**Rearrangement of 2,3-Dihydro-2,5-dimethyl-6-phenyl-4*H*-1,2-diazepin-4-one (3).**—A solution of 604 mg. of **3** in 3 ml. of methanol and 2.5 ml. of aqueous 5% sodium hydroxide was refluxed (70°) for 3 hr. under a stream of nitrogen. The solution was cooled then and neutralized with dilute hydrochloric acid. A white precipitate, total of 570 mg. in several crops, was collected, washed with water, and dried. The material could not be sublimed without extensive decomposition. Recrystallization was finally accomplished with extensive loss from a very small volume of methanol to give colorless crystals of 3-hydroxy-4-methyl-2-methylamino-5-phenylpyridine (**11**), m.p. 200° dec., p$K_A$ 5.7 and 9.7 (50% MeOH), $\lambda_{max}^{MeOH}$ 276 (infl.) and 310 mμ (ε 10,000), $\lambda_{max}^{MeOH,\ HCl}$ 258 and 313 mμ (11,000), $\lambda_{max}^{MeOH}$ 319 mμ (12,800).

*Anal.* Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 73.11; H, 6.67; N, 12.99.

A solution of 37 mg. of the base in 1 ml. of methanol was treated with 0.5 ml. of concentrated hydrochloric acid. Evaporation of the methanol gave a crystalline mass which was collected and washed with a very small volume of iced water. Recrystallization from methanol–ether gave colorless needles of the **hydrochloride**, m.p. 235–240° dec.

*Anal.* Calcd. for $C_{13}H_{14}N_2O \cdot HCl$: C, 62.27; H, 6.03. Found: C, 62.45; H, 6.08.

**3-Acetoxy-4-methyl-2-methylacetamido-5-phenylpyridine.**—A solution of 300 mg. of the above base in 1.8 ml. of acetic anhydride and 3 ml. of pyridine was allowed to stand overnight at 25° and then was concentrated at reduced pressure to about one-third volume. Methanol was added, the solution was again evaporated, the residue was then dissolved in ether, and the solution was washed with dilute aqueous acid, base, and water and then evaporated to give 228 mg. of colorless solid. Recrystallization from acetone–ether gave colorless prisms, m.p. 135–136°, $\lambda^{KBr}$ 3.32, 5.69, and 6.04 μ.

*Anal.* Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.39; H, 6.24; N, 9.21.

**Acknowledgment.**—We wish to thank Miss Barbara Garland for obtaining the n.m.r. data, and Dr. John M. Vandenbelt and Mrs. Carola Henrich Spurlock, Parke, Davis and Company, for the p$K_A$ and ultraviolet data.

# Heterocyclic Studies. XIII. The Aldol Condensation of 2,3-Dihydro-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one and Rearrangement to a Pyridazine[1]

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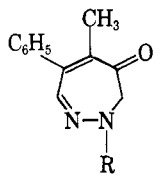
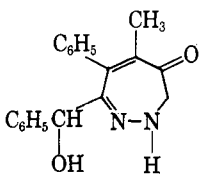
The aldol condensation of the diazepinone **1a** with benzaldehyde gives the 3α-hydroxybenzyl compound **3**, which is dehydrated to the 2-acetyl-3-benzylidene derivative **7** with acetic anhydride. Rearrangement of **7** to benzyl 3-(4-methyl-5-phenylpyridazinyl) ketone **8** occurs on hydrolysis. The structure **8** was based on degradation to the pyridazine carboxylic acid **12**, the pyridazine **13**, and the dicarboxylic acid **15a**. By carrying out the sequence of reactions with **1a** labeled at C-3 with $C^{14}$ it was shown that C-3 is extruded in the ring contraction to **8**. The mechanisms of the aldol condensation and rearrangement and the instability of diazatropone and diazatropilidene derivatives are discussed.

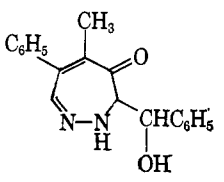
One of the reactions of the diazepinone **1a** mentioned in the first report[2] of the compound was the base-catalyzed condensation with benzaldehyde to give an aldol product considered to be **2**.[3] Physical data and evidence from a degradative sequence now require revision to structure **3**.



**1a**, R = H
**b**, R = $CH_3$



**2**



**3**

The infrared and ultraviolet spectra of the aldol, which were very similar to those of **1a**, did not clearly distinguish between **2** and **3**, but the n.m.r. spectrum, obtained after chemical evidence for **3** was in hand, was consistent only with this structure. In $CDCl_3$ solution (TMS) containing $D_2O$ the C-3 and benzyl protons formed a pair of doublets (C-3, δ = 3.35 and 3.47 p.p.m.; benzyl, δ = 5.18 and 5.30 p.p.m.; $J_{AB}$ = 7.5 c.p.s.) in addition to the single peaks at 1.92 and 6.99 p.p.m. due to methyl and C-7 protons, respectively, and phenyl multiplet at 7.2–7.7 p.p.m. Without $D_2O$, peaks due to N–H at 6.87 p.p.m. and OH at 4.0–4.2 p.p.m. (doublet, position concentration dependent) were also present, and the peak due to the benzyl proton was further split into a complex multiplet at 5.2–5.5 p.p.m.

The aldol product was remarkably resistant to acid-catalyzed dehydration and was recovered unchanged from acid treatment sufficient to cause the rearrangement of **1a** to the 1-aminopyridine.[4] Treatment with thionyl chloride in pyridine gave a dark tar. With polyphosphoric acid a small amount of the parent ketone **1a** was isolated. In contrast to **1a**, neither an oxime nor semicarbazone could be prepared from the aldol. Mixtures of unstable products which could not be characterized were obtained with dimethyl sulfate.

The formation of **3** can be viewed as a simple aldol condensation of the C-3 enolate of **1a** with benzaldehyde. It has been shown by n.m.r. studies[5] that the protons at both C-3 and C-7 in **1a** exchange with deuterium in NaOD. This work also revealed that ring contraction of **1a** and **1b** to α-aminopyridines occurs in alkaline solution, presumably by cleavage of the C-3 enolate anion. A point that must be accounted for in formulating the conversion of **1a** to **3** is the fact that the 2-methyldiazepinone **1b** does not undergo an analogous condensation; under a variety of conditions only the 2-methylaminopyridine was obtained. The product was isolated as a complex of unknown nature, and the pyridine structure was not established until the completion of the work described in the preceding paper.[5]

(1) Supported in part by a grant from the Geschickter Fund for Medical Research.

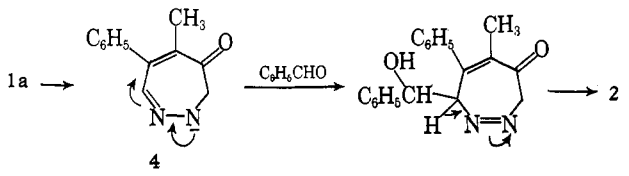
(2) J. A. Moore, *J. Am. Chem. Soc.*, **77**, 3417 (1955).

(3) The structure originally proposed[2] was based on an enolic formula for **1a**.

(4) J. A. Moore and J. Binkert, *J. Am. Chem. Soc.*, **81**, 6029 (1959).

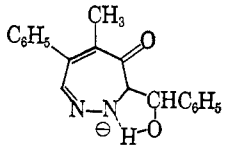
(5) J. A. Moore and E. C. Zoll, *J. Org. Chem.*, **29**, 2124 (1964).

The contrasting behavior of **1a** and **1b** was originally accounted for by formulating the condensation of **1a** as a reaction of the C-7 enolate **4**, leading to **2**, but, with the establishment of **3** as the aldol, another explanation is required.




