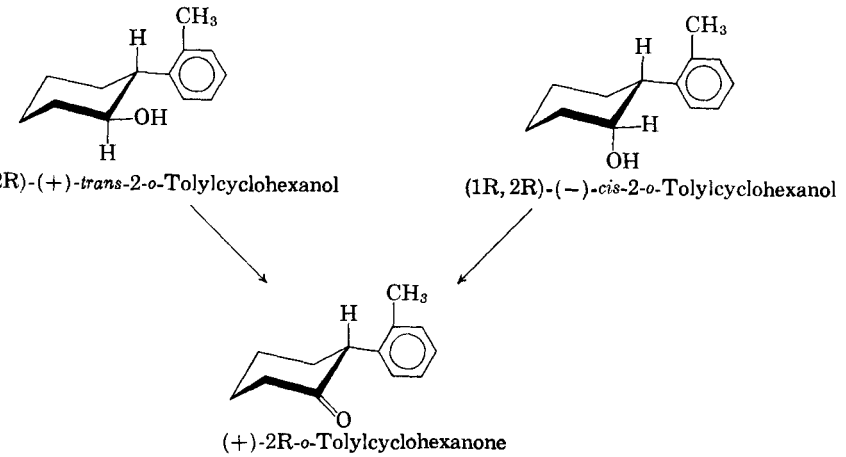
Absolute Configuration of *trans*- and *cis*-2-*o*-Tolylcyclohexanols

By DONALD R. GALPIN* and ALAIN C. HUITRIC

Optically active *trans*- and *cis*-2-*o*-tolylcyclohexanols were obtained by basic hydrolysis of their (−)-menthoxyacetate esters previously prepared and separated. Oxidation of (1S, 2R)-(+)-*trans*- (I) and (1R,2R)-(−)-*cis*-2-*o*-tolylcyclohexanol (II) yielded the same ketone, 2R-(+)-*o*-tolylcyclohexanone (III). The absolute configuration of III was established from ORD and CD measurements. This also established the absolute configuration of I and II. I and II have the same absolute configuration about C-2, but the signs of their Cotton effect in the aromatic region are opposite.

THE ABSOLUTE CONFIGURATION of an optically active ketone is available from optical rotatory dispersion (ORD) and/or circular dichroism (CD) studies to determine the sign of the Cotton effect associated with the carbonyl chromophore (1). If the conformation or significant conformations are known or can be predicted, then an application of the octant rule (2) or some of its extensions (3) will provide the absolute configuration. This rule is limited almost exclusively to ketones,[1] but since optically active secondary alcohols can be oxidized to their corresponding carbonyl compounds with retention of optical activity (4), their absolute configuration can be obtained by this method.



Recently the benzene ring has received attention as a chromophore for ORD and CD studies (5–7). The relatively scant information available concerning the anomalous dispersion of the long wavelength transition of this chromophore has precluded the formulation of a definite rule for the correlation of absolute configuration with the sign of the Cotton effect. As with the carbonyl group the Cotton effect associated with the benzene ring is conformationally dependent (5–7) and since most of the studies involving this chromophore have been conducted on compounds with aliphatic side chains of which there are several rotameric forms, the observed ORD and CD data result from a composite of the various conformers present. Brewster and Buta (5) attempted to circumvent this problem by examining rigid 1-substituted indans and based upon their observations suggested that an octant rule might also be applicable to the benzene ring. Because *trans*- and *cis*-2-*o*-tolylcyclohexanol have been shown by NMR to exist very predominantly in the chair conformation with the tolyl group in equatorial orientation (8a), these compounds appeared to provide excellent systems for the investigation of the Cotton effect in the 260 mμ region of the aromatic ring and the influence of a β axial and equatorial hydroxyl group on the optical activity of this transition.

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[1] An octant rule for azides has recently been formulated; see Djerassi, C., Moscowitz, A., Ponsold, K., and Steiner, G., *J. Am. Chem. Soc.*, **89**, 347(1967).

We wish to report on the absolute configuration of (+)-*trans*- (I) and (−)-*cis*-2-*o*-tolylcyclohexanol (II) obtained from ORD and CD measurements on (+)-2-*o*-tolylcyclohexanone (III), the oxidation product of these alcohols, and the anomalous dispersion of the aromatic ring in these compounds.

RESULTS AND DISCUSSION

The resolution of racemic I and racemic II was accomplished through their (−)-menthoxyacetate esters (9). Racemic I and II have been reported previously and some of their pharmacological properties have also been reported (8b, c). The diastereomeric esters of I were separated by fractional recrystallization and column chromatography over neutral alumina and those of II exclusively by column chromatography over this same adsorbent.[2] The progress of both separations was followed by NMR (9). The individual esters were hydrolyzed in an aqueous ethanol solution of 10% sodium hydroxide to obtain the enantiomers.

