aminobutyric acid, 10549-02-7; (*R*)-(−)-2-aminobutyric acid, 10333-83-2; DNP-(*R*)-(−)-2-aminobutyric acid, 10549-04-9; (*S*)-(+)-α-phenylglycine, 2935-35-5; DNP-(*S*)-(+)-α-phenylglycine, 10549-06-1; (*R*)-(−)-α-phenylglycine, 875-74-1; DNP-(*R*)-(−)-α-phenylglycine, 6367-35-7; (*S*)-(−)-phenylalanine, 10549-09-4; DNP-(*S*)-(−)-phenylalanine, 10549-10-7; (*R*)-(+)-phenylalanine, 10549-11-8; DNP-(*R*)-(+)-phenylalanine, 10549-12-9; (*S*)-(+)-glutamic acid, 10549-13-0; DNP-(*S*)-(+)-glutamic acid, 10549-14-1; N-(*R*)-(+)-α-methylbenzylbenzoylformamide, 10549-15-2; N-(*S*)-(−)-α-methylbenzylbenzoylformamide, 10549-16-3; N-(*R*)-(+)-α-ethylbenzylbenzoylformamide, 10549-17-4; N-(*S*)-(−)-α-ethylbenzylbenzoylformamide, 10549-18-5; (*R*)-(−)-alanine isobutyl ester *p*-toluenesulfonate, 10549-19-6; (*S*)-(+)-alanine isobutyl ester *p*-toluenesulfonate, 10549-20-9; (*R*)-(−)-valine isobutyl ester *p*-toluenesulfonate, 13018-44-5; (*S*)-(+)-valine isobutyl ester *p*-toluenesulfonate, 13018-45-6; DNP-(*S*)-(+)-valine, 10549-21-0.

Acknowledgments.—This work was supported by Grant No. NsG-689 of the National Aeronautics and Space Administration. The authors wish to express their thanks to Dr. Howard B. Powell for his valuable discussion. Thanks are extended to Dr. Yuzo Inoue for measurements of optical rotatory dispersion curves, and to Mr. Charles R. Windsor for amino acid analyses.

The Reaction of Nitrous Acid with Some Glyoxylic Acids[1]

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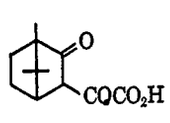
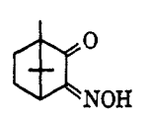
Received November 21, 1966

The product from the nitrosation of camphor-3-glyoxylic acid is shown to be 1,8,8-trimethyl-3-hydroxy-3-azabicyclo[3.2.1]octan-2-one-*exo*-4-carboxylic acid. β-Santenone-3-glyoxylic acid, but not the α isomer, undergoes an analogous rearrangement. The scope of the reaction is investigated, and a possible mechanism is described.

In the course of a study of the reactions of nitrous acid with various compounds, Chorley and Lapworth investigated the nitrosation of camphor-3-glyoxylic acid (**1**).[3] By analogy with the behavior of similar compounds, they anticipated the formation of either α-oximinocamphor (**2**) or the oximino acid **3**. A small amount of **2** was formed, but the major product was a water-soluble, crystalline acid, $C_{11}H_{17}NO_4$. Evolution of carbon dioxide was observed during the reaction, and the formation of the product was summarized by the equation, $C_{12}H_{16}O_4 + HNO_2 \rightarrow C_{11}H_{17}NO_4 + CO_2$.



1



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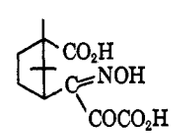
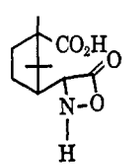


3

The new acid was monobasic, melted at 160° with loss of carbon dioxide, gave a red-violet color with ferric chloride, and showed remarkable resistance to hydrolysis by strong acids or bases. It exhibited no properties characteristic of aldehydes and ketones, and on oxidation gave camphoric acid (**5**). When the acid was refluxed with 50% aqueous potassium hydroxide, an isomeric acid was formed which had properties so similar to those of the parent acid that the acids were believed to be stereoisomers. Reduction of the parent acid with alkaline ferrous hydroxide gave an acid, $C_{11}H_{17}NO_3$, which had an indefinite melting point. This compound failed to give a ferric chloride test, and thermal decomposition of its silver salt gave α-camphidone (**8**). On this basis, the reduced acid was formulated as α-camphidonecarboxylic acid (**7**).

Methylation of the parent acid with dimethyl sulfate and alkali gave both a monomethyl and a dimethyl derivative. Neither of these derivatives gave a color with ferric chloride, and, whereas the monomethyl derivative expelled carbon dioxide from sodium bicarbonate, the dimethyl derivative was devoid of acidic properties. Treatment of the latter compound with alkali gave only ammonia and no methylamine, and it was concluded that both methyl groups were attached to oxygen.

Chorley and Lapworth, "after very long consideration" were forced to adopt **11** as the structure of the



11

acid. One of the premises from which they argued was that the molecule must contain an enolic grouping, $>C{=}C<^{OH}$ or $>N{=}C<^{OH}$ to account for the positive test with ferric chloride, and apparently they did not consider the possibility of a cyclic hydroxamic acid. Failure to consider this possibility has been noted previously,[4] and in fact the tentative structure suggested is the one which we conclude to be correct on the basis of our studies.

The product obtained by nitrosation of camphor-3-glyoxylic acid exhibited properties in agreement with those reported. Spectroscopic properties permit several conclusions about the structure. Infrared absorption bands are present at 3.12 (OH), 3.8 and 5.76 (carboxylic acid), and 6.20 μ (amide I). The nmr spectrum in dimethyl sulfoxide-d_6 shows methyl signals at τ 8.98, 9.03, and 9.13, and a two-proton hydroxyl peak at 2.33. A one-proton singlet (half-width = 4.0 cps)

(1) Taken from the Ph.D. Dissertation of L. D. Hatfield, Aug 1966.
(2) To whom inquiries should be addressed.
(3) P. Chorley and A. Lapworth, *J. Chem. Soc.*, **117**, 728 (1920).
(4) Beilstein's "Handbuch der Organischen Chemie," Vol. 27, II, Springer-Verlag, Berlin, 1955, 397.

appears at τ 6.05, which in trifluoroacetic acid-d_1 is present as a doublet at about 6.0 (J = 1.0 cps). This chemical shift corresponds to that expected for the proton at C-4 in **4**. The remainder of the spectrum consists of a five-proton multiplet in the τ 7.3–8.7 region. These data are in agreement with the hydroxamic acid formulation (**4**).