4

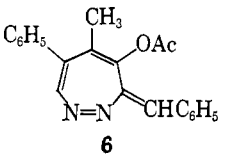
The failure of **1b** to undergo aldol condensation may simply be due to the loss of the enolate anion in the cleavage reaction, which is irreversible, at the expense of the aldol product, whose formation is readily reversible. That cleavage does not similarly occur to the exclusion of aldol formation in the case of **1a** must be due to the presence of the acidic proton at N-2 in **3**. The predominant anion **5** would be further stabilized by hydrogen bonding from the hydroxyl group, as in the familiar enhancement of the acidity of benzoic acid by *ortho*-hydroxyl groups.[6] Both reversal of the aldol condensation and the dehydration of **3** would thus be suppressed in comparison to the corresponding condensation of **1b**, although reversal of **3** does occur in aqueous alkali.



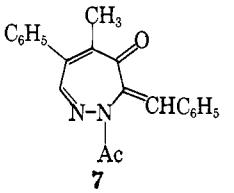
5

The only transformation product that has been obtained from the aldol **3** is an orange compound formed with acetic anhydride and pyridine whose formula corresponded to an *anhydro*-acetyl derivative. The color suggested a seven-membered ring to accomodate the chromophore, although the visible spectrum contained only strong end absorption ($\epsilon_{400\ m\mu}$ 2500), and no maximum at 408 m$\mu$ as in **1** and **3**. The infrared spectrum ($CCl_4$ solution) contained sharp bands at 1760, 1680, and 1630 cm.$^{-1}$, displaced to slightly lower frequencies (1750, 1660, and 1630) in KBr. The n.m.r. spectrum contained methyl peaks at $\delta$ = 1.70 and 2.45 p.p.m., a peak at 6.60 p.p.m. presumably due to $C_6H_5$—CH=, and the aryl C-7 multiplet at 7.3–8.0 p.p.m.

This compound was originally assigned[2] an O-acetyl structure based on the C-7 aldol structure **2**; structures **6** and **7** can be considered on the basis of the aldol **3**. The n.m.r. spectrum is not decisive in this case since so few protons are visualized; the shift upfield of the C-5 methyl peak from the position at 1.92 p.p.m. in **1a**, **1b**, and **3** indicates an appreciable change in magnetic shielding. Although the 1760-cm.$^{-1}$ carbonyl band is suggestive of an enolic acetate, structure **6** contains no carbonyl group which could give rise to the strong 1680-cm.$^{-1}$ band, and the infrared data clearly establish the N-acetyl structure **7**. The usual carbonyl frequency for an N,N-disubstituted amide is in the vicinity of 1660 cm.$^{-1}$, and the position is 1690 cm.$^{-1}$ for the acetyl group in the N-acetyl derivative of **1a**.[4] Much higher frequencies are observed, however, in acetyl derivatives of electronegative heterocyclic systems. Staab[7] has observed the parallel increase in rate of hydrolysis and carbonyl stretching frequency of the acetyl derivatives of pyrrole (1732 cm.$^{-1}$), imidazole (1747), 1,2,4-triazole (1750), and tetrazole (1779) which is due to the increased double bond character and force constant. The 1750-cm.$^{-1}$ band in the solid state spectrum of **7** may also be compared with the value (KBr spectrum) of 1740 cm.$^{-1}$ for 1-acetyl-3(5)-methyl-4-phenylpyrazole.[8]



6



7

The benzylidene ketone **7** was a stable solid, unaffected by heat or air; no reaction was observed with semicarbazide nor with maleic anhydride in refluxing benzene. In keeping with the "active acetyl" character indicated by the infrared data, however, hydrolysis occured very readily with a trace of base or, more cleanly, on brief warming with methanolic hydrochloric acid.

The hydrolysis product, obtained in 60% yield, was a colorless neutral substance, $C_{19}H_{16}ON_2$, corresponding to loss of the acetyl group (or loss of water from **3**). The infrared spectrum of this compound contained a single carbonyl band at 1700 cm.$^{-1}$; the ultraviolet spectrum had $\lambda_{max}$ 250 m$\mu$ ($\epsilon$ 9000), with marked change on addition of alkali. It was obvious from the change in color that a rearrangement, presumably ring contraction to a heteroaromatic system, had accompanied the hydrolysis. The compound formed a 2,4-dinitrophenylhydrazone and was reduced by sodium borohydride to a carbinol which was distinctly basic. It was slowly oxidized by silver oxide, but the fuschin test was negative and the general behavior suggested a readily enolized ketone rather than an aldehyde. This premise was confirmed by oxidation, with either permanganate or alkaline hydrogen peroxide, to a mixture of benzoic acid and an acid $C_{12}H_{10}O_2N_2$, both in yields greater than 50%. This demonstrated that a C-11 heterocyclic unit and the phenyl group originating from benzaldehyde were attached through a $-CH_2CO-$ bridge. Direct evidence on this point was obtained by oxidation with selenium dioxide to an $\alpha$-diketone, characterized by conversion to a quinoxaline with *o*-phenylenediamine.

Decarboxylation of the heterocyclic acid occurred very readily to give a basic oil which was identified as 4-methyl-5-phenylpyridazine (**13**) by comparison of the crystalline picrate with an authentic sample prepared from methylphenylmaleic anhydride *via* the 3,6-dichloro derivative and hydrogenolysis, thus defining the structure of the acid as **12** or the 6-isomer. (See Chart I.)

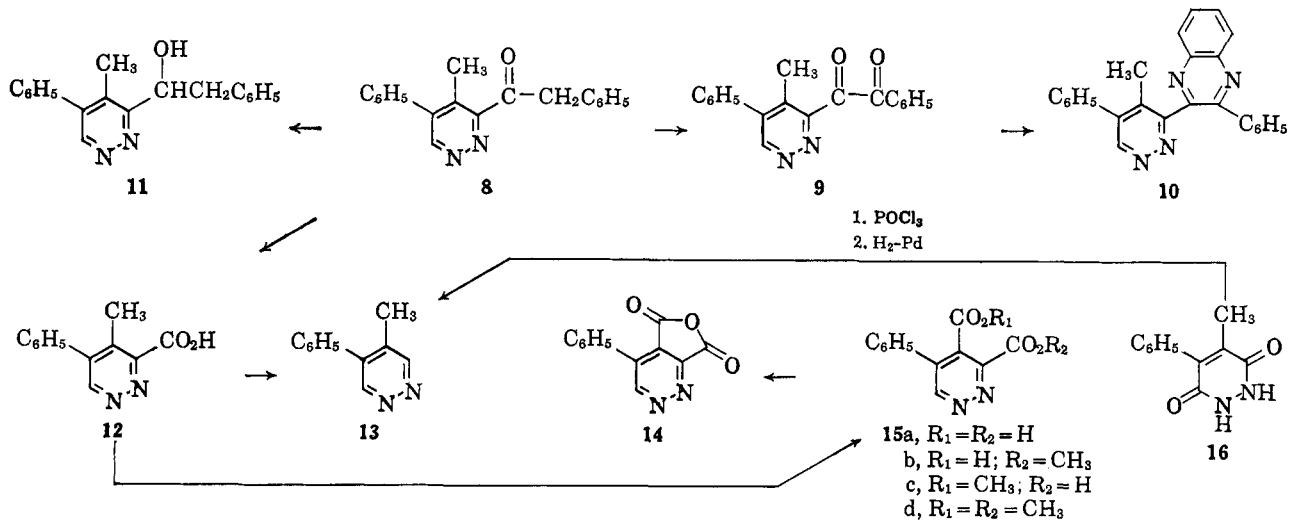
The two structural questions remaining were the placement of the C-8 side chain in **13** and the location of the carbonyl group in the two-carbon bridge. The point of attachment of the C-8 chain was approached by

(6) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, pp. 210, 211.

(7) H. A. Staab, *Chem. Ber.*, **89**, 1927 (1956); W. Otting, *ibid.*, **89**, 1940 (1956).

(8) C. L. Habraken and J. A. Moore, *J. Org. Chem.*, in press.

