[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

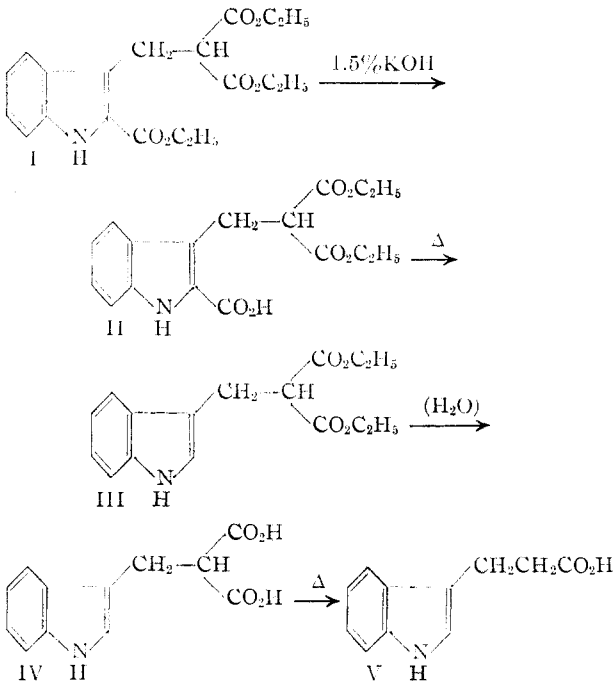
Skatylmalonic Ester

BY GILBERT STORK AND GURBAKHSH SINGH

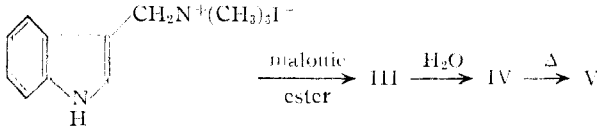
The structures of two compounds claimed to be ethyl α-carbethoxy-3-indolepropionate have been shown to be erroneous and correct structures have been established for these substances.

Three compounds are described in the literature to which the structure of ethyl α-carbethoxy-3-indolepropionate (skatylmalonic ester) (III) has been assigned by various investigators.[1,2,3]

Maurer and Moser[1] were the first to claim the synthesis of skatylmalonic ester by the route

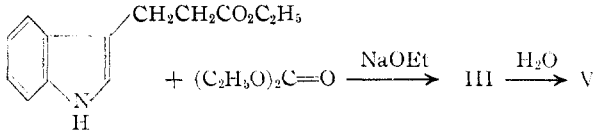


The structure of their "malonic ester," which was reported to melt at 89–90°, was presumably confirmed by its hydrolysis to a substance melting at 188–189°, claimed to be IV, and which was indeed decarboxylated on heating to the well-known 3-indolepropionic acid (V). The next synthesis to be published was that of Snyder and co-workers[2] who prepared skatylmalonic ester from gramine methiodide.



Snyder's malonic ester (III) was reported to melt at 62°, and was hydrolyzed to the malonic acid (IV), m.p. 178°, which was decarboxylated to the known 3-indolepropionic acid (V). The discrepancy in melting points between Snyder's skatylmalonic ester and acid and compounds to which the same structure was assigned by Maurer and Moser was not noted by Snyder, *et al.*, who were apparently unaware of the previous publication of these authors.

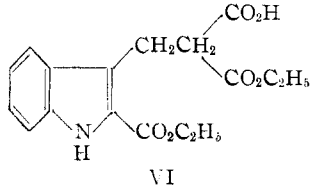
The last reported synthesis of skatylmalonic ester was that of Smith and Sogn[3] who used the method outlined



The "malonic ester" of Smith and Sogn which was prepared in 52% yield by Claisen condensation of ethyl 3-indolepropionate with diethyl carbonate melted at 77–78° and was unusual in that its hydrolysis with base gave directly 3-indolepropionic acid (V) rather than the expected malonic acid.

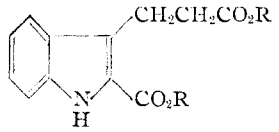
There are then three substances melting at 89–90°, 60° and 77–78° all of which are claimed to be diethyl skatylmalonate. Smith and Sogn[3] imply that these are allotropic forms of the same compound, but we considered much more likely that they were different substances. One of the syntheses is quite unambiguous, and it is evident that the compound prepared by Snyder, Smith and Stewart[2] represents the true skatylmalonic ester.

The most obvious flaw in the Maurer–Moser synthesis lies in the assumption that the carbethoxy group in the α-position of the indole ring is the first to be saponified. The reason given for this assumption is interesting though hardly logical. The substance which Maurer and Moser obtained by partial hydrolysis of I would be expected to be VI rather than II



VI

while the compound, m.p. 89–90°, obtained on decarboxylation of the latter substance and erroneously given structure III must then be VII.



VII, R = C_2H_5
VIII, R = H

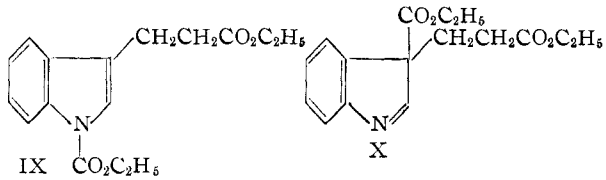
A compound which undoubtedly has structure VII is described in Maurer and Moser's own paper and melts at 94–95°, a melting point sufficiently close to that of their presumed III to be strongly suggestive of identity. Such a suggestion becomes even more compelling when one compares the melting point given for the presumed malonic acid with that reported for the diacid VIII. The former

(1) H. Maurer and E. Moser, *Z. physiol. Chem.*, **161**, 131 (1926).
(2) H. R. Snyder, C. W. Smith and J. M. Stewart, THIS JOURNAL, **66**, 200 (1944).
(3) L. I. Smith and A. W. Sogn, *ibid.*, **67**, 822 (1945).

which crystallizes in "disc like" crystals is stated to melt at 188–189° while the latter which forms "fan like" crystals melts at 194°. Repetition of the work, following Maurer and Moser's directions, showed conclusively that the diacid presumed to be IV is identical with the diacid VIII. The substance made by partial hydrolysis of the triester I melted at 194° and did not depress the melting point of authentic VIII.

