[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

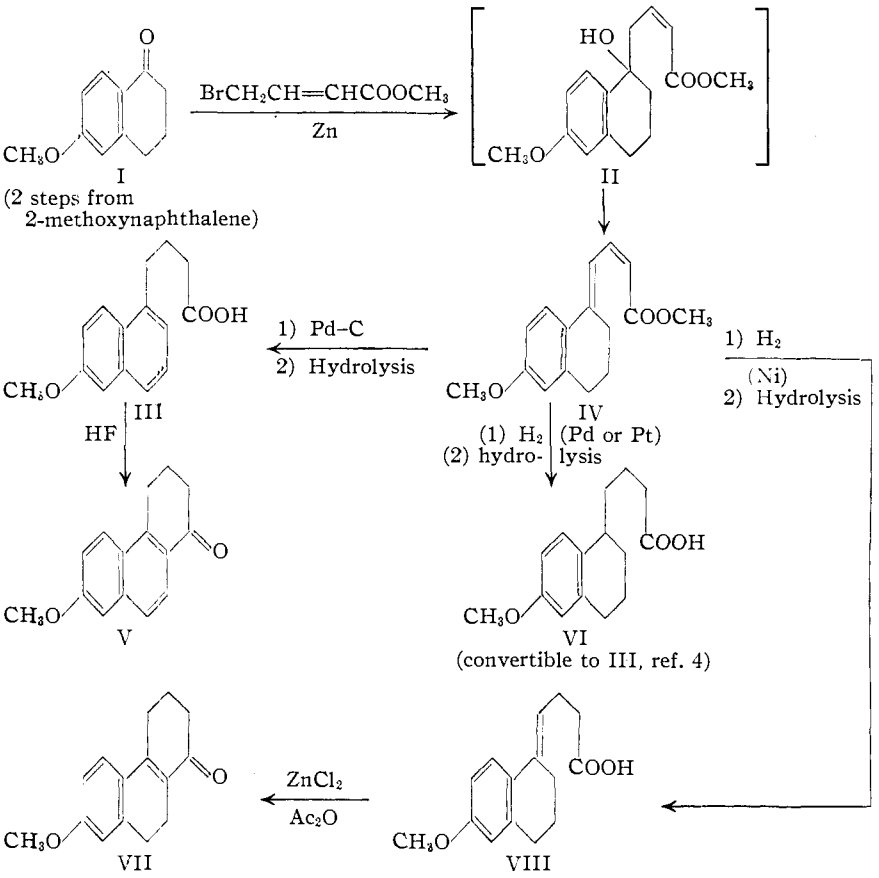
Sex Hormones. I. A Synthesis of 1-Keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene and of 1-Keto-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene

BY GILBERT STORK

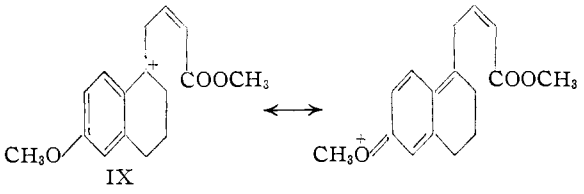
In a previous communication[1] we described a simple synthesis of 6-methoxy-α-tetralone (I) which made that compound readily available. The present paper is concerned with the extension of the ring system present in I to that of the two tricyclic ketones (V and VII).

In order to effect the desired transformation (I $\rightarrow$ V and VII), it was necessary to introduce a butyric acid grouping at the site of the carbonyl group of I. The reaction which appeared best adapted to that purpose was the Reformatsky reaction of I and methyl γ-bromocrotonate.[2]

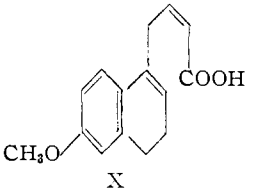
FLOW SHEET



The product of such a reaction might be expected to be the hydroxy ester (II), but it will be realized that dehydration of that intermediate will be very difficult to avoid, especially in the presence of traces of acids, because of the opportunity for resonance stabilization of a structure



such as IX. As a matter of fact, the hydroxy ester (II) could not be isolated, and the product of the reaction was the doubly unsaturated ester (IV) which was obtained as a pale yellow solid, m. p. 79–80°. Hydrolysis of IV gave the yellow acid of IV, m. p. 184.5–185.5°. The position of the double bonds in the acid of IV is unquestionably as shown, and not in the alternate arrangement shown in X,



as is evident from the color of the compound and especially from its absorption spectrum (Fig. 1, curve 1) which is closely similar to that of the chromophorically analogous piperic acid.[3] The ester (IV) shows the same absorption characteristics as the acid obtained from it on hydrolysis (except that the bands are shifted 5 mμ further toward the visible), so that the ester may be correctly represented as IV.

