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SELECTIVE RING EXPANSION OF $\Delta^{5,10}$-OCTALIN-1,6-DIONES VIA THE SCHMIDT REACTION

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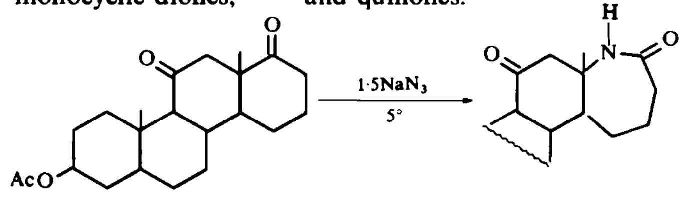
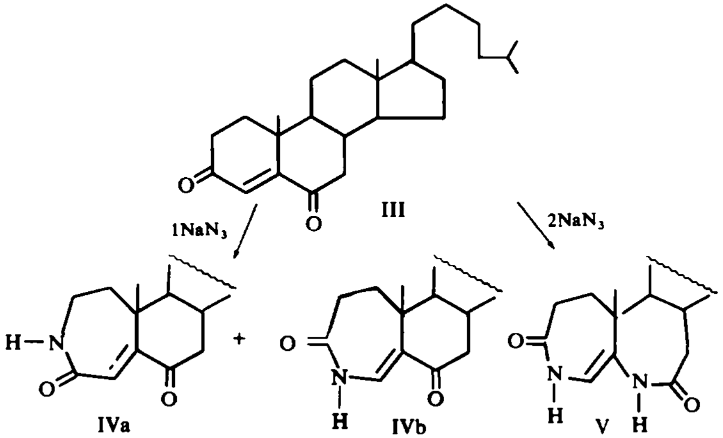
Abstract—Two octalindiones, namely 9-methyl-$\Delta^{5,10}$-octalin-1,6-dione (VI) and 5,9-dimethyl-$\Delta^{5,10}$-octalin-1,6-dione (VII), each consisting of a Δ^{1}-cyclohexenone ring (ring A) fused to a cyclohexanone ring (ring B), underwent selective expansion to lactams by the Schmidt reaction depending upon the acid medium employed. The cyclohexanone ring rearranged in concentrated sulfuric acid to a substituted caprolactam. An α,β-unsaturated lactam resulted from expansion of ring A in both conc hydrochloric and molten trichloroacetic acids. Unexpectedly, the reaction of VI in trichloroacetic acid produced an enamine lactam (XIII).

INTRODUCTION

THE Schmidt reaction[1,2] on cyclic aliphatic ketones has been the subject of some study through the years. Among these have been studies on fully saturated ring systems, both unsubstituted and substituted, as well as more recent work on those carbocyclic compounds containing α,β-unsaturation relative to the CO function.[3–7] In addition, the Schmidt reaction was applied to cyclic ketones containing heteroatoms,[8–11] monocyclic diones,[12–16] and quinones.[17–22]



I II



III IVa IVb V

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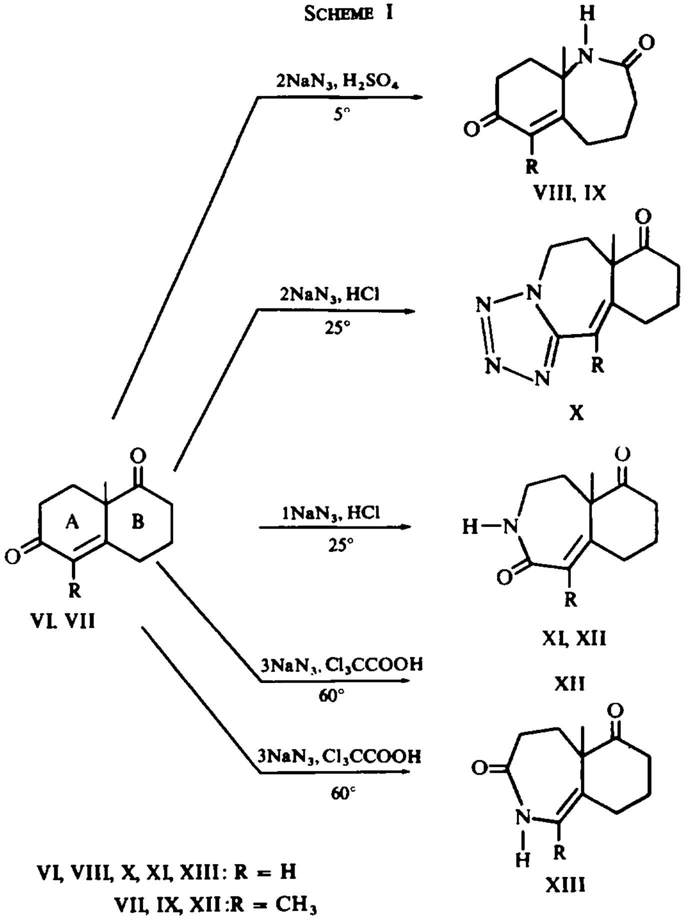
Only two reports have described this reaction with bicyclic diones wherein each of the two fused rings contained a CO function. Barton, *et al.*,[23] found that 3-β-acetoxy-D-homoandrostane-11,17a-dione (I) reacted with sodium azide in sulfuric acid–chloroform to afford one mono-aza compound II. Sing and Padmanabahn's[24] reaction of 4-cholesten-3,6-dione (III) resulted in two monolactams, IVa and IVb, with one molar equivalent of sodium azide in polyphosphoric acid (PPA). Only one bis-lactam, V, was isolated from reaction of III with two molar equivalents of the azide.

