Anal. Calcd. for $C_{27}H_{31}N_5O_6$: C, 62.18; H, 5.99. Found: C, 62.50; H, 6.14.

2-Bromobenzsuberone (XIV).—Bromine (6.2 cc.) was added with shaking as fast as the color disappeared, to a solution of 18.4 g. of benzsuberone in 150 cc. of anhydrous ether in an ice-bath. The solution was allowed to stand for 1 hr., then was poured on ice, the ether layer separated and the aqueous layer was extracted with ether. The combined extracts were washed with dilute sodium bicarbonate, then with water, dried and the solvent was removed. Distillation of the residue gave 24.77 g. (91%) of product, b.p. 140–142° (1 mm.), $n^{13}D$ 1.6006. The analytical sample was prepared one week before analysis, and apparently had lost a trace of bromine.

Anal. Calcd. for $C_{11}H_{11}BrO$: C, 55.25; H, 4.64. Found: C, 55.95; H, 4.40.

2-Cyanobenzsuberone (XV).—The best yields were obtained when the 2-bromobenzsuberone was not isolated. Benzsuberone (4.0 g.) in 100 cc. of dry ether was brominated as described above. The ether and hydrogen bromide were removed by distillation and 80 cc. of alcohol was added. The solution was heated to boiling, and sodium cyanide (1.83 g.) in 8 cc. of water was added. The solution was stirred and heated under reflux for 30 min., then was poured onto ice and extracted twice with ether. The extracts were dried, the solvent was removed, and the residue was distilled, giving 3.33 g. (72%) of product, b.p. 119° (0.3 mm.), $n^{23}D$ 1.5466.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99. Found: C, 77.48; H, 5.67.

Attempts to form an oxime and a 2,4-dinitrophenylhydrazone yielded only starting material; attempts to add hydrogen cyanide were also unsuccessful.

ROCHESTER, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

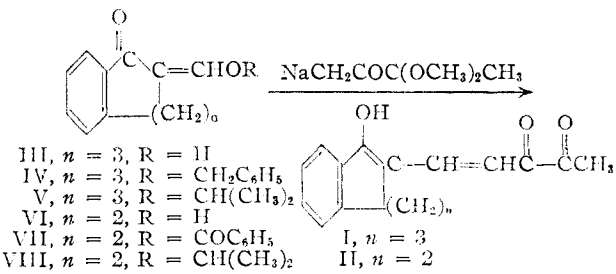
Syntheses in the Colchicine Field. The Condensation of 2-Isopropoxymethylenebenzsuberone and Related Compounds with Biacetyl Monoketal[1]

BY EDWARD OTT AND D. S. TARBELL

RECEIVED JUNE 25, 1952

Condensation of 2-isopropoxymethylenebenzsuberone and of the corresponding tetralone derivative with the sodium derivative of biacetyl monoketal gives satisfactory yields of the expected products I and II, which are of interest because of the possibility of cyclization to form tropolones analogous to colchicine. I and II undergo oxidative cyclization to form furan derivatives, one of which is identified by conversion to α-naphthofuran. Periodate oxidation of II also yields 2-carboxymethinyl-1-tetralone (XVII), identified by synthesis, which proves the position of the side-chain in I and II. The physical and chemical properties of I and II are described, and numerous derivatives are characterized.

In the preceding paper,[2] it was reported that the Mannich base of benzsuberone condensed with biacetyl monoketal to give compound I (or a tautomer). This substance was of considerable interest because of the possibility of cyclizing it to a tricyclic tropolone, which would contain the essential features of the ring system of colchicine. The yield of I from the Mannich reaction, however, was too low to allow a study of the compound or to make it useful as a synthetic intermediate. The present paper reports the preparation of I, and of its homolog II derived from α-tetralone, by a much better method, describes the chemistry of these compounds and their derivatives, and presents evidence for the structures assigned.



III, $n = 3$, R = H
IV, $n = 3$, R = $CH_2C_6H_5$
V, $n = 3$, R = $CH(CH_3)_2$
VI, $n = 2$, R = H
VII, $n = 2$, R = COC_6H_5
VIII, $n = 2$, R = $CH(CH_3)_2$

I, $n = 3$
II, $n = 2$

The O-isopropyl derivative of 2-formylbenzsuberone[2] (V) was prepared in practically quantitative yield, and was shown to be almost exclusively the O-alkylated product.[3] This compound was very sensitive to air, and was stable for appreciable periods only if stored under dry nitrogen at Dry Ice temperatures. However, it could be condensed with the sodium derivative of biacetyl monoketal[4] to yield, after acid hydrolysis, a yellow crystalline product having the composition expected for structure I. The best conditions discovered—sodium hydride in tetrahydrofuran at Dry Ice and then at room temperatures—gave a 35% yield of crystalline I.[5]

The properties of this compound were in accord with the proposed structure. It formed a mono- and bissemicarbazone, a dioxime and a quinoxaline, it gave a transient brown color with ferric chloride, and dissolved in 1% alkali or 10% sodium carbonate, but not in bicarbonate. The solutions of the salt were intense orange or red in color, and the original compound could be recovered from them by acidification.[6] The infrared spectrum of I agrees with the proposed structure, showing (Fig. 2) a hydroxyl band at 3.01 μ (3327 cm.$^{-1}$) and a conjugated carbonyl band at 6.0 μ (1667 cm.$^{-1}$).

(1) Aided by a grant from the National Cancer Institute.

(2) D. S. Tarbell, H. F. Wilson and K. Ott, THIS JOURNAL, **74**, 6263 (1952).

(3) The general procedure of W. S. Johnson and H. Posvic, *ibid.*, **69**, 1361 (1947), was followed for the alkylation and determination of the proportion of O-alkyl compound. Alkylation with benzyl chloride or bromide yielded only 20–35% of the O-alkyl compound IV.

(4) D. S. Calder and K. B. Fleer, U. S. Patent 2,401,336 (*C. A.*, **40**, 5069 (1946)); L. I. Smith and W. L. Dale, *J. Org. Chem.*, **15**, 835 (1950).

(5) A further modification in the procedure used with the tetralone derivative VIII gave a 69% yield of II; this last procedure has not yet been tried for the preparation of I.