CHART I




further oxidation of the pyridazine acid with hot permanganate to a diacid which was obtained as a hydrate and characterized as the dimethyl ester. One of the two possible diacids, 5-pyridazine-3,4-dicarboxylic acid (**15**), had been previously reported as a hydrate[9]; several salts were also described, but not the ester. The melting point of our hydrated diacid was unsharp and was accompanied by decomposition, but the literature values was duplicated by using a preheated block. Proof for structure **15a** was obtained by conversion of the diacid to a cyclic anhydride. On heating with thionyl chloride or acetic anhydride, a substance was obtained which was isolated by sublimation, pointing to a monomeric composition. The infrared spectrum had bands at 5.34 and 5.60 $\mu$, consistent with structure **14**, but brief exposure to air generated the diacid, and analytical evidence was not obtained. The very rapid hydrolysis of anhydrides derived from azine-*o*-dicarboxylic acids has been observed on several occasions.[10] To further characterize the substance as an anhydride, a freshly prepared sample was treated with methanol and two products, evidently the isomeric monomethyl esters, were obtained. By fractional crytallization one of these products was obtained in pure form; a negative color test with ferrous sulfate[11] indicated that this was the 3-carbomethoxy-4-carboxylic acid **15b**, which would be expected to predominate in the ring opening of **14**. The other isomer gave a pink color with ferrous sulfate, expected for **15c**, with a carboxyl group adjacent to the hetero atom. Both monomethyl esters on treatment with diazomethane gave the diester **15d**, also obtained from **15a**.

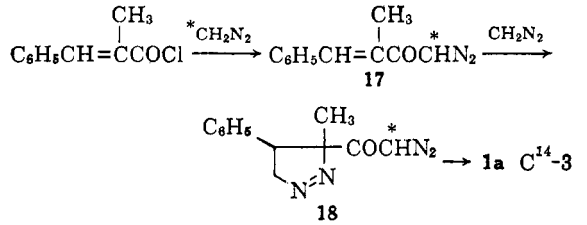
With the establishment of structure **12**, it remained to decide between the benzyl pyridazinyl ketone and phenyl pyridazinemethyl ketone structures. Since a crystalline oxime could not be obtained for Beckmann rearrangement, the Baeyer–Villiger oxidation was employed. Treatment of the ketone with perbenzoic acid gave a product containing an additional oxygen atom, but the infrared carbonyl stretching frequency was unchanged and the compound could not be saponified, indicating that N-oxide formation had occurred rather than the desired ketone cleavage. Oxidation was then carried out with persulfuric acid in benzene solution. The concentrated sulfuric acid layer contained the pyridazine acid **12**, and no benzoic acid. After concentration of the benzene layer, the sweet smelling oily residue was distilled to give a clear oil with an infrared spectrum identical with that of authentic diphenylmethane. The findings are consistent with the conversion of **8** to the benzyl ester of **12**, followed by alkylation of solvent benzene in the presence of concentrated sulfuric acid.[12]

These experiments unequivocally established structure **8** for the rearrangement product, as well as structure **11** for the derived carbinol. Several attempts to characterize the $-CHOHCH_2-$ system of **11** by dehydration produced no trace of the disubstituted ethylene. The carbinol was recovered unchanged after prolonged refluxing with concentrated hydrochloric acid; refluxing acetic anhydride gave the acetate. Similar difficulty in the dehydration of 1-(2- or 4-pyridyl)-1-ethanol has been reported[13–15] and variously attributed to inductive[13,14] and resonance[15] effects imparted by the hetero atom. The same influences apparently operate to prevent dehydration in **11** and also account for the marked depression of the basicity of the ketone **8**.

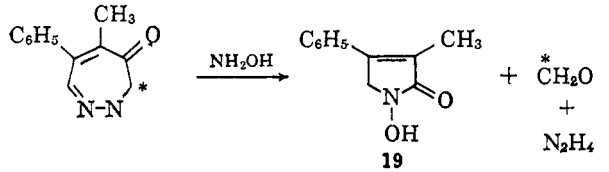
The ketone structure **8** provided strong support for the C-3 attachment of the benzyl group in the diazepine precursors, but, to rule out the possibility of rearrangement of the C-5–N-2 chain during the ring contraction, the reaction sequence was carried out with **1a** labeled at C-3 with $C^{14}$. Some modification in the standard preparative procedure for **1a** was required to introduce $C^{14}$ selectively at C-3. Both C-3 and C-7 are derived from diazomethane,[16] and, although the diazo ketone **17** has been isolated,[17] much better over-all yields of **1a** are obtained by use of large excess of diazomethane to convert $\alpha$-methylcinnamoyl chloride to a mixture of **17**

(9) R. Stoermer and H. Fincke, *Ber.*, **42**, 3128 (1909).
(10) *Inter alia*, E. Täuber, *ibid.*, **28**, 451 (1895); O. Mumm and H. Hüneke, *ibid.*, **50**, 1577 (1917).
(11) F. Feigl, "Spot Test in Organic Analysis," Elsevier, New York, N. Y., 1956, p. 287.
(12) O. Meister, *Ber.*, **6**, 963 (1873).
(13) G. B. Bachmann and D. Micucci, *J. Am. Chem. Soc.*, **70**, 2381 (1948).
(14) C. S. Marvel, E. L. Coleman, and G. P. Scott, *J. Org. Chem.*, **20**, 1785 (1955).
(15) W. R. Boehme and J. Koo, *ibid.*, **26**, 3589 (1961).
(16) J. A. Moore and R. W. Medeiros, *J. Am. Chem. Soc.*, **81**, 6026 (1959).
(17) J. A. Moore, *J. Org. Chem.*, **20**, 1607 (1955).

and **18**. For the present purposes it was necessary to work out optimum conditions for the preparation of **17** using the minimum amount of diazomethane, both to conserve labeled material and minimize contamination of **17** with the pyrazoline **18** which would be labeled at the diazepine position. An attempt was made to eliminate the wasteful use of one-half of the diazomethane as a base in the initial reaction with acid chloride by adding pyridine or triethylamine,[18] but the only product obtained was the hitherto unknown $\alpha$-methylcinnamic anhydride. In the conditions finally selected, the diazomethane-$C^{14}$, obtained in 71% yield from N-methyl-$C^{14}$-N-nitroso-*p*-toluenesulfonamide, was used in 2.15:1 molar ratio to give **17** in 60% total yield. Subsequent operations followed the usual procedures,[16] and the diazepinone-C-3[14] was diluted to a specific activity of $1.27 \times 10^3$ d.p.s./mmole for subsequent reactions. In order to determine the extent of labeling at C-7, **1a** $C^{14}$ was subjected to a degradation which selectively removes C-3; namely, cleavage with hydroxylamine to **19**, formaldehyde, and hydrazine.[7] The formaldehyde, isolated as the dimedon derivative, contained 94.5% of the $C^{14}$ activity, and the hydroxamic acid **19**, 6.4%.



The sequence **1a** → **3** → **7** → **8** → **12** → **13** was then carried out with labeled material after optimizing the reaction conditions for each step.

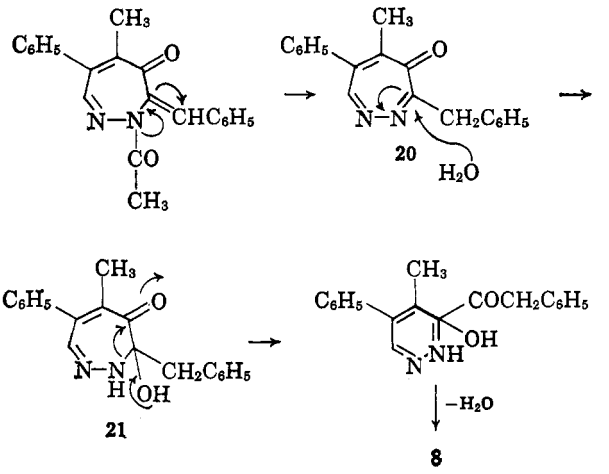


Final decarboxylation gave carbon dioxide containing 95.4% of the $C^{14}$ with 6.7% found in the picrate of the pyridazine **13**. These results agree well with those of the hydroxylamine cleavage, and provide a firm link between the diazepine and pyridazine structures.