(1) Stork, THIS JOURNAL, **69**, 576 (1947).

(2) (a) Ziegler, Schumann and Winkelmann, *Ann.*, **551**, 120 (1942); (b) Fuson, Arnold and Cooke, THIS JOURNAL, **60**, 2272 (1938); (c) Fuson and Southwick, *ibid.*, **66**, 679 (1944); (d) Cook and Schoental, *J. Chem. Soc.*, 288 (1945). Bachmann and Wendler (THIS JOURNAL, **68**, 2580 (1946)) have recently been successful in applying that reaction to α-tetralone and have mentioned their intention to apply the reactions to the 6-methoxy derivative. Their work was published after ours had been completed.

(3) Grinbaum and Marchlewski, *Bull. intern. acad. polon. sci., Classe sci. math. nat.*, **A, 156** (1937); *C. A.*, **32**, 1576 (1938). The values given for piperic acid are: $\lambda_{max.}$ 243.0 mμ (log ϵ = 4.02), and $\lambda_{max.}$ 339.5 mμ (log ϵ = 4.32).

Two routes were open from the doubly unsaturated ester (IV) to γ-(6-methoxy-1-naphthyl)-butyric acid (III). Catalytic hydrogenation of IV over Adams platinum oxide catalyst or over palladium–barium sulfate, followed by hydrolysis, gave the known saturated acid (VI), m. p. 79°, which can be dehydrogenated to III as has been shown by Haberland.[4]

A simpler and more elegant method of preparing III which accomplished both steps at once consisted in the isomerization of IV to the methyl ester of III by heating with a palladium-charcoal catalyst. This method has been used by Cook and Schoental as a step in the synthesis of a chrysene derivative, and is an application of a well-known reaction of hydrogenated ring systems with unsaturated side chains.[5]

Cyclization of the acid (III) has previously been effected in a number of ways.[6] In the present work, the tricyclic ketone (V) was conveniently prepared by the action of anhydrous hydrogen fluoride on III.

This synthesis of 7-methoxy-1-keto-1,2,3,4-tetrahydrophenanthrene represents a considerable improvement over previous methods in simplicity and in over-all yield, requiring only four steps from 6-methoxy-α-tetralone. Coupled with Johnson, Petersen and Gutsche's brilliant synthesis of equilenin from V,[7] the method described in the present paper for the synthesis of that ketone makes equilenin readily available.

Having synthesized the equilenin intermediate (V) we turned our attention to the preparation of the tricyclic ketone (VII) which is of interest in connection with the synthesis of compounds such as estrone, in which ring B is non-aromatic. Had the hydroxy ester (II) been capable of isolation, it would have been a simple matter to reduce the double bond of that compound, and to cyclize the product to VII after dehydration.[8] As we have mentioned previously, we were unable to isolate the hydroxy ester (II), and such a method could not be used.

We then considered the possibility of reducing only one of the two conjugated double bonds of the unsaturated ester (IV). Preliminary experiments with Adams platinum oxide catalyst and with palladium–barium sulfate were unsuccessful. Under the conditions employed, there was no discernible change in the rate of hydrogenation corresponding to the absorption of one mole of hydrogen.

Partial reduction of IV was successfully accomplished with Raney nickel at room temperature and pressure, a definite break occurring after the absorption of one mole of hydrogen. The ester so obtained was hydrolyzed to the corresponding acid (VIII), m. p. 73–74°, which depressed the melting point of the saturated acid (VI).

