

Acknowledgment.—The writer is greatly indebted to Dr. A. K. Balls for his suggestions and assistance in the preparation of this manuscript.

Summary

The temperature characteristics of growth of microorganisms and other organized biological processes bear a formal relation to the energies of activation of enzymically and non-enzymically catalyzed reactions. Although certain variations, observational or real, occur in these energy values with temperature, velocity extrapolations justified within reasonable limits lead to some valuable considerations. 1. Extrapolations to cold storage temperatures show the relatively enhanced importance of unorganized enzyme reactions compared to microbial action or non-enzymically catalyzed reactions. 2. Materials whose constituent ferments have high energies of activation will be aided most by storage at low

temperatures. 3. The magnitude of the various changes that occur in a single product will not all be quantitatively altered in the same degree by lowering the temperature, as evidenced by the differences in fruits ripened at low and at ordinary temperatures. 4. From the activity and temperature characteristic data of reactions in any particular product at ordinary temperatures it should be possible to predict the nature of the major changes that would occur in storage. In the critical region of temperature where liquid systems become frozen, generally 0 to -5° , the extrapolation of reaction velocities is, as might be expected, no longer readily feasible. Determinations with cathepsin, chymotrypsin and pancreas lipase show that in some, but not all, cases the velocity of simple enzyme reactions is greatly decreased when the change of state occurs.

WASHINGTON, D. C.

RECEIVED OCTOBER 21, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, VANDERBILT UNIVERSITY SCHOOL OF MEDICINE]

Diacylureas. II. Preparation and Properties of Diacylureas Derived from Branched Aliphatic Acids

BY ROGER W. STOUGHTON, H. L. DICKISON AND O. GARTH FITZHUGH

In the first paper of this series¹ a survey of the available data on diacylureas was presented and the preparation and properties of diacylureas derived from normal aliphatic acids were described. Because of the interesting hypnotic properties exhibited by these substances, this work has now been extended to derivatives of branched chain aliphatic acids. These N,N'-diacylureas were prepared by the action of an acid chloride on the appropriate monoureide. They could not be prepared by the condensation of an ester with urea in the presence of sodium ethylate, and all attempts to condense esters of both secondary and tertiary acids gave only sodium cyanate and the corresponding amide. The properties of these compounds are very similar to those reported for the straight chain analogs. It had been hoped that derivatives of secondary or tertiary acids would be more resistant to hydrolysis, but they were found to be only slightly more stable to alkali than the primary derivatives.

(1) Stoughton, *J. Org. Chem.*, **2**, 514 (1938).

A preliminary evaluation of the hypnotic activity of these compounds on white mice was made, using the procedure described in the previous paper. The data obtained are summarized in Table I.

As in the case of derivatives of normal acids, the anesthesia produced by intravenous administration lasted only a very short time, about two to four minutes. Intraperitoneally the minimum effective dose was much greater, but anesthesia lasted from fifteen minutes to one hour. The introduction of a tertiary alkyl group did not increase the activity but did increase the length of time the animals remained anesthetized. The anesthesia produced was again characterized by marked analgesia and absence of excitement.

Experimental

Monoacylureas.—All monoacylureas were prepared by the action of the proper acid chloride on urea according to the general procedure previously described for *n*-butyrylurea.¹ The isobutyryl-, 2-methylbutyryl-, and 2,2-dimethylpropionyl-ureas were recrystallized from water; the others, from dilute ethanol. Yields of 75 to

