atm.) gave fine needles, m.p. 191–192.5°. The phenylurethan of the volatile 2-hydroxybicyclo[3.2.1]octane was prepared by treating 50 mg. of phenyl isocyanate with 32 mg. of compound in 0.2 ml. of carbon tetrachloride. It had m.p. 127.5–128.0°.

Tests for S_N1 and S_N2 Reactivity.—The relative reactivity of the dichlorocarbene adducts and rearranged products was measured by their rates of reaction at room temperature with 0.1 *N* silver nitrate in ethanol, 1 *M* sodium iodide in acetone, and 15% potassium hydroxide in methanol (at 100°).

Acknowledgment.—The author is indebted to Dr. C. A. Reilly, of these laboratories, for the n.m.r. spectra and their interpretation.

Ring Expansion of 2-Alkyl-1-indanones to Isocarbostyril Derivatives[1]

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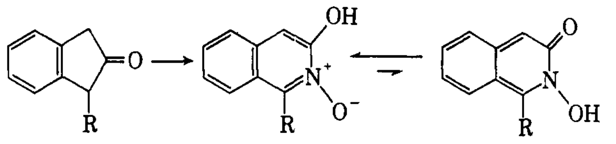
The nitrosation of 2-alkyl-1-indanones (4) under acid conditions leads to ring-expanded 2-hydroxy-3-alkylisocarbostyrils (6) in good yields *via* isolable precursors, the 2-alkyl-2-nitroso-1-indanones (5). The structure of 6 is confirmed by (i) independent synthesis–ozonization of 3-alkylisoquinoline 2-oxides (7); (ii) reduction of 6 to known 3-alkylisocarbostyril derivatives (8); and (iii) n.m.r. Tentative mechanisms for the ring expansions, 4 to 6 under strongly acid conditions and 5 to 6 in either base or acid media, are proposed.

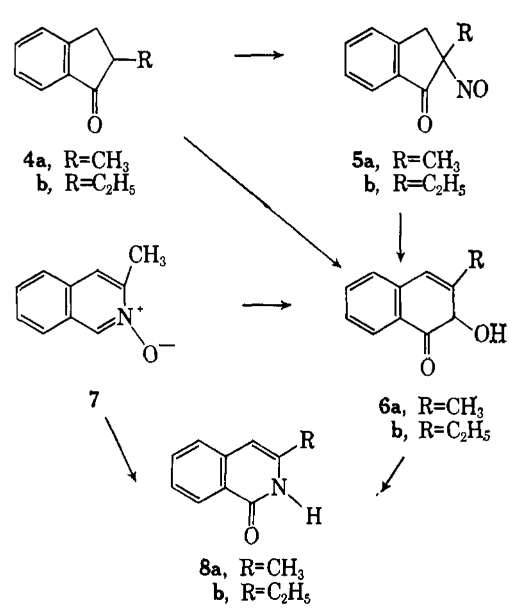
Our adventitious discovery that nitrosation of 1-alkyl-2-indanones (1) under alkaline conditions gave ring-expanded products tentatively formulated as 1-alkyl-3-hydroxyisoquinoline 2-oxides (2), or their energetically less favorable isoquinolone tautomers (3), has been reported recently.[2,3] Proof of structure of these cyclic hydroxamic acids has to date proven elusive. The postulated ring expansion, however, seemed to be in striking accord with the independent observations of Huebner and Kuehne in the nitrosation of isomeric 2-ethyl-1-indanone under acidic conditions.[4]



1a, R = CH_3
b, R = $CH_2OCH_2C_8H$ **2** **3**

In this communication we wish (i) to report that addition of *n*-butyl nitrite to a 1:1 molar equivalent of 2-alkyl-1-indanone–hydrochloric acid mixture produced 2-hydroxy-3-alkylisocarbostyrils (6) in good yield, and (ii) to provide unequivocal evidence for this novel ring expansion. Moreover, with lower acid concentration, and reversal of the mode of addition (acid to indanone–nitrite mixture), the stable precursors, 2-alkyl-2-nitroso-1-indanones (5), may be isolated. The over-all reaction sequence is shown in the diagram (col. 2).

