

Diazepines. V. The Reaction of Homophthalic Anhydride with Hydrazines (1)

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The reaction of homophthalic anhydride with hydrazine and a number of substituted hydrazines has been investigated. Only in the case of the reaction of homophthalic anhydride and 1,2-dimethylhydrazine has a diazepine been isolated. The previously reported (2) diazepine from homophthalic anhydride and hydrazine appears to be a product resulting from the reaction of two moles of homophthalic anhydride with one mole of hydrazine.

In 1944, Whitmore and Cooney (2) reported that the reaction of homophthalic anhydride (1) with hydrazine in boiling ethanol gave an 80% yield of the diazepine II, m.p. 298-300°. These authors (2) also noted that when the reaction was carried out in glacial acetic acid, the precipitate of II, that was initially obtained, rearranged upon refluxing the mixture to form III in 75% yield, m.p. 147-148°, which gave an 80% yield of a monoacetyl derivative (IV), m.p. 239-240°. In a similar manner they also reported (2) converting 4-nitrohomophthalic anhydride to the nitro and amino analogues of II. We felt that if this reaction could be generalized by use of a variety of substituted hydrazines and substituted homophthalic anhydrides that it would provide a series of 2,3-benzodiazepines, related to II, for further study.

When homophthalic anhydride (1) was reacted with phenylhydrazine in ethanol the only products isolated were the mono- and diphenylhydrazides of homophthalic acid in 53 and 21% yields, respectively. When this reaction was carried out in acetic acid the only product isolated was 2-phenylamino-1,2,3,4-tetrahydroisoquinoline-1,3-dione (V) in 68% yield. Compound V could also be obtained by refluxing homophthalic acid monophenylhydrazide in acetic acid. Reduction of V with lithium aluminum hydride gave 2-phenylamino-1,2,3,4-tetrahydroisoquinoline. Reaction of methylhydrazine with homophthalic anhydride in acetic acid proceeded in a similar manner to give VI.

Despite this lack of success with phenylhydrazine and methylhydrazine, the condensation of 1,2-dimethylhydrazine with homophthalic anhydride was studied. This reaction gave an 84% yield of 2,3-dimethyl-1,2,3,4-tetrahydro-5*H*-2,3-benzodiazepin-1,4-dione (VII). The infrared, nmr, and mass spectra of this compound were consistent

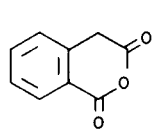
with the structure assigned. Reduction of VII with lithium aluminum hydride led to the loss of both carbonyl groups and the isolation of VIII as its picrate. Extension of this reaction to 1,2-diphenylhydrazine gave IX in 59% yield as the only pure product that could be isolated.

In view of these results with substituted hydrazines it was decided to reinvestigate the reaction (2) of hydrazine and homophthalic anhydride. Although the reaction of hydrazine and homophthalic anhydride was carried out under a wide variety of conditions, we were never able to isolate the diazepine II from this reaction. Depending upon the conditions used (see Table I) we obtained III, IV, X, or a monohydrazide of homophthalic acid, or mixtures of these. Treatment of the monohydrazide of homophthalic acid with polyphosphoric acid gave a mixture of X and III in 75 and 21% yields, respectively.

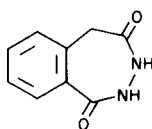
On the basis of its mass spectra structure X would appear to be more correct than one of the isomeric structures, XIa or XIb. Further, reaction of III with homophthalic anhydride gave a 75% yield of X. Such a reaction would not be likely to lead to XIa or b. When X was refluxed in glacial acetic acid, it was recovered unchanged together with a small amount of IV. Reduction of X with lithium aluminum hydride gave XII. Finally, reaction of X with mercuric oxide gave a monoamide of homophthalic acid.

It is worth noting that our compound X (not identified by Whitmore and Cooney (2)) melts at 300-302° while Whitmore and Cooney (2) report a melting point of 298-300° for II. It would appear (3) that the earlier workers (2) did not indeed obtain II but rather X from the reaction of hydrazine with homophthalic anhydride.

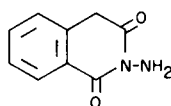
Reactions of the type noted in this paper for homophthalic anhydride have been reported for other cyclic anhydrides (4).



