[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Reactions of Hydrazine with Heterocyclic 1,2-Dicarboxylic Acid Esters

BY REUBEN G. JONES

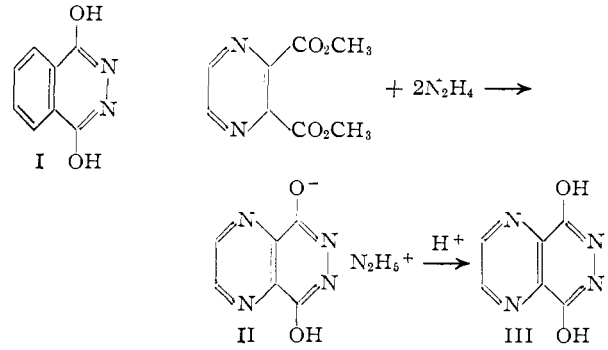
RECEIVED JULY 18, 1955

Reactions of hydrazine with 24 heterocyclic-1,2-dicarboxylic acid esters have been studied. The esters of the six-membered ring systems, pyridine, pyrazine, pyrimidine and pyridazine and of thiophene gave cyclic hydrazides (1,4-dihydroxypyridazines). The dicarboxylic esters of otherwise unsubstituted furan, pyrrole, imidazole and pyrazole gave dihydrazides. The diesters of furan, pyrrole, imidazole and pyrazole containing substituents (methyl or phenyl) on the rings adjacent to one of the carbalkoxyl groups reacted with hydrazine to form 1,4-dihydroxypyridazine compounds. Steric factors are believed to play a decisive part in these reactions. The dihydrazides were converted to pyridazines by: (1) heating with excess hydrazine hydrate, (2) heating in dilute hydrochloric acid solution. Derivatives of 3,4-furandicarboxylic acid, when heated with hydrazine, were converted to 4,4'-bis-pyrazoles.

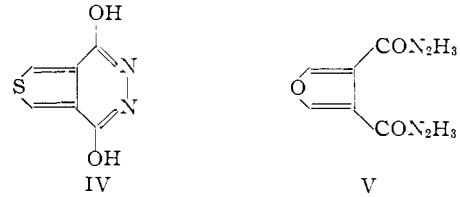
Although the reactions of hydrazine with phthalic acid derivatives to give phthalazine (1,4-dihydroxy-2,3-diazanaphthalene, I) are well known,[1] analogous reactions with other aromatic 1,2-dicarboxylic acid derivatives appear to have been studied very little. The object of the present work was to investigate the reactions of hydrazine with a series of heterocyclic 1,2-dicarboxylic acid esters for the preparation of bicyclic compounds containing the 1,4-dihydroxypyridazine ring.[2] Such compounds appeared to be of interest for cancer and virus chemotherapy testing because of the resemblance of their structures and physical and chemical properties with those of certain biologically important purines and pteridines.

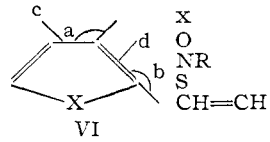
The reaction of hydrazine with 2,3-pyridinedicarboxylic acid anhydride to yield 1,4-dihydroxy-2,3,5-triazanaphthalene has been described,[3] as has also the reaction of hydrazine with dimethyl 3,4-pyridinedicarboxylate to give 1,4-dihydroxy-2,3,6-triazanaphthalene.[4] Some of the earlier investigators apparently failed to appreciate the ease with which such reactions take place. They heated the reactants together at high temperatures or for long periods of time. In the present work a number of six-membered, aromatic, 1,2-dicarboxylic acid esters were allowed to react with hydrazine. The reactants were simply mixed in methanol solution and allowed to stand or warmed briefly. In all cases reaction took place with great ease to form the dihydroxypyridazine ring.[2] The diesters used were those of pyridine, pyrimidine, pyrazine and pyridazine ring systems. The first crystalline products that separated from the methanol solutions appeared to be hydrazine salts such as II. These were quite water soluble, and, when their solutions were acidified, the bicyclic compounds exemplified by III separated as sparingly soluble, yellow to white, finely divided crystalline solids. These products are presented in the first part of Table I.

