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

Mannich Bases and Other Compounds Derived from Benzsuberone[1]

BY D. S. TARBELL, H. F. WILSON[2] AND EDWARD OTT

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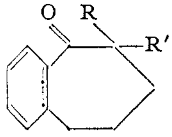
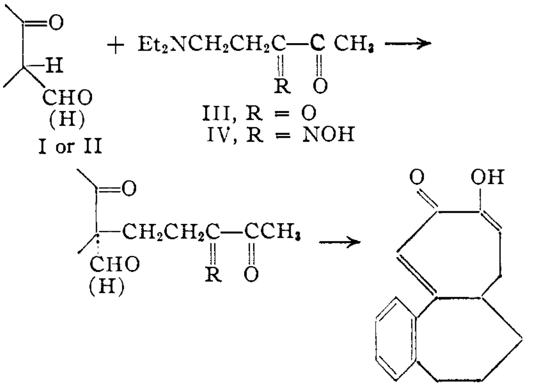
The synthesis of the colchicine ring system has been explored by applying an extension of the Robinson–Mannich reaction to benzsuberone and derivatives of biacetyl. Two Mannich bases from benzsuberone have been prepared; they readily form a dimer of methylenebenzsuberone which appears to be analogous to the dimer of methylenecyclohexanone described by Mannich. Using the Mannich base of benzsuberone and biacetyl monoketal, a small yield of the benzsuberone with the chain $=CHCH_2COCOCH_3$ in the 2-position has been obtained.

The present paper describes some results obtained in a study of several projected syntheses of the colchicine ring system. This ring system consists of a tropolone ring, a seven-membered ring and an aromatic ring, fused in the angular position.[3]



I, R = R' = H
II, R = H, R' = CHO
VII, R = $CH_2N(CH_3)_2$, R' = H
VIII, R and R' = $CH_2=$
XI, R and R' = $=CHCH_2COCOCH_3$
XII, R = H, R' = $CH_2N(CH_2)_5$
XIV, R = H, R' = Br
XV, R = H, R' = CN

An extension of the Robinson–Mannich reaction[4] to benzsuberone (I) or to formylbenzsuberone[5] (II), using a Mannich base derived from biacetyl, might be expected to yield a product (V) which could be cyclized to a partially reduced tropolone.



I or II

III, R = O
IV, R = NOH

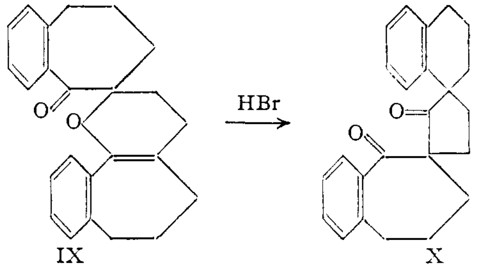
V

VI

Formylbenzsuberone (II) was readily prepared, and was converted to the O-benzoate. Numerous attempts to prepare the Mannich base from biacetyl or from biacetyl monoxime were unsuccessful; compound IV was obtained, however, by nitrosation of 5-diethylaminopentanone-2 (noval ketone), the position of the oximino group being assigned by analogy to the nitrosation of methyl ethyl ketone.[6] Preliminary experiments on the condensation of IV or its methiodide with 2-benzal-6-formylcyclohexanone were unpromising.

Attention was therefore directed to the preparation of Mannich bases derived from the cyclic ketone I, which should condense with biacetyl or a derivative to yield a compound of type V. The Mannich base VII was found to be rather unstable, and to be transformed readily by heat into a crystalline ketone shown to be the dimer of the vinyl ketone VIII; some of the dimer was also produced as a by-product during the preparation of the Mannich base.