Thus addition of excess *n*-butyl nitrite in toluene to a solution of 2-methyl-1-indanone (**4a**)/2-ethyl-1-indanone (**4b**) in toluene and 3 *N* hydrochloric acid in ethyl acetate at 0° produced, after four days, 2-hydroxy-3-methyl-isocarbostyril (**6a**)/2-hydroxy-3-ethylisocarbostyril (**6b**) in 65–68% yields. Similar reaction conditions, but a shorter reaction time, converted **4a** to the expected mixture of **5a** (6%) and **6a** (45%).



4a, R=CH_3
b, R=C_2H_5

5a, R=CH_3
b, R=C_2H_5

6a, R=CH_3
b, R=C_2H_5

8a, R=CH_3
b, R=C_2H_5

Further, the addition of several drops of concentrated hydrochloric acid to an ice-cooled solution of **4a**/**4b** and *n*-butyl nitrite in benzene gave a blue solution from which precipitated 2-methyl-2-nitroso-1-indanone (**5a**)/2-ethyl-2-nitroso-1-indanone (**5b**) in 61% yield. Upon increasing the acid concentration, but with identical reaction conditions, **4a** was converted to a mixture of **5a** (40%) and **6a** (12%). **5a** isomerized to **6a** rapidly in refluxing methanolic sodium methoxide solution and slowly in concentrated hydrochloric acid.

Threefold confirmation of the structure of the ring-expanded **6a** was achieved in the following manner.

(i) **6a** was independently synthesized in 15% yield *via* ozonization of 3-methylisoquinoline 2-oxide (**7**) in methylene chloride at 0° with one molar ozone equivalent.[5] The physical and chemical identity of the cyclic hydroxamic acid product **6a** produced by both ring expansion and ozonization are indisputable. Thus, for example, each, on treatment with benzoyl chloride in pyridine–aqueous sodium carbonate, gave identical N-benzoate esters.

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(1) (a) This research was supported in part by the U. S. Air Force under grant no. AF-AFOSR-62-18, monitored by the Air Force Office of Scientific Research, Office of Aerospace Research; (b) presented at the Metropolitan Regional Meeting, N. Y.–N. J. Sections of American Chemical Society, January 28, 1963, and at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, and at the XIXth IUPAC Congress, London, England, July 10–17, 1963.

(2) A. T. Blomquist and E. J. Moriconi, *J. Org. Chem.*, **26**, 3761 (1961).

(3) The rearrangement did not occur in acid media.

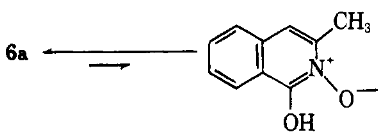
(4) Private communication from C. F. Huebner and M. E. Kuehne, Ciba Pharmaceutical Products, Inc.

(5) The scope of this ozonization reaction has been reported at the N. Y.–N. J. Metropolitan Regional Meeting of the American Chemical Society, January 22, 1962, and at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

(ii) Reduction of **6a** in glacial acetic acid with iodine and red phosphorus led, in 32% yield, to 3-methylisocarbostyril (**8a**), identical with an authentic sample of **8a** prepared by refluxing **7** with acetic anhydride.[6]

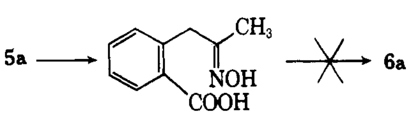
(iii) The n.m.r. spectrum of **6a** consists of four resonances with areas in the ratio of 3:1:4:1. These are assigned to a methyl group (2.53 p.p.m.), vinyl proton (6.40 p.p.m.), three ring protons plus hydroxyl proton (multiplet with one main peak at 7.47 p.p.m. and a broad base line), and the C-8 proton which is shifted further downfield by *peri*-carbonyl deshielding [doublet (J = 9 c.p.s.) centered at 8.32 p.p.m. further split into a pair of doublets (J = 3.5 c.p.s.)].[7]