The properties of the acid obtained by reduction of **4** with alkaline ferrous hydroxide substantiate the assignment of structure **7**. Carboxyl absorption is present in the infrared spectrum at 3.9 and 5.78, an amide I band appears at 6.17, and the broad hydroxyl band of the parent acid is replaced by a sharp NH stretch at 2.95 μ. The nmr spectrum contains methyl absorption at τ 9.03 (three protons), and 9.12 (six protons), and broad absorption in the 2.1–3.2 region, which can be attributed to the NH and OH functions. The C-4 proton appears as a singlet (half-width = 4 cps) at τ 6.26. In the crude product obtained from reduction of **4**, this singlet is accompanied by a weaker doublet (J = 3 cps) at τ 5.92 owing to the presence of approximately 10% of the isomeric acid **14**.

Confirmation of structure **7** was provided by an independent synthesis involving cyclization of the amino acid **12** by heating at 225°. The product obtained in this way was identical with that secured by reduction of **4**.

The monomethyl derivative, mp 172°, obtained by methylation of **4** with dimethyl sulfate, exhibited properties in agreement with Chorley and Lapworth's report, and spectroscopic properties are in agreement with structure **9**. Carboxyl and amide I bands are still present in the infrared spectrum, and the nmr spectrum shows the presence of one hydroxyl proton, τ −1.18, and a methoxyl group, 6.13. The C-4 proton signal is a singlet at τ 5.90.

In addition to the monomethyl derivative, a small amount of another compound, mp 115–118°, was isolated from the reaction described above. The infrared spectrum indicated absence of hydroxyl and carboxyl absorptions. Carbonyl bands appeared at 5.73 and 5.97 μ. This material is probably the same as the dimethyl derivative, mp 115°, reported by Chorley and Lapworth, but it is different from the dimethyl derivative described below.

Treatment of **9** with diazomethane gave a dimethyl derivative **13**, mp 102–103.5°, identical with the compound obtained by treating the parent acid **4** with excess diazomethane. The infrared spectrum shows a band for ester carbonyl at 5.75 and an amide I band at 6.00 μ. Hydroxyl and carboxyl absorptions are absent. The nmr spectrum shows methoxyl signals at τ 6.18 and 6.22. The C-4 proton resonance is a doublet (J = 1.5 cps) at τ 5.93. Lack of identity of this derivative with the one obtained by methylation with dimethyl sulfate may be due to a difference in configuration at C-4.

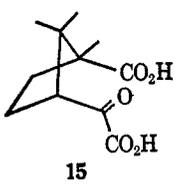
The methyl ester **10**, obtained by treating **4** with 1 equiv of diazomethane, shows infrared absorptions at 3.2 (OH), 5.77 (COOR), and 6.06 μ (amide I). This material is insoluble in sodium bicarbonate, and gives an intense red-violet color with ferric chloride. The nmr spectrum exhibits broad OH absorption centered at τ 0.9 and a methoxyl singlet at 6.20. The C-4 proton signal is a doublet (J = 1.2 cps) at τ 5.85.

The isomeric acid **6**, obtained by refluxing **4** with 50% potassium hydroxide, gives an intense red-violet color with ferric chloride, and exhibits infrared absorption 3.28 (OH), 3.8 and 5.70 (COOH), and a doublet at 6.07 and 6.17 μ (amide I).

The C-4 proton signal in the nmr spectrum is a doublet at τ 5.82 (J = 3 cps). Reduction of **6** with alkaline ferrous hydroxide gave an acid **14**, $C_{11}H_{17}NO_3$, mp 231°, which failed to give a color test with ferric chloride. Bands are present in the infrared spectrum at 2.92 (free NH), 3.05 (bonded NH), 4.0 and 5.82 (COOH), and 6.18 μ (amide I). Broad singlets appear in the nmr spectrum at τ 3.1 and 4.1, corresponding to OH and NH, while the C-4 proton signal is a doublet at 5.92 (J = 3 cps). This same acid was obtained by heating amido acid **7** to 240–250°.

The isomeric acids, **4** and **6**, and the corresponding reduced acids, **7** and **14** most likely differ in configuration at C-4, and the nmr signal of the proton attached at this position permits a stereochemical assignment. It has been shown that the *exo*-3 proton of *endo*-3-substituted bicyclo[2.2.1]heptanes is more deshielded than the *endo*-3 proton of *exo*-3-substituted derivatives.[5,6] Furthermore, the coupling constant of the *exo*-3 proton with the bridgehead proton at C-4 is greater than that of the *endo*-3 proton. Comparable differences are also noted in compounds with the bicyclo[3.2.1]octane skeleton.[7] Accordingly, in the present series of azabicyclo[3.2.1]octanes, the isomer having the more deshielded proton and the larger coupling constant with the bridgehead proton is assigned the *exo* configuration of the C-4 proton.

Chorley and Lapworth observed that the dimethyl derivative (mp 118°) gave ammonia and α-ketohomocamphoric acid **15** upon refluxing with 50% potassium hydroxide. This requires loss of methoxyl from the nitrogen, which may occur by β elimination, initiated by proton abstraction from C-4.



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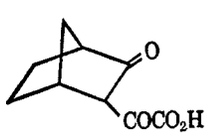
The nitrosation of several other glyoxylic acids was studied to gain information about the scope of this rearrangement. The first three were norcamphor-3-glyoxylic acid (**16**), 1-indanone-2-glyoxylic acid (**17**),



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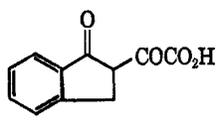

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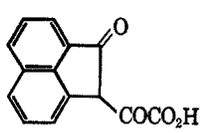

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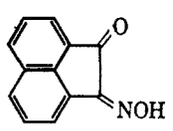


oximino ketone

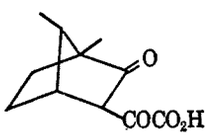
(5) W. D. Kumler, J. N. Shoolery, and F. V. Brutcher, Jr., *J. Am. Chem. Soc.*, **80**, 2533 (1958).

