[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

Wolff–Kishner Reduction of 2-Acyl-1,3-indandiones[1]

BY ROBERT A. BRAUN AND WILLIAM A. MOSHER

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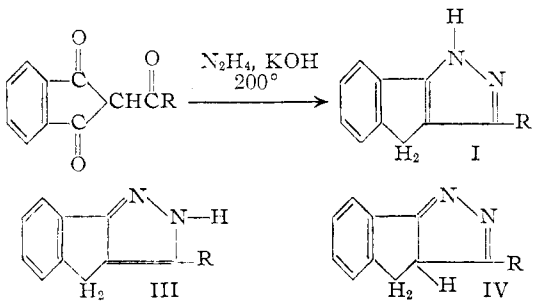
The Wolff–Kishner reduction of 2-acyl-1,3-indandiones has been found to give 1,4-dihydro-3-substituted-indeno[1,2-*c*] pyrazoles in good yields. Several of the reaction intermediates have been isolated and characterized and the course of the reaction is discussed.

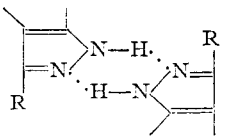
In a previous report from this Laboratory it was shown that 2-acyl-1,3-indandiones form two types of monohydrazones[2] which might be expected to cyclize to pyrazoles. The present work was undertaken to determine whether reduction, cyclization or both would occur under Wolff–Kishner conditions. Cyclization has been observed in other attempted Wolff–Kishner reactions where the intermediate hydrazone undergoes some internal condensation before it has an opportunity to experience normal reduction,[3] although there is no specific reference in the literature to an attempted Wolff–Kishner reduction of any 1,3-indandione.[4]

The Wolff–Kishner reduction, by the Huang-Minlon modification,[5] was found to give 1,4-dihydro-3-substituted-indeno[1,2-c]pyrazoles (I) in good yields. These apparently constitute a new class of compounds, the only similar compound known being 1,4-dihydro-3-carbethoxy-indeno[1,2-c]pyrazole, prepared in a completely different way.[6] The reaction seems to be general for 2-acyl-1,3-indandiones. For the few aroyl-1,3-indandiones studied no general pattern is observed. Repeated attempts to reduce 2-benzoyl and 2-*p*-methoxybenzoyl-1,3-indandione resulted in the corresponding 3-aryl-indeno[1,2-*c*]-pyrazol-4(1*H*)-one (II). The Wolff–Kishner reduction of 2-α-naphthoyl-1,3-indandione proceeded smoothly to the completely reduced 1,4-dihydro-3-α-naphthylindeno-[1,2-c]pyrazole.

There are a number of alternative structures that must be considered for the 1,4-dihydro-3-substituted-indeno[1,2-*c*]pyrazoles. Structure IV was eliminated by consideration of chemical and spectral properties of the products. Structure III must be considered, as most pyrazoles exhibit tautomerism. However, in particular cases the equilibrium is displaced to afford homogeneous pyrazoles of a fixed imino type.[7] Spectral evidence suggests that the tautomer of I, 2,4-dihydro-3-substituted-indeno[1,2-c]pyrazole (III) is absent, but we do not have unequivocal proof of this. The 1,4-dihydro-3-substituted-indeno[1,2-c]pyrazole structure is used in the subsequent discussion without excluding the possibility of the tautomeric 2,4-dihydro- structure. The structure of these materials was further confirmed by the formation of the benzenesulfonamide and benzamide of 1,4-dihydro-3-benzylindeno[1,2-c]pyrazole. Only one product was obtained for each of these reactions, indicating the presence of only one tautomer. The 1,4-dihydro-3-substituted-indeno[1,2-c]pyrazoles are white, crystalline solids. Their properties and analyses are summarized in Table I.



Each 1,4-dihydro-3-substituted-indeno[1,2-c]pyrazole was a strong band at 3.1–3.5 μ in its infrared spectrum due to an N–H group involved in intermolecular hydrogen bonding of the type



The benzenesulfonamide VIII and the benzamide have no bands in the 3.1–3.5 μ region, showing the absence of the N–H bond. Each new indeno[1,2-c]-pyrazole has a band in the 7.3±0.1 μ region. Elsner and Parker[8] studied the infrared spectra of a series of 1-alkyl and aryl-indanes and indenes, and found that the indenes had a characteristic band at 7.18 μ which was absent in the indanes. Thus a band in the 7.3 μ region indicates that the correct structure is I which contains an indene ring.