The chemical properties of the dimer (molecular weight, infrared spectrum, formation of a monoxime and uptake of one mole of bromine) are in agreement with structure IX, analogous to that demonstrated for the dimer obtained from the Mannich base of cyclohexanone.[7a] The action of hydrogen bromide in acetic acid on IX led to an isomeric compound, which appeared to be analogous to a transformation product of the dimer derived from cyclohexanone referred to above; the structure of the latter was conclusively established by Mannich,[7b] and structure X was assigned to our compound by analogy. A reasonable mechanism for the transformation in the cyclohexanone series has been proposed.[7b]



IX X

Condensation of the Mannich base VII or its methiodide with biacetyl or biacetyl monoxime did not give the desired product; with the sodio derivative of biacetyl monoketal, $CH_3COC(OCH_3)_2CH_3$, however, a small amount of the product XI was obtained.[8]

The piperidino Mannich base XII was also prepared, and was found to be somewhat more stable

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[1] Aided by a grant from the National Cancer Institute.

[2] du Pont Fellow, 1949–1950.

[3] For discussions of the structure of colchicine, see J. D. Loudon, *Ann. Repts. Chem. Soc. London*, **45**, 187 (1948); G. P. Scott and D. S. Tarbell, THIS JOURNAL, **72**, 240 (1950); W. E. Doering and L. H. Knox, *ibid.*, **73**, 828 (1951); H. Rapoport, *et al.*, *ibid.*, **73**, 1414 (1951); R. M. Horowitz and G. E. Ullyot, *ibid.*, **74**, 587 (1952); J. W. Cook, J. Jack, J. D. Loudon, G. L. Buchanan and J. MacMillan, *J. Chem. Soc.*, 1397 (1951).

[4] E. C. Du Feu, F. J. McQuillin and R. Robinson, *ibid.*, 53 (1937).

[5] *Cf.* C. H. Shunk and A. Wilds, THIS JOURNAL, **71**, 3946 (1949).

[6] O. Diels and H. Jost, *Ber.*, **35**, 3290 (1902).

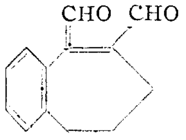
[7] (a) C. Mannich, *ibid.*, **74**, 557 (1941); (b) **74**, 565 (1941).

[8] The properties of this compound, and its preparation by a better method, are described in the accompanying paper (E. Ott and D. S. Tarbell, THIS JOURNAL, **74**, 6266 (1952)). The expected product of the above Mannich reaction would have the side chain $-CH_2CH_2-COCOCH_3$; this, if formed, either air-oxidizes or disproportionates to XI, shown below.

than the dimethyl derivative VII, although it yielded the dimer IX on heating *in vacuo*. Its reactions with biacetyl monoketal were similar to those of the dimethyl compound.

An alternative approach to the tricyclic colchicine ring system required the dialdehyde XIII, which should condense with methoxyacetone to yield the desired tropolone, analogous to the synthesis of β,γ-benzotropolone from phthalaldehyde.[9]

Some experiments were accordingly undertaken to prepare the dinitrile corresponding to XIII. It was found that hydrogen cyanide would not add to the carbonyl group of benzsuberone, even under conditions designed to circumvent the apparently unfavorable equilibrium.[10]



XIII

Treatment of the bromobenzsuberone XIV (obtained by bromination), with sodium cyanide gave the cyano ketone XV. Although it is well known that treatment of α-haloketones with cyanide may lead to products other than those due to simple replacement,[11] the structure XV was supported by the analysis and by a carbonyl absorption band in the infrared at 1660 cm.$^{-1}$. The compound did not add hydrogen cyanide, or form carbonyl derivatives.

Experimental[12]

Benzsuberone (I) was prepared by the cyclization of 8-phenylvaleric acid[13] following Plattner[14]; b.p. 108–110° (1 mm.), n^{19}D 1.5632.