(6) J. I. Musher, *Mol. Phys.*, **6**, 93 (1963); F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

(7) C. W. Jefford, S. Mahajan, F. Waslyn, and B. Waegell, *J. Am. Chem. Soc.*, **87**, 2183, 2191 (1965).

and 7-acenaphthenone-8-glyoxylic acid (**18**). With none of these was there evidence for hydroxamic acids in the products. From **16**, a mixture was formed, and attempts to separate it were unsuccessful. The infrared spectrum of the mixture, however, showed absorption at 3.1 (OH), 3.8 and 5.75 (COOH), 4.45 (CN), and a weak shoulder at 6.1 μ (>C=N). Apparently, the customary type of cleavage reactions occurred with this compound.[8] Attempted nitrosation of **17** failed owing to insolubility of the acid and its sodium salt. In each case the glyoxylic acid was recovered unchanged. Upon nitrosation of **18**, cleavage occurred to give the oximino ketone.

Failure of these compounds to undergo the rearrangement led to the suspicion that the methyl groups on the endomethylene bridge in **1** might be playing an important role, and to gain evidence on this, the behavior of α- (**19**) and β-santenone-3-glyoxylic acid (**20**) was studied.



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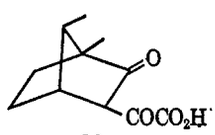
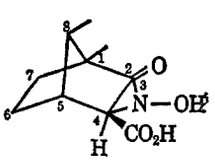


20

Upon nitrosation, the α isomer (**19**) behaved like norcamphor-3-glyoxylic acid, *i.e.*, little or no carbon dioxide was evolved, and although a green color developed during the reaction, no single pure product could be isolated from the mixture. The infrared spectrum showed bands at 4.48 (CN), 3.9 and 5.90 (CO_2H), and 3.2 μ (OH). A weak band present at 6.15 μ is ascribed to >C=N, and probably resulted from an oximino grouping, since the mixture gave a faint red color with ferric chloride.

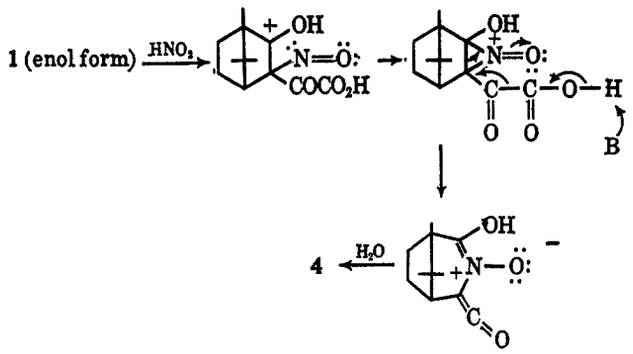
β-Santenone-3-glyoxylic acid (**20**), on the other hand, behaved like the camphor derivative. A green color developed during nitrosation, which faded to pale yellow, and steady evolution of carbon dioxide occurred. A colorless acid (**21**, $C_{10}H_{15}NO_4$) was isolated. This compound gives an intense red-violet color with ferric chloride, and its infrared spectrum shows a striking similarity to that of the camphor derivative **4**. Bands are present at 2.95 (OH), 4.0 and 5.77 (CO_2H), and 6.18 μ (amide I). The nmr spectrum shows a two-proton hydroxyl signal as a broad band from τ 0.5 to 1.5, a singlet at 8.90 (C-1 methyl), and a doublet (J = 8 cps) with peaks at 8.97 and 9.10 (C-8 methyl). A six-proton multiplet appears at τ 7.2–8.7. The C-4 proton signal appears as a singlet (half-width = 3 cps) at τ 6.06, indicating the *endo* configuration for this proton. From these data, and by analogy with the camphor derivative, structure **21** is assigned to this compound.



21

The rearrangement that occurs with **4** and **20** is the same type that occurs during nitrosation of 2-alkyl-1-indanones,[9] and can be rationalized by the sequence in Scheme I. Many variations of this same theme, differing in timing, or involving intramolecular proton transfers, or ring opening and reclosure,[10] are conceivable and cannot be evaluated with present data. Competing with the ring expansion must be the customary cleavage reactions;[8] witness the formation of a small amount of **5** from the nitrosation of **1**. Apparently, with most α-glyoxalyl ketones, the cleavage reactions are faster than ring expansion. However, the cleavage reactions do require attack by hydrolytic reagents at one of the ketone carbonyl carbons, and it is believed that the *syn*-methyl group at C-7 in the camphor and β-santenone derivatives hinders this attack sufficiently that ring expansion predominates. Steric factors that have been shown to influence the course of Baeyer–Villiger oxidations[11] may also play a role in this rearrangement. With the camphor and β-santenone derivatives, in which the nitroso group is expected to enter from the *endo* side, rearrangement is facilitated by a strain-relieving chair transition state. On the other hand, with the norcamphor and α-santenone derivatives the nitroso group should enter from the *exo* face, and the transition state for rearrangement would possess an unfavorable boat conformation. See Scheme II.

SCHEME I



Experimental Section[12]

Camphor-3-glyoxylic Acid (**1**).—From 63.0 g (0.4 mole) of camphor, 51.8 g (0.35 mole) of diethyl oxalate, and 4.6 g (0.2 g-atom) of sodium wire, mixed with 1 l. of ligroin (bp 66–75°) and treated according to the procedure described,[3,13] there was obtained 24 g of crude camphor-3-glyoxylic acid, mp 85–88°. One recrystallization from ligroin gave 20 g (45% yield) of the acid: mp 87–88° (lit.[3,12] mp 88°); infrared λ_{max} (Nujol) 2.99, 4.0, 5.25, 5.77, 5.94, 6.28, 7.45, 8.04, 8.36, 8.53, 9.02, 9.26, 9.73, 10.32, 10.80, 11.13, 11.45, 12.02, 12.30, and 12.75 μ; nmr absorptions ($CDCl_3$), singlets at τ 8.93, 8.97, and 9.12 (9 H), doublet (J = 3.8 cps) centered at 6.86 (1 H), very broad signal centered at 1.92 (0.8 H) which shifted to 5.30 on addition of 1 drop of D_2O, and a multiplet in the 7.5–8.8 region (5.3 H).