Compounds II, V, VI and VII have been prepared by the reaction of 2-acyl-1,3-indandiones with hydrazine under appropriate conditions.

From the above information it is clear that the attempted Wolff–Kishner reaction proceeds by the following route: a, the formation of a hydrazone at the extracyclic carbonyl group (except in the case of 2-diphenylacetyl-1,3-indandione in which the hydrazone is on the indan ring[2]); b, cyclization of the monohydrazone to a keto-pyrazole II; c, hydrazone formation at the remaining cyclic carbonyl; d, decomposition of the hydrazone to give the 1,4-dihydro-3-substituted-indeno[1,2-c]pyrazole.

(1) From the dissertation submitted by Robert A. Braun in partial fulfillment of the requirements for the Ph.D. degree, University of Delaware.

(2) R. A. Braun and W. A. Mosher, THIS JOURNAL, **80**, 3018 (1958).

(3) (a) C. Fisher, H. Beyer and K. Zaicker, *Ann.*, **486**, 55 (1931); (b) E. D. Bergmann and R. Ikan, THIS JOURNAL, **78**, 2821 (1956).

(4) R. Adams, "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 378, for a complete review on the Wolff–Kishner reaction up to 1951.

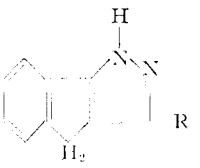
(5) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

(6) H. Leuchs and G. Kowalski, *Ber.*, **58B**, 2288 (1925).

(7) K. von Auwers, *Ann.*, **508**, 51 (1934).

(8) B. B. Elsner and K. J. Parker, *J. Chem. Soc.*, 593 (1957).

TABLE I: 1,4-DIHYDRO-3-SUBSTITUTED-INDENO[1,2-c]PYRAZOLES



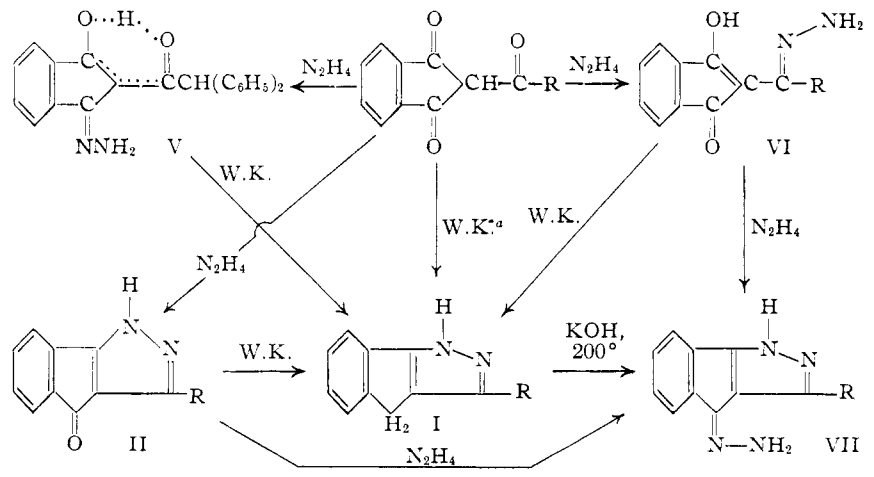
R	Method[a]	Yield, % (by Method a)	Purif. solvent	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen % Calcd.	Nitrogen % Found
CH_3	1, 4	97.2	EtOAc	183–184	$C_{11}H_{10}N_2$	77.61	77.87	5.92	5.83	16.46	16.47
C_2H_5	1, 2, 4	84.5	EtOH-H_2O	155.5–156	$C_{12}H_{12}N_2$	78.25	78.22	6.70	6.57	15.32	15.32
$CH(CH_3)_2$	1, 4	58.2	EtOAc	115–116	$C_{13}H_{14}N_2$	78.75	78.57	7.12	7.12	14.10	14.50
$C(CH_3)_3$	1, 3	91.9	EtOH-H_2O	173.5–174	$C_{14}H_{16}N_2$	79.20	79.49	7.60	7.71	13.20	13.20
$(CH_2)_4CH_3$	1	93.1	*n*-C_7H_{16}	92–93	$C_{15}H_{18}N_2$	...	...	...	...	12.41	12.39
$CH_2C_6H_5$	1, 3, 4	87.8	EtOH	154.5–155	$C_{17}H_{14}N_2$	82.90	82.87	5.73	5.76	11.38	11.67
$CH(C_6H_5)_2$	1, 2	80.0	EtOH	173–174	$C_{23}H_{18}N_2$	85.68	85.54	5.63	5.61	8.69	8.61
α-$C_{10}H_7$	1	96.2	EtOH-H_2O	122–123	$C_{20}H_{14}N_2$	85.08	84.92	5.01	5.01	9.95	10.09

