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

Monohydrazones of 2-Acyl-1,3-indandiones[1]

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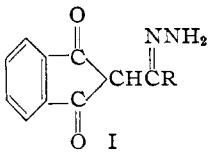
The monohydrazones of 2-acetyl-, 2-propionyl- and 2-phenylacetyl-1,3-indandione have been prepared and the hydrazone group shown to be on the side chain. 2-Diphenylacetyl-1,3-indandione 1-hydrazone was prepared by the reaction of 2-diphenylacetyl-1,3-indandione with excess hydrazine in aqueous methanol. A series of mixed azines from these hydrazones and acetophenone was prepared. The azine derived from 2-diphenylacetyl-1,3-indandione 1-hydrazone and acetophenone was strongly fluorescent.

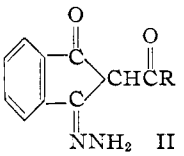
The purpose of this work was to prepare the monohydrazones of a group of 2-acyl-1,3-indandiones and to determine at which carbonyl group the hydrazine attacks. There is no record in the literature of the reaction of hydrazine with 2-acyl-1,3-indandiones.

Several 2-acyl-1,3-indandiones have been reported by Schwerin,[2] others were prepared by Kilgore,[3] and Thomas[4] synthesized 2-diphenylacetyl-1,3-indandione.

There are two possible classes of mono-hydrazones obtainable from 2-acyl-1,3-indandiones



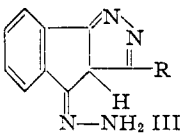
I



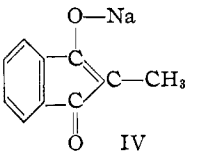
II

It has been found that an excellent yield of only one type of monohydrazone is obtained for any one 2-acyl-1,3-indandione. The type of monohydrazone obtained is determined by the nature of the R group. The monohydrazones of 2-acetyl-, 2-propionyl- and 2-phenylacetyl-1,3-indandione are readily prepared by refluxing equimolar quantities of the tri-ketone with hydrazine in ethanol for from one to three hours. The results are shown in Table I. Under the above conditions no monohydrazone of 2-diphenylacetyl-1,3-indandione could be obtained. The only product was a gummy brown material which could not be characterized. However, if a three-fold excess of hydrazine was used, with aqueous methanol as solvent, a monohydrazone of 2-diphenylacetyl-1,3-indandione could be obtained in excellent yield. The properties of this monohydrazone were quite different from those derived from the other 2-acyl-1,3-indandiones and led us to suspect a basic difference in structure for 2-diphenylacetyl-1,3-indandione monohydrazone.

The monohydrazones of 2-acetyl-, 2-propionyl- and 2-phenylacetyl-1,3-indandione gave a positive Tollens test[5] while the monohydrazone of 2-diphenylacetyl-1,3-indandione does not react. According to Mulliken[6] a positive Tollens test can be anticipated for hydrazones whenever the carbon atom of the carbonyl group that would be formed in case of hydrolysis is situated in an open chain, but it may not be satisfactory in cases when this atom is situated in a cyclic nucleus, as in structure II.[7] This test would suggest that in the monohydrazone of 2-diphenylacetyl-1,3-indandione the hydrazone group is on the indan ring while in all the other 2-acyl-1,3-indandiones studied the hydrazone group is on the side chain.



III



IV

Further support for this postulate is obtained from the reaction of the monohydrazones with dilute aqueous sodium hydroxide. 2-Acetyl-, 2-propionyl- and 2-phenylacetyl-1,3-indandione monohydrazones dissolve rapidly in dilute base to give a bright red solution. From the red solution can be recovered a red crystalline salt which also gives a positive Tollens test. This indicates that the hydrazone group is still present and is not involved in the red color formation. The color of the red solution is the same as that given in aqueous base by 1,3-indandione, 2-methyl- or 2-phenyl-1,3-indandione which Hantzsch[8] proposed was due to the formation of a salt of type IV. The red color of the alkaline solution of the monohydrazones of 2-acetyl-, 2-propionyl- and 2-phenylacetyl-1,3-indandione strongly suggests the existence of the 1,3-indandione group or its enol and the presence of the hydrazone group on the side chain. 2-Diphenylacetyl-1,3-indandione monohydrazone did not react with dilute aqueous base; however, a stable, yellow potassium salt was obtained by using warm alcoholic potassium hydroxide.

The presence of a hydrazone group in all of these compounds is further confirmed by the formation of mixed azines with acetophenone. Other workers[9] have prepared a number of mixed azines by the reaction of the hydrazone of a less reactive carbonyl compound with a reactive carbonyl compound. The only reference to azines from any indandiones is the preparation of the symmetrical azine, 2-

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

(2) W. Schwerin, *Ber.*, **27**, 104 (1894).