TABLE I
N,N'-DIACYLUREAS, R—CONHCONHCO—R', AND THEIR HYPNOTIC ACTIVITY

Urea	Minimum effective dose		M. p., °C. (corr.)	Mol. formula	N analyses, %	
	Intra-venously mg./kg.	Intra-peritoneally mg./kg.			Calcd.	Found
N-Acetyl-N'-2,2-dimethylpropionyl ^a	400	1000	105-106	C ₈ H ₁₄ N ₂ O ₃	15.05	15.02
N-Acetyl-N'-2,2-dimethylbutyryl-	225	550	118-119	C ₉ H ₁₆ N ₂ O ₃	13.99	13.94
N-Acetyl-N'-3,3-dimethylbutyryl-	200	500	120-121	C ₉ H ₁₆ N ₂ O ₃	13.99	13.88
<i>sym</i> -Di-isobutyryl ^b	110	800	111-112	C ₉ H ₁₆ N ₂ O ₃	13.99	13.92
N- <i>i</i> -Butyryl-N'-2-methylbutyryl-	90	550	92-93	C ₁₀ H ₁₈ N ₂ O ₃	13.08	13.12
N-Acetyl-N'-2,2-dimethylvaleryl ^c	120	250	63-64	C ₁₀ H ₁₈ N ₂ O ₃	13.08	13.16
N- <i>n</i> -Butyryl-N'-2,2-dimethylpropionyl-	120	650	71-72	C ₁₀ H ₁₈ N ₂ O ₃	13.08	13.05
N- <i>i</i> -Butyryl-N'-2,2-dimethylpropionyl-	140	900	170-171	C ₁₀ H ₁₈ N ₂ O ₃	13.08	13.02
<i>sym</i> -Diisovaleryl ^c	90	600	66-67	C ₁₁ H ₂₀ N ₂ O ₃	12.27	12.32
<i>sym-bis</i> -(2-Methylbutyryl) ^a	75	600	87-88	C ₁₁ H ₂₀ N ₂ O ₃	12.27	12.33
N- <i>n</i> -Butyryl-N'-2-ethylbutyryl ^c	110	500	57-58	C ₁₁ H ₂₀ N ₂ O ₃	12.27	12.26
N-Isobutyryl-N'-2-ethylbutyryl-	65	400	75-76	C ₁₁ H ₂₀ N ₂ O ₃	12.27	12.26
N-Isobutyryl-N'-2-methylvaleryl-	80	600	Oil	C ₁₁ H ₂₀ N ₂ O ₃	12.27	12.22
N-Acetyl-N'-2,2-dimethylcaproyl ^c	...	300	77-78	C ₁₁ H ₂₀ N ₂ O ₃	12.27	12.13
N- <i>n</i> -Butyryl-N'-2,2-dimethylbutyryl-	110	400	66-67	C ₁₁ H ₂₀ N ₂ O ₃	12.27	12.22
N-Isobutyryl-N'-2,2-dimethylbutyryl-	...	500	147-148	C ₁₁ H ₂₀ N ₂ O ₃	12.27	12.21
<i>sym-bis</i> -(2,2-Dimethylpropionyl)-	...	1500	206-207 (dec.)	C ₁₁ H ₂₀ N ₂ O ₃	12.27	12.38
N-2-Ethylbutyryl-N'-2-methylbutyryl-	...	450	77-78	C ₁₂ H ₂₂ N ₂ O ₃	11.56	11.52
N-2-Methylbutyryl-N'-2,2-dimethylbutyryl-	...	550	130-131	C ₁₂ H ₂₂ N ₂ O ₃	11.56	11.60
<i>sym-bis</i> -(2-Ethylbutyryl)-	...	550	86-87	C ₁₃ H ₂₄ N ₂ O ₃	10.93	10.98
<i>sym-bis</i> -(2,2-Dimethylbutyryl)-	...	800	163-164	C ₁₃ H ₂₄ N ₂ O ₃	10.93	10.93

^a Recrystallized from benzene-petroleum ether. ^b Recrystallized from hot water. ^c Recrystallized from petroleum ether.

85% were obtained. The physical properties of these compounds are recorded in Table II.