RESULTS AND DISCUSSION

To examine the effect of variation in acidity on the Schmidt ring expansion of such bicyclic diones, we chose the two octalindiones, 9-methyl-$\Delta^{5,10}$-octalin-1,6-dione (VI) and 5,9-dimethyl-$\Delta^{5,10}$-octalin-1,6-dione (VII). The results are outlined in Scheme I. In order of increasing acidity, the three solvents (and catalysts) employed were conc hydrochloric acid, trichloroacetic acid, and conc sulfuric acid. PPA, reported to be the best solvent and catalyst for the Schmidt reaction on both cycloalkanones[25] and α,β-unsaturated cycloalkenones,[3,6,7] was a very unsuitable medium for this reaction with VI and VII.

SCHEME I



VI, VIII, X, XI, XIII: R = H
VII, IX, XII: R = CH$_3$

Treatment of VI or VII with a two molar equivalent of sodium azide in conc sulfuric acid at 5°* led to VIII or IX, respectively. The cyclohexanone ring (ring B) underwent expansion in both compounds. The IR spectra (Table 1) exhibited bands

TABLE 1. SPECTRAL DATA

Compound	IR, ν_{max}^{KBr}, cm^{-1}		UV, λ_{max}^{MeOH}, mu (ε)	δ-value	NMR multiplicity[a]	No. of protons
VI	2890	1701	245	5·63	s	1
		1656	(14400)	1·42–2·97	m	10
		1610		1·38	s	3
VII	2950	1692	252	1·77–2·97	m	10
		1656	(16900)	1·69	s	3
		1608		1·34	s	3
VIII	3300	1656	217	6·25	br.s	1
	3215	1634	(13100)	5·20	s	1
	3067		230	1·44–2·47	m	10
	2941		(12100)	1·35	s	3
IX	3300	1645	209	7·40	br.s	1
	3205	1613	(8900)	1·92–2·86	m	10
	3077		247	1·81	s	3
	2933		(16800)	1·48	s	3
X	2890	1698	217	6·77	s	1
		1639	(19900)	4·56	t	2
		1515	247	1·71–3·31	m	8
			(18500)	1·51	s	3
			255			
			(15800)			
			273			
			(2520)			
XI	3279	1718	212	6·88–7·32	br.s	1
	3215	1661	(3340)	5·92	s	1
	3058			3.23–3.67	m	2
	2933			2·80–3·20	m	2
				2·16–2·69	m	4
				1·77–2·07	m	2
				1·37	s	3
XII	3226	1712	222	7·41–7·91	br.s	1
	3077	1667	(17000)	2·95–3·51	m	2
	2950	1610		2·30–2·78	m	4
				1·80–2·21	br. based sharp s.	7
				1·44	s	3
XIII	3175	1706	228	8·13	br.s	1
	3030	1664	(15800)	5·90	s	1
	2941	1600		1·62–3·39	m	10
				1·44	s	3

[a] m: multiplet, s: singlet, br.s: broad singlet, t: triplet.