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

(4) D. Thomas, U. S. Patent 2,672,483, March, 1954.

(5) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," J. Wiley and Sons, Inc., New York, N. Y., 1956, p. 162.

(6) S. P. Mulliken, "Identification of Pure Organic Compounds," Vol. 2, Stanhope Press, Boston, Mass., 1916, p. 29.

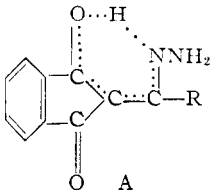
(7) Compounds III (R = CH_3–, C_2H_5) have been prepared in this Laboratory and these compounds give a negative Tollens test indicating that a 1-hydrazone group on an indan ring is unreactive with Tollens reagent.

(8) A. Hantzsch, *Ann.*, **392**, 286 (1912).

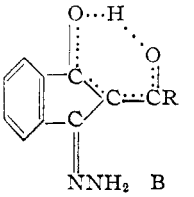
(9) (a) H. Widland and A. Roseeu, *Ann.*, **381**, 229 (1911); (b) E. R. Blout, V. W. Eager and R. M. Gofstein, THIS JOURNAL, **68**, 1983 (1946).

TABLE I

MONOHYDRAZONES OF 2-ACYL-1,3-INDANDIONES



A



B

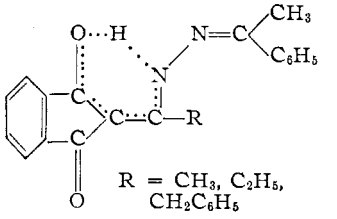
Structure	R	Yield, %	M.p., °C.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
A	CH_3	94.1	231–231.5	$C_{11}H_{10}N_2O_2$	65.33	65.38	4.99	4.94	...	...
A	C_2H_5	85.7	210	$C_{12}H_{12}N_2O_2$	...	...	..	..	12.95	12.84
A	$C_6H_5CH_2$	93.9	177–178	$C_{17}H_{14}N_2O_2$	73.48	73.36	5.06	5.10	10.17	10.09
B	$(C_2H_5)_2CH$	97.2	305	$C_{23}H_{18}N_2O_2$	77.95	77.92	5.12	5.11	7.90	8.10

[a] All compounds melt with decomposition and liberation of gas. Melting points are not corrected.

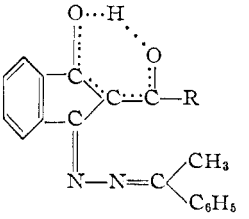
nitro-1,3-indandione azine.[10] The results of the mixed azines of acetophenone are summarized in Table II. It is of particular interest to note that compound 4 (Table II) is the only one of this group that is fluorescent in ultraviolet light and is a new type of fluorescent structure. A detailed explanation of this fluorescence will be published at a later date.

The infrared spectra of compounds 3 and 4 (Table II) were studied and were found to be consistent with the proposed structures. Neither compound has any bands in the –OH or –NH region. Compound 4 has a strong band at 5.96 μ, due to the C=N bond. There is also strong absorption in the 6.3 μ region which arises from a β-diketone group involved in conjugate chelation.[11] Compound 3 has a band at 5.92 μ (conjugated C=O) and the C=N band is shifted to 6.07 μ. There is also strong absorption in the 6.3 μ region, but in this case it is probably due to the interaction of the hydroxyl group on the indan ring and the nitrogen of the C=N bond.

TABLE II



R = CH_3, C_2H_5, $CH_2C_6H_5$



R = $CH(C_6H_5)_2$

Compound no.	R	Fluorescence	M.p., °C.[c]	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
1	CH_3	[a]	220.5–221.5	$C_{19}H_{16}N_2O_2$	9.21	9.22
2	C_2H_5	[a]	208–209	$C_{20}H_{18}N_2O_2$	8.80	8.76
3	$C_6H_5CH_2$	[a]	228.5–229	$C_{25}H_{20}N_2O_2$	7.37	7.49
4	$(C_6H_5)_2CH$	[b]	239.5–240	$C_{31}H_{24}N_2O_2$	6.13	6.02

[a] No fluorescence under ultraviolet light. [b] Strong yellow fluorescence under ultraviolet light. [c] Melting points are corrected.

A possible explanation for the difference in the position of attack by hydrazine on 2-acyl-1,3-indandiones is obtained by the examination of the Fisher–Hirschfelder models of these tri-ketones. In 2-diphenylacetyl-1,3-indandione the two phenyl groups crowd the side chain carbonyl. This could be the cause of the attack of hydrazine on the indandione carbonyl instead of on the side chain carbonyl, as was the case with the other less hindered 2-acyl-1,3-indandiones.