Seka and Preissecker[5] have described briefly reactions of hydrazine with dicarboxylic acid esters of several substituted, five-membered, aromatic, ring systems including furan, pyrrole, imidazole and 1,2,3-triazole. In some cases the fused dihydroxypyridazine ring was formed; in others dihydrazides or other products were obtained. A rather extensive investigation has now been made of the reaction of hydrazine with 1,2-dicarboxylic acid esters of furan, thiophene, pyrrole, imidazole and pyrazole.



Diethyl 3,4-thiophenedicarboxylate readily underwent reaction with excess hydrazine in methanol solution to give a crystalline product that proved to be the hydrazine salt of 4,7-dihydroxy-2-thia-5,6-diazaindene (IV). When this salt was dissolved in water and the solution acidified, IV separated as a crystalline solid. In like manner, diethyl 5-methyl-2,3-thiophenedicarboxylate with hydrazine gave the bicyclic compound, 4,7-dihydroxy-2-methyl-1-thia-5,6-diazaindene. The reaction of diethyl 3,4-furandicarboxylate with hydrazine, on the other hand, gave the dihydrazide V. So, also, did the diethyl esters of 5-methyl-2,3-furan-, 3,4-pyrrole-, 1-methyl-3,4-pyrrole-, 4,5-imidazole- and 3,4-pyrazoledicarboxylic acids react with hydrazine to form dihydrazides. The dihydrazides are presented in Table II. In none of these reactions were any pyridazine rings formed even when the re-





X	a	b	c	d
O	127°	126°	1.46Å.	1.35Å.
NR	127	126	1.46	1.35
S	123	124	1.44	1.35
CH=CH	120	120	1.39	1.39

(1) T. Curtius and E. Davidis, *J. prakt. Chem.*, **54**, 66 (1896).

(2) Throughout this paper these compounds are arbitrarily designated as 1,4-dihydroxypyridazines. Other tautomeric forms are possible and may be more probable in some cases.

(3) G. Gehorghin, *Bull. soc. chim.*, **47**, 630 (1930); K. Glen and K. Wackernagel, *J. prakt. Chem.*, **148**, 72 (1937).

(4) H. Meyer and J. Mally, *Monatsh.*, **33**, 393 (1912); H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry and J. Bernstein, THIS JOURNAL, **75**, 1933 (1953).

(5) R. Seka and H. Preissecker, *Monatsh.*, **57**, 71 (1931).

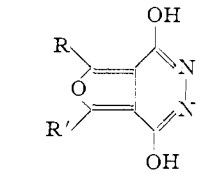
action mixtures in methanol were heated for several hours. The dihydrazides were readily distinguished from the bicyclic compounds not only by analysis but also because of the fact that the hydrazides were soluble in dilute acid solutions but insoluble in base; whereas, the bicyclic dihydroxypyridazine compounds like III and IV were soluble in dilute base and insoluble in acid.

The fact that the thiophene diester reacted to give exclusively the bicyclic compound IV, whereas the other five-membered heterocyclic diesters gave exclusively dihydrazides is probably best explained on steric grounds. The bond distances and angles of furan, pyrrole and thiophene are known,[6] and, from the published data, the angles a and b of structure VI have been calculated. It is seen that in furan and pyrroles (X = O and NR, respectively) the angles a and b are somewhat larger than in thiophene (X = S); whereas, the bond distances are the same in all three. Imidazole and pyrazole rings may be assumed to conform closely in size and shape to those of furan and pyrrole.[7] The bond angles and distances in benzene (X = CH=CH) are given for comparison. The distance between adjacent carbethoxy groups on furan, pyrrole, imidazole and pyrazole, therefore, must be somewhat greater than between such groups on thiophene. This means that, in the case of dicarbethoxythiophene, the formation of a hydrazine bridge leading to compound IV involves less strain than the formation of corresponding hydrazine bridges with dicarbethoxyfuran, pyrrole, imidazole and pyrazole. This is not meant to imply that the bicyclic dihydroxypyridazine compounds VII, VIII, IX and X are incapable of existence. Indeed, two methods were found for converting the dihydrazides to pyridazines, and these are discussed later. The most logical explanation appears to be that the reaction of the diester with excess hydrazine involves the formation first of a monohydrazide. In the case of the thiophene compounds, the second ester group is so favorably located that an internal hydrazinolysis very rapidly takes place before a second molecule of hydrazine can come in to form a dihydrazide. In the furan, pyrrole, imidazole and pyrazole compounds the second ester group is too far away, and before an internal hydrazinolysis can take place a second molecule of hydrazine from the medium reacts with the ester to form the dihydrazide which is relatively quite stable.