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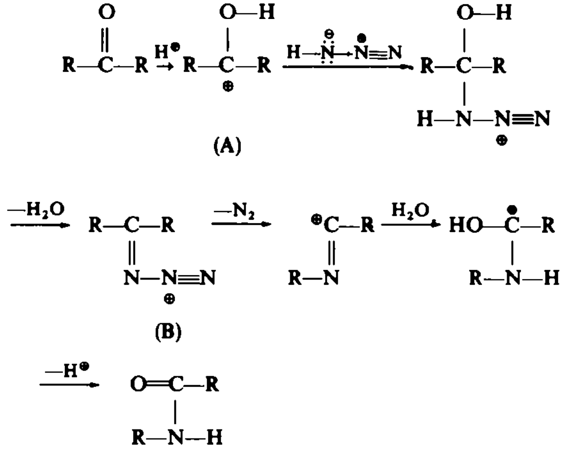
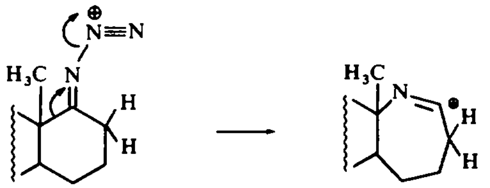
* Reactions run at room temperature failed to produce the same results. Only small amounts of intractable oil were isolated.

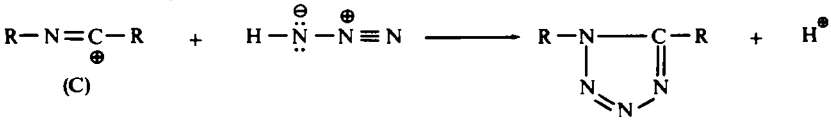
in the lactam region 3300–2940 cm^{-1} and showed no amide II bands at 1550–1530 cm^{-1}.[*] The ring B CO bands for VI (1701 cm^{-1}) and VII (1692 cm^{-1}) were shifted in the respective products to lower frequency and were screened out by the α,β-unsaturated CO absorptions at 1656 and 1645 cm^{-1} in VIII and IX, respectively. The emergence of shorter wavelength peaks in the UV spectra of VIII and IX was attributed to a bathochromic shift of the ring B CO absorption owing to conjugation with the auxochromic —NH— group.

Such products, wherein the carbon at the ring juncture migrated, were expected. It had been established earlier[26,27] that the more highly substituted C atom migrated in the rearrangement of 2-substituted cyclohexanones. The reason for this behavior can be readily be seen from the mechanism.[28] Intermediate B is so oriented that the bulkier substituent assumes a position *trans* to the leaving group, nitrogen, with the result that the less bulky group (—CH_2— in the case of VIII and IX) remains attached to carbon. The work of Barton, *et al.*,[23] is a pertinent example.





Reaction of VI, however, with two molar equivalents of sodium azide in conc hydrochloric acid at 25° led to the tetrazole X. These products are quite common[29] when two molar equivalents of sodium azide are used for each mole of CO present. Upon reacting with one mole of the hydrazoic acid formed, the ketone is converted to the intermediate iminocarbonium ion C (cf. mechanism) which then reacts with the second mole of hydrazoic acid to form the tetrazole.



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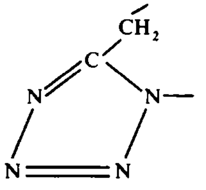
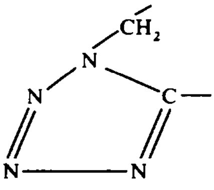
[*] Lactams show no amide II band in this region.

The IR spectrum of X showed no additional bands in the lactam region. The α,β-unsaturated CO band was no longer present, the bands at 1639 and 1515 cm^{-1} attributed to the ethylenic double bond and the —C=N— stretching frequencies, respectively.

The most revealing peak in the NMR was the multiplet centered at 4·56 δ, integrating for two protons. DiMaio and Permutti[30] have reported that the NMR spectrum of the tetrazole system XIV exhibits a complex multiplet at 2·95 δ while that of XV

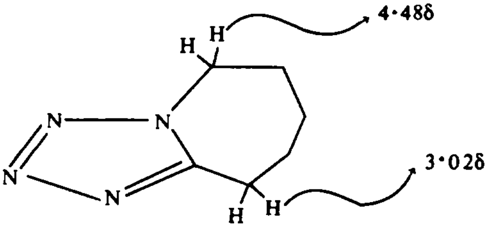


XIV



XV

absorbs near 4·95 δ. As an illustration, they cite the case of the tetrazole XVI formed from cyclohexanone. Thus, the triplet at 4·56 δ in the spectrum of X clearly eliminates the tetrazole of the isomeric lactam XIII as being the product.