(10) V. Vitols and G. Vanags, *J. Gen. Chem.* (*U.S.S.R.*), **25**, 580 (1951).

(11) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," J. Wiley and Sons, Inc., New York, N. Y., 1945, p. 123.

Experimental[12]

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

Preparation of the Monohydrazone of 2-Acetyl-1,3-indandione.—A mixture of 2-acetyl-1,3-indandione (1.9 g., 0.01 mole), 100 ml. of absolute ethanol and anhydrous hydrazine (0.34 g., 0.01 mole) was heated at reflux with vigorous stirring. After three hours the reaction mixture was cooled and filtered. The yellow crystals were washed with cold ethanol. The material was insoluble in water, ethyl alcohol and ethyl acetate but soluble in hot ethyl alcohol and ethyl acetate. The product was recrystallized from ethyl acetate and dried over P_2O_5; yield 1.9 g. (94.0%), m.p. 238–239°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.99. Found: C, 65.38; H, 4.94.

The monohydrazones of 2-propionyl- and 2-phenylacetyl-1,3-indandione were prepared in the same way (Table I).

2-Diphenylacetyl-1,3-indandione 1-Hydrazone.—To a suspension of 2-diphenylacetyl-1,3-indandione (68.00 g., 0.2 mole) in 600 ml. of water and 150 ml. of methanol was added 20.2 g. (0.6 mole) of hydrazine (95%) with vigorous stirring. A clear yellow solution was obtained. After refluxing for two hours the yellow solid that had formed was filtered, washed with three 100-ml. portions of water, then two 100-ml. portions of ether. The yellow crystals were dried at 100° and weighed 68.9 g. (97.3%). Recrystallization from ethanol–dimethylformamide gave a product which melted at 305° dec.

Anal. Calcd. for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.90. Found: C, 77.92; H, 5.11; N, 8.10.

The yield of desired product is critically affected by the solvent ratio (larger amounts of methanol decrease the yield, but with only water as solvent none of the desired product is obtained). The excess hydrazine is essential since if all other reaction conditions are kept constant and the ratio of triketone to hydrazine is changed the following yields of the monohydrazone were obtained: 1:1 ratio, 0%; 1:2 ratio, 65.4%. It was also found that the time of reflux was crucial since using the normal procedure except with a reflux period of 24 hours none of the desired product was obtained due to cyclization of the monohydrazone.

2-Acetyl-1,3-indandione 2-Azine with Acetophenone.—A mixture of 2-acetyl-1,3-indandione monohydrazone (3.00 g., 0.0149 mole) and acetophenone (1.80 g., 0.015 mole) in 30 ml. of chloroform was treated with a drop of concentrated hydrochloric acid as catalyst and the mixture was refluxed for 15 minutes. The clear yellow solution was filtered while

(12) Microanalyses are by the Geller Microanalytical Laboratories, West Englewood, N. J.

hot. Ten ml. of this was added to the filtrate and after cooling the yellow needles were collected and dried. The azine was recrystallized from methanol to give silky needles, m.p. 220.5–221.5°, yield 2.96 g. (65.3%).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: N, 9.21. Found: N, 9.22.

Compounds 2, 3 and 4 (Table II) were prepared in the same way.

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[CONTRIBUTION FROM NEW MEXICO HIGHLANDS UNIVERSITY AND ARIZONA STATE COLLEGE]

Potential Purine Antagonists. XI. Synthesis of Some 9-Aryl(alkyl)-2,6-disubstituted Purines

BY HENRY C. KOPPEL AND ROLAND K. ROBINS[1]

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The preparation of various 9-aryl(alkyl)-2,6-dihydroxypurines (III) has been accomplished by the treatment of the corresponding 9-aryl(alkyl)-2,6-dihydroxy-8-purinethiol (II) with Raney nickel. This type of synthesis has been extended to the preparation of several 2-amino-9-alkyl-6-hydroxypurines (X) from IX. 2,6-Dihydroxy-9-phenylpurine (III, R = C_6H_5) was treated with phosphorus oxychloride and phosphorus pentachloride to give 2,6-dichloro-9-phenylpurine (IV). Several new 9-phenyl-2,6-disubstituted purines have been prepared from IV. 2-Amino-9-methyl-6-purinethiol (XI) has been prepared.