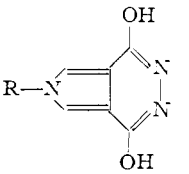
When diethyl 2-methyl-3,4-furandicarboxylate was allowed to react with hydrazine, the expected dihydrazide was not obtained. The only product was 1-methyl-4,7-dihydroxy-2-oxa-5,6-diazaindene (XI). Diethyl 1-methyl- and 1-phenyl-4,5-imidazoledicarboxylates with hydrazine gave compounds XII and XIII, respectively; diethyl 1-phenyl-4,5-pyrazoledicarboxylate gave XIV and diethyl 1-phenyl-5-methyl-2,3-pyrroledicarboxylate gave 1-phenyl-2-methyl-4,7-dihydroxy-1,5,6-triazaindene. Thus, in these reactions with hydrazine it appears that, in general, a substituent (methyl or phenyl) adjacent to one of the carbethoxy groups of the furan, pyrrole, imidazole or pyrazole diesters forces

(6) V. Schomaker and L. Pauling, THIS JOURNAL, **61**, 1769 (1939).

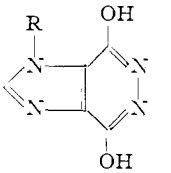
(7) This assumption is based on the fact that nitrogen and carbon have approximately the same atomic radii; see ref. 6.



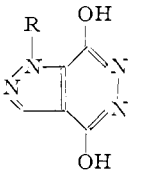
VII, R = R′ = H
XI, R = H, R′ = CH_3
XV, R = R′ = CH_3



VIII, R = H

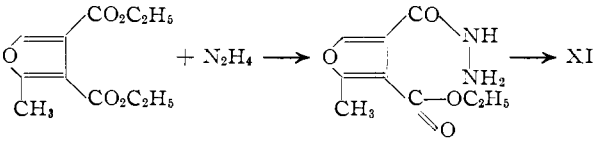


IX, R = H
XII, R = CH_3
XIII, R = C_6H_5



X, R = H
XIV, R = C_6H_5

the formation of the pyridazine ring and does not allow formation of the dihydrazides. One explanation may be that the substituent, because of its bulk, pushes the two carbethoxy groups a little closer together. A more likely explanation is that the substituent group hinders the reaction of one of the carbethoxy groups with hydrazine. The mechanism may involve first an attack of hydrazine on the less hindered ester group with formation of a monohydrazide. The remaining ester group, flanked on both sides by substituents, is shielded from attack by a second hydrazine molecule, thus allowing time for an internal hydrazinolysis with resulting formation of the pyridazine ring.



The very appreciable steric hindrance offered by a methyl group adjacent to the carbethoxy was illustrated by allowing hydrazine in methanol to react with diethyl 2,5-dimethyl-3,4-furandicarboxylate in which both ester groups are hindered. The product, XV, was obtained in only 35 to 38% yield after 24 hours at room temperature or five hours heating under reflux; 50% of the starting ester was recovered. In contrast with this, the reaction to give XI in 77% yield was complete in 12 hours; and the reaction to form the dihydrazide, V, in 90% yield was complete in one hour at room temperature.

The reaction between hydrazine and diethyl 2-mercapto-4,5-imidazoledicarboxylate gave 2-mercapto-4,7-dihydroxy-1,3,5,6-tetrazaindene instead of the dihydrazide. The influence of the mercapto group in causing formation of this ring-closed compound is not readily explained but must be due to factors other than steric ones.

Two methods were found for converting the dihydrazides of Table II to the corresponding dihydroxypyridazines,[2] Table I. The first procedure was simply to heat the dihydrazide with a large excess of hydrazine hydrate. The conversion was rather slow but was usually complete after several hours under reflux or several days on the steam-

