793. *The Reactions of Some* 1 : 4-*Dicarbonyl Systems with Hydrazine.*

By W. L. Mosby.

3 : 4-Diacetylhexane-2 : 5-dione and hydrazine yield pyrazole derivatives, whereas diacetylsuccinic ester gives both pyrazolinones and pyridazines.

3 : 4-*Diacetylhexane*-2 : 5-*dione*.—Nothing appears to have been reported concerning the reaction of 3 : 4-diacetylhexane-2 : 5-dione[1] (I) with hydrazine, although tetrabenzoylethane and its derivatives were reported[2] to give both 5- and 6-membered cyclic systems and hexane-2 : 5-dione yields[3] a mixture of 1 : 2- and 1 : 4-dihydro-3 : 6-dimethylpyridazines. The reaction of compound (I) with 2 mols. of hydrazine might, *a priori*, give either compound (II) or (III) (or a tautomer), whereas with 1 mol. of hydrazine either compound (IV) or (V) (or a tautomer) could result.

In our hands, diacetylhexanedione and an excess of hydrazine gave product (III), whilst with a single equivalent of hydrazine compound (V) was formed. The structures were assigned after a comparison of the ultraviolet spectra of the compounds with those of the tetraketone (I) and of 3 : 5-dimethylpyrazole[4] (see Fig. 1). The spectrum of hexane-2 : 5-dione (not shown) possesses two maxima (226 and 271 mμ) at much lower intensities (log ε 2·01 and 1·59, respectively). Further, the spectrum of the diester (XIX) (see below) corresponding to the diacetyl structure (IV), was quite dissimilar to that of product (V).

The dipyrazolyl (III) could not be dehydrogenated by treatment with nitric acid, mercuric acetate, lead tetra-acetate, or Tollens's reagent. Removal of the two nuclear hydrogen atoms and introduction of the intercyclic double bond would require coplanarity of the whole system, a condition made difficult, if not impossible, by interference among

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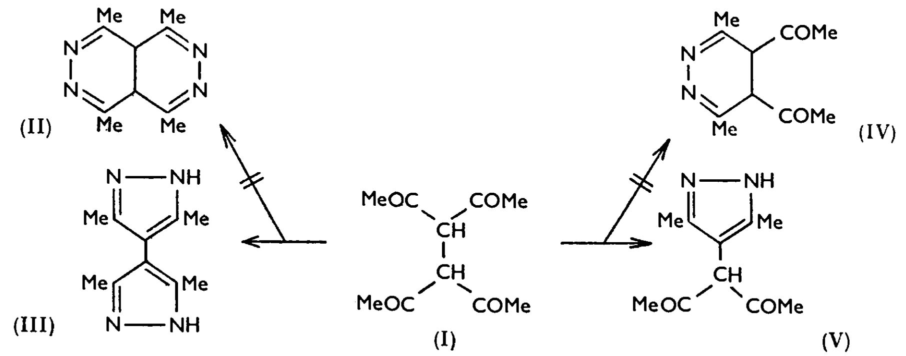
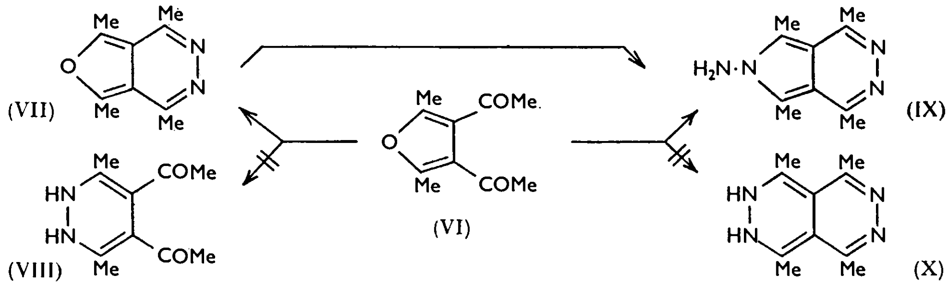
[1] Mulliken, *Amer. Chem. J.*, 1893, **15**, 523.
[2] Keller and Halban, *Helv. Chim. Acta*, 1944, **27**, 1253.
[3] Overberger, Byrd, and Mesrobian, *J. Amer. Chem. Soc.*, 1956, **78**, 1961.
[4] Rothenburg, *Ber.*, 1894, **27**, 1097.

