The Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)-dione (Isatoic Anhydride). 17 [1]. Synthesis of 2-Alkyl-4-quinolone Alkaloids *via* a One-step Reaction of *N*-Methylisatoic Anhydride with Methyl Ketone Enolates

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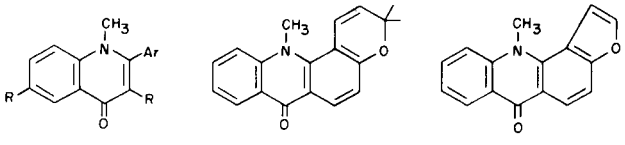
Received September 24, 1984

Lithium enolates derived from aliphatic methyl ketones react with *N*-methylisatoic anhydride (**5**) at -78° to give 2-alkyl-4-quinolone alkaloids **7** in a single step. The method was used to synthesize both double bond isomers of 1-methyl-2-(8-tridecenyl-4(1*H*)-quinolinone (**8**) thereby showing that the alkaloid evocarpine possesses the *Z*-olefin stereochemistry **8a**. Reduction of **8a** provided the alkaloid dihydroevocarpine (**16**). Compound **16** was also directly prepared from the reaction of **5** with the lithium enolate of 2-pentadecanone.

J. Heterocyclic Chem., **22**, 491 (1985).

In previous reports it has been shown that *N*-methylisatoic anhydride (**5**) reacts rapidly with lithium enolates derived from aromatic ketones to provide simple 2-aryl-4-quinolone alkaloids **1** [2] as well as the more complex ring skeletons represented by 6-demethoxyacronycine (**2**) [3] and 5-dehydroxyfuracridone (**3**) [1].

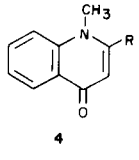


1 2 3

R = H, OCH_3

Ar = C_6H_5, 3,4-methylenedioxy-C_6H_3

Within the rutaceous plant family nature has also provided 4-quinolones **4** which are substituted in the 2-position with unbranched alkyl chains of varying length. These range from chain lengths of as little as one unit [4] (R = CH_3) to as long as 15 carbons [5] (R = $C_{15}H_{31}$).



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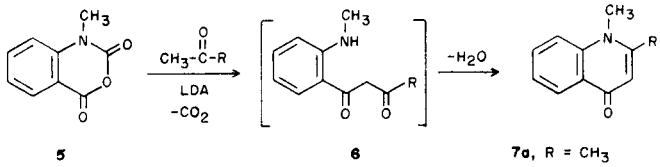
Two similar reports have appeared in the literature describing the preparation of 2-alkyl-4-quinolones and their subsequent methylations [6,7]. The *N*-unsubstituted quinolone nucleus was constructed by a Conrad-Limpach condensaion of aniline with a β-ketoester (50-55% yield). The requisite methylation was accomplished with methyl iodide in the presence of potassium carbonate. The method, however, suffers from the fact that alkylation occurs on oxygen as well as nitrogen. In fact, the *N*-methyl derivatives were only isolated as the minor product (10-11% yield) whereas the 4-methoxyquinolines were the primary product (46-54% yield) [7]. Although this two-step sequence appears to offer an easy entry into these type of systems, a 5% overall yield does not represent a useful synthetic process.

Therefore, a route which circumvents the problem of isomers must be developed which employs readily available starting materials and requires a minimum number of manipulations. It is the purpose of this paper to additionally explore the reaction of isatoic anhydrides with ketone enolates in order to expand the scope of these conversions and further demonstrate the applicability of the methodology as a general route for the facile synthesis of 4-quinolone alkaloids.

As can be seen in Scheme 1, a viable precursor for the desired product **7** is the β-diketone **6**. Such a species, can readily be prepared from the hetero ring-opening of *N*-methylisatoic anhydride (**5**) with a kinetic enolate generated from an aliphatic methyl ketone. In practice, two equvalents of the enolate are required for complete reaction to occur [8].