(6) The color of solutions of the salt of I is to be expected, *cf.* the red color of alkaline solutions of 2-hydroxy-3-methyl-1,4-naphthoquinone (R. J. Anderson and M. S. Newman, *J. Biol. Chem.*, **103**, 197 (1933)), and the yellow color of the sodium salt of ethyl α-oxalocrotonate (A. Lapworth, *J. Chem. Soc.*, **79**, 1277 (1901)). These compounds have chromophoric systems somewhat analogous to I, but we have not noted an exact parallel in the literature to I.

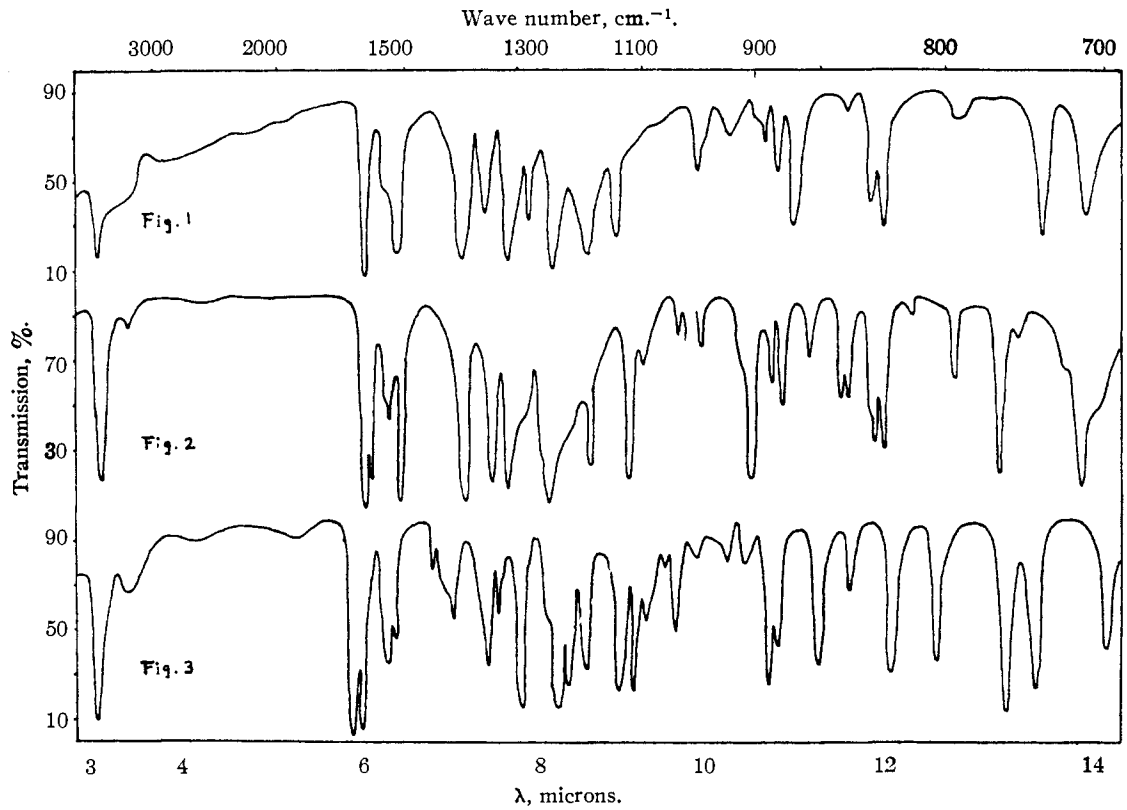


Fig. 1 (upper curve).—6-ring ketone II. Fig. 2 (middle curve).—7-ring ketone I. Fig. 3 (lower curve).—6-ring ketone IX.

Reduction of I with hydrogen and palladium yielded, when the reaction was stopped after the uptake of one mole, a dihydro compound, presumably, which was characterized as the bissemicarbazone, different from the derivative obtained from I. The dihydro compound was not stable, but rapidly air-oxidized or disproportionated, to regenerate the original compound.[7]

Oxidation experiments on I, designed to degrade the side-chain and to furnish conclusive proof of the structure, gave results that were not at first readily interpreted. Therefore, the corresponding compounds in the α-tetralone series, which are more accessible and which would furnish reference degradation products more easily, were studied.

2-Formyltetralone (VI) could not be obtained analytically pure, due to its instability, but it formed a crystalline benzoate (VII), which analyzed properly, and it gave a crystalline O-isopropyl derivative (VIII) in 92% yield. Condensation of the isopropoxy compound with biacetyl monoketal gave a 69% yield of a yellow product II, analogous to I; in addition, a few per cent. of an isomeric white compound was obtained, which was converted to the yellow compound by solution in base followed by acidification. The ultraviolet spectra of the two compounds in methylene chloride (Fig. 4) are quite different, and indicate clearly that the white compound cannot be an open-chain tautomer or *cis–trans* isomer of II, because its λ_{max} is nearly 100 mμ on the short wave length side of that of the yellow compound. The most reasonable structure for the white compound

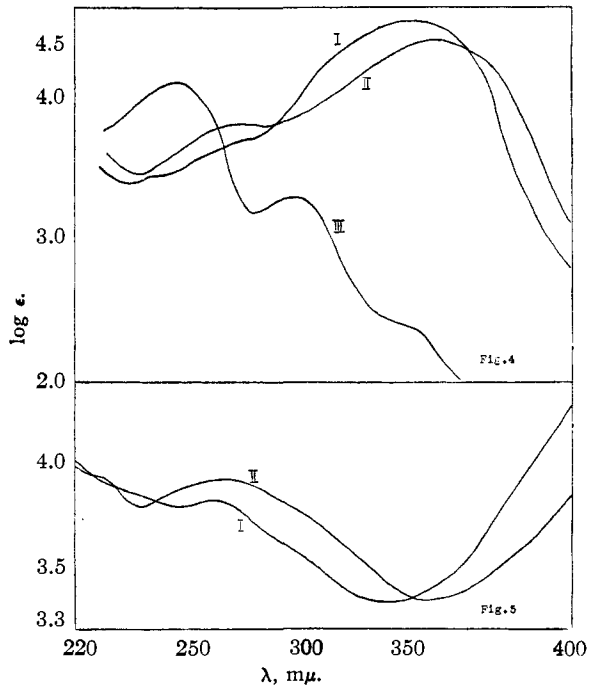
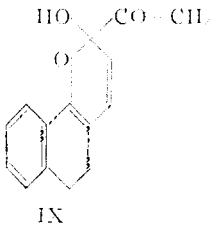


Fig. 4 (upper curve).—Ultraviolet absorption spectra (in methylene chloride): 7-ring ketone I, I; 6-ring ketone II, II; 6-ring ketone IX, III. Fig. 5. (lower curve).—Ultraviolet absorption spectra (in 0.25% sodium carbonate): 7-ring ketone I, I; 6 ring ketone II identical with IX, II.

