(180–210° at 0.5 mm.) and further recrystallization, the colorless solid melted at 151–152° with previous softening; however, when the melt was allowed to resolidify slowly, it remelted sharply at 154–155°.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.4; H, 5.9. Found: C, 78.3; H, 5.8.

3-Methoxy-16-equilenone (XI).—A mixture of 500 mg. of the methoxy ketone X (purified by evaporative distillation at 200–220° and 0.05 mm. and recrystallization from benzene–acetone), 30 cc. of purified dioxane and 200 mg. of 30% palladium–charcoal catalyst[16] was stirred with hydrogen at room temperature and atmospheric pressure until the uptake corresponded to 1.07 moles (fourteen hours). By repeated fractional crystallization of the product from methanol–acetone a total of 18% of the starting ketone was recovered, m. p. 203–206°, and from the filtrates by recrystallization from benzene was obtained 24 mg. (5%) of colorless leaflets, m. p. 185–186°. This appears to be one of the two *dl*-mixtures of the reduced ketone, **3-methoxy-16-equilenone (isomer A)**.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.2. Found: C, 81.0, 81.4; H, 7.2, 7.3.

For a second reduction the ketone was purified by refluxing in alcohol with Raney nickel catalyst and then recrystallizing; 600 mg. of ketone, 300 mg. of palladium–charcoal catalyst and 30 cc. of dioxane were used. After two hours an additional 150 mg. of catalyst was added. The reaction was allowed to proceed until the equivalent of 1.25 moles of hydrogen had been absorbed (twenty-eight hours). By repeated fractional crystallization first from benzene and then from methanol–acetone, 100 mg. of the second racemate, **3-methoxy-16-equilenone (isomer B)**, m. p. 169.5–171°, was obtained as colorless needles. The m. p. was depressed to 156–168° when this compound was mixed with the 186° isomer.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.2. Found: C, 81.4; H, 7.3.

By treating the material in the filtrates with Girard reagent P and recrystallizing the ketonic fraction many times from benzene and then from methanol–acetone, it was possible to isolate an additional 47 mg., m. p. 168–170°, bringing the total yield of isomer B to 24%. None of the pure isomer A was isolated from this run.

3-Hydroxy-16-equilenone (IV). (a) **By Reduction.**—A suspension of 500 mg. of the unsaturated phenolic ketone and 200 mg. of 30% palladium–charcoal in 35 cc. of pure dioxane was stirred at room temperature and atmospheric pressure. After three hours an additional 40 cc. of dioxane was added to effect complete solution of the compound and 100 mg. of catalyst was added. Hydrogenation was continued for a total of twenty-six hours (50 mg. of catalyst added after twenty-two hours) until the hydrogen uptake was equivalent to 1.25 moles. By repeated fractional crystallization from alcohol 72 mg. (14%) of one of the isomers, **3-hydroxy-16-equilenone (isomer B)** was obtained as colorless needles, m. p. 264–266° (vac., uncor.). This material showed no depression in melting point when admixed with the sample of phenolic ketone obtained in (b).

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8. Found: C, 81.2; H, 6.9.

(b) **By Demethylation.**—A mixture of 47 mg. of isomer B of 3-methoxy-16-equilenone (m. p. 168–170°), 4 cc. of 42% hydrobromic acid and 4 cc. of acetic acid was heated under nitrogen for three hours. After dilution and extraction with ether, the phenolic fraction was removed by repeated extraction with sodium hydroxide solution. Upon acidification 31 mg. (70%) of nearly colorless solid, m. p. 260–263° (dec.) was obtained. By recrystallization from alcohol, using Norit, cream colored leaflets, m. p. 265–266° (vac., uncor.), were obtained.

Summary

3-Hydroxy-16-equilenone, a structural isomer of the sex hormone equilenin having the keto group at C-16 instead of C-17, has been synthesized from 1-keto-2-methyl-7-methoxytetrahydrophenanthrene. An improved method of preparation is described for the latter.

MADISON 6, WIS. RECEIVED JUNE 21, 1947

(16) Linstead and Thomas, *J. Chem. Soc.*, 1130 (1940).