β-Santenone-3-glyoxylic Acid (**20**).—From 2.60 g (0.0188 mole) of β-santenone,[14] 2.74 g (0.0188 mole) of diethyl oxalate, 0.30 g (0.013 g-atom) of sodium wire, and 20 ml of ligroin, according

(8) O. Touster, *Org. Reactions*, **7**, 327 (1953).

(9) E. J. Moriconi, F. J. Creegan, C. K. Donovan, and F. A. Spano, *J. Org. Chem.*, **28**, 2215 (1963).

(10) E. J. Moriconi and F. J. Creegan, *ibid.*, **31**, 2090 (1966).

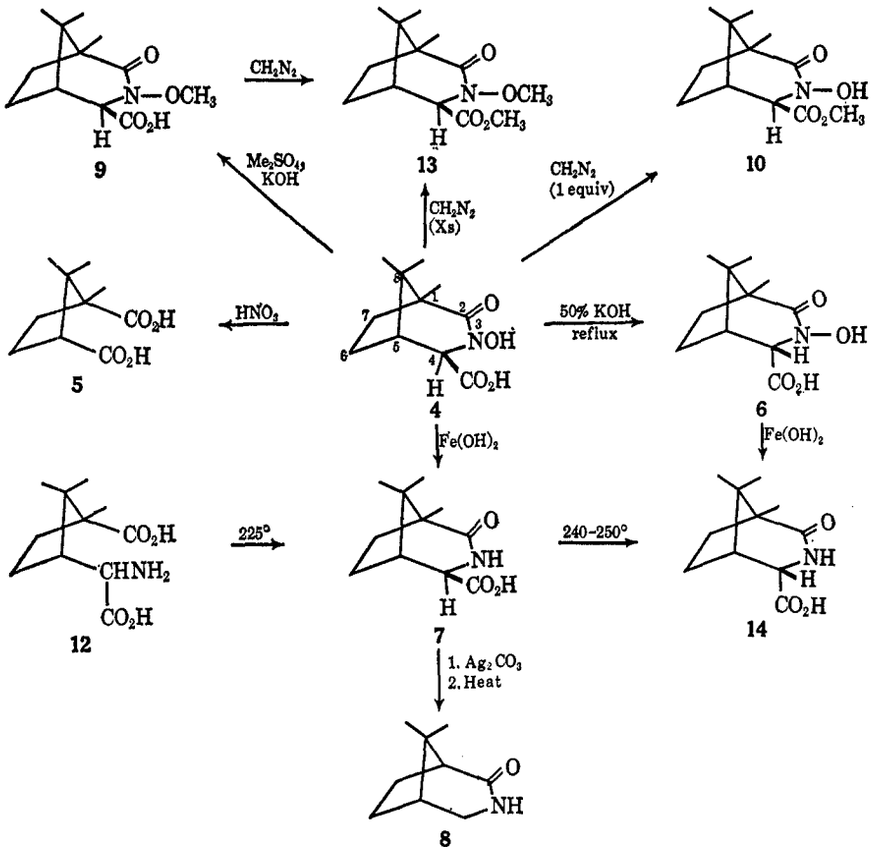
(11) J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc.*, **82**, 5235 (1960); R. R. Sauers and G. P. Ahearn, *ibid.*, **83**, 2759 (1961).

(12) Melting points and boiling points are uncorrected. Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tenn., and by Mrs. J. De Boer of this department. Infrared spectra were measured with Perkin-Elmer 21 and 237G spectrophotometers, and nmr spectra were measured with a Varian A-60 spectrometer, using tetramethylsilane as internal standard.

(13) J. B. Tingle, *Am. Chem. J.*, **19**, 393 (1897).

(14) L. D. Hatfield and W. D. Huntsman, *J. Org. Chem.*, **32**, 844 (1967).

SCHEME II



to the procedure used for 1, there was obtained 0.86 g of crude β-santenone-3-glyoxylic acid, mp 125–128°. Recrystallization from ligroin gave 0.68 g (25% yield): mp 131–132°, unchanged by sublimation at 100–105° (2 mm); infrared λ_{max} (Nujol) 3.0, 5.25, 5.80, 5.98, 6.36, 7.38, 7.45, 8.02, 8.43, 9.07, 9.84, 10.06, 10.34, 10.78, 11.10, 11.37, 12.02, 13.45, and 14.15 μ.

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.80; H, 6.58.

α-Santenone-3-glyoxylic Acid (19).—A solution of 1.05 g (0.0076 mole) of α-santenone[14] and 1.14 g (0.0078 mole) of diethyl oxalate in 2 ml of absolute ethanol was added to a solution of sodium ethoxide prepared from 0.18 g (0.0078 g-atom) of sodium and 10 ml of absolute ethanol. The flask was heated in a water bath at 55–60° for 2 hr, and the solution was poured over a mixture of 20 g of crushed ice and 1.5 ml of concentrated hydrochloric acid. The organic material was taken up in ether, and the aqueous solution was extracted with ether. The combined extracts were dried over sodium sulfate, the ether was removed on a rotary evaporator, and to the residual oil was added a solution of 1.4 g of potassium hydroxide in 20 ml of water. The mixture was warmed on a water bath at 55–60° for 1 hr, and the aqueous solution was cooled and extracted with ether. The aqueous layer was acidified with cold 6 *N* hydrochloric acid and extracted with ether, and the extract was dried over sodium sulfate. Removal of solvent on a rotary evaporator left an orange-yellow oil which was crystallized from ligroin to give 0.86 g (54% yield) of α-santenone-3-glyoxylic acid, mp 84.5–86°. A sample purified by sublimation at 65–70° (2 mm) melted at 86–87°; infrared λ_{max} (Nujol) 2.99, 4.0, 5.27, 5.78, 5.97, 6.35, 7.45, 8.04, 8.50, 8.64, 9.00, 9.25, 9.73, 9.84, 10.05, 10.38, 10.77, 11.10, 11.97, 12.04, 12.27, 12.72, 13.80, 14.00, 14.45, and 15.07 μ.