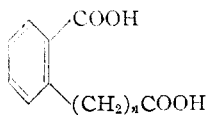
(7) Air oxidations and disproportionations of dihydro derivatives of conjugated systems similar to that in I are reported by R. E. Lutz and J. L. Wood, THIS JOURNAL, **60**, 705 (1938); also numerous examples in Kuhn's work on polyenes (*e.g.*, R. Kuhn and P. J. Drumm, *Ber.*, **65**, 1458 (1932)).

is the cyclic[8] structure IX. Isomerization of the white form to the yellow form by base must involve ring opening of IX and formation of the same anion which is obtained from the yellow form. This idea is supported by the fact that the white and yellow compounds give identical ultraviolet spectra (Fig. 5) in sodium carbonate solution. The ultraviolet spectra (Fig. 4) of the (yellow) seven-membered ring compound I and its anion (Fig. 5) are very similar to those of the lower homolog II.

The infrared spectrum of the white compound (Fig. 3) shows an OH band at 2.99 μ (3364 cm.$^{-1}$), a band in the region characteristic of the unconjugated carbonyl group, at 5.87 μ (1700 cm.$^{-1}$), which cannot be due to a conjugated carbonyl group.[9] The yellow compounds I and II (Figs. 2 and 1) both show bands in the OH region and at 1670 cm.$^{-1}$, but not in the unconjugated carbonyl region (*ca.* 1700 cm.$^{-1}$). Both yellow and white compounds (II and IX) gave a positive iodoform reaction. The yellow compound, with which most of the work was done, yielded a bissemicarbazone and a dioxime.



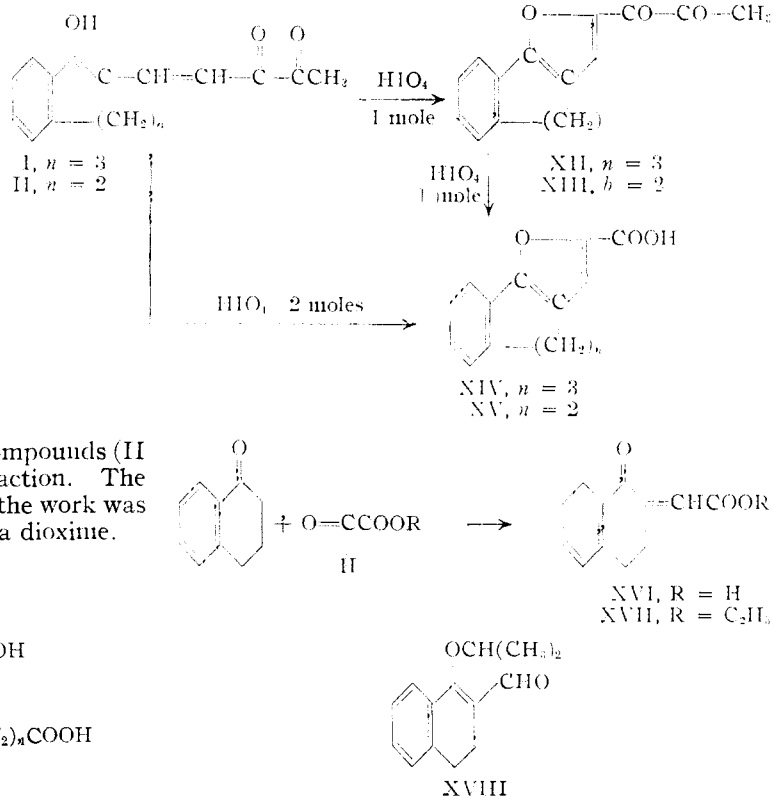
IX



X, $n = 3$
XI, $n = 2$

Both the seven-membered ring compound I and the six-membered ring analog II were oxidized by permanganate in acetone to give good yields of the expected dibasic acids, showing that the alicyclic ring was intact in each; thus, I gave γ-(*o*-carboxyphenyl)-butyric acid (X),[10] and II gave the next lower homolog, β-(*o*-carboxyphenyl)-propionic acid[11] (XI).

The action of one mole of periodic acid on I and II in aqueous tetrahydrofuran at room temperature yielded XII and XIII, respectively, which differed from the parent compounds by the loss of two hydrogen atoms; the compounds showed very similar infrared spectra with two bands in the double bond region at *ca.* 5.85 μ (1709 cm.$^{-1}$) and 6.05 μ (1654 cm.). They were insoluble in alkali, were attacked only very slowly by permanganate, and formed quinoxalines and monocarbonyl derivatives; the quinoxalines showed no carbonyl absorption in the infrared. These properties are represented adequately by the furan structures XII and XIII, which, as will be seen below, was proved definitely for XIII. Two moles of periodate with I and II gave the carboxylic acids XIV and XV, and in addition, from the tetralone derivative II, the unsaturated keto acid XVI. This compound was synthesized by condensing ethyl glyoxylate with α-tetralone in acidic or in basic media. The diketone XIII was also oxidized with one mole of periodic acid, yielding the expected acid XV in good yield. Hence the position of the side-chain in II was established, ruling out the possibility that the isopropoxy derivative VIII had structure XVIII, and that the condensation product from biacetyl monoketal had the four-carbon chain in the 1-position. Because of the complete correspondence in chemical and spectrographic properties between the seven and the six-membered ring series, there can be no doubt that the benzsuberone series has the structures an-



I, $n = 3$
II, $n = 2$

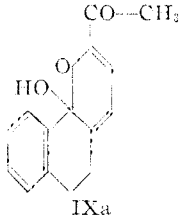
XII, $n = 3$
XIII, $n = 2$

XIV, $n = 3$
XV, $n = 2$

XVI, R = H
XVII, R = C_2H_5

XVIII

(8) For analogous cases where a marked difference in absorption properties is believed due to ring-chain tautomerism, see M. Reimer and A. L. Morrison, THIS JOURNAL, **63**, 236 (1941); H. C. Brown, *ibid.*, **63**, 882 (1941); R. E. Lutz and A. H. Stuart, *ibid.*, **58**, 1888 (1936). An alternative structure to IX is (IXa)



IXa

IX is preferred for the following reasons: (a) the ultraviolet spectrum (Fig. 4) of IX resembles more closely that of phenyl-1,3-butadiene (A. Smakula, *Angew. Chem.*, **47**, 664 (1934); O. Grummitt and F. J. Cristoph, THIS JOURNAL, **73**, 3482 (1951)) than it does that of $CH_3CH{=}CH{-}CH{=}CHCOCH_3$ (Smakula, *loc. cit.*); (b) IXa would not be expected to show absorption in the region characteristic of the unconjugated carbonyl group, but the structure IX should, as is observed.