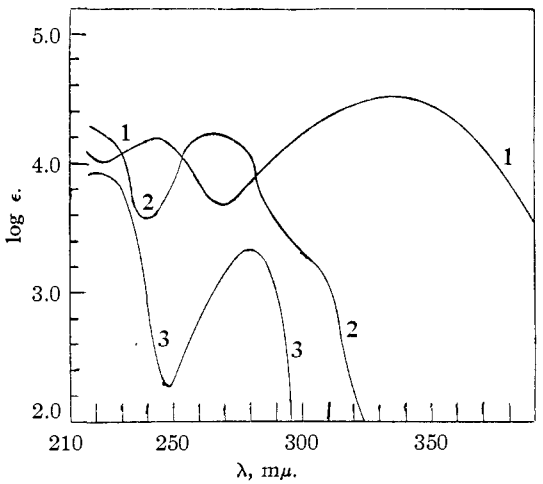


Fig. 1.—Ultraviolet absorption spectra in 95% ethanol of γ - (6 - methoxy - 1,2,3,4 - tetrahydro - 1 - naphthylidene)-crotonic acid (acid of IV) (curve 1); γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)-butyric acid (VIII) (curve 2); γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)-butyric acid (VI) (curve 3).

The absorption spectrum of the acid (VIII), Fig. 1, curve 2, is that of a substituted anethole such as 6-methoxy-3,4-dihydronaphthalene[9] and differs strongly from that of the saturated acid (VI) which has a typical anisole spectrum[10] (Fig. 1, curve 3). This leaves no doubt that the double bond of VIII is conjugated with the benzene ring. It is impossible to decide on the basis of the absorption spectrum of VIII whether the double bond is exo- or endocyclic. The endocyclic compound is reported to melt at 79°.[11]

It is interesting to consider the catalytic reduction of the doubly unsaturated ester (IV) in the light of the suggestion that when two different structures may be expected *a priori* from a catalytic hydrogenation over Raney nickel, that one will be formed which is the more stabilized by resonance energy (or, alternately, which has lost the less).[1] Application of this principle to the partial reduction of sorbic acid would give the α,β-unsaturated acid as the product, rather than its γ,δ-isomer. This has been found to be the case.[12]

$$CH_3CH{=}CHCH{=}CHCOOH \longrightarrow CH_3CH_2CH_2CH{=}CHCOOH$$

(4) Haberland, *Ber.*, **69**, 1380 (1936).

(5) See, for instance, Bachmann and Wilds, THIS JOURNAL, **60**, 624 (1938); Burnop, Elliott and Linstead, *J. Chem. Soc.*, 727 (1940).

(6) Butenandt and Schramm, *Ber.*, **68**, 2083 (1935); Cohen, Cook and Hewett, *J. Chem. Soc.*, 53 (1936); Bachmann, Cole and Wilds, THIS JOURNAL, **62**, 824 (1940).

(7) Johnson, Petersen and Gutsche, THIS JOURNAL, **67**, 2274 (1945).

(8) The reduction of the hydroxy ester from the reaction of benzaldehyde with methyl γ-bromocrotonate and subsequent dehydration of the product to methyl 5-phenyl-4-pentenoate were carried out by Ziegler, *et al.* (ref. 2a). A similar scheme was employed by Bachmann and Wendler (ref. 2) with the reaction product of methyl γ-bromocrotonate and α-tetralone.

(9) Woodward and Eastman, THIS JOURNAL, **66**, 674 (1944).

(10) Wolff and Herold, *Z. physik. Chem.*, **B13**, 201 (1931).

(11) Chuang, Tien and Huang, *Ber.*, **70**, 860 (1937); Robinson and Thompson, *J. Chem. Soc.*, 1739 (1939). The compound obtained by Burnop, Elliott and Linstead (ref. 5) and claimed to have this structure is undoubtedly the fully aromatic naphthalene derivative which is much higher melting.

(12) Farmer and Hughes, *J. Chem. Soc.*, 1929 (1934).

The same principle applied to the doubly unsaturated ester (IV) makes it evident that, in spite of a superficial analogy with sorbic acid, one might expect that the bond which is conjugated with the ester group should be reduced in this case, with the formation of the methyl ester of VIII. As we have shown above, that is the case. It should perhaps be pointed out that the formation of VIII is not likely to be due to a primary 1,4-addition of hydrogen, followed by migration of the bond, as it has been shown, in the pertinent case of 5-(4-methoxyphenyl)-3-pentenoic acid, that the double bond migrates to conjugation with the *carboxyl group* under the influence of base[13]

$$p\text{-}CH_3OC_6H_4CH_2CH{=}CHCH_2COOH \longrightarrow p\text{-}CH_3OC_6H_4CH_2CH_2CH{=}CHCOOH$$