the methyl groups. It is significant, in this connection, that tetrabenzoyl*ethylene* did not react with more than 1 mol. of hydrazine, and gave [2] only a *mono*pyrazolyl derivative. It was, however, possible to prepare *NN'*-diacyl derivatives of compound (III). In these derivatives the rings are, obviously, fixed in a true pyrazole configuration, and an *iso*-pyrazole structure, such as might be envisaged for compound (III), is impossible.



Dehydration of diacetylhexanedione was known [1,5] to produce 3 : 4-diacetyl-2 : 5-dimethylfuran (VI), which was found to react with one equivalent of hydrazine to yield a product for which structures (VII) (monohydrate) and (VIII) (or a tautomer) were considered. The infrared spectrum of the product showed no carbonyl absorption, but a strong band in the 3 μ region confirmed the suspicion of a hydrated structure. The preparation of a non-hydrated monopicrate further supports structure (VII).* The tetraphenyl analogue of (VII) is known,[2] but unfortunately its ultraviolet spectrum was not shown. However, considerable resemblance between the shape of the curve of compound (VII) (see Fig. 2) and that of 1 : 3-diphenyl*iso*benzofuran [7] may be noted.

With 2 mols. of hydrazine, compound (VI) [or (VII) with a second mol. of hydrazine] yielded a product ($C_{10}H_{14}N_4$) thought to have either structure (IX) or (X) (or a tautomer). The ultraviolet (see Fig. 2) and infrared spectra were inconclusive, although the similarity of the former to that of the furanopyridazine (VII) might be taken as evidence in favour of structure (IX). Treatment of the product with nitrous acid gave a deamino-derivative, and as *N*-aminopyrroles are known [8] thus to be deaminated, this was taken as evidence in favour of structure (IX).



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* Bradley and Watkinson [6] treated diacetyldimethylfuran in acetic acid with hydrazine and obtained a product of the same empirical formula, m. p. 136—140° (decomp.) [the monohydrate of (VII) has an instantaneous m. p. of 144°]. They consider their product to be the monohydrazone of (VI), but in the absence of evidence to the contrary it seems probable that their product is also the hydrate of (VII).

[5] Zanetti, *Gazzetta*, 1893, **23**, 307.

[6] Bradley and Watkinson, *J.*, 1956, 319.

[7] Adams and Gold, *J. Amer. Chem. Soc.*, 1940, **62**, 2038.

[8] Bülow and Klemann, *Ber.*, 1907, **40**, 4749.

Efforts to prepare other derivatives of the $C_{10}H_{14}N_4$ product were, for the most part, unsuccessful. A monopicrate was easily formed, but reactions with acetic anhydride, benzoic anhydride, benzoyl chloride, toluene-*p*-sulphonyl chloride, benzaldehyde, and phenyl *iso*cyanate gave only oily yellow mixtures. The compound gave a precipitate with Tollens's reagent, but was unchanged when heated with mercuric acetate in acetic acid or with palladium-charcoal in triethylbenzene; heating with sulphur caused decomposition and evolution of ammonia and hydrogen sulphide.

Reaction of *NN*-dimethylhydrazine with the furopyridazine was attempted, since it could yield only a product of type (IX) and not (X). The furanopyridazine failed to react, however, which is surprising in view of its ready reaction with hydrazine and the fact that dimethylhydrazine reacts normally with a number of carbonyl compounds (although *not* with diacetylhexanedione or with diacetylsuccinic ester).

FIG. 1.