2-Formylbenzsuberone (II).—Sodium methoxide, prepared from 4.8 g. of sodium, was baked at 200° under reduced pressure.[15] The white cake was broken up, the flask was evacuated, and nitrogen was bubbled in. A solution of 14.8 g. of distilled ethyl formate in 160 cc. of dry benzene was added, and the mixture was cooled in an ice-bath. A solution of 16.0 g. of benzsuberone in 180 cc. of dry benzene was added with shaking. The mixture was allowed to come to room temperature, and was then heated gently on the steam-bath; reaction started at once, and the mixture set to a mush. After 30 min., water was added, the benzene layer was extracted twice with 10% alkali, the combined alkaline extracts were shaken with ether, cooled and acidified. An oil separated, the aqueous layer was saturated with salt and extracted four times with ether. After drying the ether extracts and removing of the solvent, the residue was distilled, giving 17.9 g. (95%) of product, b.p. 122–123° (0.5 mm.), n^{24}D 1.6092.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.82; H, 6.21.

The **benzoate**, prepared in the usual way using benzoyl chloride and pyridine, was purified by chromatography on florisil and crystallized from absolute alcohol, m.p. 128.5–129°.

Anal. Calcd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.76; H, 5.25.

5-Diethylamino-3-oximino-2-pentanone (IV).—Noval ketone[16] (15.7 g.) was dissolved in 20 cc. of absolute ethanol and 10 cc. of concentrated hydrochloric acid was added slowly with stirring, keeping the temperature below 50°. The solution was then heated to 40°, and freshly distilled isoamyl nitrite (23.4 g.) was added slowly with stirring, keeping the reaction temperature at 40–50°. The homogeneous solution was stirred for an additional hour, and the temperature was allowed to fall to room temperature. The flask was then tightly stoppered and allowed to stand overnight. The solution was poured into water, saturated with salt and extracted with ether. Sodium bicarbonate was then added until carbon dioxide was no longer evolved. The aqueous solution was extracted six times with chloroform, the combined extracts were dried and the solvent was removed at the water-pump. Heating above 50° must be avoided. The oil obtained was triturated with a little ether to yield 5.1 g. of a tan solid which melted at 65–67°. The analytical sample was purified by high vacuum sublimation and it had m.p. 67.5–68°. Additional product could be obtained by combining the aqueous layers from several experiments and extracting continuously with ether for two days. Thus 5.5 g. was obtained from aqueous layers of four experiments.

Anal. Calcd. for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74. Found: C, 58.16; H, 9.42.

The **methiodide** was obtained as white crystals from absolute ethanol–ethyl acetate and melted at 203–203.5°.

Anal. Calcd. for $C_{10}H_{21}IN_2O_2$: C, 36.59; H, 6.45. Found: C, 36.44; H, 6.23.

2-Benzal-6-formylcyclohexanone.—This compound was prepared from 2-benzalcyclohexanone[17] by the method described above for 2-formylbenzsuberone in 60–65% yield, and was purified by chromatography on florisil, m.p. 79–80°. Even when a freshly prepared sample was analyzed, the carbon values were high.[18]

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 79.29; H, 6.45, 6.49.

The **benzoate**, prepared in the usual way using benzoyl chloride and pyridine, was purified by chromatography on florisil and crystallized from absolute ethanol, m.p. 128.5–129°. Even when a freshly prepared sample was analyzed, the results indicated some decomposition had occurred.

Anal. Calcd. for $C_{21}H_{18}O_3$: C, 79.22; H, 5.70. Found: C, 78.32, 78.36; H, 5.42, 5.85.

The monosemicarbazone was obtained as yellow needles from ethanol, m.p. 208.5–210° dec.

Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32. Found: C, 66.60; H, 6.34.