Scheme I



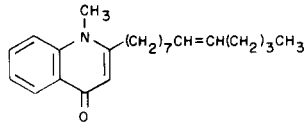
5 6

7a, R = CH_3
b, R = $(CH_2)_8CH_3$
c, R = $(CH_2)_{10}CH_3$

Thus, when acetone, 2-undecanone, or 2-tridecanone are treated with lithium diisopropylamide (LDA) at -78° followed by **5**, an extremely rapid reaction ensues and **5** is completely consumed within two minutes. Quenching the reaction with ammonium chloride produces an intensely yellow solution whose color is characteristic of intermediates such as **6** [9,10]. Evaporation of the solvent causes the yellow color to fade (due to dehydration) and products **7** are isolated directly in good yield. Compounds **7a** - **7c** are natural products isolated from *Platydesma companulata* [4], *Ruta graveolens* [11], and *Evodia rutaecarpa* [5] respectively. All physical data obtained for the synthetic alka-

loids are in complete agreement with that reported in the literature for the naturally occurring materials.

From the fruits of the same species *Evodia rutaecarpa* were isolated two additional alkaloids, evocarpine (**8**) [12] and its dihydro derivative **4** (R = $(CH_2)_{12}CH_3$) [5]. It was determined by ozonolysis that the site of unsaturation in the side chain of **8** was in the $\triangle^{8'}$ -position, however, nmr analysis, which exhibited a two-proton triplet at δ 5.29, did not establish the stereochemistry of the olefin.



8a, Z-Isomer
b, E-Isomer

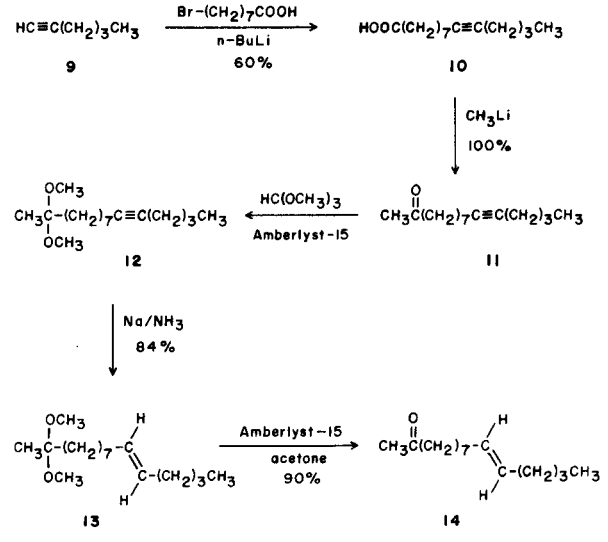
If both isomers of **8** could be synthesized, the spectral characteristics associated with the olefin should be different enough so an assignment can be made regarding the geometry of the natural product. Utilizing the presently described methodology, the construction of **8** can be realized providing that the appropriate methyl ketone component can be prepared. Scheme 2 outlines a route which will provide side chains leading to either isomer of **8** (Scheme 3).

The initial sequence begins with the alkylation of 1-hexyne (**9**) with 8-bromooctanoic acid. The resulting 9-tetradecynoic acid (**10**), when treated with two equivalents of methyllithium, produces 10-pentadecyn-2-one (**11**) in quantitative yield. The carbonyl is protected as a dimethylacetal using the procedure of Patwardhan and Dev [13], then the acetylene portion of the molecule is reduced to the (*E*)-olefin with sodium in liquid ammonia [14]. The conversion to **13** only proceeds in 30% yield with the remaining 70% of the mixture being unreacted **12**. However, when this crude mixture is recycled twice and subjected to the same reaction conditions, the desired olefin **13** is obtained in 84% yield. Deprotection of the acetal with Amberlyst-15 in acetone [15] then affords the desired methyl ketone **14** in 90% yield.