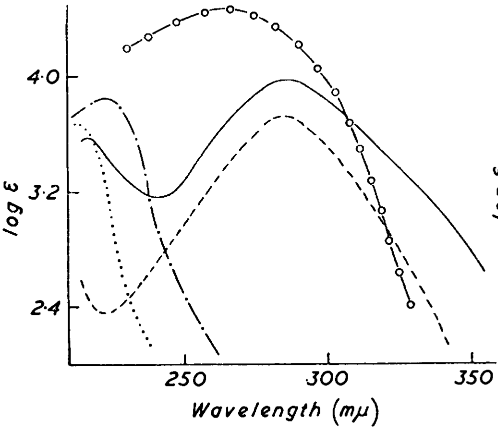


FIG. 2.

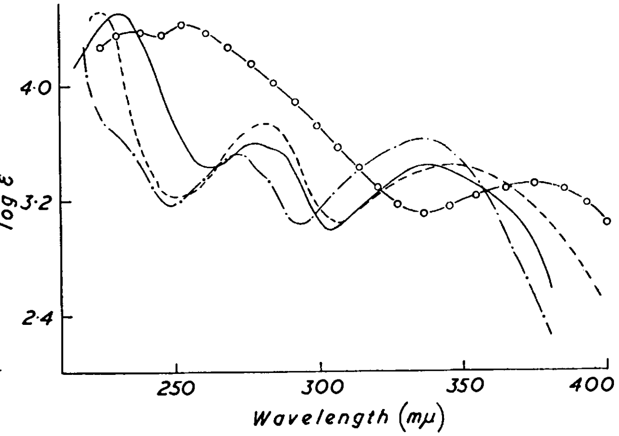
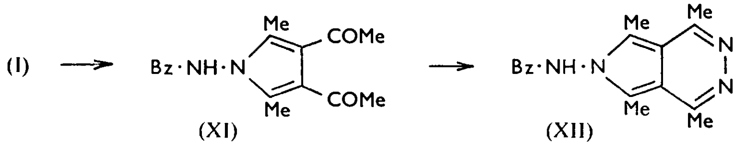


FIG. 1. 3 : 4-*Diacetylhexane*-2 : 5-*dione* (I) (– – –); 3 : 5-*dimethylpyrazole* (. . .); 3 : 5 : 3′ : 5′-*tetramethyldipyrazol*-4-*yl* (III) (— · —); 3-(3 : 5-*dimethylpyrazol*-4-*yl*)*pentane*-2 : 4-*dione* (V) (——); NN′-*dibenzoyl derivative of* (III) (— ○ —). (*All in* EtOH.)

FIG. 2. 1 : 4 : 5 : 7-*Tetramethylfuro*[3 : 4-d]*pyridazine* (VII) (*in* EtOH) (— · —); 6-*amino*-1 : 4 : 5 : 7-*tetramethylpyrrolo*[3 : 4-d]*pyridazine* (IX) (*in* EtOH) (——); 6-*benzamido*-1 : 4 : 5 : 7-*tetramethylpyrrolo*[3 : 4-d]*pyridazine* (XII) (*in* MeOH) (— ○ —); 1 : 4 : 5 : 7-*tetramethyl*-6H-*pyrrolo*[3 : 4-d]-*pyridazine* (*in* MeOH) (– – –).

It is noteworthy that the same product $C_{14}H_{10}N_4$ was obtained from the reaction of diacetylhexanedione with hydrazine in hot acetic acid. As it was known [9-11] that 1 : 4-diketones react with benzhydrazide to yield *N*-benzamidopyrroles, compound (I) was similarly treated, and the two products thereby obtained were, upon the basis of spectra and elemental analysis, assigned structures (XI) and (XII). The ultraviolet spectrum of compound (XI) is quite similar (see Fig. 3) to those of the esters (XIV) and (XV) (see p. 4000), showing with respect to the curve of the latter a bathochromic shift similar to that shown



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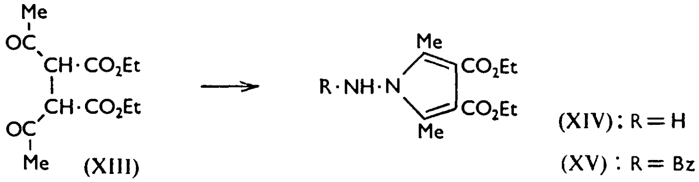
[9] Bülow, *Ber.*, 1902, **35**, 4311.