2-Dimethylaminomethylbenzsuberone (VIII).—Freshly distilled benzsuberone (15 g., 0.094 mole), 8.95 g. of dimethylamine hydrochloride (0.11 mole) and 5.4 g. of formaldehyde (0.18 mole, in a 35% aqueous solution) were stirred under nitrogen for 30 min. at room temperature and 2.5 hr. on the steam-bath. The cold suspension was taken up in water, was thoroughly extracted with ether, and the ether extracts were washed with water. The combined aqueous solutions were cooled to 0°, ice was added and the *p*H was brought carefully to 8 by addition of dilute ammonium hydroxide. The mixture was taken up in ether and washed with water to remove excess dimethylamine; the ether solution of the Mannich base was acidified to congo red with hydrochloric acid and thoroughly extracted with water. The aqueous extracts were concentrated *in vacuo*, absolute ethanol was added and the solution was repeated five times, until most of the water was removed. The viscous oil was then dissolved in tetrahydrofuran, cooled with Dry Ice–acetone, the very hygroscopic hydrochloride

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(9) D. S. Tarbell, G. P. Scott and A. D. Kemp, THIS JOURNAL, **72**, 379 (1950); D. S. Tarbell and J. C. Bill, *ibid.*, **74**, 1234 (1952).

(10) A. Lapworth and R. H. F. Manske, (*J. Chem. Soc.*, 2548 (1928)) showed that the equilibrium for the addition of hydrogen cyanide to α-tetralone was very unfavorable.

(11) E. P. Kohler and F. W. Brown, THIS JOURNAL, **55**, 4299 (1933); the action of cyanide ion on bromotetralone does not appear to have been investigated.

(12) All melting points corrected.

(13) J. W. Cook, R. Philip and A. R. Somerville, *J. Chem. Soc.*, 164 (1948).

(14) P. A. Plattner, *Helv. Chim. Acta*, **27**, 801 (1944); polyphosphoric acid has recently been recommended for the cyclization (W. J. Horton and F. E. Walker, THIS JOURNAL, **74**, 758 (1952)).

(15) W. S. Johnson, *et al.*, *ibid.*, **66**, 218 (1944).

(16) We are indebted to Professor R. C. Elderfield for a gift of this material.

(17) Poggi and Gustalla, *Gazz. chim. ital.*, 61, 405 (1931).

(18) W. S. Johnson and H. Posvic, THIS JOURNAL, **69**, 1361 (1947), have reported difficulty in obtaining good carbon analyses for 2-formylcyclohexanone compounds.

(13.8 g., 58%) was obtained as fine needles; it melted at 130–133° after recrystallization from alcohol–tetrahydrofuran.

The free base was obtained by shaking 0.66 g. of the hydrochloride with 5 cc. of 5% ammonium hydroxide containing some ice; the solution was extracted with ether, the extract was washed with saturated ammonium chloride solution, then with water and was then dried and evaporated *in vacuo.* The residue (0.42 g.) was a pale yellow oil, which could not be crystallized, and which decomposed on standing in air or heating on the steam-bath.

The picrate was obtained, after recrystallization from methanol, as rhombic leaflets, m.p. 147.2–147.4°.

Anal. Calcd. for $C_{20}H_{22}N_4O_8$: C, 53.81; H, 4.93. Found: C, 53.85; H, 5.09.

Dimer of Methylenebenzsuberone (IX).—The ether-soluble part of the reaction mixture in the preparation of the above Mannich base hydrochloride consisted of 8.85 g. of a viscous yellow oil, from which 5.6 g. of white crystals were obtained by the addition of methanol; this product after recrystallization from methanol, melted at 128°. The same product was obtained when the free Mannich base was heated *in vacuo* (1 mm.) to about 100°. From the solution of the viscous residue in methanol, the product crystallized out in white leaflets, m.p. 128° after three crystallizations from methanol. The mixed m.p. showed no depression.

Anal. Calcd. for $C_{24}H_{24}O_2$ (IX): C, 83.68; H, 7.02; mol. wt., 344. Found: C, 83.53; H, 7.07; mol. wt. (Rast), 321.