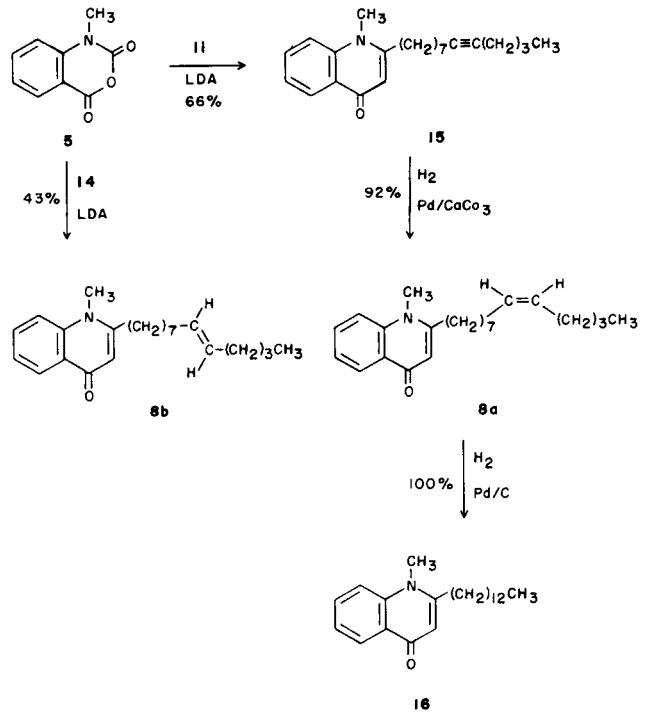
The alkenyl methyl ketone possessing the (*Z*)-olefin was not synthesized because it was felt that the introduction of the required stereochemistry (by catalytic hydrogenation) could be accomplished after the construction of the heterocycle since the remainder of the molecule should not be sensitive to such a transformation. Thus, when the lithium enolate of **11** is allowed to react with *N*-methylisatoic anhydride, the desired 4-quinolone **15** is produced in 66% yield (Scheme 3). Partial catalytic reduction of the acetylene function is accomplished at one atmosphere over palladium on calcium carbonate and the (*Z*)-tridecenylquinolone **8a** is isolated in 92% yield. The (*E*)-isomer **8b** is produced directly from the reaction of the lithium enolate of **14** with **5**.

Having both isomers in hand, spectral comparisons of both **8a** and **8b** were made. The olefinic region of **8a** exhibited a two-proton triplet at δ 5.34 (J = 5.1 Hz), whereas the signal for the analogous protons of **8b** were observed as a complex multiplet at δ 5.40. In order to further establish the integrity of the stereochemical assignments for isomers **8a** and **8b**, their carbon-13 nmr spectra were studied.

Scheme 2



Scheme 3



It is known that in a series of linear olefins, the carbon signals for the sp^2 carbons as well as their α-carbons appear further upfield for the (*Z*)-isomer versus the (*E*)-isomer [16]. The olefinic carbon signals for **8b** appear at δ 130.49 and 130.05 while the carbons α to the double bond are observed at δ 32.47 and 32.24. In isomer **8a**, the olefin carbons fall at δ 130.09 and 129.60 in conjunction with an upfield shift of 3-5 ppm for the α-carbons. This additional piece of evidence strongly supports the assignment of olefin geometry for both isomers of **8**.

Consequently, the correlation of our spectral data with that reported in the literature indicates that evocarpine is equivalent to isomer **8a** and, therefore, possesses a (*Z*)-stereorelationship of the olefin. Subsequent catalytic reduction of the double bond of **8a** over palladium on carbon easily furnishes the alaloid dihydroevocarpine (**16**).

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on either Perkin-Elmer Model 257 and 457, or Analect FX-6200 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on EM-360 and JOEL FX-90-Q spectrometers using TMS as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Mass spectra were recorded on a LKB 9000 spectrometer.

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a JEOL FX-200 spectrometer system. The spectra were obtained at an observing frequence of 50.1 MHz. Sample concentrations were *ca.* 0.1 molar 5 mm (od) sample tubes. General nmr spectral and instrumental parameters employed were: Internal deuterium lock to the solvent; spectral width of 10000 Hz; a pulse width of 3 μs corresponding to a 45° pulse angle, and a pulse repetition time of 1.8 seconds. For all spectra, 16K time-domain points were used. All shifts reported are referenced to internal TMS and are estimated to be accurate to $\pm$ 0.05 ppm.

Enolate generating reactions were conducted under a nitrogen atmosphere using tetrahydrofuran which was freshly distilled over lithium aluminum hydride. No attempt has been made to optimize the yields of the described reactions.