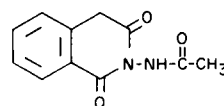
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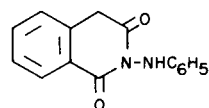
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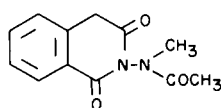
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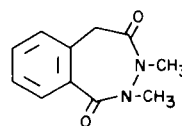
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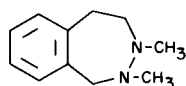
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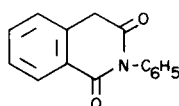
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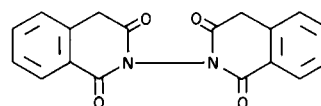
VII



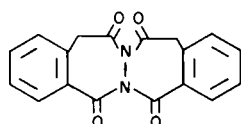
VIII



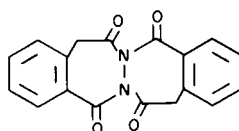
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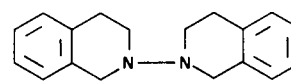
X



XIa



XIb



XII

EXPERIMENTAL (5)

Reaction of Homophthalic Anhydride with Phenylhydrazine.

(a) In Ethanol.

To a solution of 5 g. (0.031 mole) of homophthalic anhydride in 40 ml. of ethanol was added 3.06 ml. (0.031 mole) of phenylhydrazine and the solution was refluxed for 6 hours. After cooling, the mixture was filtered, the residue was washed with dilute acetic acid and recrystallized from ethanol to give 4.43 g. (53%) of the monohydrazide, m.p. 173-175°.

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.18; N, 10.30. Found: C, 66.44; H, 5.15; N, 10.35.

When the above filtrate was diluted with acetic acid, the solid obtained was recrystallized from ethanol to give 1.14 g. (21%) of the dihydrazide, m.p. 223-225°.

Anal. Calcd. for $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.55. Found: C, 70.16; H, 5.04; N, 15.62.

(b) In Glacial Acetic Acid.

To a solution of 8.1 g. (0.05 mole) of homophthalic anhydride in 40 ml. of glacial acetic acid was added 5.4 g. (0.05 mole) of phenylhydrazine and the mixture was refluxed for 30 minutes and cooled. Filtration and recrystallization from ethanol gave 8.6 g. (68%) of compound V, m.p. 173-175°.

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.79; N, 11.11. Found: C, 71.43; H, 4.61; N, 11.34.

This same product was obtained when the monophenylhydrazide of homophthalic acid was reacted with refluxing glacial acetic acid.

2-Phenylamino-1,2,3,4-tetrahydroisoquinoline.

To 0.03 g. of lithium aluminum hydride in 30 ml. of anhydrous ether was added 1 g. of 2-phenylaminoisoquinoline-1,3-dione (V) and the mixture was refluxed for 2 hours. After cooling and distillation of the lithium aluminum hydride the solvent was concentrated to give 0.62 g. (71%) of a white solid, m.p. 74-76°.

TABLE I

Reaction of Homophthalic Anhydride with Hydrazine (a)

Solvent	Temp.	Time	X (b)	IV (c)	Products (% Yield)	
					III (c)	Monohydrazide of Homophthalic Acid (d)
gl. HOAc	Ref.	12 hr	46.5	7.5	40	---
gl. HOAc (e)	Ref.	12 hr	---	52	10	---
gl. HOAc	Ref.	0.5 hr	---	---	---	79
50% HOAc	Ref.	6 hr	---	---	---	62
gl. HOAc	25°	16 hr	---	---	---	72
DMF	0°	4 hr	---	---	---	78
DMF	Ref.	2.5 hr	---	---	80	---
DMSO	0°	6 hr	---	---	---	75
DMSO	Ref.	2 hr	---	---	85	---
C ₆ H ₆	Ref.	6 hr	---	---	48	---
EtOH (f)	Ref.	6 hr	---	---	---	90

(a) Reaction of equimolar quantities of homophthalic anhydride and 95% hydrazine unless other wise noted. (b) See Experimental Section for analysis and spectral data. (c) M.p. identical with those reported (2). (d) *Anal.* Calcd. for C₉H₁₀N₂O₃: C, 55.60; H, 5.16; N, 14.41. Found: C, 55.62; H, 5.06; N, 14.14. Infrared (potassium bromide), 3450, 3200, 3050-2850, 1700, 1610 cm⁻¹. (e) Two moles of hydrazine to one mole of anhydride. (f) Hydrazine hydrate used.