[10] Capuano, *Gazzetta*, 1938, **68**, 521.

[11] Yale, Losee, Martins, Holsing, Perry, and Bernstein, *J. Amer. Chem. Soc.*, 1953, **75**, 1933.

by the curve of the ketone (I) with respect to that of the ester (XIII). Efforts to debenzoylate the hydrazide (XI) gave only dibenzoylhydrazine, whilst treatment with hydrazine gave a 40% yield of compound (XII) and a 60% yield of dibenzoylhydrazine.



Diacetylsuccinic Ester.—This ester * (XIII) was used to prepare compounds (XIV) and (XV) by Bülow's method[9] (ultraviolet spectra, see Fig. 3). Although diethyl 2 : 5-dimethylpyrrole-3 : 4-dicarboxylate is reported[13] to react with hydrazine, compound (XIV)

FIG. 3.

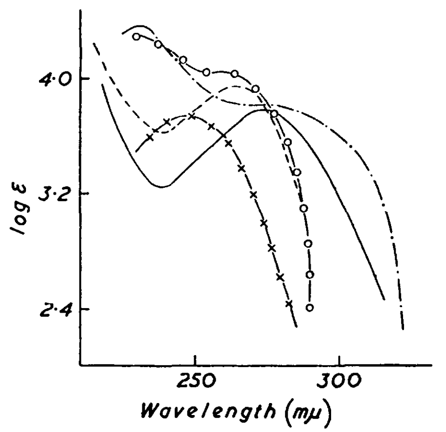


FIG. 4.

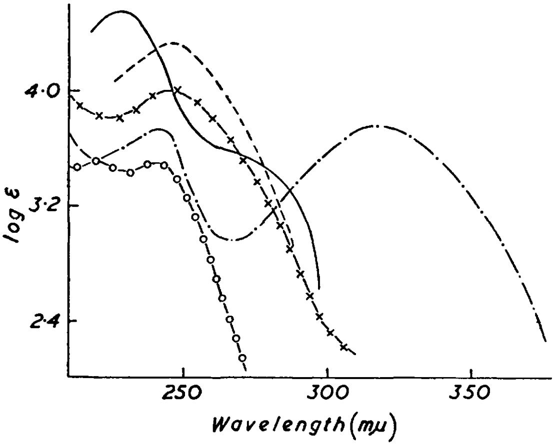


FIG. 3. 3 : *4-Diacetyl-2 : 5-dimethylfuran* (VI) (*in* EtOH) (——); *diethyl 1-amino-2 : 5-dimethylpyrrole-3 : 4-dicarboxylate* (XIV) (*in* EtOH) (– – –); 3 : *4-diacetyl-1-benzamido-2 : 5-dimethylpyrrole* (XI) (*in* MeOH) (— · —); *diethyl 1-benzamido-2 : 5-dimethylpyrrole-3 : 4-dicarboxylate* (XV) (*in* MeOH) (— ○ —); *diethyl diacetylsuccinate* (XIII) (*in* MeOH) (—×—×—).

FIG. 4. *Diethyl* 1 : *4-dihydro-3 : 6-dimethylpyridazine-4 : 5-dicarboxylate* (XIX) (*in* EtOH) (— · —); *3-methylpyrazolin-5-one* (*in* EtOH) (— ○ —); 3 : *3′-dimethyl-5 : 5′-dioxo-4 : 4′-dipyrazolinyl* (XVII) (*in* EtOH *containing a trace of* N-NaOH) (—×—×—); *dibenzoyl derivative of compound* (XVII) (*in* MeOH) (——); *tetra-acetyl derivative of compound* (XVII) (*in* MeOH) (– – –).

was unchanged when boiled overnight with hydrazine in dimethylformamide. Further, it was not hydrolysed by brief treatment with boiling alcoholic potassium hydroxide.

