{15}	*n*-C_7H_{15}	136–138	1.5	43	$C_{17}H_{33}N$	5.55	5.41
n-C_4H_9	*n*-C_7H_{15}	*n*-C_7H_{15}	161–162	2	62	$C_{26}H_{39}N$	4.78	4.79
$C_5H_{10}NCH_2$	*n*-C_4H_9	*n*-C_4H_9	145–147	4	93	$C_{16}H_{20}N_2$[b]	11.66	11.43
$(C_2H_5)_2NCH_2$	*n*-C_4H_9	*n*-C_4H_9	132	4	71.5	$C_{15}H_{30}N_2$[b]	11.76	11.81
$(C_2H_5)_2NCH_2$	*n*-C_4H_9	H	93–95	2	16	$C_{11}H_{22}N_2$[c]	15.35	15.11
C_6H_5	*n*-C_4H_9	*n*-C_4H_9	135–140	1.5	66	$C_{16}H_{23}N$[d]	6.11	6.74

[a] Ref. 3. [b] The starting nitrile was prepared by the reaction of piperidine and diethylamine, respectively, with acrylonitrile; Whitmore, *et al.*, THIS JOURNAL, 66, 725 (1944). [c] Isolated from the forerun in the alkylation of β-diethylaminopropionitrile with butyl bromide and sodium amide. [d] Jullien, *Bull. soc. chim.*, 6, 1252 (1939), reported a boiling point of 172–175° (25 mm.).

TABLE II

TRISUBSTITUTED ACETAMIDES, RR'R"C—$CONH_2$

R	R'	R"	B. p., °C.	Mm.	M. p., °C.	Yield, %	Empirical formula	Analyses, % nitrogen Calculated	Found
n-C_3H_7	*n*-C_3H_7	*n*-C_3H_7	145–147	2	69–70.5	41	$C_{11}H_{23}ON$[a]	7.57	7.51
n-C_4H_9	*n*-C_4H_9	*n*-C_4H_9	160–162	3.5	58–60	85–90	$C_{14}H_{29}ON$[b]		
n-C_4H_9	*n*-C_5H_{11}	*n*-C_5H_{11}	165–166	1.5	41.5–42	83.5	$C_{16}H_{33}ON$[a]	5.49	5.28
n-C_5H_{11}	*n*-C_5H_{11}	*n*-C_5H_{11}	179–182	3	62.5–63.5	89			
CH_3	*n*-C_7H_{15}	*n*-C_7H_{15}	182–185	2		81	$C_{17}H_{35}ON$	5.20	5.41
n-C_4H_9	*n*-C_7H_{15}	*n*-C_7H_{15}	192–195	2		90.5	$C_{29}H_{41}ON$	4.50	5.12
$C_5H_{10}NCH_2$	*n*-C_4H_9	*n*-C_4H_9	178–181	6		85	$C_{16}H_{32}ON_2$	C, 71.56	C, 71.26
								H, 12.02	H, 11.69
$(C_2H_5)_2NCH_2$	*n*-C_4H_9	*n*-C_4H_9	158–160	3	53.5–54		$C_{15}H_{32}ON_2$[c]	10.93	10.94
C_6H_5	*n*-C_4H_9	*n*-C_4H_9	168–170	0.5		76	$C_{16}H_{25}ON$[d]	5.67	5.91
								C, 77.67	C, 77.24
								H, 10.19	H, 10.26

[a] Ref. 3 describes the compounds, but no physical constants are reported. [b] See (a) constants given. [c] This amide readily hydrolyzed to the acid, but the latter could not be isolated. [d] Jullien (*Bull. soc. chim.*, 6, 1252 (1939)) obtained this compound in small yield, m. p. 76°.