The details of the ring contraction whereby C-3 is extruded can be represented by a very simple sequence (Chart II). Hydrolysis of **7** with concomitant tautomerization leads to the intermediate diazatropone **20** which undergoes addition of water. The resulting carbinolamine **21** could then revert to an acyclic aminodiketone followed by recyclization, or, more simply, the ring contraction may be viewed as an example of the general $\alpha$-oxo alcohol rearrangement[19] as illustrated in **21**. The stage is apparently set for the rearrangement when C-3 becomes trigonal, and it may be predicted that, if the direct dehydration of the aldol **3** could be effected, ring contraction to **8** would follow spontaneously, although this has not been observed.

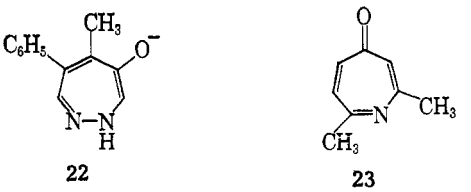
The rearrangement of **7** to **8** represents an additional example of a general type of heterocyclic rearrangement

CHART II



involving the disruption of the ring by solvolytic attack at a hetero atom and re-establishment of a new heterocyclic or carbocyclic system by participation of a neighboring reactive center. These may occur with ring contraction as in the present case, ring expansion as in the formation of pyridines from $\alpha$-aminomethyldimethoxydihydrofurans,[20] or without change in ring size as in the conversion of acyl-1,3,5-triazines to aminopyrimidines[21] or pyrylium salts to benzenes,[22] to cite a few typical examples. Ring contractions occurring by this process are particularly common among unsaturated seven-membered heterocycles,[7,23-25] since there is usually a strong driving force in the formation of an aromatic system.

It is noteworthy that the rearrangement of **7** must involve at some stage, such as **20**, a heterocyclic counterpart of the aromatic tropone system.[26] Very few examples of azepines or diazepines at this oxidation level are known. There has been considerable speculation about the degree of aromatic character that may be present, although there is very little evidence of stabilization in these systems, from either experimental or theoretical standpoints.[25,27] A remarkable exception to this generalization appears to be the azatropone **23** recently reported, without experimental details, by Johnson and co-workers.[28] The facile ring cleavage of



(18) M. S. Newman and P. Beal, *J. Am. Chem. Soc.*, **71**, 1506 (1949).
(19) S. Selman and J. F. Eastham, *Quart. Rev.* (London), **14**, 221 (1960).
(20) N. Clauson-Kaas, N. Elming, and Z. Tyle, *Acta Chem. Scand.*, **9**, 1 (1955).
(21) D. R. Osborne and R. Levine, *J. Org. Chem.*, **27**, 2933 (1963).
(22) K. Dimroth in "Neuere Methoden der Praparativen Organischen Chemie," W. Foerst, Ed., Verlag Chemie, Weinheim/Bergstr., 1961, p. 239.
(23) R. Huisgen, D. Vossius, and M. Appl, *Chem. Ber.*, **91**, 1 (1958).
(24) E. Schmitz and R. Ohme, *ibid.*, **95**, 2012 (1962).
(25) (a) J. A. Barltrop, C. G. Richards, D. M. Russel, and G. Ryback, *J. Chem. Soc.*, 1132 (1959); (b) L. N. Sternbach, E. Reeder, A. Stempel, and A. I. Rachlin, *J. Org. Chem.*, **29**, 332 (1964).
(26) T. Nozoe in "Non-Benzenoid Aromatic Compounds," D. Ginsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1959, p. 399.
(27) R. W. Schmid, *Helv. Chim. Acta*, **45**, 1992 (1962).
(28) (a) E. Bullock, B. Gregory, and A. W. Johnson, *J. Am. Chem. Soc.*, **84**, 2260 (1962). (b) NOTE ADDED IN PROOF.—A revision of the azatropone structure **23** to a furopyridine has now been made: E. Bullock, B. Gregory, and A. W. Johnson, *J. Chem. Soc.*, 1632 (1964).

the enolic diazatropilidene structure, **22**,[5] and the rearrangement of the diazatroponoid structure **20** provide additional indications of the lack of aromatic stability in these aza analogs.

## Experimental[29]

**2,3-Dihydro-3-(α-hydroxybenzyl)-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one (3).**—A solution of 7.0 g. of diazepine **1a** and 13 ml. of freshly distilled benzaldehyde in 150 ml. of 0.2 *N* sodium ethoxide in ethanol was allowed to stand at room temperature for 4 days. About half of the ethanol was removed at reduced pressure; the solution was then acidified with 1 *N* hydrochloric acid and the remaining alcohol was removed. More water was then added and the suspension was extracted with ether; the ether solution was dried and concentrated and the benzaldehyde was then removed at 1.0 mm. The dark red sirup crystallized on addition of ether to give 4.8 g. (45%) of yellow solid, m.p. 134–137°. Recrystallization from ether and then methanol–water gave a mass of pale lemon-yellow filaments, m.p. 145–146°; $\lambda_{max}^{EtOH}$ 245 (infl.), 309 (ε 5200), 395 mμ (2700); $\lambda_{max}^{0.1\ N\ NaOH}$ 243 (ε 26,000), 344 (2700), 412 mμ (5400); $\lambda^{KBr}$ 3.09, 6.10 μ.

*Anal.* Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.59, 74.39; H, 6.06, 5.94; N, 9.33.

The compound was freely soluble in 10% aqueous alkali, and separated unchanged on prompt acidification. On standing overnight the solution developed a strong benzaldehyde odor. For preparative reversal of the condensation, 100 mg. of **3** in 0.2 *N* sodium ethoxide solution was stored for 5 days, acidified with dilute hydrochloric acid, and extracted with ether. After evaporation, the orange residue crystallized on addition of a drop of methanol. A total of 30 mg. of orange prisms of **1a**, m.p. 130–145°, was obtained in three crops. Recrystallization gave dark yellow prisms, m.p. and m.m.p. (with authentic **1a**) 145–148°.

After treatment of 306 mg. of **3** with methanolic semicarbazide acetate for 3 days, a total of 302 mg. of unreacted starting material, m.p. 143–145°, was recovered. Under the same conditions, **1a** gave a crystalline semicarbazone after 1 hr.

**Sodium Borohydride Reduction of 3.**—A solution of 40 mg. of sodium borohydride in 2 ml. of 50% ethanol was added during 15 min. to a suspension of 616 mg. (2 mmoles) of the aldol **3** in 10 ml. of ethanol. The resulting pale yellow solution was kept at room temperature for an additional 15 min. The excess hydride was decomposed with a few drops of acetic acid and the solvent evaporated under reduced pressure. The residue was washed with water and a small amount of ethanol, and then dissolved in ethanol, filtered, and slowly precipitated with ether in several crops. The over-all yield of crystalline product was 437 mg. (71%), m.p. 160–165°. Recrystallization from ethanol–ether raised the melting point to 174–175°.

*Anal.* Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 73.93; H, 6.75; N, 8,96,

**2,3-Dihydro-3-(α-hydroxy-*p*-chlorobenzyl)-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one.**—A solution of 350 mg. of **1a** and 910 mg. of recrystallized *p*-chlorobenzaldehyde in 7 ml. of 0.2 *N* sodium ethoxide was stored for 2 days at room temperature. The solution was then concentrated, diluted with water, acidified, and extracted with ether. Evaporation of the dried ether solution gave 227 mg. (39%) of bright yellow crystals. Recrystallization from methylene chloride–ether and then ethanol–water gave yellow blades, m.p. 148–150°.

*Anal.* Calcd. for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.08. Found: C 66.84; H, 4.96.