TABLE I

BICYCLIC DIHYDROXYPYRIDAZINES FROM HYDRAZINE AND HETEROCYCLIC DICARBOXYLIC ESTERS

Name[a]	Empirical formula	Parent ester ref.	Method of prepn.[a]	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
5,8-Dihydroxy-1,4,6,7-tetrazanaphthalene	$C_6H_4N_4O_2$	14	A	95	280 dec.	43.91	43.93	2.46	2.65	34.14	34.11
1,3-Dimethyl-5,8-dihydroxy-2,6,7-triazanaphthalene	$C_9H_9N_3O_2$	12	A	97	302 dec.					21.98	21.87
2-Amino-5,8-dihydroxy-1,3,6,7-tetrazanaphthalene[d]	$C_6H_5N_5O_2$	15	A	93	>400					39.10	39.07
2-Cyano-3-methyl-5,8-dihydroxy-4,6,7-triazanaphthalene	$C_9H_6N_4O_2$	13	A	85	320 dec.	53.46	53.51	2.99	2.68	27.71	27.78
2-Cyano-3,8-dimethyl-5-hydroxy-4,6,7-triazanaphthalene	$C_{10}H_8N_4O$	13	A	89	338–340	59.99	59.81	4.03	3.92	27.99	28.04
1,4-Dimethyl-5,8-dihydroxy-2,3,6,7-tetrazanaphthalene	$C_8H_8N_4O_2$	11	A	73	320 dec.	49.99	48.77	4.20	4.06	29.16	29.19
4,7-Dihydroxy-2-thia-5,6-diazaindene[c]	$C_6H_4N_2O_2S$	16	A	92	328–330	42.86	42.82	2.40	2.51	16.67	16.78
2-Methyl-4,7-dihydroxy-1-thia-5,6-diazaindene	$C_7H_6N_2O_2S$	17	A	90	294–295	46.14	46.17	3.32	3.51	15.37	15.53
4,7-Dihydroxy-2-oxa-5,6-diazaindene	$C_6H_4N_2O_3$	16	C	70	>300	47.37	47.56	2.65	2.86	18.42	18.38
1-Methyl-4,7-dihydroxy-2-oxa-5,6-diazaindene	$C_7H_6N_2O_3$	16	A	77	282–283	50.60	50.88	3.64	3.72	16.86	16.75
1,3-Dimethyl-4,7-dihydroxy-2-oxa-5,6-diazaindene	$C_8H_8N_2O_3$	18	A	83	345 dec.	53.33	52.85	4.48	4.27	15.55	15.77
2-Methyl-4,7-dihydroxy-1-oxa-5,6-diazaindene	$C_7H_6N_2O_3$	17	B, C	96[b]	290–292	50.60	51.03	3.64	3.80	16.86	17.35
4,7-Dihydroxy-2,5,6-triazaindene	$C_6H_5N_3O_2$	16	B, C	90[b,e]	>310	47.68	47.72	3.34	3.34	27.81	28.20
2-Methyl-4,7-dihydroxy-2,5,6-triazaindene	$C_7H_7N_3O_2$	16	B, C	89[b]	339–340	50.91	51.02	4.27	4.40	25.45	25.38
2-Methyl-4,7-dihydroxy-1,5,6-triazaindene	$C_7H_7N_3O_2$	17	B		355 dec.					25.45	25.17
1-Phenyl-2-methyl-4,7-dihydroxy-1,5,6-triazaindene	$C_{13}H_{11}N_3O_2$	17	A	89	335–337	64.72	64.87	4.60	4.94	17.42	17.60
4,7-Dihydroxy-1,2,5,6-tetrazaindene	$C_5H_4N_4O_2$	15	B	79	385 dec.	39.48	39.65	2.65	2.99	36.84	37.08
1-Phenyl-4,7-dihydroxy-1,2,5,6-tetrazaindene	$C_{11}H_8N_4O_2$	15	A	61	315–316	57.89	57.83	3.53	3.72	24.55	24.51
4,7-Dihydroxy-1,3,5,6-tetrazaindene	$C_5H_4N_4O_2$	19	B, C	92[b]	>400	39.48	39.38	2.65	2.80	36.84	36.62
2-Mercapto-4,7-dihydroxy-1,3,5,6-tetrazaindene	$C_5H_4N_4O_2S$	19	A	67	>400	32.61	32.06	2.19	2.57	30.42	30.38
1-Methyl-4,7-dihydroxy-1,3,5,6-tetrazaindene	$C_6H_6N_4O_2$	19	A	78	354–356	43.37	43.13	3.64	3.87	33.72	34.48
1-Methyl-2-mercapto-4,7-dihydroxy-1,3,5,6-tetrazaindene	$C_6H_6N_4O_2S$	19	A	93	>330	36.36	35.90	3.05	3.12	28.27	28.15
1-Phenyl-4,7-dihydroxy-1,3,5,6-tetrazaindene	$C_{11}H_8N_4O_2$	19	A	89	315–316	57.89	57.80	3.53	3.59	24.55	24.42
1-Phenyl-2-mercapto-4,7-dihydroxy-1,3,5,6-tetrazaindene	$C_{11}H_8N_4O_2S$	19	A	97	367 dec.	50.76	50.12	3.10	3.59	21.53	21.53