The compound was insoluble in concentrated alkali, gave no color with ferric chloride, reacted immediately with potassium permanganate and absorbed almost exactly 1 mole of bromine (by titration). The bromination product, after crystallization from pentane, melted at 150–151°, but could not be obtained analytically pure. The infrared spectrum showed bands at 5.91 μ (1692 cm.$^{-1}$), (attributed to the conjugated carbonyl group), at 6.06 μ (1653 cm.$^{-1}$), (the enolic carbon–carbon double bond) and at 8.98 μ (1131 cm.$^{-1}$), (the C–O–C vibration of the enol ether), among others,

A monoxime was obtained by refluxing the compound with an excess of hydroxylamine hydrochloride and pyridine in absolute ethanol for 20 hr. It crystallized in leaflets after triturating in water, and melted at 185–187° after six crystallizations from benzene–cyclohexane and ethanol–water.

Anal. Calcd. for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01. Found: C, 80.29; H, 7.16.

Isomerization of IX to X.—The dimer IX (0.25 g.) was boiled for 1 min. in a mixture of 4 cc. of glacial acetic acid and 1 cc. of 48% hydrobromic acid. The brown reaction mixture was neutralized with 10% ammonium hydroxide and extracted with ether containing 10% of chloroform. The dried extract yielded 0.21 g. of dark material, from which 0.16 g. of crystalline material, m.p. 151–152°, was obtained. After four crystallizations from methanol and cyclohexane alternately, it melted at 153–153.5°.

Anal. Calcd. for $C_{24}H_{24}O_2$: C, 83.68; H, 7.02. Found: C, 83.36; H, 6.83.

The oxime was prepared by refluxing 30 mg. of X in 0.25 cc. of benzene with 14 mg. of hydroxylamine hydrochloride in 0.75 cc. of alcohol and 2 drops of pyridine for 24 hr. The solvent was evaporated *in vacuo*, and the addition of a little ethanol and water caused the separation of 28 mg. of white needles, m.p. 179–181°. After eight recrystallizations alternately from ethanol–water and benzene, the m.p. was 197–201°, it was possibly a mixture of *syn-* and *anti*-oximes.

Anal. Calcd. for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.02. Found: C, 80.19; H, 6.99.

The compound X was also formed from IX by refluxing for 6 hr., but not for 10 min., with a mixture of concd. hydrochloric acid and glacial acetic acid. Compound X was insoluble in concd. alkali, gave no ferric chloride test, and no acetate, either with acetic anhydride or acetyl chloride. It was not affected by bromine in carbon tetrachloride or by permanganate. The compound shows a strong band at 5.77 μ (1733 cm.$^{-1}$) (due to the carbonyl in the five-membered ring, probably) and another at 6.02 μ (1662 cm.$^{-1}$) (the carbonyl in the seven-membered ring, adjacent to the benzene ring). It showed no absorption in the hydroxyl region.

Condensation of Dimethylaminomethylbenzsuberone (VII) with Biacetyl Monoketal.—The following reaction only is described out of a considerable number which were tried, utilizing various combinations of the compounds described in this paper. The hydrochloride of VII (2.54 g.) was suspended in a mixture of 10 cc. each of dry benzene and ether, which had been saturated with ammonia. The mixture was shaken and allowed to stand for 30 min. keeping the temperature below 0°, the ammonium chloride was filtered off and washed with a little ether.

The sodium enolate was prepared from 1.32 g. of biacetyl monoketal[19] by stirring with 0.23 g. of powdered sodium at −15° in 8 cc. of dry ether. All of the sodium had dissolved after 8 hr. The solution of the enolate was added to the solution of the Mannich base, stirred for 1 hr. at room temperature, and the ether was evaporated through a warm reflux condenser, followed by an 11-hr. period of refluxing the benzene solution. The benzene was evaporated *in vacuo*, the residue was taken up in water, and extracted with ether. Chromatography of the residue from the ether extract did not lead to any crystalline material.

The aqueous solution was neutralized with mineral acid to a *p*H of 6, ammonium chloride was added to saturation, and the solution was extracted with ether. The red viscous oil obtained from the ether (0.374 g.) was refluxed with methanolic hydrochloric acid to convert the ketal functions to carbonyl groups. The methanol was evaporated *in vacuo*, and the residue extracted with ether; from this, 259 mg. of red material was obtained, which yielded 65 mg. of yellow crystals on triturating with ether. The compound melted at 162.4–162.8° after three crystallizations from benzene–cyclohexane. It was shown to be identical with the compound obtained from 2-isopropoxymethylenebenzsuberone and biacetyl monoketal, whose structure is demonstrated in the accompanying paper to be XI.