**Reaction of 2-Methyldiazepinone Ib with Benzaldehyde and Sodium Ethoxide.**—A solution of 1.0 g. of **1b** and 1.80 ml. of benzaldehyde in 50 ml. of 0.1 *N* ethanolic sodium ethoxide was stored at room temperature for 4 days. After dilution with 30 ml. of water and chilling, the solution was just neutralized with hydrochloric acid and extracted with five 20-ml. portions of methylene chloride. After drying and evaporation, the crystalline residue was collected and recrystallized from a mixture of ethyl acetate and ether to give 775 mg. (78%) of nearly colorless crystals, m.p. 197–200° dec. The compound darkened rapidly on attempted recrystallization from methanol or ethanol. Recrystallization from ether–benzene gave white needles, m.p. 202–204° dec.; $\lambda_{max}^{EtOH}$ 275, 310 mμ (ε 12,400); $\lambda_{max}^{EtOH\ +\ HCl}$ 259, 313 mμ (ε 13,500); $\lambda_{max}^{EtOH\ +\ NaOH}$ 319 mμ (ε 15,500); $pK_A$ (50% MeOH) 6.0 and 9.8; estimated mol. wt., 261.

*Anal.* Calcd. for $C_{16}H_{18}N_2O$ ($C_{13}H_{11}N_2O_2 \cdot C_3H_4O$) (mol. wt., 270.2): C, 71.09; H, 6.71; N, 10.36. Found (Bly): C, 71.34; H, 6.38; N, 10.31. Found (Zoll): C, 70.89; H, 6.54; N, 10,32; (N)-$CH_3$, 5.71 (calcd. for one (N)-$CH_3$: 5.65).

These analyses were obtained on different samples—one recrystallized from ethyl acetate and one from benzene–ether, both dried at 100°, one sample prepared a year after the other. The same product, with essentially the same infrared spectrum (not well resolved—few sharp bands), was obtained when the reaction was carried out in methanolic solution with benzaldehyde, in ethanolic solution with *p*-chlorobenzaldehyde, and *no* aldehyde in a nitrogen atmosphere (without nitrogen or aldehyde, which apparently served as an antioxidant, the yield was very low). The n.m.r. spectrum in $D_2O$ plus a trace of NaOD contained small impurity peaks, a triplet and quartet upfield and downfield, respectively, from two methyl singlets.

This substance was eventually shown to be a solvated form of 2-methyl amino-2-hydroxy-4-methyl-5-phenylpyridine by conversion to an acetylation product identical with the diacetate described in the preceding paper.[5] The nature of the persistent $C_3O_4$ fragment is completely unknown. Material with correct analytical values for the pyridine was eventually obtained[3] by avoiding all contact with any organic compounds or solvents except methanol, from which it was recovered with substantial losses.

**2-Acetyl-2,3-dihydro-3-benzylidene-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one (7).**—A solution of 2.40 g. of **3** in 4 ml. of pyridine and 7 ml. of acetic anhydride was allowed to stand at room temperature overnight and was then concentrated at reduced pressure (70°). The residue was treated with water and the resulting orange gum crystallized on addition of a little methanol. The solid was collected and washed with cold methanol to give 1.7 g. (66%) of orange prisms, m.p. 166–169°. These were recrystallized from methanol–ether and ethanol–hexane mixtures, m.p. 169–170°; $\lambda_{max}^{EtOH}$ 227 (ε 18,300), 304 (23,600), 335 mμ (infl.), strong end absorption; infrared, see discussion.

*Anal.* Calcd. for $C_{21}H_{18}N_2O_2$: C 76.34; H, 5.49; N 8.48. Found: C 76.55; H, 5.40; N, 8.42.

The compound was recovered unchanged from treatment with semicarbazide acetate under the conditions described for **3**.

**2-Acetyl-2,3-dihydro-3-*p*-chlorobenzylidene-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one.**—A solution of 120 mg. of the 3-(α-hydroxy-*p*-chlorobenzyl)diazepinone described above and 0.9 ml. of acetic anhydride in 1 ml. of pyridine was stored at room temperature for 24 hr. After addition of water the product was extracted with methylene chloride and the extract was washed, dried, and evaporated to give an orange oil which crystallized on addition of methanol and water. A total of 83 mg. of crystals was obtained; after recrystallization from methanol and then ether–pentane, the melting point was 163–164°; $\lambda^{KBr}$ 5.70, 6.10, 6.20 μ.

*Anal.* Calcd. for $C_{21}H_{17}O_2N_2Cl$: C, 69.13; H, 4.70. Found: C 69.12; H, 4.73.

**Benzyl 3-(4-Methyl-5-phenylpyridazinyl) Ketone (8).**—To a solution of 3.3 g. of the acetate **7** in 300 ml. of methanol was added 75 ml. of 10% hydrochloric acid and 150 ml. of a 1:4 mixture of concentrated hydrochloric acid and methanol. The solution was heated at 40° for 30 min.; the color gradually changed from orange to pale yellow. The solution was concentrated under reduced pressure to about half of its original volume, and cooled in an ice bath; 120 ml. of 10% potassium hydroxide was added. The pale yellow precipitate was collected and washed with a small amount of chilled ether, giving 1.60 g. of white plates, m.p. 123–125°. The aqueous filtrate was extracted with ether and the extract was combined with the ether washings of the first crop. The combined ether extract was washed with water, 1 *N* sodium bicarbonate, and again with water. The ether was dried and evaporated under reduced pressure. The oily residue was seeded with some of the previously obtained crystalline product and a small amount of ether was added. The crystals were filtered and washed with ether as before to give an additional 0.27 g. of product. The combined yield was 1.87 g. (65%). Recrystallization from chloroform–hexane gave 1.63 g. of colorless material, m.p. 125–126°; $\lambda_{max}^{EtOH}$ 250 (ε 9000), 310 mμ (about 900); $\lambda_{max}^{0.2\ N\ NaOH}$ 291 (ε 14,600), 345 mμ (6100); $\lambda^{KBr}$ 5.89 μ.

(29) Melting points were taken on a Fisher-Johns block with a calibrated thermometer. Infrared spectra were obtained in KBr pellets except where otherwise noted. Ether and methylene chloride solutions were dried with anhydrous sodium sulfate.

*Anal.* Calcd. for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.15; H, 5.80; N, 9.78.

The product was insoluble in aqueous 1 *N* hydrochloric acid or 1 *N* sodium hydroxide. However, addition of sodium hydroxide to 2 *N* ethanol solution gave a bright yellow color and enhanced the solubility in this solvent.

The **2,4-dinitrophenylhydrazone of 8** was prepared in the usual way from 30 mg. of **8**. An amorphous solid separated which was redissolved in ethanol and precipitated as an oil by addition of water. This oil was then triturated with water to give crystals, m.p. 97–100°. After crystals were obtained, repeated crystallization from methanol and ethanol gave yellow prisms, m.p. 160–161°. On repeating the preparation, oily material and then solid, m.p. 97–100°, were always obtained initially even when high melting seed was available.

*Anal.* Calcd. for $C_{25}H_{20}N_6O_4$: C, 64.09; H, 4.30; N, 17.94. Found: C, 64.06; H, 4.43; N, 18.03.

**2-Phenyl-1-[3-(4-methyl-5-phenylpyridazyl)]-1-ethanol (11).**—To a suspension of 145 mg. (0.5 mmole) of **8** in 5 ml. of ethanol was added dropwise a solution of 20 mg. of sodium borohydride 2 ml. of 50% ethanol. Gradually the starting material dissolved and the initial bright yellow color disappeared. The solution was allowed to stand at room temperature for 20 min.; the excess hydride was then decomposed with a few drops of acetic acid and the solution was concentrated to a 2-ml. volume. Water (10 ml.) was added and the resulting suspension was extracted with ether. Evaporation of the ether under reduced pressure gave 143 mg. (98%) of pale yellow crystals, m.p. 106–109°. Recrystallization from methanol–water and treatment with charcoal gave white plates, m.p. 111–112°; $\lambda_{max}^{EtOH}$ 251 mμ (ε 8100); $\lambda_{max.}^{0.1\ N\ HCl}$ (infl.) 251 (ε 6400), 301 mμ (5000).

*Anal.* Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.67; H, 6.46; N, 9.37.

The alcohol was insoluble in aqueous 1 *N* sodium hydroxide but dissolved readily in 1 *N* hydrochloric acid. Addition of sodium hydroxide to an ethanolic solution failed to give the bright yellow color observed with the ketone.