The chromic acid oxidation (4) of I and II in a two-phase system of ether and water yielded III in both instances. Although I was optically pure and II was approximately 85% one enantiomer (about 70% optical purity), the ketone III isolated from I and II had comparable rotations. The oxidation method is reported to result in little enolization of optical centers adjacent to the carbonyl group (4) but a small degree of racemization through enolization cannot be ruled out. In the oxidation of racemic *trans*-2-*o*-tolylcyclohexanol by this method on a larger scale we obtained about 10% of the keto acid ring opening product (10). This indicates that the rate of oxidation of the enolized form is faster than the rate of racemization, since racemization, if it occurred, was very slight during the oxidation of the optically active alcohols. The progress of oxidation of the optically active alcohols was followed by gas chromatography. Gas chromatography analysis of the purified ketone III obtained from I and II showed only one volatile component. Compounds I, II, and III have different emergence times on the column employed.

The ORD data for the compounds of this study are recorded under *Experimental*. All curves were determined in methanol on two separate samples. On one of each of these samples the determination was repeated on the solution which had been stored for 24–48 hr. The curves were reproducible to within 2% over the region of interest and no change was noted in the curves of the samples which had been stored.

Figure 1 shows the ORD and CD[3] curves for III.

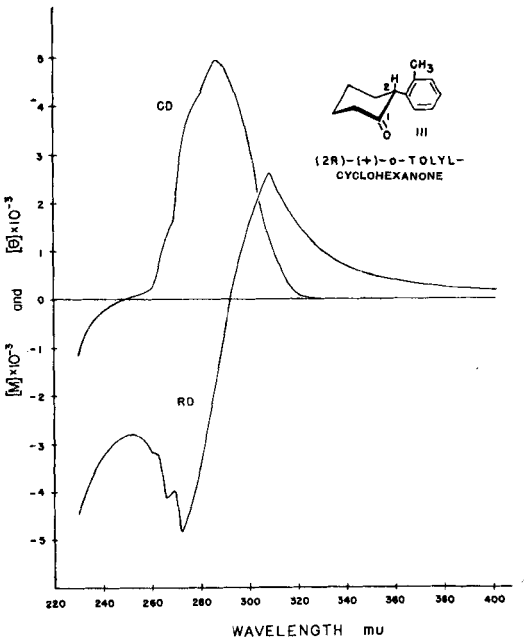
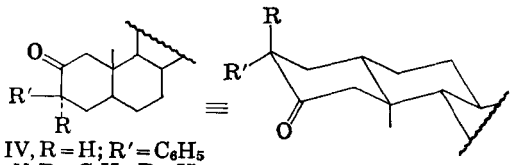


Fig. 1—Rotatory dispersion and circular dichroism curves for 2R-(+)-o-tolylcyclohexanone in menthanol; [M] is molecular rotation and [θ] is molecular ellipticity.

The Cotton effect associated with the carbonyl group is positive as well as the overlapping bands of the aromatic nucleus which appear as shoulders on the CD curve at 274 and 266 mμ. The sign of the Cotton effect of the carbonyl absorption is in agreement with the absolute configuration depicted based upon the octant rule (2) and its extensions (3).



IV, R = H; R′ = C_6H_5
V, R = C_6H_5; R = H

This assignment is supported by the work of Cookson and Hudec (11) who have shown that for the isomeric 3-phenylcholestan-2-ones, the 3-β-isomer IV (phenyl group equatorial) has a molecular amplitude[4] of somewhat less than +53, in which the presence of the aromatic ring gives a negative contribution to the amplitude of the Cotton effect when compared to the unsubstituted cholestan-2-one which has a molecular amplitude of +122 (12). Conversely, in the 3-α-isomer V, which has a molecular amplitude of +303,[5] the axial aromatic ring gives a large positive contribution to the Cotton effect as a result of homoconjugation of the benzene and carbonyl π electrons (3, 11).

The NMR spectrum of III (13) is consistent with the conformation shown in which the tolyl group is equatorially oriented and rules out any large populations of twist or axial conformers. Since the Cotton

[2] Pure (+)-*trans*-2-*o*-tolylcyclohexyl (−)-menthoxyacetate has $[\alpha]_D^{27}$ −32.5° (c 10, chloroform); pure (−)-*trans*-2-*o*-tolylcyclohexyl (−)-menthoxyacetate has $[\alpha]_D^{28}$ −67.9° (c 10, chloroform). The most pure sample of (−)-*cis*-2-*o*-tolylcyclohexyl (−)-menthoxyacetate isolated has $[\alpha]_D^{28}$ −143.5° (c 10, chloroform) and was judged to be at least 95% pure on the basis of its NMR spectrum; the sample of this ester from which II was obtained had $[\alpha]_D^{25}$ −123° (c, 0.1026 methanol) and was considered approximately 85% pure on the basis of its optical rotation and NMR spectrum (9).