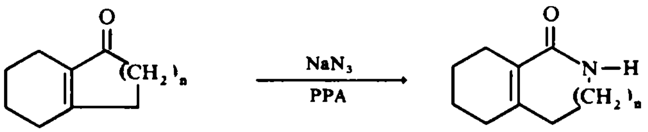


XVI

With one molar equivalent of sodium azide in conc hydrochloric acid at 25°, VI or VII rearranged to XI or XII, respectively. With these two lactams, the IR bands for the ring B as well as ring A CO group remained in both products. This indicated that the cyclohexanone CO was not involved in a vicinal relationship with the —NH— group as was the case with VIII and IX. The UV spectra showed a shift of the α,β-unsaturated CO absorptions to lower wavelength in both products. It has been reported[3,6,7,31,32] that the maximum absorption of α,β-unsaturated lactams appears at about 218 mμ while with enamine lactams, wherein the —NH— is located between the CO and ethylenic double bond, the absorption lies at about 237 mμ.

A study of the NMR spectra of XI and XII after deuterium exchange revealed the disappearance of the amide proton peaks centered at 7·10 and 7·68 δ, respectively, while the respective methylene absorptions centered at 3·33 and 3·22 δ were changed in contour. These two absorptions were assigned to the protons adjacent to the —NH— group in both lactams. Singh and Padmanabahn[24] reported similar absorptions in their compound (IVa) to be situated at 3·25 δ. The olefinic methyl proton absorption at 1·69 δ in VII was shifted downfield somewhat so that in XII it merged with a methylene multiplet representing four protons.

The apparent anomaly presented by XI and XII as compared to reported results with benzalacetone[33,34] was not surprising in view of the fact that in other such ring systems migration of the methylene group occurred irrespective of the substituent on the ethylenic carbon. Mitsuhashi, *et al.*,[7] reported that 4,5,6,7-tetrahydroindanone (XVII) and 3,4,5,6,7,8-hexahydro-1(2*H*)-naphthalenone (XVIII) each resulted in lactams wherein the alkyl and not the α-substituted olefinic C atom migrated.



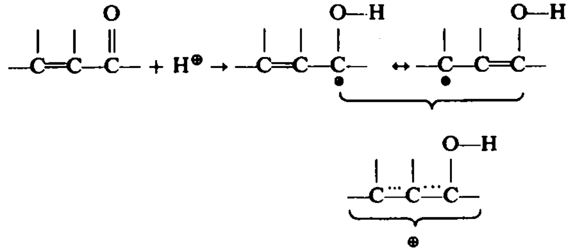
XVII: n = 1
XVIII: n = 2

Further evidence for the unpredictability of migration of the substituted ethylenic double bond was presented by the results of the reaction in molten trichloroacetic acid. Compound VII led to the same α,β-unsaturated lactam, XII, which was obtained using conc hydrochloric acid. The dione VII, however, unexpectedly underwent reaction to produce the enamine lactam XIII.

The principle IR bands of XIII were similar to those of XI and XII. However, absorption in the UV was shifted to 228 mμ, the result being that XIII absorbed at a wavelength 16 mμ longer than its isomer XI. Also, a comparison of the NMR spectra of XI and XIII showed that the amide proton absorption of the latter was shifted further downfield due to increased deshielding by conjugation with the ethylenic double bond.

All of the results clearly show that when conc sulfuric acid is used in the Schmidt reaction, the ring containing the cycloalkyl CO group (ring B) undergoes expansion, whereas use of conc hydrochloric or molten trichloroacetic acid brings about enlargement of the ring containing the α,β-unsaturated CO group. Smith[28] has done a study of the Schmidt reaction on a variety of ketones in different acids and solvents and came to certain conclusions regarding the relative basicities of ketones.

