arm capillary. An oil-bath at 100° kept the anhydride melted and mercury, which was dropped in through a capillary jet, forced the anhydride at a uniform rate into the top of the vertical hot reaction tube. The reaction products were condensed in a side-arm flask, attached to the bottom of the tube. The flask was cooled in ice and connected to a gas collecting bottle. The tube was flushed out with nitrogen before each run.

The effective hot volume of the reaction tube was 87 cc. This volume makes allowance for the volume of the thermocouple well. The tube was electrically heated in a furnace whose temperature was recorded and controlled by a Leeds and Northrup potentiometer-type recorder-controller.

In the first run at 450°, 20 g. of diglycolic anhydride was passed through the tube during eighty minutes (contact time, about forty seconds). From the reaction products was obtained 15.5 g. of diglycolic anhydride and 1.2 g. of diglycolic acid. Hence, 3.3 g. of the anhydride was the amount pyrolyzed. The furan derivative weighed 3.2 g. From Table I it may be assumed that this represents 95% of the maleic anhydride present. Hence, the corrected yield of maleic anhydride, based on the diglycolic anhydride not recovered, was 71%.

The second run was performed also with 20 g. of diglycolic anhydride during eighty-seven minutes (contact time, forty-two seconds). There was recovered 10.2 g. of the anhydride and 1.5 g. of diglycolic acid; therefore, 8.3 g. of the anhydride was pyrolyzed. The furan derivative weighed 4.9 g. With the 95% correction factor, this represents a 44% yield of maleic anhydride.

The gas evolved in runs 1 and 2, respectively, measured 600 and 2500 cc. The gas was analyzed for CO_2, unsaturates, H_2 and CO. These relative amounts were formed in run 1 (% by volume): 16.6, 4.7, 20.7, 58.0. In run 2: 13.1, 21.6, 20.7, 44.6.

Ketene in the Products.—An 8-g. sample of diglycolic anhydride was pyrolyzed in the same apparatus at 500°. The gases which were evolved were passed through a low-pitched coil condenser cooled to −15° by ice and salt, and the uncondensed gas was conducted through standard alkali. The ketene in the gas stream neutralized 0.56 cc. of 2.218 *N* sodium hydroxide. This represents 0.00124 mole of ketene or 0.052 g. This is a 4% yield, calculated on the basis of 3.3 g. of unrecovered diglycolic anhydride.

Summary

Diglycolic anhydride undergoes pyrolysis at 450–500° into maleic anhydride. This reaction involves lengthening of the carbon chain. Concurrently, a small yield of ketene is obtained. A method for the separation of mixtures of diglycolic anhydride and maleic anhydride is included.

EVANSTON, ILLINOIS RECEIVED OCTOBER 25, 1939

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DEPAUW UNIVERSITY]

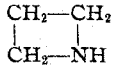
Azetidine Derivatives. I. 2,4-Diketo-3-hydroxy-3-arylazetidines

BY J. L. RIEBSOMER, HOWARD BURKETT, THOMAS HODGSON AND FRED SENOUR

The five- and six-membered heterocyclic compounds are well known since they are found in such important substances as pyrrole and pyridine. Interest in the structure and synthesis of such compounds has been fostered by the study of natural products in which these basic structures are often found.

On the other hand, four-membered heterocyclic compounds containing nitrogen in the ring have been found difficult to prepare and since no relationship between their structure and important natural products has been observed, this field of chemistry has been almost neglected.

Azetidine, or trimethyleneimine, has been known since about 1890[1] when it was prepared by the distillation of trimethylenediamine hydrochloride and by heating γ-bromopropylamine with alkali.[2]

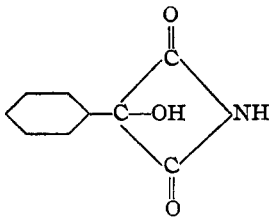


A few syntheses of substituted azetidines have been reported such as the synthesis of 3,3-dimethylazetidine,[3] N-phenyl-3,3-diphenyl-2,4-diketo-azetidine,[4] O-methylol-O-benzyleneimine,[5] 3-hydroxy-3-2,4,6-trimethoxyphenyl-2,4-diketo-azetidine,[6] and others.[7,8,9,10]

The purpose of this paper is to present a new method for the synthesis of substituted diketo-azetidines and to report certain pharmacological studies of these new compounds.