[a] A, direct action of hydrazine with the diester; B, heating the dihydrazide with excess hydrazine hydrate; C, heating the dihydrazide with dilute hydrochloric acid. [b] Yield is for preparation of method B. [c] Hydrazine salt recrystallized from methanol, white needles, unmelted up to 300°. *Anal.* Calcd. for $C_6H_8N_4O_2S$: N, 27.98. Found: N, 28.20. [d] Ammonium salt, sparingly soluble in cold water, lost ammonia when heated to 200°. *Anal.* Calcd. for $C_6H_8N_6O_2$: N, 42.85. Found: N, 42.89. [e] Yield after heating dihydrazide with excess hydrazine on steam-bath 24 hours, 50%; 40% dihydrazide recovered; yield after 60 hours, 90%

TABLE II

DIHYDRAZIDES A $(CON_2H_3)_2$

Parent acid A	Ref.	Empirical formula	Yield, %	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
4,5-Imidazole	19	$C_5H_8N_6O_2$	99	>375	45.64[a]	45.74
3,4-Pyrazole	15	$C_5H_8N_6O_2$	98	>300	45.64	45.65
3,4-Furan	16	$C_6H_6N_4O_3$	88	270d.	30.43	30.07
5-Methyl-2,3-furan	17	$C_7H_{10}N_4O_3$	94	196	28.27	28.55
3,4-Pyrrole	16	$C_6H_9N_5O_2$	95	>300	38.24	38.35
1-Methyl-3,4-pyrrole	16	$C_7H_{11}N_5O_2$	90	330d.	35.52	35.86

[a] *Anal.* Calcd.: C, 32.61; H, 4.65. Found: C, 32.87; H, 4.57.

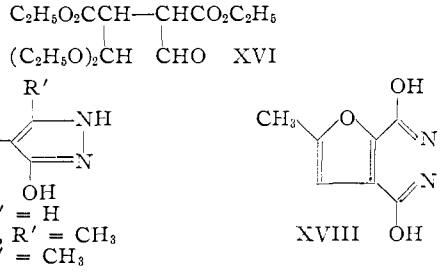
bath. This method could not be used to prepare VII from V because of opening of the furan ring as discussed below.

The second general method of converting the dihydrazides to pyridazines was discovered quite by accident when a solution of V in dilute hydrochloric acid was heated on the steam-bath. The pyridazine VII separated from the solution in good yield. The other dihydrazides of Table II were similarly treated with dilute hydrochloric acid, and in all cases but one, ring closure took place to yield the dihydroxypyridazines. The exception was 3,4-pyrazoledicarboxylic acid dihydrazide from which was obtained a monohydrazide, presumably 3-carboxy-4-pyrazolecarboxylic acid hydrazide. Although a mechanism is not proposed, it seems probable that monohydrazides are not intermediates in those cases where ring closure to pyridazines takes place.

The pyridazine VII was not formed when 3,4-furandicarboxylic acid dihydrazide (V) was heated with excess hydrazine hydrate. Instead, a crystalline compound with the formula $C_6H_6N_4O_2$ was isolated in high yield. It was soluble in base and

(8) T. Curtius, *J. prakt. Chem.*, **50**, 519 (1894).
(9) R. Seka and H. Preissecker, *Monatsh.*, **57**, 81 (1931).
(10) C. Bülow, *Ber.*, **37**, 91 (1904).
(11) C. Paal and J. Ubber, *ibid.*, **50**, 1568 (1917).
(12) O. Mumm and H. Hüneke, *Ber.*, **50**, 1568 (1917).
(13) E. M. Bottorff, R. G. Jones, E. C. Kornfeld and M. J. Mann, THIS JOURNAL, **73**, 4380 (1951).
(14) S. Gabriel and A. Sonn, *Ber.*, **40**, 4850 (1907).
(15) R. G. Jones and C. W. Whitehead, *J. Org. Chem.*, **20**, 1342 (1955).
(16) E. C. Kornfeld and R. G. Jones, *ibid.*, **19**, 1671 (1954).
(17) R. G. Jones, THIS JOURNAL, **77**, 4069 (1955).
(18) L. Knorr, *Ber.*, **17**, 2863 (1884).
(19) R. G. Jones, THIS JOURNAL, **74**, 1085 (1952).