The basicity of a CO function is related to the propensity of its non-bonding electrons on oxygen towards protonation. The extent to which species A is formed (cf. mechanism) determines the likelihood of the reaction occurring. Of the two CO functions present in VI and VII, the more basic is the α,β-unsaturated.[35] Upon protonation, the hydroxy carbonium ion formed is resonance stabilized. The acidity of the medium is inversely related to basicity of a CO compound, i.e., the stronger the basicity of the ketone, the less acidic the solvent required to promote reaction. In fact, Smith found that for a given ketone, the least acidic medium which brings about reaction in a reasonable time gave the purest products.



$$-\overset{|}{C}=\overset{|}{C}-\overset{\overset{O}{\|}}{C}- + H^{\oplus} \rightarrow \underbrace{-\overset{|}{C}=\overset{|}{C}-\underset{\bullet}{\overset{\overset{O-H}{|}}{C}}- \leftrightarrow -\underset{\bullet}{\overset{|}{C}}-\overset{|}{C}=\overset{\overset{O-H}{|}}{C}-}$$

$$\underbrace{-\overset{|}{C}\overset{\cdots}{-}\overset{|}{C}\overset{\cdots}{-}\overset{\overset{O-H}{|}}{C}-}_{\oplus}$$

In order of increasing acidity, the three solvents we employed can be arranged hydrochloric < trichloroacetic < sulfuric. The Δ^1-cyclohexanone ring (ring A), being the more strongly basic, underwent rearrangement in both conc hydrochloric and trichloroacetic acid. Conc sulfuric acid was such a strong catalyst that reaction of the α,β-unsaturated CO function was completely inhibited. This is in accordance with Smith's observation that the stronger the acidity of the medium, the lower the yield of product for a given ketone. The more weakly basic cyclohexanone ring, rearranged very readily in sulfuric acid. The other two catalysts were therefore found to be too weak in acid strength to bring about rearrangement of ring B.

EXPERIMENTAL

All m.ps (uncorrected) were determined on a Mel-Temp m.p. apparatus. All combustion analyses were performed by Alfred Bernhardt Microanalytical Laboratories, West Germany and Childers Microanalytical Laboratories, Milford, New Jersey. IR spectra were determined on a Perkin–Elmer Model 137 using the KBr pellet technique. UV absorption spectra were determined with a Bausch and Lomb Spectronic 505 spectrophotometer, all samples being dissolved in MeOH. NMR spectra were obtained on a Varian A60A spectrometer using TMS as an internal standard, all samples being dissolved in $CDCl_3$. Mol wt by mass spectrograph was obtained from Morgan-Schaffer Corporation, Quebec, Canada. The starting materials (VI and VII) were obtained commercially from Aldrich Chemical Company, Inc., Cedar Knolls, New Jersey.

Schmidt reaction on 9-methyl-$\Delta^{5,10}$-octalin-1,6-dione (VI)

A. *Using concentrated sulfuric acid.* Two grams (0·0112 mole) of VI was dissolved in 40 ml conc H_2SO_4. The soln was cooled to 5° in an ice bath and 1·46 g (0·0224 mole) NaN_3 was added in portions over a 45 min period. Thereafter, the reaction mixture was stirred an additional hr at 5° and then poured onto 200 g ice. The resulting aqueous soln was then extracted with ten 50 ml portions CH_2Cl_2, the combined extracts washed once with 50 ml 5% KOH, once with 50 ml water, dried over $MgSO_4$, and then evaporated *in vacuo* to give a solid, yield, 1·60 g (74%); m.p. 221–231°. It was recrystallized twice from EtOAc to give 1·00 g (46%) of VIII, m.p. 234–236°. (Found: C, 68·49; H, 7·81; N, 7·27. $C_{11}H_{15}NO_2$ requires: C, 68·39; H, 7·77; N, 7·25%).

B. *Using concentrated hydrochloric acid*—(i) *With two moles of sodium azide.* To a soln of 1·00 g (0·0056 mole) of VI in 10 ml conc HCl was added in portions over a 15 min period 0·74 g (0·0104 mole) NaN_3. The reaction mixture was then stirred an additional 40 min at room temp after which it was poured onto 100 g ice. The resulting aqueous soln was then extracted 5 times with 50 ml portions CH_2Cl_2. The combined extracts were washed once with 20 ml 5% KOH, once with 20 ml water, dried over $MgSO_4$, and then evaporated *in vacuo* to produce a solid, yield, 1·00 g (78%); m.p. 100–108°. After two recrystallizations from EtOAc–light petroleum, 0·45 g (35%) of X was recovered, m.p. 114–115·5°. (Found: C, 60·80; H, 6·11; N, 25·64; Mol. Wgt. (Rast), 229. $C_{11}H_{14}N_4O$ requires: C, 60·55; H, 6·42; N, 25·68%; Mol. Wgt., 218).