General Procedure for the Preparation of 2-Alkyl-4-quinolones **7**.

To a solution of 2.0 g (0.02 mole) of diisopropylamine in 75 ml of tetrahydrofuran (at -30°) was added 1.28 g (0.02 mole) of *n*-butyllithium (1.6 *M* in hexane). After cooling to -78°, a solution of 0.02 mole of the methyl ketone in 20 ml of tetrahydrofuran was added dropwise and the mixture was stirred at -78° for 1 hour. To this was added slowly a solution of 1.77 g (0.01 mole) of N-methylisatoic anhydride (**5**) in 40 ml of tetrahydrofuran and the mixture was stirred at -78° for 15 minutes. The reaction was quenched with saturated ammonium chloride and the organic phase was separated. The aqueous phase was extracted twice with methylene chloride and then the organic layers were combined and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using 2% methanol chloroform to elute the product.

1,2-Dimethyl-4(1*H*)-quinolinone (**7a**).

Prepared in 75% yield according to the general procedure. The product was crystallized from ethyl acetate, mp 175-178°; Lit. [4] mp 178-179°; ir (chloroform): 1620 cm^{-1}; nmr (deuteriochloroform): δ 8.37 (dd, 1H), 7.72-7.1 (m, 3H), 6.05 (s, 1H), 3.57 (s, 3H), 2.33 (s, 3H).

1-Methyl-2-nonyl-4(1*H*)-quinolinone (**7b**).

This compound was prepared in 74% yield according to the general procedure. The product was crystallized from cold ethyl acetate, mp 82-84°, lit [11] mp 71-75°; ir (chloroform): 1620, 1599 cm^{-1}; nmr (deuteriochloroform): δ 8.45 (dd, 1H), 7.8-7.15 (m, 3H), 6.20 (s, 1H), 3.68 (s, 3H), 2.68 (m, 2H), 1.80-0.70 (m, 17H); ms: (70 eV) m/e 285 (M^+).

Anal. Calcd. for $C_{19}H_{27}NO$: C, 80.0; H, 9.5; N, 4.9. Found: C, 79.9; H, 9.2; N, 4.9.

1-Methyl-2-undecyl-4(1*H*)-quinolinone (**7c**).

This compound was prepared in 81% yield according to the general procedure. The product was crystallized from cold ether, mp 66-69°, lit [5] mp 68.5-70°; ir (chloroform): 1625, 1595 cm^{-1}; nmr (deuteriochloroform): δ 8.4 (dd, 1H), 7.8-7.1 (m, 3H), 6.16 (s, 1H), 3.66 (s, 3H), 2.91-2.46 (m, 2H), 1.85-0.75 (m, 21H); ms: (70 eV) m/e 313 (M^+).

9-Tetradecynoic Acid (**10**).

To a solution of 4.0 g of 1-hexyne in 50 ml of HMPA (under a nitrogen atmosphere) at 0° was added dropwise 3.1 g of *n*-butyllithium (1.6 *M* in hexane). After stirring at 0° for 30 minutes, the flask was placed under vacuum in order to remove the hexane. To the resulting mixture was added dropwise a solution of 5.0 g of 8-bromooctanoic acid in 15 ml of HMPA. Stirring was continued at 0° for 4 hours. The light orange solution was poured into 500 ml of water. The mixture was acidified with 2 *N* hydrochloric acid and the product was extracted into ether (3 × 200 ml). The combined organic phases were successively washed with water and saturated sodium chloride solution. After drying over sodium sulfate, the solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using hexane/ethyl acetate (4:1) to elute the product, 3.0 g (60%) of **10**. The material crystallized on standing, mp 35-38°, lit [17] mp 31.5-32°.

10-Pentadecyn-2-one (**11**).

To a solution of 2.2 g of **10** in 70 ml of ether at 0-5° was added dropwise 12.5 ml of methyllithium (1.6 *M* in ether). Initially, a precipitate formed which then slowly went into solution. The mixture was stirred at room temperature for 4 hours then was poured into cold water. The organic material was extracted into ether (1 ×) and methylene chloride (2 ×). The organic phases were combined and dried over sodium sulfate. The solvent was removed under reduced pressure to give 2.2 g (100%) of **11** as an oil; ir (chloroform): 1705 cm^{-1}; nmr (deuteriochloroform): δ 2.42 (t, 2H), 2.26-2.00 (m, 4H), 2.13 (s, 3H), 1.75-1.15 (m, 14H), 0.92 (t, 3H).