in mineral acid. The same compound was obtained from the reaction of hydrazine with diethyl 1-formyl-2-diethoxymethylsuccinate (XVI). On the basis of analysis and reactions by which it was formed, the most probable structure of the new compound appeared to be XVIIa. When the furanopyridazines XI and XV were heated with hydrazine hydrate, compounds XVIIb and XVIIc, respectively, were obtained. The formation of compounds XVII involves a cleavage, by hydrazine, of the furan ring carrying carboxyl residues in the 3,4-position. 2-Methyl-4,7-dihydroxy-1-oxa-5,6-diazaindene (XVIII) in which carboxyl residues are attached to furan in the 2,3-position was not affected when it was heated with hydrazine hydrate.

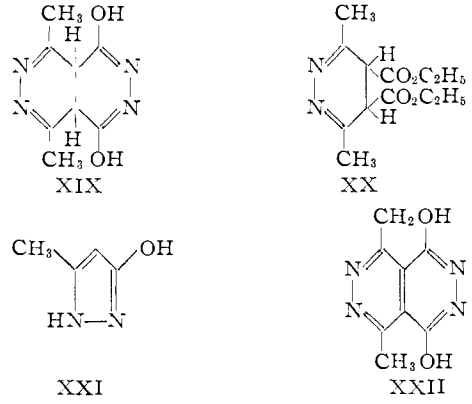


XVI

XVIIa, R = R′ = H
b, R = H, R′ = CH_3
c, R = R′ = CH_3

XVIII

An examination of the older literature revealed that Curtius[8] had prepared compound XVIIc from the reaction of diethyl 1,2-diacetylsuccinate with excess hydrazine. Later, Seka and Preissecker[9] obtained the same compound by heating diethyl 2,5-dimethyl-3,4-furandicarboxylate with hydrazine. They did not isolate the intermediate pyridazine XV, but they formulated the Curtius compound as a dihydropyridazopyridazine (XIX). This formulation was first proposed by Bülow,[10] who, following Curtius, examined again the reaction of hydrazine with diethyl diacetylsuccinate. When equimolar quantities of the reactants were used, it was possible to isolate diethyl 3,6-dimethyl-4,5-dihydropyridazinedicarboxylate[8,11] (XX). Bülow reasoned that XX would react with more hydrazine to give structure XIX and not XVIIc. He further showed that the Curtius compound was amphoteric and that it formed a tetrabenzoyl derivative. On the basis of these facts, he chose structure XIX instead of XVIIc.



XIX XX

XXI XXII

In the light of present evidence structure XVIIc originally proposed by Curtius[8] and structures XVIIa and b for the new analogs of this group appear to be correct, and structure XIX of Bülow[10] and Seka and Pressecker[9] is wrong. The fully aromatic system represented by XVII would be more stable than the dihydroaromatic system XIX. There is no reason to assume, as did Bülow, that XVIIc would not form a tetrabenzoyl derivative or would not be amphoteric. Attempts to titrate XVIIc were not successful because of its insolubility; however, the model XXI did have two titratable groups, an acid one with pK'_a 10.2 and a basic one with pK'_a 3.3 in 66% dimethylformamide. The infrared spectrum of the model compound XXI was very similar to the spectra of XVIIa and c, whereas other models like XX and XXII had spectra completely different from those of XVIIa and c.

Acknowledgment.—The author is grateful to W. L. Brown, H. L. Hunter, G. M. Maciak and G. Beckmann for the microanalyses and to Dr. H. E. Boaz and associates for physical-chemical measurements.