(ii) *With one mole of sodium azide.* To 1·00 g (0·0056 mole) VI dissolved in 10 ml conc HCl was added in portions over a 30 min period 0·37 g (0·0056 mole) NaN_3. The reaction mixture was then allowed to stir at room temp for 15 hr. It was then poured onto 100 g ice. The resulting aqueous soln was then extracted 5 times with 50 ml portions CH_2Cl_2, the combined extracts washed once with 25 ml 5% KOH, once with 25 ml water, dried over $MgSO_4$, and evaporated *in vacuo* to give an oil. The oil was washed several times with EtOAc–ethyl ether (15:50) to produce a solid, yield, 0·51 g (47%); m.p. 141–151°. This solid was taken up in boiling EtOAc, Norit added, and after 15 min the soln passed through fluted filter paper. All solvent was then evaporated *in vacuo* and the residue recrystallized several times from EtOAc to give an analytical sample of XI, m.p. 160–161·5°. (Found: C, 68·00; H, 7·49; N, 6·98. $C_{11}H_{15}NO_2$ requires: C, 68·39; H, 7·77; N, 7·25%).

Schmidt reaction on 5,9-dimethyl-$\Delta^{5,10}$-octalin-1,6-dione (*VII*)

A. *Using concentrated sulfuric acid.* Procedure same as that used for the reaction of VI in conc H_2SO_4 using 2·00 g (0·0104 mole) VII in 40 ml of the acid with addition of 1·36 g (0·0210 mole) NaN_3. The crude product was an oil which when washed first with chloroform–light petroleum, then with light petroleum, produced a solid, crude yield, 1·10 g (51%); m.p. 187–190°. After two recrystallizations from EtOAc–light petroleum, 0·75 g (35%) IX was obtained, m.p. 192–194°. (Found: C, 69·39; H, 8·21; N, 6·93; Mol. Wgt. (mass spec), 207. $C_{12}H_{17}NO_2$ requires: C, 69·53; H, 8·27; N, 6·76%; Mol. Wgt., 207).

B. *Using concentrated hydrochloric acid.* Same procedure as that used for the reaction of VI in conc HCl using 2·00 g (0·0104 mole) VII in 25 ml of the acid with addition of 0·68 g (0·0104 mole) NaN_3. Stirring, however, was continued after complete addition of the azide for only 2 hr. The crude yield of solid product amounted to 0·90 g (43%); m.p. 145–151°. After two recrystallizations from chloroform–hexane, 0·53 g (25%) XII was obtained, m.p. 161–162·5°. (Found: C, 69·50; H, 8·32; N, 6·66. $C_{12}H_{17}NO_2$ requires: C, 69·53; H, 8·27; N, 6·76%).

Schmidt reaction using molten trichloroacetic acid

A. *On 9-methyl-$\Delta^{5,10}$-octalin-1,6-dione* (VI). One gram (0·0056 mole) VI was dissolved in 15 g Cl_3CCOOH at 60°. To this soln was added all at once 1·10 g (0·0168 mole) NaN_3. After stirring at 60° for 2·5 hr, 100 ml water was added and the resulting aqueous soln neutralized with a few ml NH_4OH. It was then extracted with ten 25 ml portions of CH_2Cl_2, the combined extracts dried over $MgSO_4$, and evaporated *in vacuo* to produce an oil. After washing twice with EtOAc–pentane, a solid resulted, crude yield, 0·75 g (69%); m.p. 109–120°. The solid was taken up in boiling EtOAc, treated with Norit, and after 15 min the soln was filtered. The filtrate was then evaporated *in vacuo* to produce a residue which was recrystallized a few times from EtOAc–pentane to give 0·22 g (20%) XIII; m.p. 142·5–144·5°. (Found: C, 68·14; H, 7·74; N, 7·42. $C_{11}H_{15}NO_2$ requires: C, 68·39; H, 7·77; N, 7·25%).

B. *On 5,9-dimethyl-$\Delta^{5,10}$-octalin-1,6-dione* (VII). Procedure same as that used above with 1·00 g (0·0052 mole) VII and 1·00 g (0·0156 mole) NaN_3 except that the reaction mixture was stirred only 2 hr. Workup produced a small amount of a dark red oil which solidified after washing with EtOAc–pentane. Following treatment with Norit as described above, the residue was recrystallized once from ethyl ether, yield, 0·06 g (5·5%); m.p. 159–162°. A mixture m.p. with XII was not depressed. An IR spectrum of the material was identical to that of XII.