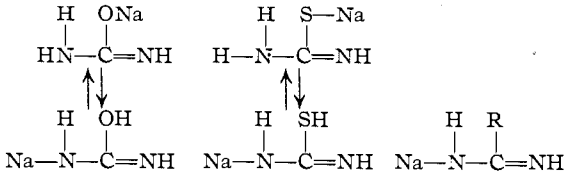
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

Condensations of α-Alkyl-α-carbethoxy-γ-butyric Lactones

BY GLENN S. SKINNER, ARTHUR STOKES[1] AND GEORGE SPILLER[1a]

The discovery that α-alkyl-α-carbethoxy-γ-butyric lactones[1b] can be substituted for malonates in the preparation of barbituric acid derivatives immediately suggested that thiourea and amidines could be used in place of urea.

It has long been the belief of many chemists that the tautomeric forms of these reagents are the most reactive ones. With sodium ethoxide the driving force of the reaction is evidently the capacity of sodium to displace hydrogen with the ultimate formation of a compound that has still greater capacity of neutralizing the sodium ethoxide. Amidines, however, can compete with the alcohol for the sodium only by substitution for the hydrogen linked to nitrogen. According to the application of the above view to this reaction the concentration of the intermediates would be less in the case of amidines and the reaction should be expected to proceed less easily. This has been found to be the case. As indicated by yields from the lactone esters at the lowest practical reaction temperature the relationship is thiourea > urea > benzamidine.



The lactone esters in common with numerous other ring systems possess the structural characteristic for increased reactivity at position 3 in

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(1b) Last previous report of this series: Skinner and Mitchell, THIS JOURNAL, **67**, 1252 (1945).

which the lactone ring plays the same role as a double bond. They should therefore be expected to react more readily than dialkylmalonic esters. Actually this increased reactivity has permitted the reaction to be conducted at temperatures low enough to isolate an intermediate compound. The intermediate once isolated can be washed with boiling alcohol. The intermediate is very insoluble in cold alcohol but does not separate immediately by cooling the reaction mixture that has been refluxed although fairly good yields of the barbituric acid are obtained. When the intermediate is stirred into a mixture of ice and hydrochloric acid the alkylhydroxyethylbarbituric acid at once precipitates. In comparative experiments ethylisoamylmalonic ester gave no barbituric acid at 25° for a period of twenty-four hours but α-isoamyl-α-carbethoxy-γ-butyric lactone gave 80–90% yields of the corresponding barbituric acid derivative.

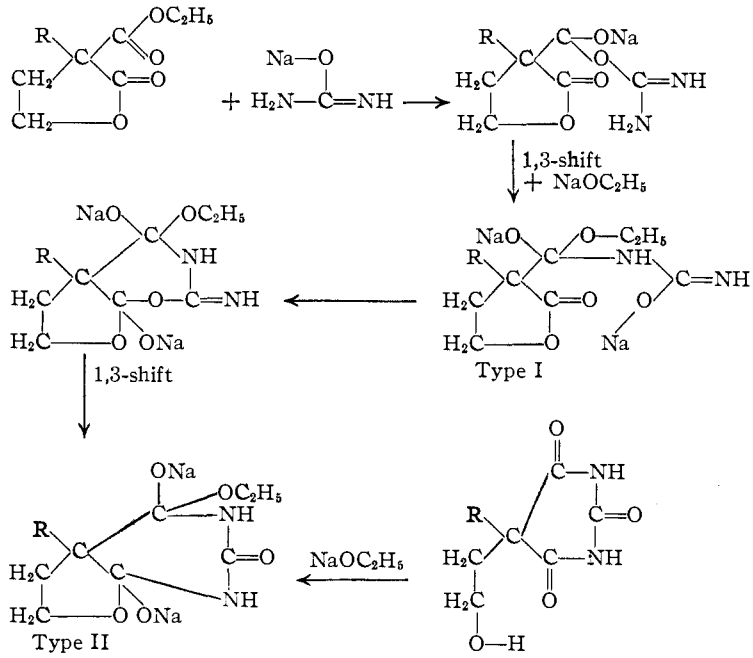
Although α-alkyl-α-carbethoxy-γ-butyric lactones readily undergo the first stage (Type I) of the condensation with benzamidine, ring closure is not effected even by heating at a temperature of 75°. The product behaves as an inner salt whose formation can be explained by the action of aqueous alkali on a product[2] analogous to the lactone thioureide (Type I). The yield is increased by using a lower reaction temperature (about 45°). It is thus established that the reaction proceeds fundamentally in the same way as with thiourea in the initial stages.