TABLE II
MONOACYLUREAS

Urea	M. p., °C. (corr.)	Formula	N analyses, %	
			Calcd.	Found
Isobutyryl-	175-176	C ₅ H ₁₀ N ₂ O ₂	21.53	21.33
Isovaleryl ^a	204-205	C ₆ H ₁₂ N ₂ O ₂	19.43	19.43
2-Methylbutyryl ^b	179-180	C ₆ H ₁₂ N ₂ O ₂	19.43	19.50
2,2-Dimethylpropionyl-	147-148	C ₆ H ₁₂ N ₂ O ₂	19.43	19.48
2-Ethylbutyryl ^c	206-207	C ₇ H ₁₄ N ₂ O ₂	17.71	17.66
2-Methylvaleryl-	152-153	C ₇ H ₁₄ N ₂ O ₂	17.71	17.75
2,2-Dimethylbutyryl-	121-122	C ₇ H ₁₄ N ₂ O ₂	17.71	17.69
3,3-Dimethylbutyryl-	173-174	C ₇ H ₁₄ N ₂ O ₂	17.71	17.78
2,2-Dimethylvaleryl-	116-117	C ₈ H ₁₆ N ₂ O ₂	16.27	16.36
2,2-Dimethylcaproyl-	108-109	C ₉ H ₁₈ N ₂ O ₂	15.04	15.20

^a Moldenhauer, *Ann.*, **94**, 102 (1855). ^b Fischer and Dilthey, *ibid.*, **335**, 367 (1904). ^c Fischer and Dilthey, *ibid.*, **335**, 366 (1904); Newberry, *J. Chem. Soc.*, **125**, 295 (1925).

N,N'-Diacylureas.—The general procedure, described previously¹ for the preparation of diacylureas by the reaction of an acid chloride with a monoacylurea, was used, but the product was isolated in a slightly different manner. Six to twelve hours of heating was necessary before the evolution of hydrogen chloride ceased and a clear solution was obtained. After cooling, the reaction mixture was washed with a saturated sodium bicarbonate solution, the benzene removed under reduced pressure, and the residue recrystallized from an appropriate solvent. Except as otherwise noted, dilute methanol was found to be most satisfactory for this purpose. The physical proper-

ties of these compounds are recorded in Table I. Yields of between 75 and 85% usually were obtained. Better over-all yields were obtained when the monoureide of the acid with the higher molecular weight was prepared first and then treated with the chloride of the other acid.

Properties of the N,N'-Diacylureas.—These compounds—with the exception of one, which was an oil—were white, nicely crystalline solids, soluble in most organic solvents but only slightly soluble in water and cold petroleum ether. They were soluble in dilute alkali but were hydrolyzed by it (usually within two or three minutes at room temperature) to monoureides and fatty acid salts. Compounds with less than ten or eleven carbon atoms in the molecule dissolved completely on the addition of one equivalent of sodium hydroxide, but those with a greater molecular weight required an excess of alkali to effect solution before the monoureide began to precipitate. The acyl group with the smaller molecular weight or the least amount of branching in the carbon chain was always hydrolyzed off more rapidly. Nevertheless, compounds with the most highly branched chains [*e. g.*, *sym-bis*-(2,2-dimethylpropionyl)-urea] were completely hydrolyzed within twenty minutes. Similarly, sodium in absolute alcohol produced alcoholysis with the formation of a monoureide and a fatty acid ester.

These branched chain diacylureas were decomposed on heating in the same way and as easily as the normal derivatives; for example, on heating diisobutyrylurea to 200°, it was found that approximately two-thirds had decomposed into isobutyramide, isobutyronitrile and carbon dioxide, and one-third had formed diisobutyramide and cyanuric acid.

Summary

A series of twenty-one diacylureas derived from branched chain aliphatic acids has been prepared by the reaction of an acid chloride with a monoacylurea. The chemical characteristics of these compounds are similar to the analogous de-

rivatives of the normal acids with the exception that the more highly branched compounds are very slightly more stable to alkali. These substances were found to have hypnotic properties, and their relative activity has been evaluated.