**Acetate of 11.**—A solution of 100 mg. of the alcohol in 1 ml of pyridine and 4 ml. of acetic anhydride was heated at 70° for 10 min. The solution was cooled in an ice bath and treated with water to decompose the excess acetic anhydride. The aqueous solution was decanted and the gummy residue was dissolved in ether and dried with anhydrous sodium sulfate. Evaporation of the ether gave 105 mg. of a pale yellow oil which crystallized slowly when a small amount of methanol was added. One recrystallization from methanol–water followed by two recrystallizations from ether gave white needles, m.p. 93°.

*Anal.* Calcd. for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.07. Found: C, 76.04; H, 6.38.

**4-Methyl-5-phenylpyridazine-3-carboxylic Acid (12). A. Permanganate Oxidation.**—To a stirred solution of 500 mg. (1.72 mmoles) of the ketone **8** in 2 ml. of acetone was added in small portions during 2 hr. 515 mg. (3.26 mmoles) of potassium permanganate. The mixture was stirred at room temperature for an additional 30 min. A few drops of ethanol were added to decompose any unchanged permanganate and the precipitated manganese dioxide was filtered and washed with 0.5 *N* sodium hydroxide and with acetone. The washings were combined with the filtrate and most of the acetone evaporated under reduced pressure. The remaining alkaline solution was diluted with water to about 30 ml., saturated with salt, and washed with ether to remove a trace of nonacidic products. The solution was then acidified with hydrochloric acid and extracted first with two 15- and 20-ml. portions of ether and then with three 15- to 20-ml. portions of chloroform. The ether and the chloroform extracts were dried separately and evaporated under reduced pressure. The chloroform extract gave 120 mg. of crystalline material, m.p. 130–134°. The ether extract gave 400 mg. of a semioily residue which upon recrystallization from benzene gave 90 mg. of a crystalline product, m.p. 132–135°. This was combined with the material obtained from the chloroform extract to give a total of 210 mg. (61%) of the pyridazine carboxylic acid **12**. The benzene mother liquor was evaporated under reduced pressure and the residue sublimed to give 163 mg. (79%) of benzoic acid, m.p. and m.m.p. 120–122°.

The acid **12** was recrystallized from chloroform, giving colorless prisms, m.p. 135–136° dec.; $\lambda_{max}^{EtOH}$ 255 mμ (ε 7100); $\lambda_{max}^{0.2\ N\ KOH}$ 246 mμ (ε 7400); $\lambda^{KBr}$ 3.05, 4.17, 4.45, 5.15, 5.90 μ.

*Anal.* Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.38; H, 4.64; N, 13.15. Found: C, 67.28; H, 4.71; N, 13.08.

Occasionally this acid precipitated in a different crystalline form which melted at about 80°; when the melt was seeded with the higher melting crystals, it solidified and then melted at 135°.

The acid reacted with diazomethane to give a **methyl ester**, m.p. 104, $\lambda^{KBr}$ 5.81 μ.

**B Hydrogen Peroxide Oxidation.**—To a solution of 73 mg. (0.25 mmole) of the ketone **8** in 2 ml. of methanol and 0.25 ml. of 1 *N* sodium hydroxide was added dropwise at 10-min. intervals 30% hydrogen peroxide. The solution changed from dark yellow to a pale straw color. About 5 ml. of water was added and the alkaline solution was extracted with ether. Evaporation of the ether extract gave 20 mg. of a light brown oil which was not identified. The aqueous solution was acidified and extracted with two 3-ml. portions of ether and three 5-ml. portions of chloroform. Both extracts were dried and evaporated under reduced pressure. The residue from the ether extract was a mixture of benzoic acid and the pyridazine carboxylic acid **12**, which were separated by washing with a small amount of ether to give 18 mg. (65%) of benzoic acid. The acid **12** from the two extracts was combined to give 33 mg. (61%).

**4-Methyl-5-phenylpyridazine (13). A. From 12.**—Fifty milligrams of the acid **12** was placed in a sublimator and heated under vacuum to 140°. The acid melted with rapid gas evolution and a colorless liquid collected on the cold finger. The distillate was dissolved in 2 ml. of ethanol and an equal volume of a saturated solution of picric acid in ethanol was added. The precipitate which formed after a few minutes was filtered and washed with methanol to give 63 mg. (59%) of yellow needles of the **picrate**, m.p. 133–135°. Recrystallization from methanol gave raised m.p. 136–137°, m.m.p. (with authentic picrate from B) 136–137°. The infrared spectra of the two samples were identical.

*Anal.* Calcd. for $C_{17}H_{13}N_5O_7$: C, 51.13; H, 3.28; N, 17.54. Found: C, 51.20; H, 3.41; N, 17.33.

**B. From 16. 4-Methyl-5-phenylpyridazine-3,6-dione (16).**—**16** was prepared by refluxing a solution of 2.4 g. of 3-methyl-4-phenylmaleic anhydride,[30] m.p. 94–95°, and 1.7 g. of hydrazine sulfate in 15 ml. of water and 25 ml. of acetic acid for about 3 hr. The solution was then evaporated to small volume and diluted with water. The resulting gelatinous precipitate was collected and refluxed in acetone to remove unchanged anhydride. A total of 740 mg. of white powder was obtained, m.p. 322–326° (sealed capillary); $\lambda_{max}^{EtOH}$ 257 (ε 4700), 313 mμ (3400); $\lambda_{max}^{EtOH\ +\ NaOH}$ 339 mμ (ε 2800).

**3,6-Dichloro-4-methyl-5-phenylpyridazine.**—A solution of 300 mg. of the above dione in 3.5 ml. of phosphorus oxychloride was refluxed for 30 min. The amber solution was then concentrated at reduced pressure and the dark brown residue was treated with water, then made slightly alkaline, and extracted with ether. The dried ether solution was evaporated to give a semicrystalline residue which was recrystallized from methanol–water to give 116 mg. of cream-colored prisms, m.p. 112–116°. Further recrystallization from methanol–water gave shiny colorless cubes, m.p. 120–122°; $\lambda_{max}^{EtOH}$ 260 mμ (ε 4000) (no change with acid or base).

*Anal.* Calcd. for $C_{11}H_8Cl_2N_2$: C, 55.25; H, 3.37; N, 11.72. Found: C, 55.35; H, 3.44; N, 12.14, 12.01.

**4-Methyl-5-phenylpyridazine.**—A solution of 112 mg. of the above dichloropyridazine in 8 ml. of ethanol was stirred in a hydrogen atmosphere with 200 mg. of 10% palladium–charcoal for 20 hr. The solution was then filtered and evaporated, and the residue was taken up in 10 ml. of water. A small amount of oily material was extracted with ether, the clear aqueous solution was made basic with potassium hydroxide, and the oil was extracted with ether. Evaporation of the ether solution gave 47 mg. of pale yellow oil which was distilled at 50° in a short-path still to give 36 mg. of colorless mobile oil, $pK_A$ 3.3, $\lambda_{max}^{EtOH}$ 245 mμ, $\lambda_{max}^{0.1\ N\ HCl}$ 297 mμ (ε 2000).

*Anal.* Calcd. for $C_{11}H_{10}N_2$: N, 16.46. Found: N, 16.45.

Solutions of 16 mg. of the above base in ether and 22 mg. of picric acid in ether containing a few drops of ethanol were combined and an oil separated. The supernatant solution was decanted, and the oil was crystallized from 0.2 ml. of ethanol at 0°. A total of 6.0 mg. of yellow prisms of the picrate was obtained, m.p. 137–138° after drying at 0.1 mm.

(30) J. A. Moore and F. J. Marascia, *J. Am. Chem. Soc.*, **81**, 6049 (1959); the material used in the present work was from the same sample described in this reference, obtained by bromination and dehydrobromination of 3-methyl-4-phenylsuccinic acid.