Curtius[14] found that diacetylsuccinic ester reacted with 1 or 2 mols. of hydrazine to yield products which he formulated as (XVI) and (XVII), respectively. Re-investigation[9] of these reactions showed that Curtius's first product was converted into the second by reaction with 1 mol. of hydrazine, and this led Bülow[15] to assign structure (XVIII) instead

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* The so-called β-modification (m. p. 88—90°), evidently a diketo-form from its negative ferric chloride reaction, was used in this work. In an effort to utilize the oily congeners of the β-form, purification by vacuum-distillation was attempted: the only pure product isolated, however, was ethyl 4-acetyl-4 : 5-dihydro-2-methyl-5-oxofuran-3-carboxylate ("*iso*carbopyrotritartaric ester," m. p. 110°; strong blue colour reaction with ferric chloride) known[12] to result from the pyrolysis of diacetylsuccinic ester.

[12] Knorr and Haber, *Ber.*, 1894, **27**, 1151.

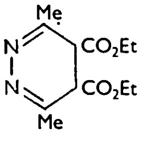
[13] Seka and Preisecker, *Monatsh.*, 1931, **57**, 81.

[14] Curtius, *J. prakt. Chem.*, 1894, **50**, 508.

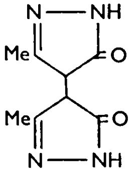
[15] Bülow, *Ber.*, 1904, **37**, 91.

of (XVII) to the second product. Seka and Preisecker,[13] who also obtained this product from condensation of hydrazine with either diethyl diacetylsuscinate (XIII) or diethyl 2 : 5-dimethylfuran-3 : 4-dicarboxylate, assigned the product structure (XVIII).

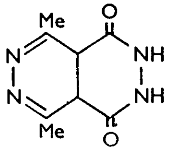
The infrared spectrum of the dihydropyridazine ester [9,14,15] disclosed a strong >NH absorption at 3·1 μ and *two* ester bands, at 5·83 and 5·93 μ. Of the six possible tautomeric structures of this compound, three are excluded by the absence of an >NH group, and two others by the presence of but a single type of ester group. These results suggest that the ester has structure (XIX) rather than (XVI). The ultraviolet spectrum of the ester (see Fig. 4) had previously been measured,[16] but was not reported in a convenient form. It is quite different from the spectrum of diethyl 3 : 6-dimethylpyridazine-4 : 5-dicarboxylate [17] ($\lambda_{max.}$ 231, 240·5, 274 mμ; log ε 3·36, 3·25, 3·46), which resembles the curves [18] of some of the simpler substituted pyridazines.



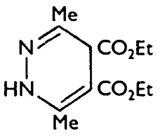
(XVI)



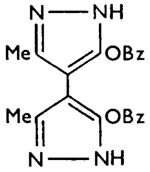
(XVII)



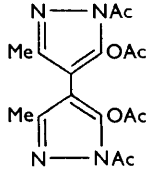
(XVIII)



(XIX)



(XX)



(XXI)

The ultraviolet spectra of Curtius's second product ($C_8H_{10}O_2N_4$), and of its dibenzoyl and tetra-acetyl derivatives, so closely resemble that of 3-methylpyrazolin-5-one (see Fig. 4), and are so dissimilar to the curves of the pyridazine derivatives that structure (XVII) is undoubtedly correct and not (XVIII). This conclusion was evidently also reached by Jones,[19] although no evidence was presented. The infrared spectrum of the dibenzoyl derivative of compound (XVII) shows an >NH absorption at 3·18 μ and an ester band at 5·69 μ, but no amide absorption, so the dibenzoyl derivative is formulated as (XX) (or its tautomer) and the tetra-acetyl derivative as (XXI).