REFERENCES

[1] H. Wolff, *Organic Reactions* 3, 307 (1946)

[2] P. A. S. Smith, *Molecular Rearrangements* (Edited by Paul de Mayo) Vol. I, chpt. 8, p. 457. Interscience, New York (1963)

[3] K. Mitsuhashi and K. Nomura, *Chem. Pharm. Bull.* **13**, 951 (1965)

[4] H. Singh, V. Parashar and S. Padmanabahn, *J. Sci. Ind. Res.* **25**, 200 (1966). *Chem. Abstr.* **65**, 12249 (1966)

[5] B. Matkovics, G. Gondos and Z. Tegyey, *Acta. Chim. Acad. Sci. Hung.* **53**, 417 (1967). *Chem. Abstr.* **68**, 59795 (1968)

[6] K. Mitsuhashi, K. Nomura, I. Watanabe and N. Minami, *Chem. Pharm. Bull.* **17**, 1572 (1969)

[7] K. Mitsuhashi, K. Nomura, N. Minami and M. Matsuyama, *Ibid.* 1578 (1969)

[8] S. C. Dickerman and A. J. Besozzi, *J. Org. Chem.* **19**, 1855 (1954)

[9] S. C. Dickerman and E. J. Moriconi, *Ibid.* **20**, 206 (1955)

[10] E. E. Miklina, *et al.*, *Zh. Organ. Khim.* **1**, 1336 (1965) (Russ); *Chem. Abstr.* **63**, 13257 (1965)

[11] K. Hohenlohe-Oeringen, *Monatsh. Chem.* **96**, 257 (1965)

[12] R. Fusco and S. Rossi, *Gazz. Chim. Ital.* **81**, 511 (1951); *Chem. Abstr.* **46**, 5550 (1951)

[13] H. Watanabe, S. Kuwata and S. Koyama, *Chem. Pharm. Bull.* **9**, 834 (1961)

[14] M. Rothe and R. Timler, *Chem. Ber.* **95**, 783 (1962)

[15] M. I. Vinnik and N. G. Zarakhani, *Dokl. Akad. Nauk. SSSR* **152**, 1147 (1963)

[16] H. Sekiguchi, *Bull. Soc. Chim. Fr*, 691 (1965)

[17] E. Stephenson, *J. Chem. Soc.* 2620 (1949)

[18] G. M. Badger and J. H. Seidler, *Ibid.* 2329 (1954)

[19] K. N. Carter, *J. Org. Chem.* **31**, 4257 (1966)

[20] R. W. Richards and R. M. Smith, *Tetrahedron Letters* 2361 (1966)

[21] G. Jones, *J. Chem. Soc.* 1808 (1967)

[22] H. Moore and H. R. Sheldon, *J. Org. Chem.* **32**, 3602 (1967)

[23] D. H. R. Barton, A. da S. Campos-Neves and A. I. Scott, *J. Chem. Soc.* 2698 (1957)

[24] H. Singh and S. Padmanabahn, *Chem. & Ind.* 118 (1967)

[25] R. T. Conley, *Ibid.* 438 (1958)

[26] H. Schecter and J. C. Kirk, *J. Am. Chem. Soc.* **73**, 3087 (1951)

[27] R. T. Conley, *J. Org. Chem.* **23**, 1330 (1958)

[28] P. A. S. Smith, *J. Am. Chem. Soc.* **70**, 320 (1948)

[29] F. R. Benson, *Chem. Rev.* **41**, 1 (1947)

[30] G. DiMaio and V. Permutti, *Tetrahedron* **22**, 2063 (1965)

[31] R. H. Mazur, *J. Org. Chem.* **26**, 1289 (1961)

[32] C. W. Shoppee, G. Kruger and R. N. Mirrington, *J. Chem. Soc.* 1050 (1962)

[33] P. A. S. Smith and J. P. Horowitz, *J. Am. Chem. Soc.* **72**, 3718 (1950)

[34] L. H. Briggs, G. C. DeAth and S. R. Ellis, *J. Chem. Soc.* 61 (1942)

[35] E. F. Pratt and K. Matsuda, *J. Am. Chem. Soc.* **75**, 3739 (1953)