During the course of a program designed for the preparation of new biologically active purine antagonists, it appeared desirable to synthesize certain 9-aryl-2,6-disubstituted purines. A survey of the literature revealed only a patent reference[2] to the preparation of 9-phenylxanthine (9-phenyl-2,6-dihydroxypurine). Biltz and co-workers[3] successfully synthesized 2,6-dihydroxy-9-methylpurine by the treatment of uramil with methyl isothiocyanate and cyclized the substituted thiourea (I, R = CH_3) with concentrated hydrochloric acid to give 2,6-dihydroxy-9-methyl-8-purinethiol (II, R = CH_3). This compound (II, R = CH_3) was then treated with nitrous acid to give 2,6-dihydroxy-9-methylpurine (III, R = CH_3). This synthetic route succeeded for the preparation of 2,6-dihydroxy-9-ethylpurine (III, R = C_2H_5), but when 2,6-dihydroxy-9-phenyl-8-purinethiol (II, R = C_6H_5) was treated with nitrous acid by Biltz, *et al.*,[3] the expected 2,6-dihydroxy-9-phenylpurine (III, R = C_6H_5) was not obtained. Blicke and Schaaf[4] have recently utilized Raney nickel to remove the 8-mercapto group of several 9-alkyl-1,3-dimethylpurine - 2,6 - dione - 8 - thiols. Following this lead, 2,6-dihydroxy-9-phenyl-8-purinethiol (II, R = C_6H_5) was treated with Raney nickel in a sodium hydroxide solution to yield 2,6-dihydroxy-9-phenylpurine (III, R = C_6H_5) in 46% yield, or an over-all yield of 18% from uramil. In a similar manner, 9-*p*-chlorophenyl-2,6-dihydroxypurine (II, R = ClC_6H_4) was prepared from uramil in an over-all yield of 12%. This work was extended to include the preparation of -9-ethyl, -9-isobutyl and -9-methyl-2,6-dihydroxypurine by the removal of the 8-mercapto group with Raney nickel.

Since a rather large quantity of uramil was required for this study, it was found convenient to nitrosate barbituric acid after the manner of Bayer[5] and to reduce this product (violuric acid) with sodium hydrosulfite to give uramil. This procedure was found to be superior to the nitration of barbituric[6a] acid followed by the reduction of the 5-nitrobarbituric acid with stannous chloride to give uramil.[6b] Gulland[7] has reported that the chlorination of 2,6-dihydroxy-9-methylpurine with phosphorus oxychloride at 140° in a sealed tube gives 2,6 - dichloro - 9 - methylpurine. Preliminary efforts in this Laboratory to chlorinate 2,6-dihydroxy-9-methylpurine by refluxing phosphorus oxychloride with or without N,N-dimethylaniline were not successful. Treatment with phosphorus oxychloride and phosphorus pentachloride appeared to lead to degradation products. When 2,6-dihydroxy-9-phenylpurine (III, R = C_6H_5) was treated with phosphorus oxychloride for a relatively short period of time in the presence of phosphorus pentachloride, an ether-insoluble, phosphorus-containing compound was isolated from the reaction mixture. However, when the amount of phosphorus pentachloride was increased and the chlorination time extended to 40 hr., a 50% yield of 2,6-dichloro-9-phenylpurine (IV) was obtained. Treatment of IV with thiourea in refluxing alcoholic solution gave 9-phenyl-2,6-purinedithiol in good yield. When IV was treated with various amines in alcoholic solution, the corresponding 2-chloro-9-phenyl-6-substituted aminopurine (V) was obtained. Boiling dilute sodium hydroxide converted IV to 2-chloro-6-hydroxy-9-phenylpurine (VII). The assignment of structures of V and VII was made since Montgomery and Holum[8] recently have shown that with 2,6-dichloropurine the "6"-position is most readily attacked by nucleophilic reagents.

Treatment of III, R = C_6H_5, with phosphorus pentasulfide in pyridine gave 2-hydroxy-9-phenyl-6-purinethiol (VI). The assignment of structure to VI was made from the ultraviolet absorption spectrum which exhibited λ_{max} of 340 mμ at *p*H 11. The ultraviolet absorption above 300 mμ is characteristic of a 6-mercapto group.[9] This reaction is

(1) Department of Chemistry, Arizona State College, Tempe, Arizona. To whom inquiries regarding this paper should be sent.

(2) German Patent 120,437; *Chem. Zentr.*, **72**, I, 1219 (1901).

(3) H. Biltz, K. Strufe, E. Topp, M. Heyn and R. Rohl, *Ann.*, **423**, 200 (1921).

(4) F. F. Blicke and R. L. Schaaf, THIS JOURNAL, **72**, 5857 (1956).

(5) A. von Bayer, *Ann.*, **127**, 210 (1920).

(6) (a) W. W. Hartman and O. E. Shephard, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 440; (b) p. 617.

(7) J. M. Gulland, *J. Chem. Soc.*, 647 (1938).

(8) J. A. Montgomery and L. B. Holum, THIS JOURNAL, **79**, 2185 (1957).

(9) A. G. Beaman, *ibid.*, **76**, 5633 (1954).