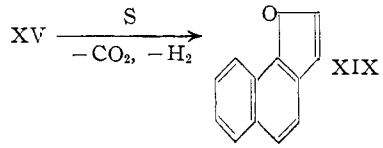
(9) *cis*- and *trans*-phenyl-1,3-butadiene show numerous bands in the double bond region in the infrared (Grummitt and Cristoph, ref. 8).

(10) We are indebted to Professor W. S. Johnson for an authentic sample of X for a mixed m.p.; *cf.* (a) W. S. Johnson and W. E. Shelberg, THIS JOURNAL, **67**, 1754 (1945); (b) W. Hückel and E. Goth, *Ber.*, **57**, 1289 (1924).

(11) A sample of XI (A. F. Titley, *J. Chem. Soc.*, 2575 (1928)) was kindly furnished by Dr. G. A. Page of this Laboratory.

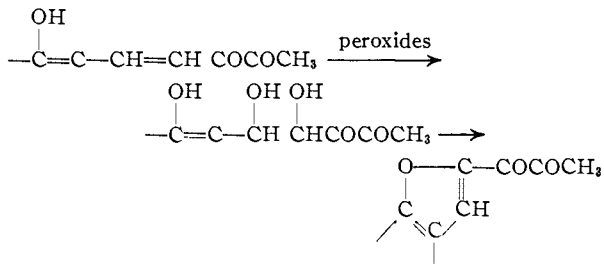
alogous to the six-membered ring series, which have been assigned.

The structure of the dihydronaphthofuroic acid XV was established by heating with sulfur, which caused simultaneous decarboxylation and dehydrogenation to the known naphthofuran XIX; this was synthesized by condensing α-naphthol with



chloroacetal,[12] and the two samples were compared through the crystalline picrate and trinitrobenzene complex.

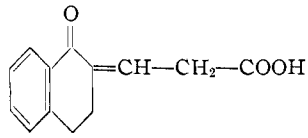
The mechanism of the oxidative cyclization of I and II to XII and XIII is not clear; periodic acid is not necessary for the reaction, because treatment of II with dilute sulfuric acid in tetrahydrofuran at room temperature for two weeks gave a non-crystalline product, from which the quinoxaline of XIII was obtained. It is possible that the reaction involves formation of an enolic peroxide[13] yielding finally a chain of the type (including the ring carbonyl)—CO—C=CH—CHOHCOCOCH$_3$, which then cyclizes to the furan with dehydration. Oxidation by peroxides might cause hydroxylation of the double bond as follows,[14] which could cyclize to the furan with the loss of two molecules of water.



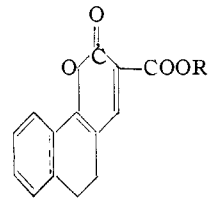
The formation of the acid XVI from II with periodate appears to require likewise the postulation of an intermediate oxygenated on the carbon which becomes the carboxyl group in XVI.

Experiments on the cyclization of I and II to tropolones, using basic catalysts, were not successful, probably due to the formation of the stable anion by the base. Some alkylation experiments did not lead to the desired enol ether. Cyclization experiments on the dihydro derivative of II were also unsuccessful.

When the periodate oxidation experiments were started, it was expected that the acid XX or a tautomer would be the product, and experiments were therefore started to synthesize a related compound for identification; condensation of 2-isopropoxymethylenetetralone (VIII) with sodiomalonic ester led to two compounds, whose properties agreed with the structures XXI and XXII. Saponification of the ester XXI yielded the acid XXII. At this point the nature of the oxidation products of I and II were clarified, and XXI and XXII were not investigated further.



XX



XXI, R = C_2H_5
XXII, R = H

Experimental[15]

2-Isopropoxymethylenebenzsuberone (V).—Freshly distilled 2-formylbenzsuberone[2] (4.5 g.), 4.28 g. of ignited potassium carbonate and 4.93 g. of dry iodine-free isopropyl iodide were refluxed in 18 cc. of dry acetone with stirring under dry nitrogen for 6 hr., at which time there was no longer a quick ferric chloride test. The refluxing was continued for 1 hr. The solvent was evaporated *in vacuo*, and the residue was taken up with water. Distillation of the residue from the dried ether solution was carried out with a nitrogen capillary, and yielded 5.13 g. (94%) of yellow oil, b.p. 144–145° (2 mm.). It could not be crystallized, was very sensitive to air, and had to be stored under dry nitrogen at Dry Ice temperatures. An assay[8] showed 95–100% of O-alkyl compound. The analytical sample was distilled in a molecular still just before analysis, $n^{27}D$ 1.5652.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 77.86; H. 7.77.

2-Benzyloxymethylenebenzsuberone (IV) was obtained by a similar procedure, best using benzyl bromide. The distilled product b.p. 160–172° (0.4 mm.) contained 30–35% of O-alkylated product.

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 82.00; H, 6.80.

2-Formyltetralone (VI).—This compound, prepared in essentially the same manner as 2-formylbenzsuberone,[2] was obtained in 43% yield,[16] b.p. (1 mm.) 105–107°, $n^{19}D$ 1.6341. The compound decomposed slowly in air, and a satisfactory analysis could not be obtained, even on a freshly distilled sample.

The benzoate (VII) was prepared using benzoyl chloride and pyridine, and, after five crystallizations from absolute alcohol, melted at 115–115.5°.

Anal. Calcd. for $C_{18}H_{14}O_3$: C, 77.68; H, 5.08. Found: C, 77.96; H, 5.39.