Experimental

Reactions of Hydrazine with Dicarboxylic Acid Esters to Form Dihydroxypyridazines, Table I, Method A.—A solution of 0.1 mole of the dicarboxylic acid ester in 25–50 ml. of methanol was treated with 15 g. (0.3 mole) of hydrazine hydrate. Often an exothermic reaction took place. The mixture was either allowed to stand at room temperature for several hours, or heated on the steam-bath for 0.5 hour, and the methanol removed by evaporation. The crystalline product was taken up in the minimum quantity of hot water (usually about 50–500 ml.) containing 5 ml. of concentrated ammonium hydroxide. If necessary the solution was filtered and then acidified with excess acetic or hydrochloric acid. The crystalline precipitate was collected on a filter, washed successively with cold water, alcohol and ether and air-dried. Samples for analysis were prepared by recrystallizing from water, or, if too insoluble, solution in dilute ammonium hydroxide and reprecipitation with acid. Usually the sample was sublimed under reduced pressure at about 250–275°.

Conversion of Dihydrazides to Pyridazines, Method B.—A mixture of 0.05 mole of the dihydrazide with 50 ml. of hydrazine hydrate was heated under reflux (2–8 hours) or on the steam-bath (9–72 hours) until the solid had dissolved. The solution was then evaporated under reduced pressure on the steam-bath to remove all of the hydrazine. The solid residue was taken up in about 50–200 ml. of hot water, and the solution was acidified with acetic or hydrochloric acid. After cooling, the crystalline product was collected, washed and air-dried.

Method C.—A solution of 0.05 mole of the dihydrazide in 100 ml. of 2 *N* hydrochloric acid was heated on the steam-bath for six hours. The mixture was cooled, and the crystalline precipitate that had separated was collected on a filter and air-dried. Analytical samples were sublimed under reduced pressure.

Preparation of Dihydrazides, General Method.—A solution of 0.1 mole of the diester in about 50 ml. of methanol was treated with 15 g. (0.3 mole) of hydrazine hydrate. After standing for several hours or heating for 0.5 hour on the steam-bath the mixture was thoroughly cooled and the crystalline product was collected and air-dried. Analytical samples were recrystallized from water or alcohol or, if too insoluble in either of these, the sample was dissolved in dilute acid and reprecipitated by addition of ammonium hydroxide.

The dihydrazides are listed in Table II. They were entirely stable and could be heated, recrystallized, or dissolved in acid and reprecipitated by base without change. Heating in acid solution for extended periods of time converted them to pyridazines.

3,3′-Dihydroxy-4,4′-bis-pyrazole (XVIIa).—A mixture of 16 g. of 3,4-furandicarboxylic acid dihydrazide and 25 ml. of hydrazine hydrate was heated on the steam-bath for six hours. The resulting brown solution was evaporated under reduced pressure, and the residue was taken up in 100 ml.

of dilute sodium hydroxide solution. After treating with carbon the solution was filtered and acidified with acetic acid. The crystalline precipitate was collected and air-dried; yield 13 g. (90%). An analytical sample was recrystallized from water, darkened but unmelted at 360°.

Anal. Calcd. for $C_6H_8N_4O_2$: C, 43.37; H, 3.64; N, 33.73. Found: C, 43.57; H, 3.87; N, 33.98, 33.55.

The same compound was obtained in 50% yield by treating diethyl 1-formyl-2-diethoxymethylsuccinate[18] in ethanol with excess hydrazine. It was identified by infrared spectrum.

3,3'-Dihydroxy-5-methyl-4,4'-bis-pyrazole (XVIIb).—This was obtained in 90% yield by heating 10 g. of 1-methyl-4,7-dihydroxy-2-oxa-5,6-diazaindene (XI) with 20 ml. of hydrazine hydrate on the steam-bath for eight hours. A sample for analysis was sublimed at 275° under 0.1 mm. pressure; m.p. above 360°.

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.66; H, 4.76; N, 31.11.

In the same way 3,3'-dihydroxy-5,5'-dimethyl-4,4'-bis-pyrazole (XVIIc) was prepared in 52% yield by heating 1,3-dimethyl-4,7-dihydroxy-2-oxa-5,6-diazaindene (XV) with hydrazine under reflux for 15 hours; m.p. above 375°.

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.55; H, 5.32; N, 28.88.

A sample prepared by the method of Curtius[8] had an infrared spectrum identical with that of the product described above.

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF BOSTON UNIVERSITY]

Preparation and Constitution of Nonadiyne-1,4

BY WALTER J. GENSLER, A. P. MAHADEVAN AND JOSEPH CASELLA, JR.