It has been reported that γ-lactones[3] are converted by sodium alkoxides to esters of γ-hydroxy acids at temperatures below 55°. Since the hydroxyethylbarbituric acids are formed with great ease at these temperatures it is quite evident that the reaction does not proceed through the intermediate formation of alkylhydroxyethylmalonates as dialkylmalonic esters under the same conditions show relatively little tendency to react.

In order to remove this possibility α-isoamyl-α-carbethoxy-γ-butyric lactone was allowed to stand with the sodium ethoxide solution prior to the addition of the urea. This did not result in the rupture of the lactone ring but in the partial cleavage of the carboxethyl group with the formation of α-isoamyl-γ-butyric lactone. The remaining portion of the reactant reacted rapidly after the manner of the lactone esters to yield the alkylhydroxyethylbarbituric acid and not with the comparative slowness of the dialkylmalonic esters. It is therefore evident that the lactone ring of these compounds remains intact in the initial stages of the condensation.

Furthermore, tetrahydropyrimidine derivatives are formed at 70–75° from esters of dialkylmalonic acids.[4] If the cleavage of the lactone ring by sodium ethoxide were a prior step for the formation of the barbituric acid or the tetrahydropyrimidine derivative, ring closure should be effected when the lactone esters are used under the same conditions.

Since the Type II compound can be made either by carrying out the condensation with urea and with thiourea or by treating the hydroxyethylbarbituric acid with sodium ethoxide solution one may inquire as to whether the hydroxyethylbarbituric acid is formed first. If this were correct the necessary hydroxyl could have become available only by a prior opening of the lactone ring which is quite unlikely in view of the unreactivity of the dialkylmalonic esters under the optimum conditions for the lactone esters. The following scheme is therefore tentatively proposed as the one best explaining the facts.



Since the chief objective is the employment of the lactone esters for synthetic purposes it may be stated that the β-hydroxyl and other similarly placed functional groups in these barbituric acid derivatives are smoothly displaced. β-Aminoethylbarbituric acids are formed from the corresponding bromo acids in 75–80% yields. The aminoethylisoamylbarbituric acid is diazotized quantitatively to yield the original hydroxyethyl compound. The xanthate is formed from β-bromoethylisoamylbarbituric acid in more than 87% yield.

(2) The lactone amidine has been isolated in collaboration with Ethel Anderson and will be reported in the next paper of this series.

(3) Spencer and Wright, THIS JOURNAL, **63**, 1281 (1941).

(4) Dox and Yoder, *ibid.*, **44**, 361 (1922).

TABLE I

BARBITURIC ACIDS RR'(CONH)$_2$CO

R	R'	M. p., °C.	Yield, %	Nitrogen, % Found	Calcd.
C_2H_5—	$BrCH_2CH_2$—	164–165	96	10.65[c]	10.65
C_2H_5—	H_2N—CH_2CH_2—	226–228	75	21.18[c]	21.09
iso-C_5H_{11}—	H_2N—CH_2CH_2—	212–213	81	17.39[c]	17.41
iso-C_5H_{11}—	CH_3—CO—NH—CH_2CH_2—	237–238	94	14.81	14.84
C_2H_5—	CH_3—CO—NH—CH_2—CH_2—	239–240	75	17.25	17.42
iso-C_5H_{11}—	CH_3—O—CS—S—CH_2—CH_2—	172	87[a]	8.47	8.43
n-C_4H_9—	H_2N—CH_2—CH_2—	204 dec.	75	18.24	18.50
n-C_4H_9—	$(CH_3)_3NBr$—CH_2CH_2—	250–251 dec.	74	22.4[b]	22.8[b]

[a] Sulfur, %: found, 19.30; calcd., 19.31. [b] Bromine. [c] Analyses by George Limperos.