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.68; H, 6.52.

Norcamphor-3-glyoxylic Acid (16).—A solution of 11.0 g (0.1 mole) of norcamphor, and 14.6 g (0.1 mole) of diethyl oxalate in 15 ml of absolute ethanol was heated to 50° in a water bath, and a solution of sodium ethoxide prepared from 2.3 g of sodium and 100 ml of absolute ethanol was added dropwise with stirring during 20 min. The mixture was stirred for 3 hr, the solution was poured onto a mixture of 200 g of crushed ice and 15 ml of concentrated hydrochloric acid, and the organic material was taken up in ether. The aqueous layer was extracted with ether, and the extracts were washed with saturated salt solution and dried over sodium sulfate. The solvent was removed on a rotary evaporator, and the residual oil was distilled to give 13.2 g (63% yield) of ethyl norcamphor-3-glyoxalate: bp 118–120° (2 mm); $n^{25}D$ 1.5062; infrared λ_{max} (neat) 3.0, 3.38, 3.48, 5.76, 5.92, 6.15, 6.78, 6.88, 7.18, 7.28, 7.49, 7.70, 7.88, 8.05, 8.40, 9.10, 9.32, 9.68, 9.78, 10.57, 10.92, 11.08, 11.55, 12.02, 12.66, and 14.25 μ.

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 63.15; H, 6.60.

Ethyl norcamphor-3-glyoxalate (10.5 g, 0.05 mole) was dissolved in 40 ml of cold 10% sodium hydroxide, and the yellow solution was stirred for 0.5 hr at 10–15°, and for 0.5 hr at 25–30°. The mixture was cooled and acidified with 6 *N* hydrochloric acid, and the mixture was extracted with two 100-ml portions of ether. The combined extracts were dried over sodium sulfate, the ether was removed on a rotary evaporator, and the residue was recrystallized from carbon tetrachloride to give 5.9 g (65% yield) of norcamphor-3-glyoxylic acid: mp 112–113°; infrared λ_{max} (Nujol) 3.05, 4.2, 5.40, 5.77, 5.96, 6.27, 7.40, 7.55, 7.65, 8.05, 8.50, 8.68, 8.80, 9.05, 9.41, 9.74, 10.07, 10.38, 10.51, 11.05, 12.60, 12.80, 13.85, and 14.35 μ.

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.26; H, 5.69.

7-Acenaphthenone-8-glyoxylic Acid (18).—Ethyl 7-acenaphthenone-8-glyoxylate[15,16] (2.68 g, 0.01 mole) was dissolved in 20 ml of 1 *N* sodium hydroxide and the solution was warmed at 40–50° for 1 hr. The solution was filtered and the filtrate was added dropwise to 25 ml of hot 10% hydrochloric acid with vigorous stirring. The mixture was filtered and the precipitate was washed thoroughly with water and dried in a vacuum desiccator. Recrystallization from acetone–benzene gave 1.97 g (82% yield) of **18**: mp 239–240°; infrared λ_{max} (Nujol) 3.05, 3.8, 5.80, 6.04, 6.13, 6.23, 6.42, 7.48, 7.80, 7.95, 8.25, 9.15, 9.64, 9.90, 10.16, 11.20, 12.07, 12.48, 12.84, 13.10, 13.69, and 14.18 μ.

Anal. Calcd for $C_{14}H_8O_4$: C, 70.00; H, 3.36. Found: C, 70.13; H, 3.29.

(15) J. B. Duthie and S. G. Plant, *J. Chem. Soc.*, 1900 (1952).

(16) J. N. Chatterjea and K. Prasad, *J. Indian Chem. Soc.*, **34**, 375 (1957).

1-Indanone-2-glyoxylic Acid (17).—This acid was prepared as described:[16,17] mp 219–220 (lit.[16,17] mp 215, 218°); infrared λ_{max} (Nujol) 3.05, 5.82, 6.05, 6.19, 6.50, 7.45, 7.70, 8.02, 8.60, 9.83, 9.97, 10.34, 11.26, 12.42, 12.57, and 13.46 μ.

Nitrosation of Camphor-3-glyoxylic Acid.—From 20.0 g (0.09 mole) of camphor-3-glyoxylic acid dissolved in 40 ml of 10% sodium hydroxide, and treated with 65 ml of 10% sodium nitrite and then 100 ml of 10% hydrochloric acid according to the procedure described,[3] there was obtained 11.5 g (55% yield) of 1,8,8-trimethyl-3-hydroxy-3-azabicyclo[3.2.1]octan-2-one-*exo*-4-carboxylic acid (**4**): mp 160° dec (lit.[3] mp 160° dec); infrared λ_{max} (KBr) 3.12, 3.8, 5.76, 6.20, 6.75, 6.80, 6.90, 7.15, 7.26, 7.40, 7.87, 8.24, 8.49, 8.58, 9.00, 9.55, 9.98, 10.13, 10.58, 10.90, 11.45, 11.82, 12.80, 13.47, 14.22, and 14.62 μ; nmr spectrum (DMSO-d_6) a broad singlet at τ 2.33 (2 H), a singlet (half-width = 4 cps) at 6.05 (1 H), a complex multiplet in the 7.3–8.7 region (5 H), and singlets at 8.98, 9.03, and 9.13 (9 H), In trifluoroacetic acid-*d*, the singlet at τ 6.05 appeared as a doublet (J = 1 cps) at about 6.0.

Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16. Found: C, 58.09; H, 7.53; N, 6.09.