2-Isopropoxymethylenetetralone (VIII).—2-Formyltetralone (49.2 g.) was refluxed with 57.8 g. of isopropyl iodide and 51.0 g. of potassium carbonate in 150 cc. of acetone under nitrogen for 42 hr., at which time there was still an immediate ferric chloride color. The reaction was worked up as described previously, and distillation of the neutral fraction yielded 47.1 g. (77%) of product, b.p. 145–150° (2 mm.), $n^{14}D$ 1.5851. It solidified when chilled in Dry Ice, and, after three recrystallizations from pentane, was obtained as white needles, m.p. 52.5–53°. It was soluble in all organic solvents, and slowly decomposed in air.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.98; H, 7.50.

The alkali-soluble portion of the reaction product yielded 8.0 g. of formyltetralone; this raises the yield of ether to 92%.

Alkylation of Biacetyl Monoketal by 2-Isopropoxymethylenebenzsuberone. Preparation of I.—Solutions of 13.1 g. of the isopropoxy compound V, of 8.55 g. of the monoketal[4] and of 1.56 g. of sodium hydride, each in a separate 25-cc.

(12) (a) J. Hesse, *Ber.*, **30**, 1438 (1897); **31**, 601 (footnote) (1898); (b) R. Stoermer, *Ann.*, **312**, 311 (1900).

(13) E. P. Kohler and W. E. Mydans, THIS JOURNAL, **54**, 4667 (1932), for example.

(14) We are indebted to a referee for this suggestion.

(15) All m.ps. corrected; microanalyses by Miss Claire King.

(16) α-Tetralone was synthesized through air oxidation of tetralin, *cf. Org. Syntheses*, **20**, 94 (1940). Using this method, α-tetralol may be found in considerable amounts besides the ketone; *cf.* W. G. Brown, A. H. Widiger and N. J. Letang, THIS JOURNAL, **61**, 2601 (1939). In the above formylation 49% of α-tetralol was obtained as a side product. It is believed that the α-tetralone used was actually a mixture of the ketone and alcohol.

portion of pure dry tetrahydrofuran, were mixed at Dry Ice temperatures in a nitrogen atmosphere; the mixture was stirred under nitrogen for 40 hr. at 0° and for 8 hr. at room temperature. Ether was added to the reaction mixture, which was extracted once with water and six times with 1% sodium carbonate. The basic extract soon formed a precipitate of cotton-like yellow needles, probably the sodium salt of the enol ketal, with the side-chain =CH—CH=C(OH)C(OCH$_3$)$_2$CH$_3$. It was very soluble in water, ethanol and moist benzene. It decomposed partially during crystallization from moist benzene, and also on standing in aqueous solution; the crude salt melted at 165–167°. An attempt to obtain the free ketal crystalline by liberating it from the salt at *p*H 5 yielded a yellow oil, which on acidification formed crystalline I.

The bulk of the basic extract from the reaction mixture was acidified with hydrochloric acid to *p*H 2–3 and shaken for 18 hr. The brownish precipitate was collected, suspended in a little ether and washed twice with water, giving 4.56 g. of almost pure I on filtration; from the ethanol filtrate was obtained 3.68 g. of yellow oil, from which was obtained, by digestion with cyclohexane, 0.71 g. of additional product. The total yield was 5.13 g. (35%). The pure material (m.p. 162–162.5°)[17] was obtained after four crystallizations from benzene–cyclohexane, and was identical with the substance obtained previously[2] from the Mannich reaction.

Anal. Calcd. for C$_{16}$H$_{16}$O$_3$: C, 74.98; H, 6.29. Found: C, 75.21; H, 6.39.

The monosemicarbazone melted after four crystallizations from methanol at 186–186.5°; it was yellow, and dissolved in 10% sodium carbonate to give a deep yellow solution.

Anal. Calcd. for C$_{17}$H$_{19}$N$_3$O$_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.46; H, 6.27; N, 13.36.

The bissemicarbazone was prepared using 3 moles of semicarbazide; it melted at 246–246.5° after three crystallizations from alcohol. It was white and insoluble in alkali.

Anal. Calcd. for C$_{18}$H$_{22}$N$_6$O$_3$: C, 58.36; H, 5.99; N, 22.69. Found: C, 58.46; H, 6.22; N, 22.99.

The dioxime was prepared using pyridine. After three recrystallizations from aqueous alcohol, it melted at 198.5–199°.

Anal. Calcd. for C$_{16}$H$_{18}$N$_2$O$_3$: C, 67.11; H, 6.34. Found: C, 66.76; H, 6.33.

The quinoxaline was prepared from 29 mg. of I and 12.5 mg. of *o*-phenylenediamine in 2 cc. of absolute alcohol on the steam-bath for 30 min. Water (3 drops) was added, and after standing 24 hr., the white crystals were collected and recrystallized four times from chloroform–ethanol, m.p. 243–244°. The compound gave a green fluorescent dye when treated with concentrated sulfuric acid.

Anal. Calcd. for C$_{22}$H$_{20}$N$_2$O: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.31; H, 6.02; N, 9.27.

Catalytic Reduction of I.—Reduction with platinum catalyst led to an uptake of nearly 3 moles of hydrogen, and no pure products could be isolated. With 5% palladium-on-calcium carbonate in ethanol the uptake stopped at approximately 1.5 moles; the product turned yellow in air, especially in the presence of base. Extraction of the ether solution of the hydrogenation product with 10% sodium carbonate gradually regenerated all of the starting material I. In a similar run, a bissemicarbazone prepared from the hydrogenation product melted at 233–233.5°, after three recrystallizations from alcohol; it was only slightly soluble and was difficult to purify, but was different from the bissemicarbazone of I, as shown by a mixed m.p.

Anal. Calcd. for C$_{17}$H$_{24}$N$_6$O$_3$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.38; H, 6.85; N, 22.50.

In a run in pure ethyl acetate, with palladium-on-calcium carbonate, 1.2 moles of hydrogen was absorbed, and the above bissemicarbazone was obtained in 58% yield.

Alkylation of Biacetyl Monoketal by 2-Isopropoxymethylenetetralone (VIII). Preparation of II and IX.—The isopropoxy compound VIII (12.0 g.) in 30 cc. of dry tetrahydrofuran, 8.3 g. of biacetyl monoketal in 20 cc. of tetrahydrofuran, and 1.44 g. of sodium hydride in the same solvent were mixed under nitrogen at Dry Ice temperatures. The mixture was stirred under *nitrogen* for 30 min. at 40°. The reaction mixture was taken up in ether and a little water, and was extracted five times with 10% sodium carbonate. The basic extracts were acidified with concd. hydrochloric acid to *p*H 1, and shaken for 42 hr. The brown crystalline mass was collected, washed thoroughly with water, suspended in a little ether, filtered again and dried in a vacuum desiccator. The greenish-yellow crystals of II (9.3 g., 69%) were dissolved in benzene–ether, washed twice with water and recrystallized from benzene containing a little cyclohexane. A yield of 8.3 g. of II, m.p. 154–156°, was obtained. The m.p. was raised to 157–158° by four crystallizations from benzene–cyclohexane.