Regardless of whether the double bond be exo- or endocyclic in VIII, addition of a proton will produce the same intermediate, and in either case the compound should cyclize to the desired phenanthrene derivative. As a matter of fact, treatment of VIII with a zinc chloride–acetic anhydride mixture[14] was found to proceed as expected with the formation of the tricyclic ketone (VII) which gave its highly characteristic dark purple dinitrophenylhydrazone.[15]

Experimental

Methyl γ-(6-Methoxy-1,2,3,4-tetrahydro-1-naphthylidene)-crotonate (IV).—The zinc strips used in this preparation were cleaned by washing with dilute acid, water and acetone. They were dried before use for a short time at 100°. To 45 g. of zinc strips covered with 110 ml. of dry benzene was added 2–3 g. of dry mercuric chloride. After allowing to stand for half an hour, a solution of 42.9 g. of methyl γ-bromocrotonate[2] and 42 g. of 6-methoxy-α-tetralone[1] (m. p. 78.4–79°) in a mixture of 110 ml. of dry ether and 30 ml. of dry benzene was added all at once, followed by a crystal of iodine. The mixture was refluxed with occasional shaking or stirring. Three additional portions of 22 g. of zinc, 13.5 g. of bromoester and a crystal of iodine were introduced at one and one-half hour intervals. The mixture was colored orange or green at various times during the reaction. The refluxing was continued for three hours after the last addition, and the mixture was cooled and poured on ice. The mixture was acidified with acetic acid and extracted with ether. The benzene–ether solution was washed with 5% aqueous ammonia (three times, or until the aqueous extracts became but slightly yellow), water and finally saturated salt solution. The solvent was removed and the residue distilled under the vacuum of an oil pump. A considerable forerun (b. p. 145–165° at 1 mm.) was obtained which soon solidified. This was unchanged 6-methoxy-α-tetralone (20 g.). The next fraction was a thick yellow oil, b. p. 182–188° (1.3 mm.) which consisted of the desired ester (29 g.). This represents a 48% yield (93% on the basis of recovered 6-methoxy-α-tetralone).

A small sample of the compound was submitted to evaporative distillation under a high vacuum, giving a light yellow oil which crystallized on long standing. Recrystallization from petroleum ether (40–60°) with the help of a Dry Ice-acetone mixture gave the pure ester as a yellow compound, m. p. 79–80° with previous sintering. The absorption spectrum of the compound in 95% ethanol showed $\lambda_{max.}$ 248 mμ (log ε = 4.10) and $\lambda_{max.}$ 343 mμ (log ε = 4.43).

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.31; H, 6.96.

The acid of IV was prepared by refluxing 1 g. of the above methyl ester under nitrogen for one and a half hour with a mixture of 5 ml. of water, 5 ml. of 95% alcohol and 1 g. of potassium hydroxide. After cooling and ether extraction to remove any alkali insoluble material, the mixture was acidified giving the acid as a yellow precipitate. This (0.9 g.) was recrystallized from a mixture of benzene and petroleum ether giving yellow crystals, m. p. 184.5–185.5°. The absorption spectrum of the acid is shown on Fig. 1, curve 1.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.74; H, 6.60. Found: C, 73.40; H, 6.65.

γ-(6-Methoxy-1-naphthyl)-butyric Acid (III).—A mixture of 19 g. of the ester (VI) as obtained from the first distillation (not crystalline) and 1 g. of a 30% palladium–charcoal catalyst[16] was heated under a carbon dioxide atmosphere to 280–290° for three to four hours. After cooling under carbon dioxide, ether was added, and the catalyst was filtered off. After removal of the ether the residue was hydrolyzed to the desired acid by refluxing under nitrogen for three to four hours with a mixture of 10 g. of potassium hydroxide, 110 ml. of 95% ethyl alcohol and 110 ml. of water. After allowing to cool, water was added, and the solution was extracted with ether to remove any base-insoluble material. The aqueous solution was poured in a thin stream into a mixture of 20 ml. of concentrated hydrochloric acid and ice to precipitate the acid. The white precipitate was filtered off and weighed 17.7 g. after air drying. Recrystallization from aqueous methanol (charcoal) gave 14 g. of the acid (III), m. p. 151° as reported.[4,6]