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.0; H, 11.8. Found: C, 81.0; H, 11.8.

14,14-Dimethoxy-5-pentadecyne (**12**).

To a solution of 2.6 g of **11** in 30 ml of trimethyl orthoformate was added 1.0 g of Amberlyst-15 resin. After stirring at room temperature for 18 hours, the resin was filtered from the reaction mixture and the excess trimethyl orthoformate was removed under reduced pressure to give 1.8 g (58%) of **12** as an oil. This material was used in the next step without any further purification; nmr (deuteriochloroform): δ 3.14 (s, 6H), 2.25-1.93 (m, 7H), 1.72-1.15 (m, 16H), 0.90 (t, 3H).

(*E*)-14,14-Dimethoxy-5-pentadecene (**13**).

To 85 ml of liquid ammonia was added a solution of 1.8 g of **12** in 1.5 ml of methanol. Sodium was then added at such a rate as to keep the blue color visible. After 4 hours, the ammonia was allowed to evaporate then water was cautiously added. The mixture was extracted with methyl *t*-butylether (MTBE) and dried over sodium sulfate. The solvent was removed under reduced pressure to give the product **13** contaminated with **12**. This mixture was recycled twice in order to achieve total reduction of the starting material; overall yield 1.5 g (84%) of **13** as an oil. This material was used in the next step without any further purification; ir (chloroform): 2931, 2859, 1216 cm^{-1}; nmr (deuteriochloroform): δ 5.37 (m, 2H), 3.16 (s, 6H), 2.28-1.82 (m, 7H), 1.72-1.15 (m, 16H), 0.90 (t, 3H).

(*E*)-10-Pentadecen-2-one (**14**).

To a solution of 1.1 g of **13** in 20 ml of acetone containing 0.3 ml of

water was added 0.2 g of Amberlyst-15 ion exchange resin. After stirring at room temperature for 4 hours, the resin was filtered from the reaction mixture and the solvent was removed under reduced pressure to give 0.82 g (90%) of **14** as an oil; ir (chlorofom): 2928, 2859, 1710 cm^{-1}; nmr (deuteriochloroform): δ 5.37 (m, 2H), 2.41 (t, 2H), 2.18 (s, 3H), 2.17-1.85 (m, 4H), 1.78-1.10 (m, 14H), 0.90 (t, 3H).

Anal. Calcd. for $C_{15}H_{20}O$: C, 80.3; H, 12.6. Found: C, 80.7; H, 12.4.

1-Methyl-2-(8-tridecynyl)-4-(1*H*)-quinolinone (**15**).

To a solution of 1.0 g (0.01 mole) of diisopropylamine in 30 ml of tetrahydrofuran (at -30°) was added 0.64 g of *n*-butyllithium (1.6 *M* in hexane). After cooling to -78°; a solution of 2.2 g (0.01 mole) of **11** in 10 ml of tetrahydrofuran was added dropwise. After stirring at -78° for 1 hour, a solution of 0.9 g (0.005 mole) of **5** in 15 ml of tetrahydrofuran was added slowly then stirring was continued at -78° for 20 minutes. The reaction was quenched with saturated ammonium chloride solution and the organic phase was separated. The aqueous layer was extracted twice with methylene chloride and the organic solutions were combined and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on a Waters Prep-500 chromatography apparatus using ethyl acetate to elute the product, 1.1 g (66%) of **15** as an oil; ir (chloroform): 1620 cm^{-1}; nmr (deuteriochloroform): δ 8.41 (dd, 1H), 7.76-7.22 (m, 3H), 6.20 (s, 1H), 3.69 (s, 3H), 2.68 (t, 2H), 2.26-1.99 (m, 4H), 1.80-1.26 (m, 14H), 0.90 (t, 3H); ms (70 eV): m/e 337 (M^+).