TABLE III

TRISUBSTITUTED ACETIC ACIDS, RR'R"C—COOH

R	R'	R"	B. p. °C.	Mm.	Yield, %	Empirical formula	Analyses, % Calculated C	H	Found C	H	Maximum effective dilution $BaCl_2$[a] × 10^6	Doryl[b] × 10^5
n-C_3H_7[c]	*n*-C_3H_7	*n*-C_3H_7	114–117	5[d]	82	$C_{11}H_{22}O_2$	70.89	11.94	71.18	12.44	0.2	Inactive
n-C_4H_9	*n*-C_4H_9	*n*-C_4H_9	136–137	2[e]	90	$C_{14}H_{28}O_2$	73.61	12.35	74.02	11.92	0.6	Inactive
n-C_4H_9	*n*-C_5H_{11}	*n*-C_5H_{11}	157–160	2.5	50	$C_{16}H_{32}O_2$	74.91	12.60	75.49	12.90	6.0	3.8
n-C_5H_{11}	*n*-C_5H_{11}	*n*-C_5H_{11}	167–168	2	94	$C_{17}H_{34}O_2$	75.47	12.68	75.37	12.47	2.0	3.0
CH_3	*n*-C_7H_{15}	*n*-C_7H_{15}	169–171	2	83	$C_{17}H_{34}O_2$	75.47	12.68	76.36	12.65	2.0	2.5
n-C_4H_9	*n*-C_7H_{15}	*n*-C_7H_{15}	177–179	1	82	$C_{20}H_{40}O_2$	76.92	12.82	78.15	12.83	1.5	0.5
$C_5H_{10}NCH_2$	*n*-C_4H_9	*n*-C_4H_9			60	$C_{16}H_{32}O_2NCl$[f]	N, 4.58		N, 4.76			

[a] Papaverine activity, 1×10^5. [b] Atropine activity, 1000×10^5. [c] Trimethylacetic acid exhibited no musculotropic or neurotropic activity. [d] M. p. 65.5–67.5°. [e] M. p. 35–37°, literature,[19] m. p. 38°. [f] Obtained as the hydrochloride, m. p. 178–178.5°.

Experimental

I. **Trisubstituted Acetonitriles.**—The synthesis of tributylacetonitriles by methods (a) and (b) will illustrate the general procedure used for the preparation of the nitriles listed in Table I.

(a) **From Capronitrile:** In a two-liter, three-necked flask, fitted with an efficient stirrer, condenser and a 500-cc. dropping funnel, was placed a mixture of 100 g. of redistilled capronitrile, 300 g. of butyl bromide and 300 cc. of dry toluene. A suspension of sodium amide in a total of 400 cc. of toluene was prepared from 53 g. of sodium[13] and the stirred sodium amide suspension was added from a dropping funnel as described by Ziegler and Ohlinger.[10] The flask was warmed to 80° and the sodium amide suspension was added at such a rate that gentle refluxing resulted. After the addition of the sodium amide was completed, the reaction mixture was stirred and refluxed for an additional hour. The flask was cooled in an ice-bath and the reaction product decomposed with 500 cc. of water. The toluene layer was separated, washed with water, the solvent removed *in vacuo* and the residue fractionated. A 10-g. forerun, b. p. 95–97° (8 mm.), was identified as dibutylacetonitrile. The main fraction, b. p. 107–110° (1.5 mm.), amounted to 177.3 g. (81%); $n^{24}D$ 1.4390. The residue (24 g.) was a black, viscous liquid, presumably consisting of tributylacetamidine.

(13) "Organic Reactions," Vol. I, p. 99.

The latter may be prepared as follows: Tributylacetonitrile (21 g., 0.1 mole) was added to a suspension of sodium amide (prepared from 4.0 g. of sodium and liquid ammonia) in 75 cc. of toluene and the mixture refluxed and stirred for five hours. The flask was cooled and the excess sodium amide was decomposed with water. The toluene layer was separated, the aqueous layer saturated with potassium hydroxide and ether extracted. The ether–toluene layer was dried over potassium hydroxide pellets, the solvents removed *in vacuo* and the residue distilled; yield 20 g. (88%); b. p. 134–136° (0.5 mm.); colorless, viscous oil.

Anal. Calcd. for $C_{14}H_{30}N_2$: N, 12.38. Found: N, 11.84.