EXPERIMENTAL

M. p.s were taken in Pyrex capillaries, in a Hershberg m. p. apparatus (Ace Scientific Co.) with Anschütz thermometers. The ultraviolet spectra were measured with a Cary automatic recording spectrophotometer (Model 10).

3 : 4-*Diacetylhexane*-2 : 5-*dione* (I).—Pentane-2 : 4-dione (b. p. 133—134°; 200 g.) was added, under nitrogen, during 6 hr., to a stirred slurry of sodium hydride (48 g.) and ether (1500 ml.). More ether (approx. 2 l.) was then added and the mixture heated so that ether extracted iodine (254 g.) from a thimble placed below the condenser. The cooled slurry was filtered, and the solid was washed and crystallized from acetic acid. The ketone (139 g., 70·2%) recrystallized from acetic acid in platelets, m. p. 189—190° (lit.,[1] m. p. 191°), $\lambda_{max.}$ 285 mμ (log ε 3·71).

3 : 5 : 3′ : 5′-*Tetramethyldipyrazol*-4-*yl* (III).—Diacetylhexanedione (I) (19·8 g.) was added

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[16] Korschun and Roll, *Bull. Soc. chim. France*, 1926, **39**, 1223.

[17] Paal and Koch, *Ber.*, 1903, **36**, 2538.

[18] Eichenberger, Rometsch, and Druey, *Helv. Chim. Acta*, 1954, **37**, 1298; Horning and Amstutz, *J. Org. Chem.*, 1955, **20**, 1069.

[19] Jones, *J. Amer. Chem. Soc.*, 1956, **78**, 159.

portionwise to 85% hydrazine hydrate (30 ml.) as rapidly as possible. The mixture was cooled and filtered, and the crystals were washed with ice-water. When a hot, clarified (charcoal) methanolic solution of the product was diluted with water, the *dipyrazolyl* crystallized (15·6 g., 82%), m. p. 299—300°, $\lambda_{max.}$ 223 mμ (log ε 3·84 (Found: C, 63·3; H, 7·1; N, 29·3. $C_{10}H_{12}N_4$ requires C, 63·8; H, 6·4; N, 29·8%). The *dinitrate* was prepared from the base and concentrated nitric acid (Found: C, 37·7; H, 5·05; N, 26·9. $C_{10}H_{12}N_4,2HNO_3$ requires C, 38·0; H, 5·1; N, 26·6%). The NN′-*diacetyl derivative*, obtained by the use of acetic anhydride and pyridine, crystallized from ligroin in white lozenges, m. p. 123·5—125·0°, $\lambda_{max.}$ 252 mμ (log ε 4·40) (Found: C, 61·2; H, 6·6; N, 21·1; O, 11·4. $C_{14}H_{18}O_2N_4$ requires C, 61·3; H, 6·6; N, 20·4; O, 11·7%). The NN′-*dibenzoyl derivative*, prepared from (III), benzoyl chloride, and pyridine, after two crystallizations from *cyclo*hexane–ligroin, melted at 126·0—128·5° and had $\lambda_{max.}$ 270 mμ (log ε 4·65) (Found: C, 72·2; H, 5·6; N, 14·2; O, 8·3. $C_{24}H_{12}O_2N_4$ requires C, 72·4; H, 5·53; N, 14·1; O, 8·04%).

3-(3 : 5-*Dimethylpyrazol*-4-*yl*)*pentane*-2 : 4-*dione* (V).—Hydrazine hydrate (0·6 ml.; 85% solution) was added dropwise to a stirred slurry of diacetylhexanedione (2·0 g.) and boiling ethanol (50 ml.). The clarified (charcoal) hot solution was evaporated *in vacuo* and the resulting oil crystallized. After trituration with water and drying, the crude *diketone* weighed 1·3 g. (65·5% yield). Crystallization from water gave 0·9 g. of colourless needles. On immersion at 130° it melted at 134—140°; if immersed at lower temperatures, the compound decomposed gradually. Aqueous solutions give a deep red colour with ferric chloride. $\lambda_{max.}$ were 217 and 285 mμ (log ε 3·59 and 3·97) (Found: C, 58·9; H, 7·4; N, 13·3. $C_{10}H_{14}O_2N_2,\frac{1}{2}H_2O$ requires C, 59·1; H, 7·4; N, 13·8%).