Spectral evidence [absence of N-oxide absorption at 7.55 μ and 8.44 μ, both present as strong bands in 3-methylisoquinoline 2-oxide (**7**); an ultraviolet absorption spectrum more like 3-methylisocarbostyril (**8a**) than **7**], N-benzoate formation,[14] and failure of picrate formation[2] suggest the preponderance of **6a** rather than the tautomeric **9a**. Positive color tests, however, were obtained with ferric chloride[8] and acidified, alcoholic dimethylaniline (N-oxide).[9]



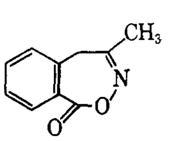
9a

It was of interest to determine whether the observed ring expansion **5a** → **6a** proceeded *via* the intermediacy of the ring-opened oximino acid **10**.



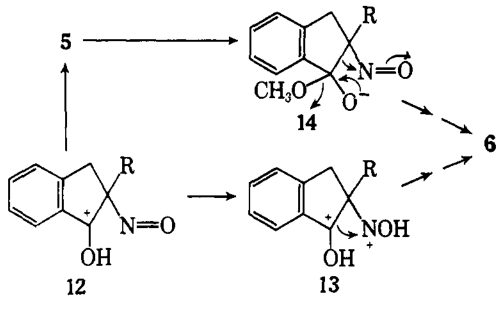
10

Treatment of **10**, however, under the conditions of acid-catalyzed isomerization of **5a** to **6a** led to an 87% recovery of **10** and no **6a**. Further, fusion of **10** at 165–175° for fifteen minutes produced Gottlieb's "anhydro derivative" as red-orange needles of probable structure **11**.[10]



11

Perhaps the simplest mechanism to explain all the facts would initially involve nitrosation of the enolic form of **4** in acid media to yield **12**. In low acid concentration, loss of a proton from this conjugate acid would lead to the observed intermediate **5**, while further protonation of **12** under more strongly acidic conditions would lead to **13** and thence to **6**. The base-catalyzed conversion of **5** to **6** is also depicted as a concerted elimination–ring expansion without ring opening *via* **14**.[11]



Experimental

The n.m.r. spectrum was taken in deuteriochloroform with tetramethylsilane as internal reference, using a Varian Associates spectrometer Model A-60 Mc./sec. Infrared spectra were recorded on Perkin-Elmer Models 21 and 137 recording infrared spectrophotometers with sodium chloride optics unless otherwise stated. Ultraviolet spectra were run on a Cary 15 recording spectrophotometer. Melting points were determined on a Kofler micro hot stage and are corrected. The ozonator used in this research was a Welsbach Corporation T-23 laboratory ozonizer. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory.

2-Hydroxy-3-methyl-isocarbostyril (6a) and 2-Hydroxy-3-ethylisocarbostyril (6b).—To a solution of 8.0 g. (0.055 mole) of 2-methyl-1-indanone [b.p. 83–85° (2.5 mm.); lit.[12] b.p. 88–90° (3 mm.)] in 100 ml. of toluene at 0° was added with stirring, 70 ml. of 3 N hydrochloric acid in ethyl acetate. To this solution was then added slowly 8 ml. (0.068 mole) of freshly prepared n-butyl nitrite in 25 ml. of toluene. The solution was stirred for 1 hr. at 0° and an additional hour at room temperature. Color changes during the reaction ranged from green to bright orange. The resulting two layers were separated; the more dense layer on refrigeration (4 days) gave crude **6a**, while the upper layer upon concentration *in vacuo* and refrigeration also gave impure **6a**. Recrystallization of the combined solids from carbon tetrachloride gave **6a** (6.6 g., 69%) as white plates, m.p. 172.5–173° (sublimed). Infrared: $\lambda_{\max}^{\mathrm{KBr}}$ 6.02 μ s (C=O), 6.14 s and 6.25 s (C=C)[13]; no free OH. Ultraviolet: $\lambda_{\max}^{\mathrm{EtOH}}$ 249 mμ (ϵ 9100), 291 (8500).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.52; H, 5.05; N, 8.00.