The ester (IV) was catalytically reduced and hydrolyzed to the **tetrahydro acid** (VI): a solution of 0.22 g. of IV in 10 ml. of absolute alcohol was reduced at atmospheric pressure and room temperature in the presence of 9.8 mg. of Adams platinum oxide catalyst. The theoretical quantity of hydrogen was taken up in thirty minutes, and the originally yellow solution had become colorless. The catalyst was filtered off, 5 ml. of 95% ethyl alcohol, 15 ml. of water and 0.2 g. of potassium hydroxide was added to the alcohol solution of the reduced compound. The mixture was refluxed under nitrogen for three and a half hours. Most of the alcohol was removed by heating on the steam-bath under an air jet, the aqueous solution was extracted once with ether, and the oil which separated on acidification of the basic solution was taken up in ether. The ether extracts were washed with water and saturated salt solution and dried over anhydrous sodium sulfate. The oil left on removal of the ether was taken up in petroleum ether (30–60°) and, after standing in the cold room, the acid (VI) (0.15 g.) crystallized in white prisms m. p. 79°.[4]

The absorption spectrum of the compound is shown on Fig. 1, curve 3.

The reduced acid (VI) may be dehydrogenated to III by heating with sulfur, as has already been shown by Haberland.[4]

1-Keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene (V).—Cyclization of III was accomplished by allowing a solution of 14 g. of the acid in about 150 ml. of anhydrous hydrogen fluoride to remain in a platinum flask kept in an ice-bath for two hours. The hydrogen fluoride was allowed to evaporate, and the residue was poured in water. The precipitate was filtered off and washed thoroughly with water and potassium carbonate solution. The crude ketone was dissolved in boiling acetone, filtered from any insoluble residue, charcoaled, and allowed to crystallize after the addition of water to turbidity. The ketone was sometimes quite difficult to obtain absolutely white. In

(13) Vorländer and Gieseler, *J. prakt. Chem.*, [2] **121**, 247 (1929).

(14) This reagent has been utilized with conspicuous success by Johnson and co-workers for similar cyclizations: W. S. Johnson, H. C. E. Johnson and J. W. Petersen, THIS JOURNAL, **67**, 1306 (1945); W. S. Johnson and J. W. Petersen, *ibid.*, **67**, 1366 (1945); W. S. Johnson, H. C. E. Johnson and Betty Petersen, *ibid.*, **68**, 1926 (1946).

(15) Robinson and Schlittler, *J. Chem. Soc.*, 1288 (1935).

(16) Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

those cases it was very conveniently purified by passing its solution in benzene over a column of alumina.[17] The same weight of alumina as of compound was sufficient to remove any color from the ketone. Elution with benzene and benzene–ether gave the perfectly white ketone (V) m. p. 99–100°,[4,6] which was thus obtained in 85% yield.

γ-(6-Methoxy-1,2,3,4-tetrahydro-1-naphthylidene)-butyric Acid (VIII).—Attempts to add only one mole of hydrogen to IV were unsuccessful with Adams platinum oxide catalyst as well as with a 5% palladium–barium sulfate catalyst. Raney nickel proved satisfactory for our purpose: To a solution of 0.23 g. of ester (IV) in 10 ml. of absolute alcohol was added 0.21 g. of Raney nickel catalyst[18] (wet with alcohol) and the mixture was reduced with hydrogen in a low pressure apparatus. After half an hour, the theoretical quantity of hydrogen for reduction of one double bond had been absorbed and the rate of hydrogenation had slowed down considerably.

After removal of the catalyst, the ester was hydrolyzed and worked up exactly as described above for the ester of VI, giving 0.16 g. of the acid (VIII), m. p. 73–74°. The absorption spectrum of this compound is shown on Fig. 1, curve 2.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.22; H, 7.65.