Anal. Calcd. for C$_{15}$H$_{14}$O$_3$ (II): C, 74.36; H, 5.82. Found: C, 74.74; H, 5.98.

The bissemicarbazone from II melted, after four crystallizations from alcohol, at 258–259°.

Anal. Calcd. for C$_{17}$H$_{22}$N$_6$O$_3$: C, 56.96; H, 6.19. Found: C, 56.59; H, 6.27.

The dioxime melted at 234–235° after four crystallizations from alcohol.

Anal. Calcd. for C$_{15}$H$_{16}$N$_2$O$_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.12; H, 6.10; N, 9.63.

The ketone II gave a reddish-brown color with ferric chloride and reduced permanganate instantly.

The above aqueous acidic filtrate from the crude brown II was saturated with ammonium chloride and extracted with ether–benzene; the extract yielded 0.45 g. of yellow oil which crystallized on standing. Digestion with ether gave 0.29 g. of white needles of IX which, after five crystallizations from benzene–cyclohexane, melted at 145.5–146°, and gave a large depression on mixed m.p. with II.

Anal. Calcd. for C$_{15}$H$_{14}$O$_3$: C, 74.36; H, 5.82. Found: C, 74.35; H, 5.83.

When the white ketone IX was dissolved in warm 10% sodium carbonate, reprecipitated with acid, and crystallized from benzene–cyclohexane, the yellow ketone II, m.p. 157–158°, was obtained. Ketone IX gave the same ferric chloride color as II; both II and IX yielded about 15–20% of crystalline iodoform when treated with alkaline hypoiodite solution. A number of other ill-defined oxidation products was obtained.

Permanganate Oxidation of II to β-(*o*-Carboxyphenyl)-propionic Acid (XI).—The yellow ketone II (488 mg.) in 30 cc. of acetone was treated with 980 mg. of powdered potassium permanganate, added in small portions during 0.5 hr. at 2–5°. Stirring was continued for 80 min. at 0°. The acetone was evaporated in an air stream, 30 cc. of water was added, and the manganese dioxide was reduced, with cooling in an ice–salt-bath, with sodium bisulfite and sulfuric acid. The product was taken up in ether, washed with ammonium chloride, and extracted with saturated bicarbonate solution. The acidic material obtained (0.305 g.) was subjected to steam distillation to remove volatile acids, the residue was taken up in ether and was treated with charcoal. The solid obtained (m.p. 162–185°) could not be purified by fractional crystallization from benzene–ethyl acetate, and was finally chromatographed on dry silica gel from hot benzene (279 mg. of acidic material in 15 cc. of solvent). Elution with a total of 500 cc. of benzene yielded a total of 178 mg. of crystalline acid, m.p. 162–166°, which was raised to 166–167° by two crystallizations from benzene, followed by two from water. The m.p. and neutral equivalent checked for the acid XI, and there was no depression on mixed m.p. with an authentic sample.[11]

Permanganate Oxidation of I to γ-(*o*-Carboxyphenyl)-butyric Acid (X).—The compound I (767 mg.) was oxidized as described above with 1.66 g. of permanganate. The crude acid (565 mg.) was purified by chromatography as described above, and 240 mg. of X obtained, m.p., after one crystallization from benzene and two from water, 138–139°. No depression was observed on mixed m.p. with an authentic sample.[10]

Periodic Acid Oxidation of I to XII.—The ketone I (256 mg., 1.0 mmole) was heated to 35° in 10 cc. of purified tetrahydrofuran, and 240 mg. (1.05 mmoles) of paraperiodic acid (HIO$_4$·2H$_2$O) in 2.5 cc. of water was added. After 2.5 hr., there was no longer any color formed when sodium car-

(17) The analytical sample was obtained from an earlier run in which the alkylation was carried out in dry ether, and the sodium derivative of biacetyl monoketal was prepared with powdered sodium; the yield was 21%.

bonate was added to a test portion of the solution. The solvent was evaporated *in vacuo* at room temperature, and the brown residue was taken up in ether and was washed four times with small portions of water. Extraction with bicarbonate yielded only 18 mg. of tarry material; the ether solution was washed with water and with ammonium chloride solution, and was dried and evaporated *in vacuo*, giving a yellow oil (239 mg.). From this was obtained 169 mg. (66%) of yellow crystals of XII, m.p. 70–72°. Five crystallizations from hexane raised the m.p. to 79°.

Anal. Calcd. for $C_{16}H_{14}O_3$ (XII): C, 75.57; H, 5.55. Found: C, 75.96; H, 5.58.

The compound gave no color with ferric chloride, was insoluble in 10% aqueous alkali, but was decomposed when methanol was added to the basic solution or when it was heated. It was attacked only slowly by permanganate in acetone.

The orange **monodinitrophenylhydrazone** melted at 265–266° after four crystallizations from chloroform.

Anal. Calcd. for $C_{22}H_{18}N_4O_6$: C, 60.86; H, 4.18; N, 12.89. Found: C, 60.75; H, 4.43; N, 12.85.

The **monosemicarbazone** was only slightly soluble in organic solvents, and melted at 236.5–237° after five crystallizations from ethanol.

Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.62; H, 5.50; N, 13.50. Found: C, 65.94; H, 5.44; N, 13.99.

The **quinoxaline** was obtained in quantitative yield as yellow needles, m.p. 153–154, after four crystallizations from alcohol. It showed strong green fluorescence in chloroform or benzene solution; with 12 *N* hydrochloric acid it formed a dark blue dye, and with 4 *N* acid a red one.

Anal. Calcd. for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56. Found: C, 81.27; H, 5.61.