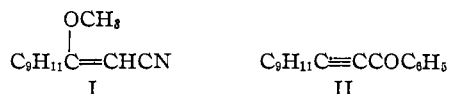
NASHVILLE, TENNESSEE RECEIVED NOVEMBER 25, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Benzoylmesitylacetylene¹

BY REYNOLD C. FUSON, G. E. ULLYOT AND J. L. HICKSON

Among the products obtained by treating the enol methyl ethers (I) of 2,4,6-trimethylbenzoylacetonitrile with phenylmagnesium bromide there were found varying amounts of a ketone whose identity was for a long time in doubt and whose origin is still not entirely clear.² The present paper reports a study of the reactions of this unusual compound. The results showed it to be benzoylmesitylacetylene (II)—a conclusion which has been confirmed by an independent synthesis of the compound in question.

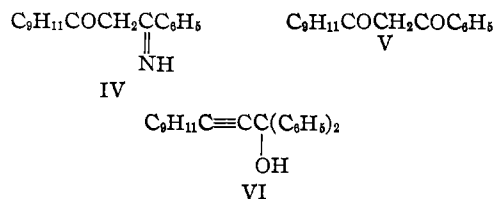


Actually the acetylenic compound was not obtained directly by the interaction of the enol ethers (I) with phenylmagnesium bromide. A yellow amorphous solid appeared to be its precursor; this solid contained nitrogen and halogen, but was not obtained in pure form. When it was dissolved in boiling 95% alcohol the acetylenic ketone was formed. Boiling glacial acetic acid converted the precursor into the imino ketone (IV), showing that the skeletal structure is $\text{C}_6\text{H}_{11}\text{C}-\text{C}-\text{CC}_6\text{H}_5$.

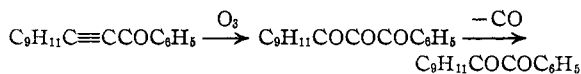
The presence of an unhindered carbonyl group in the acetylenic ketone was shown by the formation of a semicarbazone and by the reaction with phenylmagnesium bromide. The latter reagent converted the ketone to the corresponding carbinol (VI). The latter absorbed three moles of hydrogen in the presence of Raney nickel. Ozonization of the acetylenic ketone gave β -isodurylic acid, benzoic acid and a small amount of mesityl phenyl diketone.

(1) Original manuscript received June 18, 1938.

(2) Fuson, Ulllyot, Stedman, Gehrt and Tawney, *THIS JOURNAL*, **60**, 1447 (1938).



It was this information which suggested that the ketone might be benzoylmesitylacetylene. Mesityl phenyl triketone would be expected as a product of the action of ozone, and the diketone is known to be a decomposition product of the triketone.³



Further evidence in favor of the acetylenic structure for the unsaturated ketone is its conversion into 2,4,6-trimethyldibenzoylmethane (V) by the action of sulfuric acid. Nef⁴ used this method to prove the structure of benzoylphenylacetylene.

Reduction of the ketone (II) with hydrogen in the presence of Raney nickel gave benzoylmesitylthane, the structure of which was confirmed by synthesis of the compound from β -chloropropiophenone and mesitylene by the Friedel-Crafts method.

A more satisfactory synthesis⁵ of the ethane was developed by use of α -chloroisodurene made by the method of Nauta and Dienske.⁶ This chloride condensed with the sodium derivative of ethyl benzoylacetate to give a solid which was presumably ethyl α -isodurylbenzoylacetate. The latter was subjected to hydrolysis without purification. Decarboxylation of the resulting acid gave the desired ethane.

(3) Fuson, Weinstock and Ulllyot, *ibid.*, **57**, 1803 (1935).

(4) Nef, *Ann.*, **308**, 277 (1899).

(5) This synthesis was carried out by Mr. J. J. Denton.

(6) Nauta and Dienske, *Rec. trav. chim.*, **55**, 1000 (1936).