[a] (1) Wolff–Kishner reduction of 2-acyl-1,3-indandione. (2) Wolff–Kishner reduction of monohydrazone of 2-acyl-1,3-indandione. (3) Wolff–Kishner reduction of 3-substituted-indeno[1,2-c]pyrazol-4(1*H*)-one (VI). (4) Reaction of 3-substituted-indeno-[1,2-c]pyrazol-4(1*H*)-one hydrazone (VII) with potassium hydroxide at 200°.

Experimental[9]

2-Acyl-1,3-indandiones.—The 2-acyl-1,3-indandiones were prepared by the reaction of dimethyl phthalate and the corresponding methyl ketones in the presence of sodium methoxide according to the method of Kilgore.[10]

Monohydrazones of 2-Acyl-1,3-indandiones.—The preparation and proof of structure of these compounds has been described earlier.[2]



[a] W.K. = Reaction under conditions of the Huang-Minlon modification of the Wolff–Kishner reduction.

1,4-Dihydro-3-*t*-butylindeno(1,2-c)pyrazole (Wolff–Kishner Reduction of 2-Pivalyl-1,3-indandione).—A mixture of 2.00 g. (0.0087 mole) of 2-pivalyl-1,3-indandione and 30 ml. of diethylene glycol was treated with 1.0 ml. (0.03 mole) of hydrazine hydrate. The mixture was heated gradually over a period of one hour to a temperature of 150° in an open flask. Excess potassium hydroxide (1 g.) was added and the temperature was raised to 200° and kept at this temperature for one hour. After cooling, the clear yellow solution was poured into 200 ml. of ice-water and the resulting white precipitate was filtered, washed with water and dried (1.69 g., 91.9%). 1,4-Dihydro-3-*t*-butylindeno(1,2-c)pyrazole had m.p. 173.5–174° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.20; H, 7.70; N, 13.20. Found: C, 79.49; H, 7.71; N, 13.20.

(9) Microanalyses are by the Geller Microanalytical Laboratories, West Englewood, N. J. All melting points are corrected.

(10) L. B. Kilgore, J. H. Ford and W. C. Wolfe, *Ind. Eng. Chem.*, **34**, 494 (1942).

The preparation and properties of the other compounds of this type are summarized in Table I. The same method of synthesis was used. All of these compounds have a strong band at 3.10–3.30 μ (hydrogen bonded N–H) in their infrared spectra. The band at 6.21–6.31 μ is due to the C=C and/or C=N bonds. Other maxima that these compounds have in common are: 6.80–6.85, 9.19–9.34 and 10.07–10.13 μ.

Benzenesulfonamide of 1,4-Dihydro-3-benzylindeno(1,2-c)-pyrazole (VIII).—A 0.50-g. (0.0024 mole) sample of 1,4-dihydro-3-benzylindeno(1,2-c)-pyrazole was mixed with 10 ml. of 10% aqueous sodium hydroxide and 1.0 ml. of benzenesulfonyl chloride. The mixture was shaken vigorously at room temperature. The heavy, oily solid was filtered, washed with ether and dried to give 0.62 g. (79.0%) of the benzenesulfonamide. Recrystallization from ethanolic dimethylformamide gave white crystals, m.p. 169.5–170.5°.

Anal. Calcd. for $C_{23}H_{18}N_2SO_2$: C, 71.48; H, 4.69; N, 7.25. Found: C, 71.45; H, 5.09; N, 7.24.