In an attempt to condense phenylhydroxymalonic esters[11] with urea in the presence of sodium ethylate to produce the corresponding barbituric acid derivatives, there were produced instead imides or azetidine derivatives such as

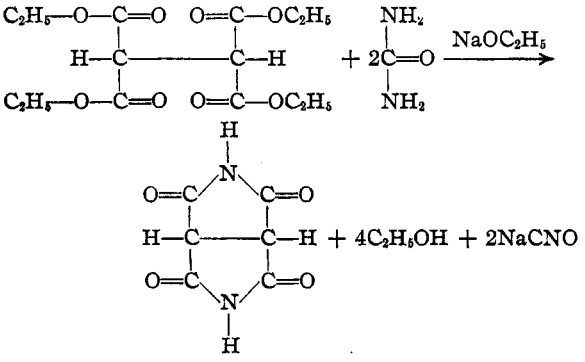
(1) Ladenburg and Sieber, *Ber.*, **23**, 2727 (1890).
(2) Gabriel and Weiner, *ibid.*, **21**, 2675 (1888).
(3) Komppa and Sevon, *Ann. Acad. Sci. Fennicae*, **37A**, 7, 8 (1933).
(4) Staudinger, Göhring and Schöller, *Ber.*, **47**, 46 (1914); Staudinger and Becker, *ibid.*, **50**, 1016 (1917).
(5) Orlov, *Chem. Zentr.*, **76**, 674 (1905); **77**, 1413 (1906).
(6) Szeki, *Ber.*, **56**, 2464 (1923).
(7) Gibbs and Marvel, THIS JOURNAL, **56**, 725 (1934); *ibid.*, **57**, 1137 (1935).
(8) Govaert, *Proc. Acad. Sci. Amsterdam*, **37**, 156 (1934).
(9) LeFèvre, *J. Chem. Soc.*, 733 (1929).
(10) Warren and Briggs, *Ber.*, **64B**, 26 (1931).
(11) Riebsomer, Irvine and Andrews, THIS JOURNAL, **60**, 1015 (1938).



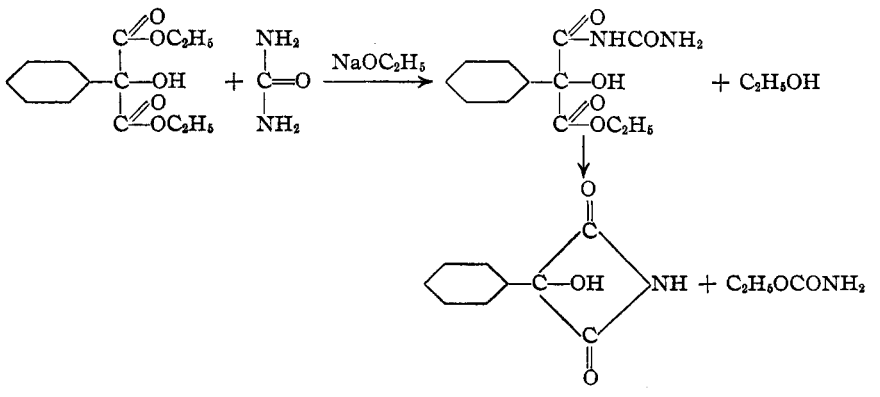
Further investigation proved that gaseous ammonia passed into the mixture of substituted malonic ester, and sodium ethylate dissolved in alcohol, produced the same substituted azetidines as when urea was added, though in lower yields.

This formation of azetidine derivatives is not so unusual as might be expected when one considers that urea has been used under similar conditions to synthesize five-membered heterocyclic nitrogen compounds.

Roeder[12] treated diethyl succinate with urea in the presence of sodium ethylate and produced succinimide. In the same publication Roeder reported a reaction very similar to the one by which we have prepared substituted azetidines and wrote the equation

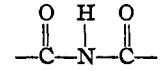


On the basis of such experience it would seem reasonable to represent the reactions by which we have prepared azetidine derivatives thus



Or since ammonia may be substituted for urea to produce the same azetidine derivatives one might reasonably postulate that urea is first decomposed by the sodium ethylate to produce ammonia which would then react to give the imide and ethyl alcohol.

Since these azetidine derivatives contain the grouping



which is associated with many compounds possessing hypnotic activity,[13] it seemed justifiable to expect some hypnotic activity when these compounds were administered to animals. All the compounds prepared in this series, however, proved to be inactive as hypnotics when given to rabbits. Not only are they inactive as hypnotics but they are toxic to rabbits in relatively small doses.

Experimental

General Method of Preparation.—Since these compounds were all prepared by essentially the same procedure, it is necessary to describe in detail the preparation of only one. For the preparation of 2,4-diketo-3-phenyl-3-hydroxy-azetidine, 25 g. of phenylhydroxymalonic ester was added to a sodium ethylate solution prepared from 80 g. of absolute alcohol and 7.5 g. of sodium. The mixture was placed in a 3-necked flask equipped with a stirrer, condenser and addition tube and was heated to 115–120° with an oil-bath and 10 g. of urea was added. After stirring at 115–120° for five hours 10 g. more urea was added and the stirring and heating continued for about eleven hours.