1,8,8-Trimethyl-3-azabicyclo[3.2.1]octan-2-one-*exo*-4-carboxylic Acid (7). By Reduction of 4.—Treatment of 5.0 g of **4** in 120 ml of 20% potassium hydroxide with 28 g of ferrous ammonium sulfate in 100 ml of water according to the published procedure,[3] gave 4.4 g of the reduced acid **7**, with indefinite melting point, from shrinkage at 200° to complete liquefaction at 228°. A sample purified by repeated recrystallization from acetone melted at 201–203°; infrared λ_{max} (Nujol) 2.95, 3.9, 5.78, 6.17, 7.42, 8.22, 9.02, 9.78, 10.95, 11.22, 12.70, 13.37, 13.75, and 14.65 μ; nmr spectrum (DMSO-d_6), broad band at τ 2.1–3.2 (2 H), singlet (half width = 4 cps) at 6.26 (1 H), methyl signals at 9.03 (3 H) and 9.12 (6 H), and multiple peaks in the 7.2–8.8 region. The crude product exhibited a weak doublet (J = 3 cps) at τ 5.92, but this signal was not present in the purified material.

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.53; H, 8.11; N, 6.63. Found: C, 62.69; H, 8.11; N, 6.58.

1,8,8-Trimethyl-3-azabicyclo[3.2.1]octan-2-one-*exo*-4-carboxylic Acid (7). By Cyclization of 12.—A 0.10-g sample of amino acid **12**[18] was placed in a sublimation apparatus, evacuated to 2 mm, and heated in an oil bath at 225°. The sublimate (75 mg, mp 184–191°) was recrystallized from acetone–ligroin, to give 45 mg of colorless crystals, mp 200–201°. The infrared spectrum of this material was identical with that of the sample obtained by reduction of **4**, and no depression was observed for the mixture melting point of the two samples.

1,8,8-Trimethyl-3-methoxy-3-azabicyclo[3.2.1]-octan-2-one-*exo*-4-carboxylic Acid (9).—From 4.7 g of acid **4**, 6.0 g of dimethyl sulfate, and 5.0 g of potassium hydroxide in 75 ml of methanol, treated as described,[3] there was obtained 25 mg of neutral material which was isolated as brown, granular crystals, mp 115–118°. The infrared spectrum of this material indicated the absence of hydroxyl and carboxyl functions, and showed carbonyl bands at 5.73 and 5.97 μ. This material was not investigated further.

Fractional crystallization of the acidic material from ethyl acetate gave 1.40 g of colorless crystals, mp 128–130°, and 1.87 g of material, mp 170°. Neither of the fractions gave a color test with alcoholic ferric chloride, and both expelled carbon dioxide from 5% sodium bicarbonate.

The lower melting fraction was recrystallized twice from acetone and once from ethyl acetate to give 0.86 g of the methoxy derivative **9**. The infrared and nmr spectra of this compound were identical with those of the higher melting fraction described below, and hence the two are different crystalline modifications.

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.57; H, 7.91; N, 5.68.

The higher melting fraction was recrystallized three times from ethyl acetate to give 1.53 g of material: mp 173–174° (lit.[3] mp 172°); infrared λ_{max} (KBr) 2.9, 3.9, 5.70, 6.15, 6.78, 6.90, 7.05, 7.09, 7.14, 7.23, 7.25, 7.38, 7.90, 8.25, 8.50, 8.61, 9.00, 9.52, 9.82, 10.00, 11.50, 13.40, 14.28, 14.47, 14.63, and 15.55 μ; nmr spectrum ($CDCl_3$), broad singlet (half-width = 4 cps) at τ 5.90 (1 H, singlet at 6.13 (3 H), methyl singlets at 8.85, 8.91, and 9.07 (9 H), broad singlet at −1.18 (1 H), and a multiplet in the 7.2–8.7 region (5 H).

(17) H. Leuchs and G. Kowalski, *Ber.*, **58b**, 2288 (1925).

(18) W. Eckert and N. Ottawa, German Patent 1,019,296 (Nov 14, 1957); *Chem. Abstr.*, **54**, 1475 (1960).

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.66; H, 7.92; N, 5.71.

Methyl 1,8,8-Trimethyl-3-hydroxy-3-azabicyclo[3.2.1]octan-2-one-*exo*-4-carboxylate (10).—From the reaction of 0.23 g (0.001 mole) of **4** in 30 ml of 1:1 methylene chloride–ether, and 27.0 ml (0.001 mole) of 0.037 *M* diazomethane in ether, there was obtained 0.11 g of the methyl ester **10**, mp 129.5–131°. This product was insoluble in 5% sodium bicarbonate, and gave an intense red-violet color with ferric chloride. Recrystallization from petroleum ether (bp 20–40°) gave 0.10 g: mp 131.5–132°; infrared λ_{max} (Nujol) 3.2, 5.77, 6.06, 7.70, 7.96, 8.47, 9.00, 9.51, 9.85, 9.92, 10.10, 10.33, 10.64, 11.62, 11.88, 12.63, 13.20, 14.00, and 14.46 μ; nmr spectrum ($CDCl_3$), a broad band centered at about τ 0.9 (1 H), a doublet (J = 1.2 cps) at 5.85 (1 H), singlet at 6.20 (3 H), singlets at 8.87, 9.03, and 9.07 (9 H), and a multiplet in the 7.2–8.6 region (5 H).

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.70; H, 7.82; N, 5.67.

Methyl 1,8,8-Trimethyl-3-methoxy-3-azabicyclo[3.2.1]octan-2-one-*exo*-4-carboxylate (13). From 9.—The methoxy derivative **9** (0.26 g, 0.0011 mole), was dissolved in 30 ml of 1:1 ether–methylene chloride and 35 ml of 0.037 *M* diazomethane in ether was added. After 1 hr the solvent was removed, and the residue was crystallized from ethyl acetate–petroleum ether to give 0.21 g of **13**, mp 102–103.5°. This compound was insoluble in sodium bicarbonate, and gave no color with ferric chloride; infrared λ_{max} (Nujol) 5.68, 5.75, 6.00, 6.98, 7.08, 7.86, 8.00, 8.28, 8.60, 9.02, 9.53, 9.67, 9.84, 10.07, 10.25, 10.48, 10.76, 11.60, 12.02, 13.23, 14.03, and 14.50 μ; nmr spectrum ($CDCl_3$), a doublet (J = 1.5 cps) at τ 5.93 (1 H), singlets at 6.18 (3 H) and 6.22 (3 H), singlets at 8.87, 9.00, and 9.08 (9 H), and a multiplet at 7.3–8.3 (5 H).

Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29; N, 5.49. Found: C, 61.15; H, 8.35; N, 5.59.

Methyl 1,8,8-Trimethyl-3-methoxy-3-azabicyclo[3.2.1]octan-2-one-*exo*-4-carboxylate (13). From 4.—To a solution of 0.50 g of acid **4** in 30 ml of 1:1 ether–methylene chloride was added at 0.037 *M* solution of diazomethane in ether until the yellow color persisted. The solution was allowed to stand overnight and filtered, and the solvent was distilled. The oily residue was crystallized from benzene–petroleum ether to give 0.10 g of the dimethyl derivative **13**, mp 98.5–102°. This material was identical with the dimethyl derivative described above.

1,8,8-Trimethyl-3-hydroxy-3-azabicyclo[3.2.1]octan-2-one-*endo*-4-carboxylic Acid (6).—A solution of 2.0 g of **4** in 20 ml of 50% potassium hydroxide was refluxed for 24 hr, and the mixture processed as described[3] to give 1.10 g of **6**, mp 203–205° (lit.[3] mp 205°). This compound gave an intense red-violet color with ferric chloride; infrared λ_{max} (Nujol) 3.25, 5.70, 6.07, 6.17, 7.80, 8.40, 8.60, 9.00, 9.98, 10.05, 10.44, 11.50, 12.97, 13.40, 14.50 and 15.22 μ; nmr spectrum (DMSO-d_6), broad signal in the τ 2.2–3.5 region (2 H), a doublet (J = 3 cps) at 5.82 (1 H), a multiplet in the 7.2–8.8 region (5 H), and singlets at 9.02 (3 H) and 9.08 (6 H).

Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16. Found: C, 58.09; H, 7.53; N, 6.09.

1,8,8-Trimethyl-3-azabicyclo[3.2.1]octan-2-one-*endo*-4-carboxylic Acid (14). From 6.—To a solution of 0.20 g of **6** (0.0009 mole) in 6 ml of 20% potassium hydroxide was added 1.4 g (0.005 mole) of ferrous ammonium sulfate in 7 ml of water. The mixture was treated as described[3] to give 0.15 g of a gray solid, mp 228–230°. Recrystallization from acetone–ligroin raised the melting point to 231°; infrared λ_{max} (Nujol) 2.92, 3.05, 4.0, 5.82, 6.18, 7.78, 8.02, 8.10, 8.20, 8.67, 9.02, 10.43, 10.60, 11.28, 11.98, 12.78, 13.37, 13.88, and 14.60 μ; nmr spectrum (DMSO-d_6), broad singlets at τ 3.15 (1 H) and 4.13 (1 H), a doublet (J = 3.5 cps) at 5.92 (1 H), a complex pattern at 7.2–8.8 (5 H), and singlets at 9.02, 9.04, and 9.07 (9 H).

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.53; H, 8.11; N, 6.63. Found: C, 62.40; H, 7.95; N, 6.59.

1,8,8-Trimethyl-3-azabicyclo[3.2.1]octan-2-one-*endo*-4-carboxylic Acid (14). From 7.—The amido acid **7** (0.50 g) was heated in an oil bath at 240–250° under a nitrogen atmosphere for 0.5 hr, and then recrystallized twice from acetone to give 0.22 g of **14**, mp 227–229°. This sample was identical (mixture melting point and infrared spectrum) with the sample prepared by reduction of **6**.

***syn*-1,8-Dimethyl-3-hydroxy-3-azabicyclo[3.2.1]octan-2-one-*exo*-4-carboxylic Acid (21).**—Into a 50-ml, three-necked flask equipped with a stirrer, side-arm dropping funnel, and exit

tube for gases was placed 5.0 ml (5 mmoles) of 1 *N* sodium hydroxide followed by 0.50 g (2.4 mmoles) of β-santenone-3-glyoxylic acid (**20**) and then 0.18 g (2.5 mmoles) of sodium nitrite. The flask was immersed in a water bath at room temperature and 2.5 ml of 10% hydrochloric acid was added dropwise during 15 min. Each drop of acid produced a light green precipitate which immediately redissolved forming a green solution. The green color rapidly faded to a pale yellow and carbon dioxide was evolved at the rate of 1 bubble every 3–4 sec. The aqueous solution, which gave an intense red-violet color with ferric chloride, was stirred for 1 hr and was then evaporated to dryness on a rotary evaporator at 50–60° and aspirator pressure. The residue was extracted with two 25-ml portions of boiling ethyl acetate and the hot extracts were filtered, combined, and evaporated to a volume of approximately 3 ml on a steam bath. A small volume of ligroin, bp 66–75°, was added and the solution was cooled in an ice box for 2 days to give 0.20 g (39% yield) of nearly colorless, granular crystals of the hydroxamic acid **21**, mp 156–158° with gas evolution. The product gave an intense red-violet color with ferric chloride and dissolved in 5% sodium bicarbonate with evolution of carbon dioxide. A sample, recrystallized from ethyl acetate, melted at 162–163° with gas evolution; infrared λ_{max} (KBr) 2.95, 4.0, 5.77, 6.18, 6.86, 7.18, 7.47, 7.73, 8.05, 8.15, 8.45, 8.77, 9.20, 9.55, 9.83, 10.03, 10.58, 11.47, 11.76, 12.02, 12.74, 13.75, and 14.68 μ; nmr spectrum (DMSO-d_6), a broad signal from τ 0.5 to 1.5 (2 H), a singlet (half-width = 3 cps) at 6.06 (1 H), a methyl singlet at 8.90 and a methyl doublet (J = 8 cps) with peaks at 8.97 and 9.10, and multiple peaks in the 7.2–8.7 region (6 H).

Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.32; H, 7.09; N, 6.71. Found: C, 56.20; H, 7.06; N, 6.70.

Nitrosation of α-Santenone-3-glyoxylic Acid.—Into a 50-ml, three-necked flask equipped with a magnetic stirrer, pressure-equalizing dropping funnel, and exit tube for gases were placed 4.0 ml of 1 *N* sodium hydroxide, 0.42 g (2.1 mmoles) of α-santenone-3-glyoxylic acid (**19**), and then 0.15 g (2.1 mmoles) of sodium nitrite. The flask was immersed in a water bath at room temperature and 2.0 ml of 10% hydrochloric acid was added dropwise with stirring during 15 min. Each drop of acid produced an intense green color which rapidly faded. Very little gas was evolved from the reaction mixture. After approximately one-half the acid had been added, a yellow precipitate was observed but this redissolved rapidly. The mixture was stirred 1 additional hr at room temperature and the nearly colorless, aqueous solution, which gave a very light red color with ferric chloride, was extracted with two 15-ml portions of ether. The combined extracts were dried over anhydrous sodium sulfate. Removal of the solvent on a rotary evaporator at room temperature and aspirator pressure left 0.23 g of a pale yellow oil that darkened rapidly on standing. The infrared spectrum (chloroform solution) exhibited absorption at 4.48 (C=N), 3.9 and 5.90 (carboxylic acid), 3.2 (OH), and 6.15 μ (C=N). Extraction of the residue (in chloroform solution) with sodium bicarbonate, followed by acidification of the aqueous solution, extraction with chloroform, and drying over anhydrous sodium sulfate gave a solution whose infrared spectrum was nearly identical with that of the original mixture. The initial chloroform solution, after extraction with sodium bicarbonate and drying over anhydrous sodium sulfate, exhibited absorption at 3.08, 5.75, and 5.98 with a shoulder at 6.08 μ.

Nitrosation of Norcamphor-3-glyoxylic Acid.—The apparatus was the same as that used in the preceding reaction. Into the flask were placed 10 ml of 1 *N* sodium hydroxide, 1.82 g (0.01 mole) of norcamphor-3-glyoxylic acid (**16**), and 0.70 g (0.01 mole) of sodium nitrite. The flask was immersed in a water bath at room temperature and 6 ml of 10% hydrochloric acid was added dropwise during 40 min. Each drop of acid produced a green color which soon disappeared. Very little gas was evolved during the course of the reaction. The solution was stirred for 1 hr at room temperature. A colorless solid separated which was filtered, washed with water, and air dried to give 0.25 g of material which melted with decomposition above 275°. The infrared spectrum (Nujol mull) exhibited only six very broad bands at 3.0, 5.75, 6.2, 8.1, 9,7, and 13.9 μ. A gray residue remained when a sample was ignited; when dissolved in a few drops of water this residue gave a solution with pH 10.

The combined filtrate and washings above gave only a very weak color with ferric chloride. Water was evaporated on a rotary evaporator at 50–60° (aspirator pressure) and the residue was extracted with two 25-ml portions of boiling ethyl acetate. The combined extracts were filtered while hot and solvent was removed on a rotary evaporator, leaving 1.40 g of a reddish oil that darkened rapidly on standing. The infrared spectrum (liquid film) exhibited hydroxyl absorption at 3.1, carboxylic acid bands at 3.9 and 5.75, nitrile band at 4.45, and a weak C=N band at 6.1 μ. Attempts to separate the components of the mixture by column chromatography and other methods were unsuccessful.

Nitrosation of 7-Acenaphthenone-8-glyoxylic Acid.—The glyoxylic acid **18** (1.31 g, 5.5 mmoles) was dissolved in 7 ml of 1 *N* sodium hydroxide and 0.40 g (5.7 mmoles) of sodium nitrite was added. Twelve milliliters of 10% hydrochloric acid was added during 1 hr. The yellow precipitate that was produced was extracted with ether and the organic layer was dried over anhydrous sodium sulfate. Removal of the solvent on a rotary evaporator at room temperature and aspirator pressure left 0.85 g of a viscous, red oil. Crystallization from benzene gave 0.56 g of 7-oxo-8-oximinoacenaphthene, mp 219° (lit.[18] mp 220–222°).

Nitrosation of 1-Indanone-2-glyoxylic Acid.—The sodium salt (2.6 g, 0.01 mole) of 1-indanone-2-glyoxylic acid (**17**) was added to 10 ml of 1 *N* sodium hydroxide followed by 0.70 g (0.01 mole) of sodium nitrite. Ten milliliters of 10% hydrochloric acid was added dropwise during 40 min. Each drop of acid produced a white precipitate which redissolved, slowly at first, but after about one-third of the acid had been added the precipitated material failed to go back into solution. Stirring was continued for 0.5 hr, and then the solid was filtered off, washed with water, and dried in air. In this manner there was obtained 1.92 g of unchanged **17**, mp 212–215°.

In another experiment, 1.02 g (5 mmoles) of **17** was dissolved in in 10 ml of dimethyl sulfoxide and 0.40 g (5.7 mmoles) of sodium nitrite was added. Then 1.0 ml of 10% hydrochloric acid was added dropwise during 1 hr. The solution was poured over 25 g crushed ice and the yellow precipitate was filtered off, washed with water, and dried in air to give 0.82 g of unchanged **17**, mp 214–216°. The filtrate above gave no significant color test with ferric chloride.

Registry No.—**1**, 10277-34-6; **4**, 10293-72-8; **6**, 10293-73-9; **7**, 10293-74-0; **9**, 10277-35-7; **10**, 10305-69-8; **13**, 10316-14-0; **14**, 10293-75-1; **16**, 10293-76-2; **17**, 10277-36-8; **18**, 10293-77-3; **19**, 10293-78-4; **20**, 10293-79-5; **21**, 10277-37-9; nitrous acid, 7782-77-6; ethyl norcamphor-3-glyoxalate, 10293-81-9.