RECEIVED FEBRUARY 4, 1955

Hexynylmagnesium bromide and propargyl bromide in the presence of cuprous chloride couple to give the terminally unsaturated skipped diyne, nonadiyne-1,4. Available evidence shows that although an allenic impurity is present, the bulk of the coupling product has the assigned structure. Some features of terminally deuterated nonadiyne-1,4 are discussed. Dodecatriyne-1,4,7 is obtained as a minor product in the coupling reaction.

Acetylenic Grignard reagents in the presence of cuprous chloride couple with propargyl bromides to form skipped diynes.[1] In this way, for example, hexynylmagnesium bromide and 1-bromoheptyne-2 give tridecadiyne-5,8,[1] and heptynylmagnesium bromide and 1-bromoöctyne-2 give pentadecadiyne-6,9.[2] The subject of the present paper is nonadiyne-1,4 (III), a compound selected for study as a representative terminally unsaturated skipped diyne, and also for use in further synthetic work.

Coupling of hexynylmagnesium bromide (I) and

$$\underset{\text{I}}{CH_3(CH_2)_3C{\equiv}CMgBr} + \underset{\text{II}}{BrCH_2C{\equiv}CH} \longrightarrow \underset{\text{III}}{CH_3(CH_2)_3C{\equiv}CCH_2C{\equiv}CH}$$

propargyl bromide (II), although slower than the coupling of hexynylmagnesium bromide and 1-bromoheptyne-2, proceeded without difficulty to form nonadiyne-1,4 (III). The material, a water-white liquid, became yellow on standing sealed and darkened rapidly on exposure to air. The coupling product was expected to have structure III; but just as with other products from propargyl bromides, the possibility of rearrangement during or after coupling[3] made it necessary to consider isomeric structures—for example, conjugated diynes IV and V or allene acetylenes VI and VII.

$CH_3(CH_2)_3C{\equiv}C{-}C{\equiv}CCH_3$	IV
$CH_3(CH_2)_3CH_2C{\equiv}C{-}C{\equiv}CH$	V
$CH_3(CH_2)_3CH{=}C{=}CHC{\equiv}CH$	VI
$CH_3(CH_2)_3C{\equiv}CCH{=}C{=}CH_2$	VII

First, however, an estimate of homogeneity was sought.

Treatment of the coupling product with mercuric iodide dissolved in aqueous alcoholic sodium hydroxide solution[4] precipitated a crystalline mercury derivative, m.p. 109–111°, in over 90% yield. To determine whether the unmodified coupling product or *isomerized* material was the immediate precursor of the derivative, the coupling product was exposed briefly to the alkaline solution before adding mercuric iodide. The same solid was obtained, but the yield dropped sharply. Clearly, alkali under the conditions of the formation of the mercury derivative was able to modify the coupling product. But fortunately the change, whatever its nature, operated to *decrease* the yield of derivative so that the observed yields were minimal measures of the content of original hydrocarbon. These experiments showed accordingly that a single substance comprised *over 90%* of the coupling product.

Formation of nonane on addition of four moles of hydrogen to the coupling product confirmed the absence of branching. Because ozonolysis yielded valeric acid, the unsaturation was confined to the first five carbons of the chain. Furthermore the absence of any sign of caproic acid rendered structure V highly improbable. Formation of silver and copper derivatives in addition to the above-mentioned mercury derivative established the presence of a terminal acetylene grouping, and thereby eliminated the possibility of structures IV and VII.

Considerations based on molar refraction and on ultraviolet absorption favored structure III over VI or VII. The Lorenz–Lorentz value (39.95) agreed closely with the molar refraction calculated for the skipped diyne III (39.97) but was 2.26 units lower than the value expected for the allenic acetylenic structures. The observed ultraviolet

(1) W. J. Gensler and A. P. Mahadevan, THIS JOURNAL, **77**, 3076 (1955).

(2) W. J. Gensler and G. R. Thomas, *ibid.*, **73**, 4601 (1951).

(3) See the discussion in reference 1. Also note L. Piaux and M. Gaudemar, *Compt. rend.*, **240**, 2328 (1955).

(4) J. R. Johnson and W. L. McEwen, THIS JOURNAL, **48**, 469 (1926).