Benzamide of 1,4-Dihydro-3-benzylindeno(1,2-c)pyrazole (IX).—A mixture of 1,4-dihydro-3-benzylindeno(1,2-c)pyrazole (0.5 g., 0.0024 mole), 5 ml. of dry pyridine, 10 ml. of dry benzene and about 0.5 g. of benzoyl chloride was heated for 30 minutes in a hot water-bath. The mixture was poured into 100 ml. of cold water. The benzene layer was removed, washed with 5% sodium carbonate solution and dried over magnesium sulfate. The benzene solution was filtered and evaporated to dryness. The resulting sweet-smelling oil was allowed to stand at room temperature and after three days the oil crystallized. Recrystallization from anhydrous ethanol gave beautiful, white needles, m.p. 95–96°; infrared spectrum (1% in KBr), no N–H band, 5.91 μ (amide C=O), 6.22 μ (C=C and/or C=N).

Anal. Calcd. for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.06; N, 8.00. Found: C, 82.77; H, 5.07; N, 8.09.

Wolff–Kishner Reduction of the Monohydrazone of 2-Acetyl-1,3-indandione.—The monohydrazone of 2-acetyl-1,3-indandione (0.73 g., 0.0036 mole) was added to 25 ml. of diethylene glycol and treated with 1.0 ml. of hydrazine hydrate. The temperature was raised slowly to 125°. Excess potassium hydroxide (1 g.) was added and the temperature was raised to 200° and kept there for one hour. The

clear yellow solution was cooled and poured into 200 ml. of cold water. The white precipitate was filtered, washed with 50 ml. of water and dried to give 0.60 g. (98.4%) of 1,4-dihydro-3-methylindeno(1,2-c)pyrazole, m.p. 183–184°, no depression in melting point with authentic sample.

Wolff–Kishner Reduction of 2-Diphenylacetyl-1,3-indandione 1-Hydrazone.—One gram (0.0024 mole) of 2-diphenylacetyl-1,3-indandione 1-hydrazone was reduced using the same procedure as in the previous experiment. Diethylene glycol (30 ml.) was the solvent and 1.5 ml. of hydrazine hydrate and 1 g. of potassium hydroxide was used. The white crystalline product was washed with water and dried to give 0.65 g. (70.7%) of 1,4-dihydro-3-diphenylmethylindeno(1,2-c)pyrazole, m.p. 172–174°, mixed m.p. with an authentic sample was also 172–174°.

3-*t*-Butylindeno(1,2-c)pyrazol-4(1H)-one.—To 6.90 g. (0.03 mole) of 2-pivalyl-1,3-indandione in 150 ml. of ethanol was added 1.5 g. (0.03 mole) of hydrazine hydrate. The clear yellow solution was heated at reflux for 48 hours. After cooling, the solution was diluted with one liter of cold water. The white solid was filtered, dried and recrystallized from aqueous methanol (using decolorizing charcoal); m.p. 198–199°, 87.2% yield as white plates.

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38; mol. wt., 246. Found: C, 75.02; H, 6.27; N, 12.19; mol. wt. (Rast), 252.

The Wolff–Kishner reduction of 3-*t*-butylindeno(1,2-c)-pyrazol-4(1H)-one gave 1,4-dihydro-3-*t*-butylindeno(1,2-c)-pyrazole in 87.2% yield.

3-Isobutylindeno(1,2-c)pyrazol-4(1H)-one Hydrazone.—To a mixture of 2.09 g. (0.015 mole) of 2-isobutyl-1,3-indandione in 100 ml. of anhydrous ethanol was added 1.02 g. (0.032 mole) of anhydrous hydrazine. The resulting clear yellow solution was heated at reflux for 45 hours. Upon cooling, 2.08 g. (61.2%) of a white crystalline solid was obtained, m.p. 227–228° (placed in apparatus at 220°). After three recrystallizations from ethanol the m.p. was not changed; however, upon slow heating the compound did not melt up to 360°.

Anal. Calcd. for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.77. Found: C, 68.95; H, 6.13; N, 24.10.

Using the same procedure the following are prepared: **3-methylindeno(1,2-c)pyrazol-4(1H)-one hydrazone**, 88.1%, m.p. 250–255°. *Anal.* Calcd. for $C_{11}H_{10}N_4$: C, 66.65; H, 5.09; N, 28.27. Found: C, 66.33; H, 5.03; N, 28.45. **3-Ethylindeno(1,2-c)pyrazol-4(1H)-one hydrazone**, 53.4%, m.p. 263–264°. *Anal.* Calcd. for $C_{12}H_{12}N_4$: C, 67.32; H, 5.69; N, 26.34. Found: C, 67.22; H, 5.79; N, 26.34 and **3-Benzylindeno(1,2-c)pyrazol-4(1H)-one hydrazone**, 86.8%, m.p. 263–264°. *Anal.* Calcd. for $C_{17}H_{14}N_4$: C, 74.45; H, 5.15; N, 20.43. Found: C, 74.50; H, 5.33; N, 20.12. All of these compounds are converted to the corresponding 1,4-dihydro-3-substituted-indeno(1,2-c)pyrazoles in 80 to 98% yield simply by heating to 200° for one hour with excess potassium hydroxide in diethylene glycol.