The hydrochloride was prepared by dissolving 20 g. (0.076 mole) of tributylacetamidine in 250 cc. of ether and saturating with gaseous hydrogen chloride. The ether was removed *in vacuo* leaving a thick sirup which slowly crystallized upon the addition of a few drops of water; recrystallized from hot water, yield 19.0 g., m. p. 141–142°.

Anal. Calcd. for $C_{14}H_{31}N_2Cl$: N, 10.66. Found: N, 10.54.

The forerun of dibutylacetonitrile collected from a series of alkylations can be further alkylated with sodamide and butyl bromide to give tributylacetonitrile.

(b) **From Acetonitrile**[14]: A mixture of 20.5 g. (0.5 mole) of acetonitrile and 250 g. of dry butyl bromide in 250 cc. of anhydrous toluene was stirred and heated while a suspension of sodium amide (prepared from 39 g. of sodium) was added cautiously. After the addition of the sodium amide was completed, the gray reaction mixture was refluxed and stirred for two hours. The product was processed as described above; yield 94 g. (80%); b. p. 101–104° (0.5 mm.); $n^{24}D$ 1.4385.

Attempts to alkylate either capronitrile or acetonitrile with butyl chloride were less satisfactory. In one experiment, the reaction proceeded sluggishly; then suddenly became uncontrollably violent. In other experiments, crude yields of alkylated products were 22–30%. A higher amidine residue was usually obtained in these experiments.

II. **Hydrolysis of Nitriles to Acetamides.**—The following hydrolytic experiments were carried out with tributylacetonitrile as a model substance: The nitrile was recovered unchanged by reaction with hydrogen peroxide in alcoholic potassium hydroxide at 50° for three hours[15]; while refluxing with 20% potassium hydroxide in butanol for 100 hours yielded 15.5% of tributylacetamide.[16]

Hydrolysis with 80% sulfuric acid: In a two-liter, three-necked flask equipped with a Hershberg tantalum wire stirrer and reflux condenser, there were added 1500 g. of 80% sulfuric acid and 216 g. of tributylacetonitrile. The reaction mixture was heated and stirred vigorously for twelve hours on the steam-bath. The dark brown reaction product was poured on ice and the viscous oil extracted with benzene. The benzene layer was washed with 10% sodium carbonate solution, and with water. The solvent was removed *in vacuo* and the viscous residue was distilled; yield 210 g. (90%); b. p. 153–155° (1.5 mm.). The distillate slowly solidified to a waxy solid, m. p. 57–59°.[2a] The amides reported in Table II were secured by hydrolysis with 80% sulfuric acid.

Other concentrations of sulfuric acid (70–96%) were studied. With 96% sulfuric acid at 60° for eight hours, an 83% yield of the amide was obtained. In another experiment, 16 g. of tributylacetonitrile and 150 cc. of 70% sulfuric acid were heated for three hours at 145°. There was a considerable evolution of sulfur dioxide and the reaction mixture was transformed into a black tar from which none of the desired acetamide could be isolated.

III. **Hydrolysis of Acetamides to Acids.**—The synthesis of tributylacetic acid will illustrate the general procedure used for the preparation of the trisubstituted acetic acids.

(a) Acidic reagents such as phosphoric acid at 150–160° for six hours,[17] concentrated hydrochloric acid at reflux temperature for thirty hours, mixtures of sulfuric and acetic acids and ethanol–sulfuric acid gave none of the expected tributylacetic acid. Potassium hydroxide in propylene glycol or in glycerol likewise yielded no acidic product.