1 : 4 : 5 : 7-*Tetramethylfuro*[3 : 4-d]*pyridazine* (VII).—85% Hydrazine hydrate (1·8 ml.) was added to a warm solution of 3 : 4-diacetyl-2 : 5-dimethylfuran [5] (VI) (6·0 g.) in ethanol (10 ml.), after which the solution was cooled and filtered and the solid was washed and dried. The pale yellow *furopyridazine* (4·2 g., 71·7%) crystallized from benzene in buff needles (2·7 g.). On immersion much below its m. p., it melts and decomposes over a range. The instantaneous m. p. is 144°, and $\lambda_{max.}$ are 235 (infl.), 272, and 337 mμ (log ε 3·57, 3·52, and 3·60) (Found: C, 61·8; H, 7·2; N, 14·9; O, 15·9. $C_{10}H_{12}ON_2,H_2O$ requires C, 61·8; H, 7·2; N, 14·4; O, 16·5%). The *picrate* crystallized from methanol in yellow needles, m. p. 173·0—174·6° (Found: C, 47·7; H, 3·6; N, 18·0. $C_{16}H_{15}O_8N_5$ requires C, 47·5; H, 3·6; N, 17·3%).

6-*Amino*-1 : 4 : 5 : 7-*tetramethylpyrrolo*[3 : 4-d]*pyridazine* (IX).—85% Hydrazine hydrate (3·0 ml.) was added to a solution of 3 : 4-diacetyl-4 : 5-dimethylfuran (3·0 g.) in dimethylformamide (8 ml.), and the mixture was heated under reflux for 2 hr., then cooled and filtered. The *amino-compound* (IX) was washed with ethanol and dried, giving 3·1 g. (98·5%) of white crystals. Crystallization from water gave lozenges, m. p. 294—295° if immersed at about 290° but decomposing slowly if put into a bath much below 290°, $\lambda_{max.}$ 229, 278, and 342 mμ (log ε 4·48, 3·58, and 3·43) (Found: C, 63·5; H, 7·2; N, 29·7. $C_{10}H_{14}N_4$ requires C, 63·2; H, 7·4; N, 29·5%). The solid and its neutral solutions fluoresce blue under ultraviolet light, while acidified solutions show a green-blue fluorescence. The *picrate*, after three recrystallizations from methanol, melted at 189·5—191·0° (Found: C, 45·7; H, 4·1; N, 22·9. $C_{16}H_{17}O_7N_7$ requires C, 45·9; H, 4·1; N, 23·4%).

1 : 4 : 5 : 7-*Tetramethyl*-6H-*pyrrolo*[3 : 4-d]*pyridazine.*—A solution of sodium nitrite (350 mg.) in water (2 ml.) was added to a solution of the amino-compound (IX) (970 mg.) in glacial acetic acid (5 ml.) stirred at 5°. The mixture was then evaporated *in vacuo*; the residual oil was dissolved in ethanol and the solution was again evaporated *in vacuo.* A clarified (charcoal) solution in water (10 ml.) of the resulting yellow solid was basified with aqueous ammonia, whereupon 800 mg. of pale tan solid were precipitated. Two crystallizations from methanol gave nearly white *pyrrolopyridazine*, decomp. >300°, $\lambda_{max.}$ 225, 282, and 346 mμ (log ε 4·55, 3·73, and 3·43) (Found: C, 69·1; H, 7·4; N, 23·4. $C_{10}H_{13}N_3$ requires C, 68·5; H, 7·4; N, 24·0%).