Piperidinomethylbenzsuberone (XII).—Benzsuberone (32 g.), piperidine hydrochloride (26.8 g.) and 20.7 g. of a 35% solution of formaldehyde were stirred under nitrogen for 10 min. at room temperature and 30 min. on the steam-bath; 5.17 g. of formalin was added, and stirring was continued for 1 hr. Three drops of concd. hydrochloric acid was added, which caused disappearance of the upper layer, and stirring was continued for 15 min. after the solution was homogeneous. The cooled reaction mixture was taken up in water and washed with ether (from which 8.5 g. of benzsuberone was recovered). The combined aqueous extracts were evaporated *in vacuo*, absolute alcohol was added and the solvent was removed again. The residual yellow oil crystallized from dry acetone in long hygroscopic needles (39.2 g.), 3.9 g. of additional material being recovered from the mother liquor; the total yield was 93%, taking into account the recovered benzsuberone. After four crystallizations from acetone, the product melted at 165°, solidified and remelted with decomposition at 235–237°. When the compound was heated very slowly, the lower m.p. was not observed.

Anal. Calcd. for $C_{17}H_{23}NO \cdot HCl \cdot {}^1/_2H_2O$: C, 67.42; H, 8.32. Found: C, 67.61; H, 7.88.

The free base XII was obtained by dissolving the above hydrochloride in the minimum amount of water and adjusting the *p*H to 8 with ammonium hydroxide. The oil which separated soon crystallized; it was soluble in all the common organic solvents and insoluble in water. From concentrated solutions in hexane, it was obtained as hexagonal leaflets. After three crystallizations from ethanol–water, it melted at 64.6–65°.

Anal. Calcd. for $C_{17}H_{23}NO$: C, 79.38; H, 8.94. Found: C, 79.34; H, 9.14.

A crystalline picrate or styphnate could not be obtained, but the **picrolonate** formed readily; it melted at 139–139.8° after recrystallization from ethanol–cyclohexane. Heating above 50° had to be avoided, because above this temperature considerable amounts of piperidine picrolonate[20] (m.p. 247–248°) were formed, due to decomposition of the Mannich base picrolonate.

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[19] Prepared by the method of D. S. Calder and K. B. Fleer, U. S. Patent 2,401,336 (*C. A.*, **40**, 5069 (1946)). Preparation of the enolate is described by L. I. Smith and W. L. Dale, *J. Org. Chem.*, **15**, 835 (1950).

[20] An analytical sample of piperidine picrolonate melted at 247.5–248°. *Anal.* Calcd. for $C_{15}H_{19}N_5O_5$: C, 51.57; H, 5.48. Found: C 51.46; H, 5.80.

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

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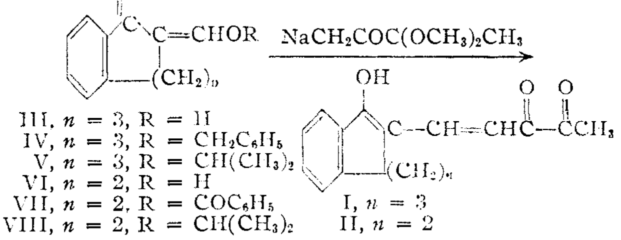
Condensation of 2-isopropoxymethylenebenzsuberone and of the corresponding tetralone derivative with the sodium derivative of biacetyl monoketal gives satisfactory yields of the expected products I and II, which are of interest because of the possibility of cyclization to form tropolones analogous to 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.$^{-1}$).

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[1] Aided by a grant from the National Cancer Institute.

[2] D. S. Tarbell, H. F. Wilson and E. 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.