Anal. Calcd. for C₁₅H₁₆N₂: C, 80.32; H, 7.19; N, 12.49. Found: C, 79.99; H, 7.29; N, 12.29.

Reaction of Homophthalic Anhydride with Methylhydrazine.

To a solution of 3 g. (0.0185 mole) of homophthalic anhydride in 25 ml. of glacial acetic acid was added 0.85 g. (0.0185 mole) of methylhydrazine. After refluxing for 12 hours, cold water was added and the mixture was extracted with chloroform. The chloroform extract was washed with 5% sodium bicarbonate and concentrated to dryness to give, after recrystallization from ethanol, 2 g. (47%) of compound VI, m.p. 211-213°.

Anal. Calcd. for C₁₂H₁₂N₂O₃: C, 62.06; H, 5.20; N, 12.05. Found: C, 62.03; H, 5.17; N, 12.07.

Reaction of Homophthalic Anhydride with 1,2-Dimethylhydrazine.

To a solution of 2 g. (0.0123 mole) of homophthalic anhydride in 20 ml. of glacial acetic acid was added 0.738 g. (0.0123 mole) of 1,2-dimethylhydrazine dihydrochloride in 10 ml. of pyridine. The solution was refluxed for 12 hours, cooled, diluted with water, and extracted with chloroform. The chloroform extract was washed with 10% hydrochloric acid and 5% sodium bicarbonate, dried over magnesium sulfate and concentrated to dryness. Dry column chromatography of the residue on alumina in ether gave 2.1 g. (84%) of compound VII which was recrystallized from hexane, m.p. 118-119°. Infrared (potassium bromide), 1680, 1610 cm⁻¹; NMR (DMSO-d₆), 2.4-2.6 (4 Ar), 6.75 (N-CH₃), 6.80 (N-CH₃), 7.2 τ (CH₂); Mass Spec., 204 (82%), 161 (11%), 146 (21%), 145 (34%), 118 (82%), 90 (100%), 89 (84%).

Anal. Calcd. for C₁₄H₁₂N₂O₂: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.57; H, 5.81; N, 13.91, 13.59.

2,3-Dimethyl-1,2,3,4-tetrahydro-5H-2,3-benzodiazepine (VIII).

A solution of 1.20 g. of VII in 75 ml. of anhydrous ether was added dropwise with stirring over 2 hours to 0.45 g. of lithium aluminum hydride in 20 ml. of anhydrous ether. The mixture was refluxed for 6 hours, hydrolyzed, and the ether evaporated to give 0.81 g. of an oil. Treatment of the oil with picric acid gave the picrate of VIII, m.p. 129-130°.

Anal. Calcd. for C₁₇H₁₉N₅O₇: C, 50.37; H, 4.72; N, 17.28. Found: C, 50.53; H, 4.50; N, 17.22.

Reaction of Homophthalic Anhydride with 1,2-Diphenylhydrazine.

To a solution of 5 g. (0.0307 mole) of homophthalic anhydride in 20 ml. of glacial acetic acid was added 5.65 g. (0.0307 mole) of 1,2-diphenylhydrazine and the mixture was refluxed for 12 hours. After cooling the mixture was poured onto ice and the solid collected was chromatographed to give 4.2 g. (59%) of IX, m.p. 190-192° from benzene. Infrared (potassium bromide), 1715, 1675 cm⁻¹; NMR (DMSO-d₆); 2.6-2.7 (9 Ar), 5.8 τ (CH₂).

Anal. Calcd. for C₁₅H₁₁N₂O₂: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.92; H, 4.73; N, 5.94.

Several minor components were also isolated from the chromatography but could not be completely characterized.

Reaction of Homophthalic Anhydride with Hydrazine.

In a typical run 0.394 g. (0.0123 mole) of 95% hydrazine was added to a solution of 2 g. (0.0123 mole) of homophthalic anhydride in 25 ml. of glacial acetic acid. After refluxing for 12 hours the mixture was cooled and filtered to give after recrystallization from dimethylformamide 0.92 g. (46.5%) of compound X, m.p. 300-302°. Infrared (potassium bromide), 1680, 1660 cm⁻¹;

Mass spec., 320 (92%), 161 (14%), 160 (9%), 145 (90%), 132 (40%), 118 (74%), 90 (100%), 89 (74%).