Oxidation of I with Two Moles of Periodic Acid to the Acid XIV.—Compound I (512 mg., 2 mmoles) in 20 cc. of tetrahydrofuran at 35° was treated with 935 mg. of paraperiodic acid (4.1 mmoles) in 5 cc. of water, and the mixture was allowed to stand 46 hr. at room temperature. The solvent was evaporated *in vacuo* without heating and the residue was taken up in ether. The ether extract was washed with water and three times with bicarbonate solution. The latter was acidified to congo red, the precipitate filtered and washed with water; 285 mg. (63%) of the white acid XIV, m.p. 206–208°, was isolated. Four crystallizations from benzene gave material melting at 208–209°.

Anal. Calcd. for $C_{14}H_{12}O_3$ (XIV): C, 73.67; H, 5.30; neut. equiv., 228. Found: C, 73.95; H, 5.35; neut. equiv., 229.

The product XIV was attacked only slowly by bromine in carbon tetrachloride; it gave no carbonyl derivatives, and did not take up hydrogen in the presence of platinum, or palladium-on-calcium carbonate.

Periodic Acid Oxidation of II to XIII.—Oxidation of 122 mg. of II with 120 mg. of paraperiodic acid, carried out essentially as described above for the seven-membered ring homolog I, yielded 96 mg. of a neutral deep yellow oil, from which 71 mg. of yellow prisms were isolated on adding hexane. After four crystallizations from pentane–hexane, it melted at 79–80°.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.98; H, 5.04. Found: C, 74.60; H, 5.00.

The compound showed the same chemical properties as XII, but gave a large depression in m.p. upon admixture with compound XII.

The **quinoxaline** was obtained, after four crystallizations from ethanol, as yellow needles, m.p. 179–180°.

Anal. Calcd. for $C_{21}H_{16}N_2O$: C, 80.74; H, 5.16; N, 8.97. Found: C, 80.72; H, 5.41; N, 9.27.

Air Oxidation of II to XIII.—II (160 mg.) was allowed to stand for two weeks at room temperature in a mixture of 8 cc. of tetrahydrofuran and 2 cc. of 3 *N* sulfuric acid. A sample still gave a red color with sodium carbonate solution. The alcohol was removed *in vacuo* without heating, and the neutral material, 81 mg. of yellow oil which could not be crystallized, was separated in the usual way. From this was obtained 49 mg. of the same quinoxaline described above, m.p. and mixed m.p. 179–180°. The original precipitate from *o*-phenylenediamine appeared to change on standing; perhaps a dehydrogenation by the diamine was also involved.

Oxidation of II by Two Moles of Periodate to the Acids XV and XVI.—In a number of oxidation experiments on II with two moles of periodate, the acids XV and XVI, as well as the diketone XIII, were obtained, although not all three products were isolated from any one run.

A. The Acid XV.—Treatment of 488 mg. of II (2 mmoles) with 935 mg. of paraperiodic acid (4.1 mmoles) in 5 cc. of water and 20 cc. of tetrahydrofuran yielded by the usual procedure, after 48 hr. at room temperature, 155 mg. of solid acidic material, when the bicarbonate extract was acidified with mineral acid. The filtered product was taken up in ether, was washed with water, and from the dried extract 144 mg. of white needles was obtained, which, after five crystallizations from benzene, melted at 222°.

Anal. Calcd. for $C_{13}H_{10}O_3$ (XV): C, 72.89; H, 4.70; neut. equiv., 214. Found: C, 72.92; H, 4.48; neut. equiv., 215.

The acid had the same properties as its homolog XIV.

From the aqueous acidic filtrate from XV, there was obtained by saturation with ammonium chloride and ether extraction, 32 mg. of the acid XVI, described below.

B. The Acid XVI.—Oxidation of 488 mg. of II with 956 mg. of paraperiodic acid under the usual conditions for 88 hr., yielded a precipitate of the furan acid XV, when the bicarbonate extract was acidified; 95 mg. (22%) of pure XV was obtained. Saturation of the filtrate from XV with ammonium chloride and ether extraction gave 88 mg. (22%) of the acid XVI, m.p. 185–186°, after two crystallizations from ethyl acetate. The analytical sample was obtained from an earlier run.

Anal. Calcd. for $C_{12}H_{10}O_3$ (XVI): C, 71.28; H, 4.98; neut. equiv., 202. Found: C, 71.34; H, 4.78; neut. equiv., 202.

The acid gave strongly positive tests for unsaturation with bromine in carbon tetrachloride, and permanganate. It turned purple after melting, and also when dissolved in 10% alkali and allowed to stand in air. It gave no ferric chloride test.

The ethyl ester (XVII) was prepared from absolute alcohol and 2 drops of hydrochloric acid, and was obtained as pale yellow needles, m.p. 109–109.5°, after four crystallizations from hexane.

Anal. Calcd. for $C_{14}H_{14}O_3$ (XVII): C, 73.02; H, 6.13. Found: C, 72.91; H, 6.04.

Periodic Acid Oxidation of XIII to XV.—Oxidation of 44 mg. of XIII with 42.2 mg. of paraperiodic acid in 3.5 cc. of tetrahydrofuran and 0.7 cc. of water for 60 hr. at room temperature yielded 27 mg. (68%) of bicarbonate-soluble crystalline material which, after six recrystallizations from benzene melted at 222°. No depression in m.p. was observed when mixed with the white acid obtained from direct oxidation of II.

Dehydrogenation and Decarboxylation of Acid XV to α-Naphthofuran (XIX).—The furan acid XV (74 mg.) was mixed thoroughly with 11.2 mg. of sublimed sulfur, and heated at 230–240° for 30 min., at which time gas evolution had stopped. The mixture was taken up in a little ether–benzene, treated with Darco, and was washed with bicarbonate solution, with water and with ammonium chloride solution. The yellow oil (31 mg.) obtained from the ether solution was steam distilled in a micro-apparatus, the distillate was saturated with ammonium chloride and was thoroughly extracted with ether. The product, 22 mg. of a pale yellow oil, was converted into the **picrate**, m.p. 127.5–128.5° after six crystallizations from methanol; the **trinitrobenzene compound**, m.p. 137–138°, was also prepared. Both were shown to be identical by mixed m.p. with the authentic derivative, described below.

α-Naphthofuran (XIX).—The procedure of Hesse[12a] was followed. From 9.0 g. of α-naphthol and 9.15 g. of chloroacetal, 3.29 g. of steam distilled neutral material (free of α-naphthol) was obtained. Fractional distillation yielded 2.61 g. of α-naphthofuran, b.p. 103–105° (3 mm.), $n^{14}D$ 1.6530.[18]

The **picrate**, obtained in quantitative yield, was dark yellow needles, m.p. 127.5–128° after six crystallizations from methanol. It decomposes with partial sublimation in high vacuum at 60°; the analytical sample was dried at 35° in the high vacuum. The compound has been reported to melt at 113°, and at 122–123°,[12b] and hence was analyzed.