Anal. Calcd. for $C_{23}H_{31}NO$: C, 81.8; H, 9.2; N, 4.1. Found: C, 81.4; H, 9.2; N, 4.3.

1-Methyl-2-(8-*Z*-tridecenyl)-4(1*H*)-quinolinone (Evocarpine) (**8a**).

A solution of 0.6 g of **15** in 30 ml of ethanol was hydrogenated at one atmosphere over 70 mg of 5% palladium on calcium carbonate. After 30 minutes the theoretical amount of hydrogen was absorbed. The catalyst was filtered from the mixture and the solvent removed under reduced pressure to give 0.55 g (92%) of **8a** as an oil. Upon standing, the oil crystallized, mp 34-37°; ir (chloroform): 2940, 2875, 1625, 1600 cm^{-1}; nmr (deuteriochloroform): 8.42 (m, 2H), 7.80-7.24 (m, 3H), 6.27 (s, 1H), 5.34 (t, 2H, J = 5.1 Hz), 3.76 (s, 3H), 2.72 (t, 2H), 2.18-1.88 (m, 4H), 1.65-1.14 (m, 14H), 0.90 (t, 3H); C-13 nmr (deuteriochloroform) δ 142.01, 132.09, 130.09, 129.60, 126.79, 123.43, 115.30, 111.13, 109.07, 34.80, 34.20, 31.98, 29.65, 29.22, 28.62, 27.16, 26.94, 22.34, 13.94.

1-Methyl-2-(8-*E*-tridecenyl)-4-(1*H*)-quinolinone (**8b**).

The reaction of 310 mg of **5** with 800 mg of **14** was performed under the same conditions as described for the preparation of **15**. The crude product was flash chromatographed using 2% methanol/chloroform to elute the desired material, 250 mg (43%) of **8b** as an oil; ir (chloroform): 2940, 2873, 1625, 1605 cm^{-1}; nmr (deuteriochloroform): δ 8.45 (dd, 1H), 7.77-7.25 (m, 3H), 6.24 (s, 1H), 5.40 (m, 2H), 3.75 (s, 3H), 2.74 (t, 2H), 2.22-1.84 (m, 4H), 1.70-1.18 (m, 14H), 0.90 (t, 3H); C-13 nmr (deuteriochloroform): δ 177.79; 154.75, 141.99, 132.81, 130.49, 130.05, 126.64, 126.49, 123.28, 115.28, 111.10, 34.76, 34.11, 32.47, 32.24, 31.88, 29.52, 29.20, 29.14, 28.91, 28.71, 28.57, 22.17, 13.93.

1-Methyl-2-tridecyl-4(1*H*)-quinolone (Dihydroevocarpine) (**16**).

A solution of 100 mg of **8a** in 1.5 ml of ethanol was hydrogenated over 5% palladium on carbon at 25 psi for 24 hours. The catalyst was filtered from the reaction mixture and the solvent was reduced under reduced pressure to give 100 mg (100%) of pure **16**. An analytical sample was crystallized from cold ether, mp 70-73°, lit. [5] mp 74-75°; ir (chloroform): 2945, 2878, 1620, 1598 cm^{-1}; nmr (deuteriochloroform): δ 8.46 (dd, 1H), 7.75-7.23 (m, 3H), 6.24 (s, 1H), 3.75 (s, 3H), 2.72 (t, 2H), 1.85-1.16 (m, 22H), 0.90 (t, 3H).

Dihydroevocarpine (**16**) was alternately prepared in 53% yield from the reaction of **5** with the lithium enolate generated from 2-pentadecanone, according to the aforementioned general procedure.

Acknowledgement.

The author wishes to thank Sue DiCataldo for running the nmr spectra, Frances McCrink for the ir spectra, Bertha Owens for the low resolution mass spectra, Mike Kolpak and Dr. Mike Shapiro for the carbon-13 spectra, and Jackie Misuro for the microanalyses. The author also thanks Linda Hinchman for the hplc separations on the Waters Prep-500 apparatus and Herbert Schuster for the preparation of compound **10**.

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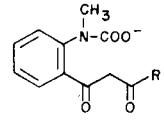

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