Experimental

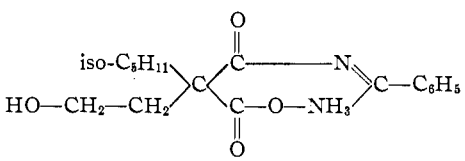
Isolation of the Intermediate II.—A solution of sodium ethoxide prepared from 13.8 g. of sodium and 200 cc. of absolute alcohol was cooled to 25° while stirring. Powdered urea (24.0 g.) and 45.6 g. of α-carbethoxy-α-isoamyl-γ-butyrolactone were stirred into the slurry. In two and one-half hours the urea had dissolved completely and stirring was stopped. The temperature of the mixture was now increased slowly in the course of four hours to 44° at which a white crystalline precipitate began to separate. It was heated for two hours longer at this temperature. After standing overnight the mixture had set to a solid mass. The solid cake was broken up and filtered with the aid of a rubber dam, washed three times with ice-cold absolute alcohol and dried to constant weight *in vacuo;* yield was 52.5 g. The barbituric acid derivative that was precipitated by the acidification of a test aqueous solution of the compound melted sharply at 178° without further purification. Five grams of the substance was recrystallized from 10 cc. of boiling absolute alcohol. The crystalline salt obtained by filtering and washing five times with ice-cold alcohol weighed 3.5 g. after drying *in vacuo*. It was dried to constant weight at 102°. *Anal.* Calcd. for $C_{13}H_{22}O_5N_2Na_2$: Na, 13.85; N, 8.48. Found: Na, 13.99; N, 8.44.

Reaction of Sodium Ethoxide upon the Lactone Ester.—To a solution of sodium ethoxide prepared from 4.6 g. of sodium and 90 cc. of absolute alcohol was added 15.3 g. of α-isoamyl-α-carbethoxy-γ-butyric lactone. After standing for fifty-one hours at 27–29° 8.0 g. of powdered urea was dissolved in the mixture by stirring for forty-five minutes at this temperature. After an additional twenty hours a 10-cc. sample was withdrawn and treated with an excess of hydrochloric acid, finely crushed ice and petroleum ether. The weight of barbituric acid derivative was 0.64 g., m. p. 177–179°. The weight of the oil from the petroleum ether washings was 0.76 g. The yield of the barbituric acid derivative did not increase after standing for twenty-four hours longer. One day later the crystalline solid had separated and did not increase in amount after standing another day. The total yield of barbituric acid derivative was 6.4 g. (39%) and that of the decarboxethylated lactone ester was 8 g. (51%), b. p. 90–93° (4 mm). The Zeisel test for $-OC_2H_5$ was negative.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.23. Found: C, 69.08; H, 10.30.

Comparison with a Dialkylmalonic Ester.—According to the procedure for converting the lactone esters to hydroxyethylbarbituric acids yields of 80–90% are obtained in twenty-four hours at similar temperatures. The reaction of 17.3 g. of ethylisoamylmalonic ester on 8.0 g. of urea in alcoholic sodium ethoxide prepared from 4.6 g. of sodium and 90 cc. of absolute alcohol gave no barbituric acid derivative at 25° for twenty-four hours. When the temperature was raised to 45° and another aliquot was withdrawn after twenty hours the yield of barbituric acid derivative was 30%. The yield was increased to 39% by heating at 65° for seven hours. After standing for two days longer at room temperature and heating again for four hours at 67° the yield of crude ethylisoamylbarbituric acid was 63%. Recrystallized once from absolute alcohol the product melted at 154–156°.

Condensation of α-Carbethoxy-α-isoamyl-γ-butyric Lactone with Benzamidine.—A hot solution of sodium ethoxide prepared from 6.9 g. of sodium and 70 cc. of absolute alcohol was cooled while stirring. To this was added 13.5 g. of benzamidine hydrochloride and 15.8 g. of the lactone ester. When well-mixed the temperature was raised to 60° in the course of two hours where it was maintained for ten hours. In two hours more the temperature was raised to 75°. After distilling the alcohol under diminished pressure the aqueous solution of the residue was extracted with ether. The oily precipitate from the water layer that was obtained by acidification was dissolved in ether. Repeated working with petroleum ether as a precipitant from ether and chloroform solution gave 6.4 g. of crystalline material dec. p. 140–145°. This was suspended in boiling chloroform and dissolved by the addition of a very small quantity of alcohol. Upon cooling there was obtained 4.5 g. of pure product which decomposed definitely at 147° with vigorous evolution of ammonia. *Anal.* Calcd. for $C_{17}H_{24}O_4N_2$: N, 8.75. Found: N, 8.70. The analysis and behavior indicate that it is an inner salt.