(b) **Organic nitrites**: In a 1-l., 3-necked flask, fitted with a gas inlet tube, dropping funnel, reflux condenser and stirrer, was placed a solution of 95 g. of tributylacetamide in 500 cc. of glacial acetic acid. Anhydrous hydrogen chloride gas was bubbled in slowly for fifteen minutes and 85 g. of freshly distilled butyl nitrite[18] was added dropwise to the stirred solution over a period of two hours. The solution assumed a deep red color and within fifteen minutes an evolution of gas was observed. After the addition of butyl nitrite was completed, the solution was stirred at room temperature two hours, and then on the steam-bath for an additional two hours. The acetic acid was removed *in vacuo* and the residue dissolved in 10% potassium hydroxide solution. The alkaline solution was decolorized with Norite, filtered and acidified with hydrochloric acid. The gummy residue was extracted with ether, dried over sodium sulfate and the ether removed. The residue was fractionated; yield 75 g. (79%); b. p. 140–143° (2 mm.). The distillate slowly crystallized; m. p. 35.5–37.5°; literature,[19] m. p. 38°. A 3-g. forerun was obtained which gave a qualitative test for nitrogen.

In subsequent experiments, solution of the reaction product in 10% potassium hydroxide was omitted. Upon removal of the acetic acid, the crude tributylacetic acid was distilled and was found to contain small amounts of the amide. The acid was obtained free of amide by a second distillation as evidenced by a negative qualitative test for nitrogen. All the acids listed in Table III were prepared by this procedure.

Benzene and dioxane gave slightly higher yields than acetic acid. In general, dioxane gave products of higher purity.

Attempts to convert tributylacetamide to tributylacetic acid by the method of Bouveault[11] using sodium nitrite and sulfuric acid were unsuccessful. Various concentrations of sulfuric acid were used including concentrated acid, but none of the expected tributylacetic acid was isolated. The use of sulfuric–acetic acid mixture was also fruitless. Tributylacetamide could not be converted to the corresponding acid in acetic acid or dioxane with sodium nitrite and anhydrous hydrogen chloride.

Nitrous anhydride is apparently also applicable to the hydrolysis of the hindered trialkylacetamides. A good yield of tributylacetic acid was obtained from tributylacetamide as follows: Nitrous anhydride[20] was passed into a solution of 10 g. of tributylacetamide in 75 cc. of glacial acetic acid, cooled in an ice-bath. The flask was allowed to stand at room temperature overnight and was heated for two hours on the steam-bath. The acetic acid was removed *in vacuo* on the steam-bath and the residue was dissolved in 10% potassium hydroxide solution. Upon

(14) Bergstrom and Agostinho (THIS JOURNAL, **67**, 2152 (1945)) monoalkylated acetonitrile with butyl bromide and sodamide in liquid ammonia and obtained a 56% yield of capronitrile and 27% of the dialkylated product.

(15) Radziszewski, *Ber.*, **18**, 355 (1885); McMaster and Langreck, THIS JOURNAL, **39**, 103 (1917); Murray and Cloke, *ibid.*, **56**, 2749 (1934).

(16) Rovira and Palfray (*Compt. rend.*, **211**, 396 (1940)) report that, although 10% of the theoretical amount of ammonia is liberated upon refluxing phenyldibutylacetonitrile with potassium hydroxide and diethylene glycol, none of the expected phenyldibutylacetic acid was isolated.

(17) Berger and Olivier, *Rec. trav. chim.*, **46**, 600 (1947).

(18) In subsequent experiments, it was established that butyl nitrate could be stored in the refrigeratior for several months without any appreciable decomposition.

(19) Whitmore, *et al.*, THIS JOURNAL, **63**, 643 (1941).

(20) "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., p. 267.

acidification of the alkaline solution with hydrochloric acid, tributylacetic acid separated as an oil which solidified upon standing; yield 8 g. (80%); m. p. 33.5–35.5°.

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Summary

1. The conversion of trialkylacetamides to trialkylacetic acids has been investigated using a number of different hydrolytic agents. Of the methods studied, the reaction of alkyl nitrites in organic solvents in the presence of gaseous hydrogen chloride gave consistently high yields of trialkylacetic acids.