**1-Phenyl-2-[3-(4-Methyl-5-phenylpyridazinyl]ethanedione (9).**—One hundred milligrams (0.35 mmole) of the ketone **8** was added to a solution of 38 mg. (0.35 mmole) of selenium dioxide in 2 ml. of dioxane and 0.01 ml. of water and heated at 80–85° for 3.5 hr. The precipitated selenium was filtered and the dioxane was evaporated under reduced pressure. Addition of a small amount of methanol to the oily residue gave 51 mg. (47%) of pale yellow crystals, m.p. 128–132°. The product was treated with charcoal and recrystallized from ether. Several recrystallizations and filtrations through a fine filter were required to remove finely dispersed selenium. The recrystallized product melted at 134–135°; $\lambda_{max}^{EtOH}$ 250 mμ (ε 16,800), inflection at about 390 mμ (ε 103); $\lambda^{KBr}$ 5.88, 6.00 μ. An analytically pure sample could not be obtained because of the difficulties in removing the last traces of selenium and the instability of the product in solution.

The **quinoxaline 10** was prepared by treatment of 20 mg. (0.065 mmole) of crude diketone with 7.6 mg. (0.070 mmole) of *o*-phenylenediamine in acetic acid for 40 min. at 80°. The acetic acid was evaporated under reduced pressure and the residue was recrystallized several times from ethanol to give 4 mg. of pale yellow crystals, double m.p. 178° and 187–190°. The infrared spectrum of this derivative no longer showed the two peaks in the carbonyl region (5.88 and 6.00 μ) which occurred in the spectrum of the starting diketone.

*Anal.* Calcd. for $C_{25}H_{18}N_4$: C, 80.19; H, 4.85; N, 14.96. Found: C, 79.75; H, 5.03; N, 15.06.

**Hydrogen Peroxide Cleavage of 1-Phenyl-2-[3-(4-methyl-5-phenylpyridazinyl)]ethanedione.**—A solution of 30 mg. (0.098 mmole) of the diketone **9** in 1.5 ml. of 30% hydrogen peroxide was allowed to stand at 5° overnight. The solution was diluted with 5 ml. of water, made alkaline, washed with three 5-ml. portions of ether, acidified, and then extracted with one 8-ml. portion of ether and three 5-ml. portions of chloroform. Both the ether and the chloroform extract were dried and evaporated under reduced pressure. The residue from the ether extract was heated with 5 ml. of hexane and filtered. The hexane was evaporated and the residue sublimed to give 11 mg. (92%) of benzoic acid, m.p. and m.m.p. 120–122°. Evaporation of the chloroform extract gave 14 mg. of crystalline residue. This was combined with the hexane-insoluble material obtained from the ether extract to give a total of 17 mg. (81%) of the pyridazine carboxylic acid **12**, m.p. 129–133°. After recrystallization from chloroform, the acid melted at 135–137° and gave no mixture melting point depression with a sample of the acid **12** obtained previously from compound **8**.

**5-Phenylpyridazine-3,4-dicarboxylic Acid (15a).**—A solution of 100 mg. (0.46 mmole) of the acid **12** in 5 ml. of 1 *N* sodium hydroxide was heated to 70°, and 150 mg. (0.95 mmole) of potassium permanganate was added in small portions during 40 min. The reaction mixture was heated at reflux for an additional 30 min., cooled to room temperature, and filtered. Acidification of the filtrate with 6 *N* hydrochloric acid gave 109 mg. (96%) of white needles. The product began to decompose above 160° and melted with decomposition at about 214–227°; when placed on the block at 200°, it melted at 225–227°. The melting point remained unchanged after recrystallization from ethanol–water; $\lambda^{KBr}$ 2.84, 2.95, 3.63, 4.25, 4.39, 5.20, 5.82–5.95 μ.

*Anal.* Calcd. for $C_{12}H_8N_2O_4 \cdot H_2O$: C, 54.96; H, 3.84; N, 10.68. Found: C, 55.55; H, 3.98; N, 10.79.

The **dimethyl ester 15d** was prepared by treatment of the diacid with excess diazomethane in ether. Recrystallization from ether and sublimation gave white crystals, m.p. 131–132°; $\lambda^{KBr}$ 5.75, 5.80 μ.

*Anal.* Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.91; H, 4.59; N, 10.46.

**5-Phenylpyridazine-3,4-dicarboxylic Acid Anhydride (14).**—A suspension of 100 mg. of the dicarboxylic acid in 2 ml. of acetic anhydride was heated at 100–110° until all of the acid dissolved. The acetic anhydride was removed *in vacuo*, and the dark residue was washed with a small amount of anhydrous ether. Sublimation gave 62 mg. of a pale yellow crystalline product which began to decompose at about 150° and melted with further decomposition at 177–185°. In contrast to the starting material the product was fairly soluble in chloroform or benzene. Recrystallization from benzene–ether gave colorless crystals, m.p. 182–185° (preheated block); $\lambda^{KBr}$ 5.34, 5.60 μ. After standing, the bands corresponding to the acid began to appear in the infrared spectrum. The analysis indicates complete conversion to the nonhydrated acid **15a**.

*Anal.* Calcd. for $C_{12}H_6O_4$: C, 59.02; H, 3.30. Found: C, 59.17; H, 3.66.

Similar material was obtained when the acid was refluxed with thionyl chloride in benzene solution.

**The Monomethyl Esters of 5-Phenylpyridazine-3,4-dicarboxylic Acid.**—The anhydride (**14**) was prepared from 105 mg. of the dicarboxylic acid as described above and immediately dissolved in 5 ml. of absolute methanol. After standing for a short time at room temperature, the pale yellow solution became colorless and was then evaporated under reduced pressure to give 93 mg. of crystalline residue, m.p. 110–145° dec. The product was boiled with 10 ml. of ether and filtered, and the ether was evaporated. The ether-insoluble fraction was recrystallized from chloroform–hexane, giving 29 mg. of white crystals of the **3-monomethyl ester 15b**, m.p. 158–170°. Further recrystallization of the first crop gave a material which melted at 178–180° and gave a negative ferrous sulfate test; $\lambda^{KBr}$ 2.90, 3.59, 3.81, 4.03, 5.21, 5.70–5.94 μ (broad peak).

*Anal.* Calcd. for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.90. Found: C, 60.78; H, 4.37.

Two additional crops of crystals were obtained from the first chloroform–hexane mother liquor by concentration, until the solution became cloudy, and subsequent cooling in ice. The second crop was combined with the residue obtained from the ether extract to give a total of 35 mg. of material which melted at 105–120°. Several recrystallizations from ether gave a small amount of the **4-monomethyl ester 15c**, m.p. 105–112°, pink color with ferrous sulfate solution; $\lambda^{KBr}$ 2.95, 4.16, 4.50, 5.17, 5.76, 5.89 μ.

Treatment of both the higher and the lower melting material with diazomethane gave the same product, identical in melting point, mixture melting point, and infrared spectrum with the 5-phenylpyridazyl-3,4-dicarboxylic acid dimethyl ester **15d** prepared by treatment of the diacid with diazomethane.

**Perbenzoic Acid Oxidation of Benzyl 3-(4-Methyl-5-phenylpyridazinyl) Ketone.**—A solution of 150 mg. (0.52 mmole) of **8** in a 0.038 *N* solution of perbenzoic acid in chloroform was allowed to stand at 5° for 10 days. The solution was extracted with 1 *N* sodium bicarbonate and with water until it gave a negative potassium iodide test, dried, and evaporated under reduced pressure. The residue was warmed with a 50:50 ether–hexane mixture and filtered to give 115 mg. of crystalline product, m.p. 142–144°. Concentration of the filtrate gave an additional 13 mg. of crystals, m.p. 139–144°. After recrystallization from chloroform–ether the product had m.p. 148–149°, $\lambda^{KBr}$ 5.87 μ.

*Anal.* Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 75.30; H, 5.36; N, 8.98.