[3] The CD curves were also obtained in methanol. The authors are deeply indebted to Dr. William F. Trager who made all the CD determinations reported in this paper while he was at the Chelsea College of Science and Technology, London, England.

[4] The trough was not quite reached in this determination. Moscowitz *et al.* (3) report a value of +45 in dioxane.

[5] Moscowitz *et al.* (3) show a value of +375.

effect of III is positive, it must have the configuration corresponding to the mirror image of the equatorially substituted 3-β-phenylsteroid IV (3). For an independent assignment of the absolute configuration of III based on chemical evidence see Huitric and Newell (14).

The influence of the *o*-tolyl methyl group on the carbonyl Cotton effect in compound II is unknown and difficult to predict. Examination of Dreiding molecular models indicates that rotation of the equatorially oriented tolyl group causes the position of the methyl group to alternate between back and front upper- and lower-left octants, but the weighted time-average positions are uncertain. There is also some question regarding the applicability of the octant rule to front-octant perturbations (15). It would appear that the predominant effect of the *ortho* methyl group is through its influence on the preferred conformation of the molecule. For example, it will decrease contribution from a chair conformation with the aromatic group in axial orientation and will also affect the rotation of the phenyl ring. It is interesting to note that in the other chair conformation of III (aromatic group axial) the phenyl ring is located in the lower-right back octant. Any contribution from this conformation would therefore also contribute to the positive Cotton effect and would also cause an enhancement of the molecular amplitude (3, 11).

The ORD and CD curves for I and II appear in Figs. 2 and 3, respectively. In both instances there is a weak multiple Cotton effect associated with aromatic absorption in the 260 mμ region. The strength of the Cotton effect is best obtained from a comparison of the CD curves. If the background curve in the ORD is steeply rising, it may obscure the Cotton effect (6, 16). Although both compounds have the same absolute configuration about the carbon atom bearing the tolyl group, the signs of their Cotton effects, measured in methanol, are opposite. The CD curve of I was determined on its enantiomer $[\alpha]_D^{26}$ −70.6° (c 10, chloroform)[6] and the mirror image is reproduced.[7] The CD curve of II, which was determined to 225 mμ, exhibits another negative transition beginning to appear at 227 mμ; the CD curve for I was measured only to 230 mμ.

In the 1-substituted indan series Brewster and Buta (5) concluded that a large Cotton effect in the 250–270 mμ region appears to be associated with the presence of a group capable of direct perturbation of the π electron cloud of the ring by hydrogen bonding or by electrostatic effects. In our systems intramolecular hydrogen bonding with the π electron cloud should be solvent dependent. The ORD curve of I measured in isooctane[8] showed a smoothing off in the region of 260–270 mμ. Our system lacks the conformational rigidity of the indans and our data on the aromatic chromophore are not yet sufficient to draw conclusions. Solvent effects will be studied more thoroughly from CD measurements and the authors are in the process of studying the *p*-tolyl isomers and the 2,6-dimethylphenyl analogs.

[6] The extremely weak pen displacements in the CD determinations of these alcohols did not permit the elucidation of fine structure. Consequently, the shape of these curves is only approximate and the sign and magnitude of the absorption are the more significant information.

[7] The ORD curve was determined on both enantiomers and the curve of (−)-I was the exact mirror image of that of (+)-I and agreed in absolute values of rotation to within 2% over the entire spectrum.

[8] The ORD curve in isooctane was determined by Todd D. Cochran.

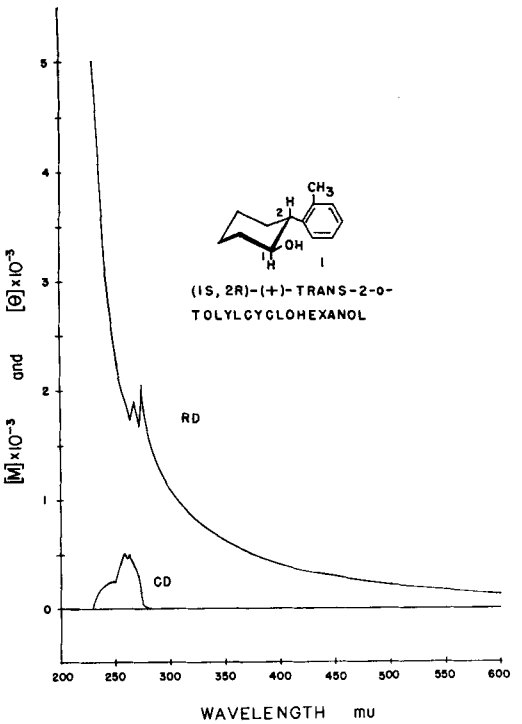


Fig. 2—Rotatory dispersion and circular dichroism curves for (1S,2R)-(+)-trans-2-o-tolylcyclohexanol in methanol; [M] *is molecular rotation and* [θ] *is molecular ellipticity.*