5-Alkyl-5-β-aminoethylbarbituric Acids.—In a typical experiment 70 g. of 5-β-bromoethyl-5-isoamylbarbituric acid that had been dissolved in 150 cc. of hot alcohol was poured in a thin stream into 470 cc. of 6% alcoholic ammonia that was cooled in a freezing mixture of salt and ice. In three hours it had warmed to room temperature and in two hours more crystals began to separate. After two days the precipitate (29 g., m. p. 204–205° dec.) was filtered. Concentration of the mother liquor gave 16.3 g., m. p. 212–213°. Further concentration of the filtrate gave 2 g. more. The two end fractions were treated with 7 cc. of aqua ammonia in 50 cc. of water. Solution was effected by gradually stirring in 8 cc. of saturated sodium hydroxide solution. The well-cooled filtrate was carefully neutralized with acetic acid. After standing in a cold bath the amino acid was filtered, bringing the total yield of product m. p. 212–213° to 44.7 g. (81%).

The amino acids are acetylated by warming and stirring on a steam-bath with three to four times their weight of acetic anhydride and an equal weight of benzene for about twenty minutes. Four to five volumes of finely crushed ice and water are then stirred into the mixture to precipitate the acetyl derivative which does not require further purification.

5-Isoamyl-5-β-methylxanthogenethylbarbituric Acid.—A mixture of 15.0 g. of 5-β-bromoethyl-5-isoamylbarbituric acid and 12.0 g. of methyl potassium xanthogenate was dissolved in absolute methyl alcohol. To this solution 8.5 cc. of a 4.5 *N* solution of hydrogen chloride in

methyl alcohol was added. After refluxing for an hour the methyl alcohol was distilled from a water-bath. The crude xanthogenic ester obtained by treating the residue with water weighed 16.0 g. The crude product was dissolved in hot methyl alcohol and filtered. By cooling the filtrate in an ice–salt-bath 14.3 g. of pure product was obtained, m.p. 172°.

Reaction with Trimethylamine.—A cold solution of 14.5 g. of 5-β-bromoethyl-5-*n*-butylbarbituric acid in 125 cc. of absolute alcohol was carefully mixed with a cold solution of 13.3 g. of trimethylamine in 65 cc. of absolute alcohol. After standing two days in the ice-box and a month at room temperature no crystals had separated. After distillation to dryness under diminished pressure and crystallization from *n*-butyl alcohol 13 g. of product melting at 245–50° and decomposing at 255° were obtained. Crystallization of this from ethyl alcohol yielded 11 g. melting at 250–251° with slight decomposition. The bromine is precipitated directly from water solution.

Summary

1. Some comparisons are made with respect to the relative ease with which urea, thiourea and benzamidine condense with an α-alkyl-α-carbethoxy-γ-butyric lactone and an alkylmalonic ester to yield compounds related to pyrimidine.

2. A tentative mechanism for the reaction is proposed which is based partly on the isolation of two types of intermediates.

3. The replacement of bromine in the β-position to the barbituric acid nucleus proceeds smoothly. The β-amino group is quantitatively diazotized to the hydroxy compound without rearrangement.

NEWARK, DELAWARE RECEIVED JULY 9, 1946

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF J. T. BAKER CHEMICAL CO.]

Some Urethans of Phenolic Quaternary Ammonium Salts

BY JOHN H. GARDNER AND JOSEPH R. STEVENS

Stevens and Beutel[1] have demonstrated the pronounced physostigmine activity of certain 3-alkyl-4-dimethylaminophenol dimethylurethan methiodides. A new series of *p*-aminophenol derivatives with other groups in the 3-position has now been prepared and shown to be physiologically active. Similar derivatives of 5-hydroxy-1,2,3-trimethylindoline and of 6- and 8-hydroxy-1-methyl-1,2,3,4-tetrahydroquinoline have also been prepared and found to be active. The properties of the dimethylurethan hydrochlorides are summarized in Table I and those of the methiodides in Table II.