(18) Stoermer (ref. 12b) reports b.p. 282–284° (755 mm.), $n^{16}D$ 1.634.

Anal. Calcd. for $C_{18}H_{11}N_3O_8$: C, 54.41; H, 2.79; N, 10.58. Found: C, 54.24; H, 3.10; N, 10.73.

The trinitrobenzene compound melted at 137–138° after three crystallizations from methanol.

Anal. Calcd. for $C_{18}H_{11}N_3O_7$: C, 56.70; H, 2.91; N, 11.02. Found: C, 56.48; H, 3.24; N, 11.18.

Ethyl Glyoxylate and Related Compounds.—Oxalic acid was reduced to glyoxylic acid as follows.[19] Zinc powder (30 g.), 47.5 g. of sodium and 700 g. of mercury were fused to a melt under dry nitrogen, and the cooled amalgam was crushed to small lumps. The amalgam was added during 2 hr. to a solution of 130 g. of oxalic acid dihydrate and 450 g. of concd. hydrochloric acid in 1200 cc. of water, the mixture being kept at 8–12°. The solution was brought to *p*H 3–4 by addition of 30% alkali, and was evaporated almost to dryness in an air stream. The glyoxylic acid was extracted from the inorganic salts with absolute ethanol in a soxhlet for 3 days. The extract (1.5 l.) was dried over calcium sulfate, saturated with hydrogen chloride and refluxed for 3 hr. The solvent was removed through a 2-ft. Vigreux column, and the residue was taken up in ether, washed with ice-cold 5% carbonate solution, ammonium chloride solution and distilled. The principal fractions were 7.9 g., b.p. 132–134° (1 atm.), $n^{14}D$ 1.4306, apparently ethyl glyoxolate or its ethyl hemiacetal[19b] and 48.6 g., b.p. 186–189° (1 atm.), $n^{18}D$ 1.4160, the diethyl acetal.[19b] Hydrolysis of the latter with 2 *N* hydrochloric acid in the cold gave ethyl glyoxylate.

Condensation of Ethyl Glyoxylate with Tetralone Forming XVI.—Ethyl glyoxalate (0.25 g.) and 0.365 g. of α-tetralone were dissolved in 2 cc. of acetic anhydride containing 1 drop of concd. sulfuric acid; the mixture was stirred under nitrogen for 16 hr. at room temperature, and was then heated on the steam-bath for 4 hr. The acetic anhydride was decomposed with a little boiling water, and the mixture was then cooled and brought to *p*H 6 with 10% carbonate. From the dried ether extract of this mixture, a yellow oil (0.49 g.) was obtained which did not crystallize; it was hydrolyzed by refluxing 4.5 hr. with 5 cc. of concd. hydrochloric acid. The hydrolysis mixture, worked up by the usual procedure, yielded 0.229 g. (46%) of bicarbonate-soluble crystalline material, which melted at 186.5–187.5° after four crystallizations from ethyl acetate, and gave no depression on mixed m.p. with XVI obtained by periodate oxidation of II. The two samples were also compared through the crystalline ethyl esters XVII, again proving identity of the material obtained by synthesis and oxidation.

Condensation of α-tetralone with ethyl glyoxylate with sodium hydride gave a poor yield of XVI.

Condensation of Isopropoxymethylenetetralone with Malonic Ester to Form XXI.—Malonic ester (1.6 g.) was converted to the sodio compound with 0.25 g. of powdered sodium in dry ether and was cooled to 0°; to this was added 2.16 g. of the isopropoxy compound in 10 cc. of dry ether under nitrogen. The mixture was stirred for 10 min. at 0°, 30 min. at room temperature, and was refluxed for 1 hr. Ice-water was added, and the mixture was extracted with ether; the latter was extracted thoroughly with 5% carbonate and then with water. Yellow prisms, m.p. 144–146° (0.75 g.) were obtained by digesting the residue from the neutral portion with ether, and, after four crystallizations from benzene–cyclohexane, they melted at 150°.

Anal. Calcd. for $C_{16}H_{14}O_4$ (XXI): C, 71.10; H, 5.22. Found: C, 71.16; H, 5.17.

The compound dissolved slowly in hot 10% alkali; it gave no carbonyl derivatives and no color with ferric chloride.

The combined basic extracts from the reaction mixture were acidified with mineral acid, and extracted with ether–benzene. The organic layer was again extracted with 5% carbonate, acidified and taken up in ether–benzene. Evaporation of the dried solution and addition of ether caused the separation of 0.16 g. of yellow needles, m.p. 197–199°. The m.p. was raised to 200° by three crystallizations from benzene.

Anal. Calcd. for $C_{14}H_{10}O_4$ (XXII): C, 69.42; H, 4.16. Found: C, 69.42; H, 4.17.

Alkaline hydrolysis of the ester XXI gave the acid XXII.

Spectra.—Infrared spectra were taken by Mr. Carl Whiteman on a Perkin–Elmer spectrograph, using Nujol suspensions. Ultraviolet spectra were taken on a Beckman instrument, and methylene chloride was used as solvent for compounds I and II because they reacted with alcohol.

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NOTES

A Synthesis of Valine

BY P. T. ADAMS AND B. M. TOLBERT[1]

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In the preparation of radioactive compounds it is often of interest to explore syntheses which, although not involving novel methods, have not been previously reported and which offer special advantages in availability of intermediates or position of label. Thus the preparation of aliphatic amino acids by the reduction of the corresponding oxazolone has been described only twice before[2,3] and in both cases with either poor or no reported yields. In fact, most authors consider this an unsatisfactory method for the preparation of aliphatic amino acids.[3,4]

This method has, however, been applied to the synthesis of valine with unexpectedly good results. Starting with 10 millimoles of glycine, 2-phenyl-4-isopropylidine oxazolone-5 has been prepared through the intermediate hippuric acid by the method of Ramage and Simonsen[5] in 57% yield with 24% recovery of unused glycine or 75% yield based on glycine used. The oxazalone was then reduced in 75% yield to valine using red phosphorus and hydrogen iodide.[6] It is possible that part of the increased applicability of this method is due to the use of newer and more efficient methods (ion

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