When the reaction was finished, the excess alcohol was evaporated to complete dryness. The dried product was dissolved in 100 cc. of water. To this solution was added 50 g. of ice and 10% hydrochloric acid was introduced slowly with stirring until the solution was acid to litmus. A large excess of acid should be avoided. The acidified solution was extracted with three 50-cc. portions of ether, and the ether solution dried over anhydrous sodium sulfate and filtered. The ether solution then was evaporated and the oily residue crystallized from a benzene–petroleum ether mixture. The yield of 2,4-diketo-3-hydroxy-3-phenylazetidine was 4.3 g., or 17% of the theoretical based on the quantity of ester used. In some cases the final purification was rather difficult and involved several crystallizations.

(12) Roeder, *Ber.*, **46**, 2561 (1913).

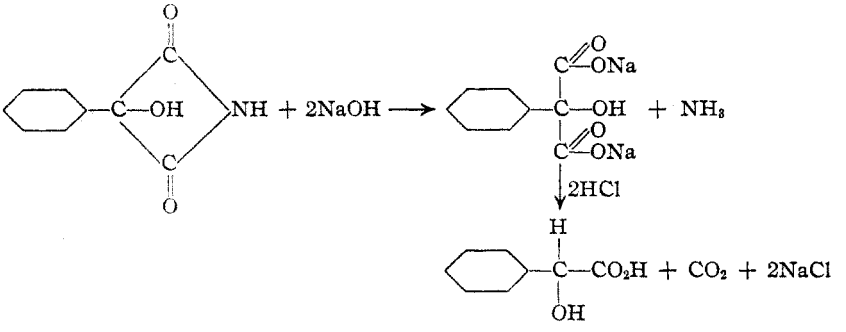
(13) Shonle, *Ind. Eng. Chem.*, **23**, 1104 (1931).

TABLE I

2,4-Diketo-3-hydroxy-3-aryl-azetidine	M. p., °C.	Analyses, Kjeldahl, % Calcd.	Found	Combustion analyses,% Calcd. C	H	Found C	H	Yield azetidine deriv., %	M. p. (acid produced upon sapon.), °C.
Phenyl	107.5–108	7.91	7.94	61.02	3.95	61.01	4.23	17	118
p-Tolyl	131	7.33	7.23	62.82	5.23	62.62	5.41	9	145
p-Ethyl	105–106	6.83	7.06	64.39	5.37	64.30	5.60	24	141–142
2,5-Dimethyl	135–136	6.83	6.70	64.39	5.37	63.98	5.45	37	116–117
Mesityl	151–152	6.39	6.29	65.75	5.94	65.79	6.02	6	147
p-*s*-Butyl	89–90	6.01	5.86	66.85	6.43	66.74	6.52	38	105–106

Synthesis Using Ammonia Instead of Urea.—In this synthesis the procedure was the same as outlined above except that dry ammonia gas was bubbled slowly into the arylhydroxymalonic ester–sodium ethylate mixture instead of adding the urea. This procedure was carried out in three different cases using phenylhydroxymalonic ester, *p*-tolylhydroxymalonic ester and *p*-ethylphenylhydroxymalonic ester as starting materials. The corresponding azetidine derivatives were formed in yields of about 3%. The melting points, mixed melting points and N, C and H analyses checked with the compounds produced from urea and the corresponding malonic esters.

Proof of Structure.—A sample of 1–2 g. of each of the substituted azetidines was saponified with excess 20% aqueous sodium hydroxide by boiling the mixture for four hours. Ammonia gas was evolved, which would be anticipated from such treatment of imides. The saponified product was strongly acidified with hydrochloric acid and boiled for four hours during which time carbon dioxide was evolved. The acidified solution was extracted with ether, the ether evaporated and the residue crystallized from benzene. The resulting products were shown by their melting points and mixed melting points to be the corresponding mandelic acids. The reactions may be explained by the typical equations shown.



A summary of the data obtained from the compounds prepared is assembled in Table I.

The authors are indebted to Dr. Robert S. Shelton of the William S. Merrell Company for the pharmacological data, and to Dean William M. Blanchard of DePauw University who was instrumental in obtaining financial aid from The National Research Council, and from Mr. J. K. Lilly of Indianapolis, Indiana.

Summary

1. Six 2,4-diketo-3-hydroxy-3-arylazetidines have been prepared by the condensation of arylhydroxymalonic esters and urea.

2. These compounds failed to show any hypnotic activity when administered to rabbits. They did prove to be moderately toxic.

GREENCASTLE, INDIANA RECEIVED AUGUST 18, 1939