If the resulting two layers were concentrated in volume until the mixture was turbid, followed by refrigeration for 3–4 hr., a mixture of **5a** and **6a** precipitated. Recrystallization of this crude material from carbon tetrachloride gave 45% of **6a**; the carbon tetrachloride-insoluble residue was triturated with ethanol to give 6% of **5a**.

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[6] M. M. Robison and B. L. Robison, *J. Org. Chem.*, **21**, 1337 (1956); M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.*, **80**, 3443 (1958).

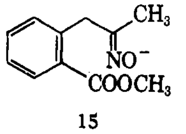
[7] We are indebted to Dr. James N. Shoolery of Varian Associates for his help in interpreting the n.m.r. spectrum.

[8] R. L. Schriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 122.

[9] N. A. Coats and A. R. Katritzky, *J. Org. Chem.*, **24**, 1836 (1959).

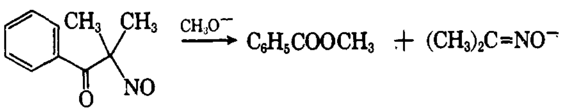
[10] J. Gottlieb [*Ber.*, **32**, 966 (1899)] cyclodehydrated **10** by heating to its melting point. The product obtained, m.p. 171–173°, had a low carbon analysis, and was later described in Beilstein [**27**, 210 (1937)] as red needles and assigned structure **11**. The nonidentity of our fused product, m.p. 175–177°, with **6a**, m.p. 172.5–173°, was established by a comparison of infrared spectra and a considerably depressed mixture melting point.

[11] A reasonable alternative pathway might be a ring opening of **14** to the oximino ester derivative **15** followed by cyclization with elimination to **6**,



15

as previously suggested for **1** → **2**.[2] Thus Huebner and Kuehne[4] have prepared the open chain nitroso ketone **16** and it reacted normally to give the expected cleavage products.



16

[12] J. Colonge and G. Weinstein, *Bull. soc. chim. France*, 462 (1952).

[13] *Cf.* with infrared absorptions reported for 2-hydroxyisocarbostyril: 6.14 μ (C=O); 6.21 μ and 6.29 μ (ring).[6]

Using a 4-day reaction time, 2-ethyl-1-indanone [b.p. 103–104° (4–4.5 mm.), lit.[12] b.p. 127° (12 mm.)] was converted in 65% yield to **6b**, m.p. 154–155° (sublimed), as white plates. Infrared: $\lambda_{\max}^{\text{KBr}}$ 6.04 μ s (C═O); 6.15 s and 6.26 s (C═C)[13]; no free OH. Ultraviolet: $\lambda_{\max}^{\text{EtOH}}$ 248 mμ (8300), 291 (7400).

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.82; H, 5.85; N, 7.42.

The N-benzoate esters of 6a and 6b were obtained on benzoylation of **6a**/**6b** with benzoyl chloride in pyridine–aqueous sodium carbonate. The N-benzoate ester of **6a** was obtained as white needles, m.p. 167–168° (from 95% ethanol). Infrared: $\lambda_{\max}^{\text{KBr}}$ 5.63 μ s and 5.95 s (C═O's).[14] Ultraviolet: $\lambda_{\max}^{\text{EtOH}}$ 233 mμ (31,000), 276 (10,200), 325 (4100).

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.14; H, 4.88; N, 4.95.