Pharmacological measurements were made in the laboratory of The Wm. S. Merrell Co., through the courtesy of Dr. Robert S. Shelton, or in the laboratory of Dr. F. O. Zillessen of Easton, Pennsylvania. For a preliminary evaluation, the toxicities were determined. These were stated as LD_{50}, in mg./kg., in mice by intravenous injection. Of the meta-substituted *p*-dimethylaminophenol derivatives, the methoxy compound was by far the most toxic (LD_{50} 1.3 mg./kg.), but the greatest toxicity of the series was shown by 8-hydroxy-1-methyl-1,2,3,4-tetrahydroquinoline dimethylurethan methiodide (0.24 mg./kg.).

Experimental

General Procedure.—For the preparation of the aminophenols, the phenols were coupled with diazotized sulfanilic acid, and the azo dye was reduced with sodium hydrosulfite with or without being isolated. The aminophenols were methylated with methyl iodide in the presence of sodium carbonate and the resulting quaternary salt was subjected to destructive distillation in vacuum. In the preparation of 4-dimethylamino-3-methoxyphenol, it was found better to decompose the quaternary salt under reflux in vacuum. The dimethylaminophenols were converted into the dimethylurethan hydrochlorides by the general procedure of Stevens and Beutel.[1] In some cases it was necessary to boil the dimethyl urethans with excess methyl iodide in acetone for several days. The indoline and quinoline dimethylurethan salts were obtained in a similar way. For illustration the preparation of 4-dimethylamino-3-isopropoxyphenol and its derivatives is described in detail.

Resorcinol Mono- and Di-isopropyl Ethers.—The monoether has been used previously in another connection[2] but its preparation has not been described. These ethers were prepared by the general method for the preparation of resorcinol mono-alkyl ethers of Klarmann, Gatyas and Shternov.[3] Resorcinol mono-isopropyl ether, yield, 27.1%, b. p. 122–125° under 3.5 mm.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.1; H, 7.9. Found: C, 71.43; H, 7.96.

Resorcinol di-isopropyl ether, yield, 11.5%, b. p. 89.5–95° under 3 mm.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.2; H, 9.3. Found: C, 74.2; H, 9.13.

4-Amino-3-isopropoxyphenol.—To a solution of 19.1 g. of sulfanilic acid, 6.5 g. of sodium carbonate monohydrate and 6.2 g. of sodium nitrite in 75 ml. of water, cooled to 2° by adding ice, 25 ml. of concentrated hydrochloric acid was added and then enough sodium nitrite to give a blue color on starch–potassium iodide paper after a minute. Urea was added to destroy the excess nitrous acid and the solution was then poured into a cold solution of 15.2 g. of resorcinol mono-isopropyl ether in 80 ml. of 10% sodium hydroxide. The mixture was allowed to stand about two hours until no test for diazo compound was obtained with an alkaline solution of β-naphthol. It was then acidified with hydrochloric acid, chilled in the refrigerator, filtered and the precipitate washed with water. The dye was dried in a vacuum at 50°. Yield was 28.4 g. (93.4%).

The dye was dissolved in a mixture of 190 ml. of water and 26 ml. of 50% sodium hydroxide. To the solution 44.5 g. of sodium hydrosulfite was added with stirring. The temperature rose to 60° and the solution became light green. It was then neutralized to a brilliant yellow end point with glacial acetic acid, chilled in the refrigerator and the light brown crystals were filtered out and dried in

(1) I. R. Stevens and R. H. Beutel, THIS JOURNAL, **63**, 308 (1941).

(2) H. H. Hodgson, R. J. H. Dyer and H. Clay, *J. Chem. Soc.*, 629 (1934).

(3) E. Klarmann, L. W. Gatyas and V. A. Shternov, THIS JOURNAL, **53**, 3397 (1931).