We now have only the Smith and Sogn synthesis to consider. The method of synthesis and the fact that 3-indolepropionic acid is obtained *directly* on base hydrolysis of the compound to which they assigned formula III leave only two possible structures for this compound: IX or X.

Repetition of Smith and Sogn's work gave their presumed malonic ester, m.p. 77–78°. This compound was not basic, a fact which rules out the



indolenine structure X, and the infrared absorption spectrum showed conclusively the absence of an N–H bond. The ultraviolet spectrum of the compound further confirmed the absence of 3,3-disubstituted indolenine structure.[4] These facts suffice to establish that the compound prepared by Smith and Sogn is ethyl 1-carbethoxy-3-indolepropionate.

(4) IX has $\lambda_{max.}$ 260 mμ (log ε = 4.03) while X would have $\lambda_{max.}$ around 245 mμ (*cf.* P. Grammaticakis, *Compt. rend.*, **210**, 569 (1940)).

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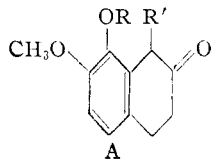
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

The Synthesis of Some 1-Substituted 7,8-Dimethoxy-2-tetralones

BY GILBERT STORK AND HAROLD CONROY[1]

The ketones, 5-bromo-7,8-dimethoxy-2-tetralone-1-acetic ester, 1-(β-dimethylaminoethyl)-5-bromo-7,8-dimethoxy-2-tetralone and 1-[β-(N-methylbenzylsulfonamido)-ethyl]-5-bromo-7,8-dimethoxy-2-tetralone were synthesized by a route starting from 2,3-dimethoxybenzaldehyde. These tetralones are of interest in connection with the possible extension of their ring system to that of a 13-substituted hydrophenanthrene typical of the morphine alkaloids.

Consideration of the possible approaches to the synthesis of the morphine alkaloids led to the belief that the use of a properly substituted 2-tetralone (of type A) would afford valuable intermediates



A

for this purpose. Two methods have been described for the preparation of 1-substituted 2-tetralones. Direct alkylation of a 2-tetralone is known to take place in the 1-position and has been used successfully in a number of instances,[2,3] although the tendency for dialkylation is so great that it is often difficult to obtain the monosubstituted derivative.[2,4] The second method, which involves the reaction of a 1-alkyl-3,4-dihydronaphthalene with peracids,[5,6] is not of general applicability.

A method for the synthesis of a compound of type A in which R′ is an acetic acid residue was devised, since such a grouping eventually should be transformable into the ethanamine chain of morphine. The starting material chosen was 2,3-dimethoxy-5-bromobenzaldehyde[7] (I), which was condensed with ethyl cyanoacetate to yield 2,3-dimethoxy-5-bromobenzylidene cyanoacetic ester (II). The addition of cyanide ion to the unsaturated system of II gave the dicyano ester (III).

Hydrolysis of III to 2,3-dimethoxy-5-bromophenylsuccinic acid (V) by a method which is successful in the preparation of phenylsuccinic acid[8] resulted in material that was obviously impure. However, the dicyano ester (III) was converted to V by reaction with methanolic hydrogen chloride in the presence of some water, when α-(2,3-dimethoxy-5-bromophenyl)-β-carbomethoxysuccinimide (IV) was obtained. Vigorous basic hydrolysis of IV gave V in excellent yield.

The lactone (VI) was obtained in good yield by treatment of the diacid (V) with a mixture of formalin and dilute sulfuric acid. A similar reaction has been used previously in the synthesis of some phthalide derivatives.[9] The lactone (VI) was opened to 2,3-dimethoxy-5-bromo-6-bromomethylphenylsuccinic acid dimethyl ester (VII) with methanolic hydrogen bromide.[10,11]

The diester (VII) was treated with a suspension

(1) Atomic Energy Commission Predoctoral Research Fellow, 1949–1950.

(2) J. W. Cornforth, R. H. Cornforth and R. Robinson, *J. Chem. Soc.*, 689 (1942).

(3) H. Andersag and W. Salzer, U. S. Patent 2,271,674 (1942) [*C. A.*, **36**, 3514 (1942)].

(4) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 676 (1946).

(5) R. Ghosh and R. Robinson, *ibid.*, 506 (1944).

(6) J. English and G. Cavaglieri, THIS JOURNAL, **65**, 1085 (1943).

(7) W. Davies, *J. Chem. Soc.*, **123**, 1575 (1923).

(8) A. Lapworth and W. Baker, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 451.

(9) R. H. F. Manske and A. E. Ledingham, *Can. J. Res.*, **22B**, 115 (1944).

(10) This reaction is similar to the formation of o-chloromethylphenylacetic ester from homophthalide (S. Murahashi, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **30**, 180 (1936)).

(11) From one early run which had not been so thoroughly cooled as the others a rather large proportion of a compound, m.p. 80°, was obtained in addition to some diester (VII). This substance contained no replaceable bromine; when it was dissolved in benzene and the cold solution saturated with hydrogen bromide VII was obtained. The compound is evidently 2,3-dimethoxy-5-bromo-6-methoxymethylphenylsuccinic acid dimethyl ester, formed by solvolysis of the intermediate benzylcarbonium ion. None of this compound was isolated from reaction mixtures which were saturated with hydrogen bromide, finally at 0°.