**Persulfuric Acid Cleavage of Benzyl 3-(4-Methyl-5-phenylpyridazinyl) Ketone.**—To a cooled slurry of 1.60 g. of potassium persulfate in 4.00 g. of concentrated sulfuric acid and 0.74 ml. of water was added a solution of 200 mg. (0.69 mmole) of **8** in 5 ml. of benzene. The reaction mixture was allowed to warm to room temperature and was then stirred for 20 min. The benzene layer was decanted and the acid layer was washed with two 3-ml. portions of benzene. The combined benzene solution was washed with sodium bicarbonate and water and dried. The solvent was removed through a Vigreux column, and the dark, sweet-smelling residue distilled under vacuum to give 25 mg. (22%) of diphenylmethane, identical in infrared spectrum with an authentic sample. The sulfuric acid layer was cooled in ice, carefully diluted with 20 ml. of water, and extracted with chloroform. The chloroform solution was washed with water and extracted with 1 *N* sodium hydroxide. The alkaline solution was acidified and again extracted with chloroform. The chloroform extract was dried and evaporated to give 58 mg. (39%) of the pyridazine carboxylic acid **12**, m.p. 130–134°. After recrystallization from chloroform the product melted at 135–137° and gave no mixture melting point depression with the acid obtained in previous experiments.

**α-Methylcinnamic Anhydride.**—To a stirred ether solution of 0.07 mole of diazomethane was added 9.7 ml. (0.07 mole) of triethylamine; standing overnight a white solid, presumably triethylamine hydrochloride, separated. This material was redissolved in ether and the solution was washed thoroughly with aqueous sodium bicarbonate. After drying and concentrating, the ether solution deposited long colorless needles, m.p. 82–83°; $\lambda^{KBr}$ 5.70, 5.94 μ.

*Anal.* Calcd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.74; H, 6.23.

**Radioactivity Measurements.**—All $C^{14}$ counting was done with a Packard-Tri-Carb liquid scintillation counter, Model 314X. The scintillation mixture contained 4 g. of 2,5-diphenyloxazole and 0.1 g. of 1,4-bis-2-(phenyloxazolyl)benzene/l. of toluene. For compounds **1a**, **3**, and **7**, all of which have strong absorption at 400 mμ, counting efficiency was too low to permit direct counting. In these cases samples were oxidized to carbon dioxide by a standard chromic acid wet combustion technique, and barium carbonate was counted in a thixotropic scintillation gel. For all other compounds, weighed samples were counted directly in the scintillation solution. All samples were counted five times, usually for 10 min., and for each sample the efficiency was determined by adding a benzoic acid-$C^{14}$-1 standard; efficiencies ranged from 44–58%. The specific activities reported below are corrected for background and counting loss.

**1-Diazo-3-methyl-4-phenyl-3-buten-2-one $C^{14}$-1 (17).**—Diazomethane-$C^{14}$ was prepared by the standard procedure[31] from 21.5 g. (0.2 moles) of N-methyl-$C^{14}$-N-nitroso-*p*-toluenesulfonamide[32] containing 0.1 mc. of $C^{14}$ activity. The yield by titration was 71%. To this diazomethane was added a solution of 5.90 g. of freshly crystallized α-methylcinnamoyl chloride. After standing at room temperature for 5 hr., the solution was evaporated at reduced pressure and the diazo ketone was collected in three crops, total yield 4.1 g. (61%), m.p. 85–89°; specific activity $9.33 \times 10^4$ d.p.s./mmole.

This diazo ketone was converted to the pyrazoline **18** with nonradioactive diazomethane in 48% yield by the usual procedure; **18** had m.p. 92–95°. This product was then diluted with unlabeled **18** to give 3.9 g., m.p. 92–93°; specific activity $2.30 \times 10^4$ d.p.s./mmole. The radioactive pyrazoline was converted to **1a** in 70% yield, and the product was again diluted with unlabeled material to give 7.7 g. of **1a**, m.p. 151–152°; specific activity $1.27 \times 10^3$ d.p.s./mmole.

Subsequent steps were then carried out by the procedures described above without further dilutions of radioactivity. Compounds **3**, **7**, **8**, and **12** had specific activities ranging from 100–103% of that of **1a**. In the decarboxylation of **12**, a slow stream of nitrogen was bled into the sublimer and the entrained carbon dioxide was absorbed in sodium hydroxide solution and then precipitated by addition of barium chloride. The barium carbonate had specific activity $1.21 \times 10^3$ d.p.s./mmole; the picrate of **13** had specific activity 85 d.p.s./mmoles.

(31) T. J. deBoer and H. J. Backer, *Org. Syn.*, **36**, 16 (1956).

(32) Obtained from New England Nuclear Corp.

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# Thiadiazoles. III. Amino-Group Exchange and Ring-Cleavage Reactions of 7-Amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidines[1]

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Displacement of the amino group of 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (I) by secondary amines was shown to occur with the formation of 7-(disubstituted amino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidines (V–VIII). Primary amines were likewise shown to effect displacement of the amino group, but cleavage of the pyrimidine ring to a 1,2,5-thiadiazole may ensue. The structure of the amino-group exchange product from I and butylamine was shown to be 7-(butylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine, rather than the 6-butyl derivative, by reduction to 4,5-diamino-6-(butylamino)pyrimidine and by independent synthesis. Products of ring cleavage of I were shown to be *N*-substituted amidines, *e.g.*, 4-amino-*N*-butyl-1,2,5-thiadiazole-3-carboxamidine (XIV). The formation of the thiadiazolopyrimidines resulting from exchange of amino groups could be favored over the formation of 1,2,5-thiadiazoles by limiting the reaction time. Exchange of one mono- or disubstituted amino group for another and the reversibility of this type of reaction were also demonstrated. Evidence that these amine-exchange reactions are influenced by the relative basicities of the attacking and departing amines and by steric effects was obtained. It is suggested that the exchange of amino groups occurs by direct displacement and that ring cleavage is an independent process.

Facile nucleophilic displacement from position 7 of substituents commonly subject to expulsion from heterocyclic rings was observed during the course of investigations on the synthesis of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines.[2] These displacements were effected by aniline generated during the formation of the thiadiazole ring by *N*-sulfinylaniline (III). Evidence was subsequently obtained that trace amounts of 7-anilino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (IV) may be formed during the preparation of 7-amino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (I) from 4,5,6-triaminopyrimidine (II, $R_1 = R_2 =$ H) and *N*-sulfinylaniline. Moreover, cleavage of the pyrimidine ring of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines bearing oxygen functions was found to proceed under comparatively mild conditions.[3] These reactions indicate an unusual lability of the pyrimidine ring that is probably ascribable to electron localization at the hetero atoms. The lability of the ring system suggested that additional studies of [1,2,5]thiadiazolo[3,4-*d*]pyrimidines might contribute to further elucidation of the course of amino-group exchange and ring-opening reactions of fused pyrimidine heterocycles.

Paper chromatographic evidence for the formation of trace amounts of the 7-anilino derivative (IV) during the preparation of the 7-amino derivative (I) was confirmed by showing that a small amount of the 7-anilino derivative (IV) could be isolated by greatly prolonging the reaction time. Interaction of pure I and refluxing aniline afforded IV in low yield. From reactions of I with refluxing morpholine and with dimethylamine at 100°, 7-morpholino[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (V) and 7-(dimethylamino)[1,2,5]thiadiazolo[3,4-*d*]pyrimidine (VI) were isolated and were shown to be identical with specimens of these compounds that had been prepared[2] from reactions of the appropriate 6-substituted 4,5-diaminopyrimidines (II) and N-sulfinylaniline (III). Similarly, reactions of I with pyrrolidine, with dibutylamine, and with certain primary amines gave the 7-(substituted amino) derivatives VII–X (Chart I).

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(2) Y. F. Shealy, J. D. Clayton, and J. A. Montgomery, *J. Org. Chem.*, **27**, 2154 (1962).

(3) (a) Y. F. Shealy and J. D. Clayton, *ibid.*, **28**, 1491 (1963); (b) Y. F. Shealy and J. D. Clayton, *ibid.*, **29**, 2141 (1964).