The N-benzoate ester of **6b** was obtained as pale, pink needles, m.p. 149–150° (from 95% ethanol). Infrared: $\lambda_{\max}^{\text{KBr}}$ 5.64 μ s and 5.94 s (C═O's).[14] Ultraviolet: $\lambda_{\max}^{\text{EtOH}}$ 231 mμ (31,400), 277 (10,500), 320 (4600).

Anal. Calcd. for $C_{18}H_{15}NO_3$. C, 73.70; H, 5.15; N, 4.78. Found: C, 73.73; H, 5.21; N, 4.60.

2-Methyl-2-nitroso-1-indanone (5a) and 2-Ethyl-2-nitroso-1-indanone (5b).—To a stirred, ice-cold solution of 3 g. (0.020 mole) of **4a** in 25 ml. of benzene was added 3.5 ml. of freshly prepared *n*-butyl nitrite. Three drops of concentrated hydrochloric acid was added. On standing at room temperature for 1 hr., crude **5a** began to precipitate from solution. After 2 hr., the precipitate was filtered and triturated with ethanol to give 2.2 g. (61%) of **5a** as pale white plates, m.p. 145–147°. Infrared: $\lambda_{\text{C=O}}^{\text{KBr}}$ 5.78 μ s.[15]

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.55; H, 5.18; N, 8.00. Found: C, 68.81; H, 5.39; N, 8.00.

Similarly **4b** led to **5b** in 61% yield, m.p. 134–135°, as white plates on trituration with ethanol. Infrared: $\lambda_{\text{C=O}}^{\text{KBr}}$ 5.77 s.[15]

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.94; H, 5.90; N, 7.70.

In experiments with higher acid concentrations, 20 drops of concentrated hydrochloric acid was used. Under these conditions, a crude mixture of **5a** and **6a** precipitated on standing at room temperature several hours. This mixture, m.p. 147–157°, was extracted with hot carbon tetrachloride. The insoluble material, on trituration with ethanol, gave 40% of **5a**. The carbon tetrachloride extract was concentrated and then refrigerated, to yield 12% of **6a**.

Ring Expansion of 5a/5b to the Corresponding 6a/6b. With Sodium Methoxide.—One gram of **5a** was refluxed for 2.5 hr. in a methanolic solution in which 0.25 g. of sodium had been previously dissolved. Upon evaporation of the solvent and cooling, the sodium salt of **6a** separated. This was filtered, dissolved in hot water, and acidified with dilute hydrochloric acid to yield crude **6a**. This material was filtered and recrystallized once from carbon tetrachloride to yield 0.80 g. (80%) of **6a**, m.p. 172–173° (sublimed). Similarly **5b** was converted to **6b** in identical yields. Extension of the reflux period to 6.5 hr. did not enhance the yields in either case.

With Concentrated Hydrochloric Acid.—One gram of **5a** was refluxed for 5 hr. in 50 ml. of concentrated hydrochloric acid. It dissolved very slowly. The yellow solution was evaporated to one-half its volume, cooled, filtered, and the solid, which was a mixture of unreacted **5a** and product **6a**, collected. This residue was extracted with hot carbon tetrachloride to lead ultimately to 0.71 g. (71%) of pure **6a**. **5b** reacted in similar fashion throughout to yield **6b**. Reduction of the reflux period to 2.5 hr. led only to a quantitative recovery of **5a**.

Ozonization of 3-Methylisoquinoline 2-Oxide (7) to 6a.—A solution of 2.4 g. (15.1 mmoles) of **7**, prepared by the peracetic acid oxidation of 3-methylisoquinoline,[6] in 200 ml. of methylene chloride was cooled to 0°, and 14 l. (15.4 mmoles of ozone) of ozone–oxygen was bubbled through the solution was complete absorption of ozone. Color changes during absorption were from pale to rich yellow. The ozonated solution was purged with nitrogen and then extracted with three 40-ml. portions of 5% sodium hydroxide solution. The combined alkaline extracts were washed with two 50-ml. portions of chloroform. Evaporation of the chloroform–methylene chloride extracts, followed by recrystallization of the residue from 1:1 benzene–cyclohexane, gave 30% of unchanged **7**.