3 : 4-*Diacetyl*-1-*benzamido*-2 : 5-*dimethylpyrrole* (XI).—A mixture of diacetylhexanedione (1·98 g.), benzhydrazide (1·36 g.), and acetic acid (5 ml.) was heated under reflux for 3 hr., then cooled and diluted with water. The solid was filtered off, washed, and dried (wt. 1·64 g.). Crystallization from methanol–water gave felted needles of the *pyrrole* (1·28 g.), m. p. 194·7—197·0° (recrystallization from ethyl acetate did not improve the m. p.), $\lambda_{max.}$ 230 and 265—276 mμ (log ε 4·36 and 3·83) (Found: C, 68·5; H, 5·5; N, 10·0; O, 15·6. $C_{17}H_{18}O_3N_2$ requires C, 68·5; H, 6·0; N, 9·4; O, 16·1%).

6-*Benzamido*-1 : 4 : 5 : 7-*tetramethylpyrrolo*[3 : 4-d]*pyridazine* (XII).—A solution of the diacetyl compound (XI) (1·20 g.) in ethanol (30 ml.) was heated under reflux with 85% hydrazine hydrate (0·50 ml.) for 4 hr. Most of the ethanol was then allowed to boil away, and the residue was cooled and filtered. The solid was washed with ethanol and dried, giving 1·10 g. of crude product, which was extracted with boiling nitromethane to remove 460 mg. of dibenzoylhydrazine (m. p. 241·0—241·8°), leaving 440 mg. (40·6%) of the yellow *benzamido-compound* (XII), m. p. 298·5—303·5°. After crystallization from methanol it had m. p. 303·5—305°, $\lambda_{max.}$ 232—246, 256, and 378 mμ (log ε 4·39, 4·43, and 3·30) (Found: C, 69·3; H, 6·05; N, 19·2; O, 5·6. $C_{17}H_{18}ON_4$ requires C, 69·4; H, 6·1; N, 19·1; O, 5·4%).

This product was obtained in 32% yield by basification with ammonia of the mother-liquors from the preparation of the diacetylpyrrole (XII).

Diethyl 1 : 4-*Dihydro*-3 : 6-*dimethylpyridazine*-4 : 5-*dicarboxylate* (XIX).—This ester was prepared in 63% yield from diethyl diacetylsuccinate (2 : 5-dioxohexane-3 : 4-dicarboxylate) (XIII) in essentially the manner described.[9, 14] Recrystallization from *cyclo*hexane gave white needles, m. p. 70—71° (lit.,[14] m. p. 68—69°), $\lambda_{max.}$ 210, 243, and 318 mμ (log ε 3·74, 3·73, and 3·75).

3 : 3′-*Dimethyl*-5 : 5′-*dioxo*-4 : 4′-*dipyrazolinyl* (XVII).—This compound, prepared in 80% yield from the dihydropyridazine ester (XIX) by Bülow's method,[15] had $\lambda_{max.}$ 247 mμ (log ε 4·00).

Schotten–Baumann benzoylation gave a *dibenzoyl derivative*, m. p. 270·2—271·2° after two recrystallizations from ethanol, $\lambda_{max.}$ 230·5 and 270 (infl.) mμ (log ε 4·54 and 3·55) (Found: C, 65·1; H, 4·6; N, 13·9. $C_{22}H_{18}O_4N_4$ requires C, 65·7; H, 4·5; N, 13·9%).

The tetrabenzoyl derivative could not be obtained by the Schotten–Baumann technique,[13] but was prepared from the pyrazolone (XVII) and benzoyl chloride in pyridine in 97% yield; it had m. p. 197—201° (lit.,[13] 190°).

The tetra-acetyl derivative was obtained by the use of acetic anhydride and pyridine. The crude product (62% yield) crystallized from *cyclo*hexane in acicular clusters, m. p. 136·0—137·5° (lit.,[13] 140°), $\lambda_{max.}$ 246 mμ (log ε 4·31).

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