NEWARK, DEL.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, RESEARCH DIVISION, AMERICAN CYANAMID CO.]

The Synthesis of Some 1,2,4-Oxadiazolidinones

BY S. R. SAFIR AND R. J. LOPRESTI

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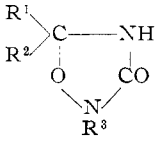
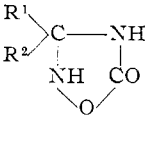
The reaction of ethyl (1,1-diphenylmethylene)-carbamate with hydroxylamine in the presence of alkoxide ion gives rise to 3,3-diphenyl-1,2,4-oxadiazolidin-5-one. The reaction of (1,1-diphenylmethylene)-carbamoyl chloride with hydroxylamine gives an isomeric product, 5,5-diphenyl-1,2,4-oxadiazolidin-3-one.

The widespread use of barbituric acid and hydantoin derivatives in medicine during the past twenty-five years has stimulated great interest in the search for related heterocyclic systems which would provide useful drugs, particularly those with action on the central nervous system. While several dozen systems have been studied, only a few, of which the 2,4-oxazolidinediones,[1] the succinimides[2] and the 2,4-piperidinediones[3] are examples, have yielded clinically useful products. The 1,2,4-oxadiazolidin-3-one nucleus (Ia), a previously unknown system combining some of the structural features of the



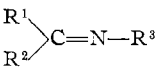


Ia, $R^1 = R^2 = R^3 = H$
Ib, $R^1 = R^2 = C_6H_5$, $R^3 = H$
Ic, $R^1 = R^2 = C_6H_5$, $R^3 = CH_3$

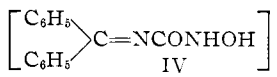
IIa, $R^1 = R^2 = H$
IIb, $R^1 = R^2 = C_6H_5$

barbiturates, the hydantoins and the oxazolidinediones, appeared to be an appropriate nucleus for investigation. The synthesis of several diphenyl derivatives of Ia and the isomeric system, 1,2,4-oxadiazolidin-5-one (IIa), is the subject of this paper.

The starting point for this work is based on the observation by Banfield, *et al.*,[4] that N-acyldiarylketimines (IIIa) form addition products with alcohols and amines. Ethyl (1,1-diphenylmethylene)-carbamate (IIIb) was prepared by the method of Banfield, *et al.*,[4] but attempts to form adducts with either methanol or acetoxime were unsuccessful. Because of this lack of reactivity it was thought that the carbamate could be made to react with hydroxylamine in the presence of alkoxide ion to give a presumably unstable hydroxamic acid IV which would then cyclize spontaneously to Ib.



IIIa, $R^1 = R^2$ = aryl, R^3 = acyl
IIIb, $R^1 = R^2 = C_6H_5$, $R^3 = COOC_2H_5$
IIIc, R^1 = aryl, R^2 = alkyl, R^3 = acyl



When this reaction was carried out, a small amount

(1) (a) M. A. Spielman, THIS JOURNAL, **66**, 1244 (1944); (b) G. M. Everett and R. K. Richards, *J. Pharmacol. Exptl. Therap.*, **81**, 402 (1944).

(2) (a) C. A. Miller and L. M. Long, THIS JOURNAL, **73**, 4895 (1951); (b) G. Chen, R. Portman, C. R. Ensor and A. C. Bratton, Jr., *J. Pharmacol. Exptl. Therap.*, **103**, 54 (1951).

(3) (a) O. Schnider, H. Frick and A. H. Lutz, *Experientia*, **10**, 135 (1954); (b) Von B. Pellmont, A. Studer and R. Jürgens, *Schweiz. med. Wochschr.*, **85**, 350 (1954).

(4) J. E. Banfield, G. M. Brown, F. H. Davey, W. Davies and T. H. Ramsay, *Austr. J. Sci. Research*, **A1**, 330 (1948).