2. Several new trialkylacetic acids are described.

3. Trialkylacetic acids having a total of 15–20 carbon atoms show musculotropic and neurotropic antispasmodic activity.

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

Spiro (Steroid) Thiazolidines[1]

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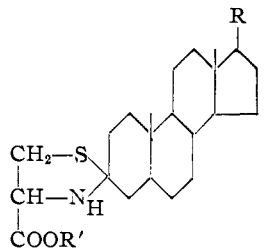
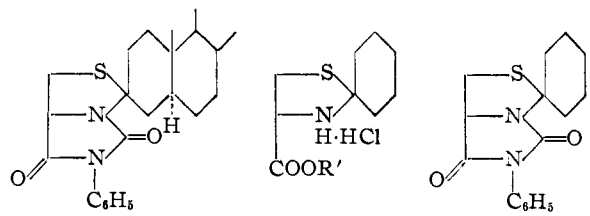
In a preliminary note[2] the preparation of several spiro (steroid) thiazolidines was reported, and the possible role such structures may have in the action of steroid hormones was discussed.

Schubert[3] in a series of papers has described the thiazolidines resulting from the condensation of cysteine with various aldehydes. Ratner and Clarke[4] studied the formation and properties of thiazolidine-4-carboxylic acid, and it has been announced[5] that the various penicillins are thiazolidine derivatives. This paper describes the thiazolidines formed by the reaction of 1(+)-cysteine with a number of 3-ketosteroids.

When an alcoholic (methanol or ethanol) solution of cholestanone was added to an aqueous alcoholic solution of 1(+)-cysteine hydrochloride buffered with potassium acetate, a heavy precipitate formed in a few minutes. The product (I) melted unsharply between 220 and 230° and was insoluble in water and very slightly soluble in organic solvents. The solubility together with the high melting point suggested that the product exists as a dipolar ion. The compound produced no color with sodium nitroprusside in the presence of ammonia or sodium bicarbonate whereas in the presence of sodium carbonate, a positive test for the free SH grouping was obtained. The compound was readily oxidized by a solution of iodine producing cystine and cholestanone. These reactions indicated that the product was (I), a thiazolidine analogous to those prepared by Schubert.[3] It was characterized as its N-acetyl derivative, m. p. 266–267°. Spiro [cholestane-3,2′-thiazolidine-4′-carboxylic acid ethyl ester] (II) prepared from cholestanone and cysteine ethyl ester hydrochloride in buffered solution reacted similarly to the free acid and when treated with phenyl isocyanate, the product isolated was the N-phenylhydantoin (III), m. p. 216–217°.



I	R = C_8H_{17}	; R′ = H
II	R = C_8H_{17}	; R′ = C_2H_5
IV	R = O	; R′ = H
IVa	R = O	; R′ = C_2H_5
V	R = $COCH_3$	; R′ = H
Va	R = $COCH_3$	; R′ = C_2H_5
VI	R = ...OH	; R′ = H
VIa	R = ...OH	; R′ = C_2H_5
VII	R = —OH	; R′ = H



III VIII R′ = H IX R′ = C_2H_5 X

Spiro-thiazolidines were prepared from the following 3-ketosteroids: androstanedione-3,17 (IV and IVa), pregnanedione-3,20 (V and Va), androstanol-17α-one-3 (VI and VIa) and its 17β isomer androstanol-17β-one-3 (VII). The products formed may exist in two possible steric modifications since the thiazolidine ring is at right angles to the plane of the steroid nucleus. Consequently one isomer can be considered to have the sulfur atom of the heterocyclic ring above the plane of the nucleus, while the sulfur atom of the second isomer would be below the plane of the nucleus. However, only one isomer has been obtained from the compounds investigated.

(1) The authors gratefully acknowledge the assistance of the Jane Coffin Childs Memorial Fund for Medical Research, the Commonwealth Fund, the Whiting Foundation, the Alfred P. Sloan, Jr., Research Fund, the Baird Foundation and the Pardee Foundation.

(2) Lieberman, *Experientia*, II, 411 (1946).

(3) Schubert, *J. Biol. Chem.*, **111**, 671 (1935); **114**, 341 (1936); **121**, 539 (1937); **130**, 601 (1939).

(4) Ratner and Clarke, THIS JOURNAL, **59**, 200 (1937).

(5) *Science*, **102**, 627 (1945).