1-Keto-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (VII).—A solution of 50 mg. of γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)-butyric acid (VIII) in 0.5 ml. of glacial acetic acid and 1 ml. of acetic anhydride was treated with 0.5 ml. of an acetic acid solution containing 20 mg./ml. of zinc chloride (fused)[14] and heated under nitrogen for four hours. The mixture was evaporated on the steam-bath after addition of methanol, and the residue was heated on the steam-bath under nitrogen for thirty minutes with 8 ml. of 5% potassium hydroxide solution. The non-acidic, insoluble material was taken up in ether, and the oil remaining after evaporation of the solvent was heated for thirty minutes with an excess of semicarbazide hydrochloride in methanol in the presence of a little pyridine. In this manner, 35 mg. of semicarbazone was obtained, m. p. 248–249°, dec. (when introduced in the heating-bath at 210°). This is higher than the m. p. previously reported for this compound (238–240°, dec.)[19] so that it was considered necessary to prepare the 2,4-dinitrophenylhydrazone of the ketone: The semicarbazone obtained above was heated for a few minutes with 12% hydrochloric acid on the steam-bath, and the yellow, fluorescent solution was extracted with ether. The oil remaining after removal of the ether was evaporatively distilled under a high vacuum, but the ketone (VII) obtained in this way was still an oil (the difficulty of crystallizing the ketone has been noted previously[15,19]). Treatment with 2,4-dinitrophenylhydrazine in alcohol, in the presence of a trace of sulfuric acid, gave after short heating on the water-bath the iodine colored, characteristic dinitrophenylhydrazone, m. p. 245–247°. On recrystallization from toluene this gave small needles, m. p. 250–252° (reported m. p. 256°,[15] 253–255°[20]). To remove any doubts about the identity of the substance, it was analyzed with the following results: Calcd. for $C_{21}H_{20}N_4O_5$: C, 61.75; H, 4.93. Found: C, 61.49; H, 5.17.

(17) Aluminum Co. of America, grade F-20, minus 80 mesh.

(18) "Organic Syntheses," Vol. 21, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 15.

(19) Robinson and Walker, *J. Chem. Soc.*, 60 (1937).

Acknowledgment.—The author wishes to thank Dr. Elkan R. Blout of Polaroid Corporation for arranging for the determination of the absorption spectra reported in this paper.

Summary

Methyl γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)-crotonate has been prepared by the reaction of 6-methoxy-α-tetralone and methyl γ-bromocrotonate in the presence of zinc. This compound was isomerized to methyl γ-(6-methoxy-1-naphthyl)-butyrate by heating with palladium–charcoal. The acid obtained from that compound on hydrolysis was cyclized with hydrogen fluoride to the equilenin intermediate 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene.

Partial reduction of methyl γ-(6-methoxy-1,2,-3,4-tetrahydro-1-naphthylidene)-crotonate was successfully accomplished with Raney nickel at atmospheric pressure and room temperature, and the resulting ester was hydrolyzed and cyclized to 1-keto-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene.

(20) Hewett, *J. Chem. Soc.*, 50 (1936).

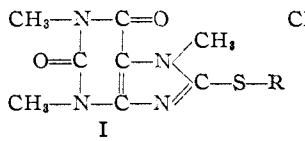
CAMBRIDGE, MASS. RECEIVED MARCH 31, 1947

[CONTRIBUTION FROM THE RESARCH LABORATORIES OF PARKE, DAVIS AND CO.]

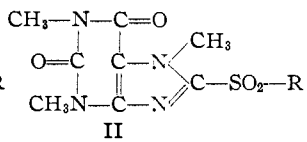
8-R-Thio- and 8-R-Sulfonylcaffeine Derivatives

BY LOREN M. LONG

During the course of our search for compounds possessing anticonvulsant activity, it became desirable to synthesize a number of 8-substituted caffeine derivatives of the type represented by (I) and (II) where R may be a simple alkyl, substituted alkyl or an aryl group.



I



II

Numerous cyclic ureides such as barbituric acids and hydantoins exhibit the property of raising the convulsive threshold in animals in which convulsive seizures are electrically induced.[1] Although most of these compounds contain at least one phenyl radical, there are several which contain only simple alkyls as substituents. Moreover, the substitution of a methyl radical on the urea portion of the molecule has at times proved to be advantageous.[2] That substitution in the 8-position of caffeine does not necessarily yield physiologically inert compounds is evidenced by the

(1) Merritt and Putnam, *Epilepsia*, **3**, 51 (1945).

(2) Lascalzo, *J. Nervous Mental Disease*, **101**, 537 (1945); Goodman and Manuel, *Fed. Proc.*, IV No. 1, 119 (1945); Everett and Richards, *ibid.*, IV No. 1 20 (1945).