Anal. Calcd. for $C_{18}H_{12}N_2O_4$: C, 67.49; H, 3.78; N, 8.75. Found: C, 67.29; H, 3.82; N, 8.76.

To the solution remaining after the filtration of X was added 150 ml. of water to give, after recrystallization from ethanol, 0.2 g. (7.5%) of compound IV, m.p. 241-242°, reported (2) m.p. 239-240°.

The remaining solution was extracted with chloroform and the chloroform was washed with 5% sodium bicarbonate. Concentration of the chloroform gave 0.86 g. (40%) of compound III, m.p. 148-149° from ethanol, reported (2), m.p. 146-148°.

The reaction of homophthalic anhydride and hydrazine was attempted under a variety of other conditions as indicated in Table I.

Reaction of the Monohydrazide of Homophthalic Acid with Polyphosphoric Acid.

A mixture of 1 g. of the monohydrazide of homophthalic acid (see Table I) and 5 g. of polyphosphoric acid was heated under nitrogen for 2 hours and poured onto ice. The solid obtained was recrystallized from dimethylformamide to give 0.65 g. (75%) of compound X which was identical with that described above. After removing X, the mother liquors were extracted with chloroform. Concentration of the chloroform extract and recrystallization from ethanol gave 0.18 g. (21%) of compound III which was identical with that described above.

Reaction of 2-Amino-1,2,3,4-tetrahydroisoquinoline-1,3-dione (III) with Homophthalic Anhydride.

A mixture of 0.08 g. (0.000454 mole) of III and 0.073 g. (0.000454 mole) of homophthalic anhydride in 10 ml. of glacial acetic acid was refluxed for 5 hours. Upon cooling a solid was obtained which was recrystallized from dimethylformamide-methanol to give 0.108 g. (74%) of X identical with that described above.

Reaction of X with Lithium Aluminum Hydride.

A slurry of 0.18 g. (0.00056 mole) of X in 10 ml. of anhydrous ether was added to 0.085 g. of lithium aluminum hydride in 25

ml. of anhydrous ether and the mixture was refluxed for 6 hours. After hydrolysis, concentration of the ether gave a solid which after chromatography on alumina gave 0.09 g. (64%) of XII, m.p. 119-120° from benzene-hexane.

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.59. Found: C, 81.78; H, 7.64; N, 10.61.

Reaction of X with Mercuric Oxide.

A mixture of 0.5 g. (0.00142 mole) of X and 0.615 g. of mercuric oxide in anhydrous ether was stirred at room temperature for 1 hour. Concentration of the ether gave 0.15 g. (59%) of a monoamide of homophthalic acid, m.p. 222-223° from ethanol.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.05; H, 4.95; N, 7.85.

REFERENCES

- (1) Part IV: R. J. Dubois and F. D. Popp, *J. Heterocyclic Chem.*, **6**, 113 (1969). A portion of this work was supported by a grant from the Schering Corporation.
- (2) W. F. Whitmore and R. C. Cooney, *J. Am. Chem. Soc.*, **66**, 1237 (1944).
- (3) We have recently prepared by a completely different route a compound we believe to have structure II and find that its m.p. differs considerably from that reported by Whitmore and Cooney (2). Using this same new procedure we have also prepared the nitro derivative of II claimed by Whitmore and Cooney and find that its properties also differ considerably from those reported (2).
- (4) For examples and leading references see: H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, **16**, (1937); E. Hedaya, R. L. Hinman, and S. Theodoropoulos, *J. Org. Chem.*, **31**, 1317 (1966); M. Ishikawa, M. Fujimoto, K. Okabe, and M. Sakai, *Chem. Pharm. Bull.*, **16**, 227 (1968).
- (5) Melting points are corrected and taken in capillaries. Analyses were by Spang Microanalytical Laboratory, Ann Arbor, Mich. Mass spectra by Morgan Schaff Corp., Montreal, Canada.

Received November 6, 1968

Potsdam, New York 13676