The alkaline extracts were then acidified with concentrated hydrochloric acid to give a brick red precipitate which was filtered; two recrystallizations of the residue from carbon tetrachloride gave **6a** in 15% yield.

The acidic filtrate was made alkaline with 10% sodium hydroxide, and the whole was refluxed with 30 ml. of 30% hydrogen peroxide for 2 hr. The solution was then cooled, acidified, and continuously extracted (48 hr.) with ether. Evaporation of the ether extracts yielded a yellow solid which on recrystallization from water was shown to be authentic phthalic acid (10%), m.p. 188–190° (sublimed).

Reduction of 6a/6b to the Corresponding 8a/8b.—A mixture of 1.75 g. (0.01 mole) of **6a**, 0.5 g. of iodine, 0.8 g. of red phosphorus, and 40 ml. of glacial acetic acid was refluxed for 14 hr. The insoluble material was removed by filtration while hot and the filtrate was evaporated to dryness *in vacuo*. This residue was extracted with aqueous sodium carbonate solution to remove any unreduced **6a**. The remaining solid material was dissolved in boiling water from which on cooling deposited 0.51 g. (32%) of 3-methylisocarbostyril (**8a**). Several recrystallizations from benzene (Norit) gave pure **8a**, m.p. 214–215°, identical (mixture melting point and superimposable infrared spectra) with authentic 3-methylisocarbostyril prepared by refluxing **7** with acetic anhydride.[6]

Similarly (no aqueous sodium carbonate extraction necessary), 1.8 g. of **6b** gave 0.64 g. (38%) of **8b**, m.p. 142.5–143.5° [from water (Norit)], lit.[16] m.p. 140–141°.

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.20; H, 6.36; N, 8.00.

Attempted Acid-Catalyzed Rearrangement of *o*-Carboxybenzyl Methyl Ketoxime (10).—**10**, m.p. 162–163°, lit.[17] m.p. 162°, was prepared by the following three-step synthesis[17]: reaction of *o*-bromobenzoic acid with acetylacetone produced phenylacetylacetone-*o*-carboxylic acid, m.p. 143° (from ethanol), lit.[17] m.p. 142°, in 64% yield; conventional ketone cleavage of this β-diketone gave *o*-carboxybenzyl methyl ketone, m.p. 119–120° (from water), lit.[17] m.p. 115°, in 25% yield; the oxime **10** was then obtained in the usual manner.

Treatment of 2 g. of **10** with 20 ml. of concentrated hydrochloric acid under reflux for 6.5 hr. resulted in the recovery of 87% of **10**; no **6a** was isolated.

Fusion of 10.—**10** was heated for 15 min. in a crucible at an oil bath temperature of 165–175°. The melt foamed throughout the heating period, and droplets of water condensed at the top of the crucible. On cooling the product, possibly **11**, was recrystallized from acetone to yield small red-orange needles, m.p. 175–177°. Infrared: $\lambda_{\text{C=O}}^{\text{KBr}}$ 5.81 μ s. A mixture melting point of **6a** and the fusion product showed a depression to 159–164°.

Acknowledgment.—We wish to thank Dr. C. F. Huebner for the use of his unpublished observations on 2-ethyl-1-indanone and Dr. D. J. Hennessy for a provocative discussion of the mechanism of this ring expansion.

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(14) O-benzoylation of **9a** would yield an ester with only one carbonyl band.

(15) The carbonyl absorption of 1-indanone appears as a broad band centered at 5.85 μ (potassium bromide wafer; our work using calcium fluoride optics).

(16) F. Damerow, *Ber.*, **27**, 2235 (1894).

(17) W. R. H. Hurtley, *J. Chem. Soc.*, 1870 (1929).