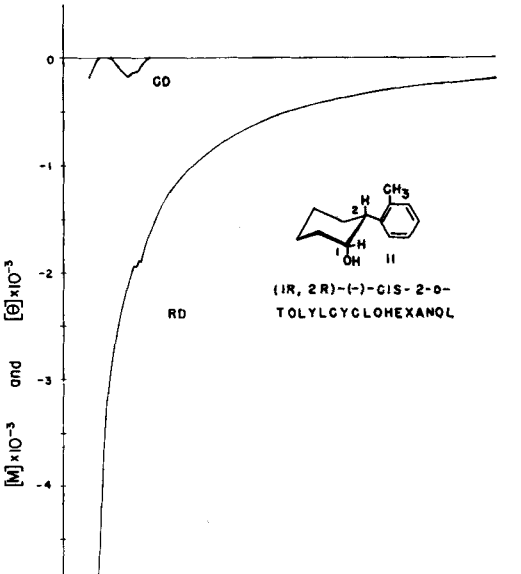


Fig. 3—Rotatory dispersion and circular dichroism curves for (1R,2R)-(−)-cis-2-o-tolylcyclohexanol in methanol; [M] *is molecular rotation and* [θ] *is molecular ellipticity.*

EXPERIMENTAL

(1S,2R)-(+)-trans-2-o-Tolylcyclohexanol (I)—A mixture of 4.0 Gm. of (+)-*trans*-2-*o*-tolylcyclohexyl (−)-menthoxyacetate (9) and 100 ml. of a 10% solution of sodium hydroxide in 70% ethanol in water was refluxed for 2.5 hr., cooled, and diluted with 100 ml. of water. The mixture was extracted four times with 50-ml. portions of ether and the combined ether extracts were washed twice with 25-ml. portions of 5% sodium hydroxide, once with 5% hydrochloric acid, then with water until the washings were neutral, and dried over anhydrous calcium sulfate. Filtration, solvent removal, and distillation yielded 1.70 Gm. of I, b.p. 81–82° at 0.20 mm.; $[\alpha]_D^{26}$ +70.6° (c 10 chloroform). Analysis of this alcohol by VPC on a Carbowax 20 M column at 190° showed a single volatile component present. The IR spectrum on sodium chloride plates was essentially the same as racemic I, exhibiting minor variations in the fingerprint region; RD in methanol (c 0.1096) showed $[M]_{600}$ +132°, $[M]_{589}$ +141°, $[M]_{500}$ +222°, $[M]_{400}$ +399°, $[M]_{300}$ +1084°, $[M]_{273}$ +2056° (peak), $[M]_{270}$ +1671° (trough), $[M]_{266}$ +1900° (peak), $[M]_{263}$ +1730° (trough), $[M]_{230}$ +4999°.

The levorotatory enantiomer was obtained by the same method, $[\alpha]_D^{26}$ −71.1° (c 10, chloroform); the ORD curve was the exact mirror image of that of (+)-I.

Acidification of the combined basic solutions and workup yielded after distillation 1.82 Gm. of (−)-menthoxyacetic acid, b.p. 108–110° at 0.4 mm.; $[\alpha]_D^{26}$ −94.7° (c 10, chloroform). Reported: b.p. 134–137° at 2 mm. (17); $[\alpha]_D^{25}$ −91.5° (c 2, 95% ethanol) (18).

(1R,2R)-(−)-cis-2-o-Tolylcyclohexanol (II)—A 2.1-Gm. sample of the *cis* esters ($[\alpha]_D^{25}$ −123° [c 0.1026, methanol]), approximately 85% (−)-*cis*-2-*o*-tolylcyclohexyl (−)-menthoxyacetate (9), was hydrolyzed as described for the isolation of I. Following workup the product was distilled to give 0.85 Gm. of II, b.p. 76–78° at 0.18 mm.; $[\alpha]_D^{25}$ −102° (c 0.1280, methanol). Analysis of this alcohol by VPC on a Carbowax 20 M column at 190° showed it to be free of volatile contaminants. The IR spectrum on sodium chloride plates was identical to racemic II. The reported b.p. of racemic II is 76–78° at 0.15–0.17 mm. (8). On the basis of the specific rotation and NMR spectrum (9) of the starting ester the compound is estimated to be about 85% one enantiomer (about 70% optical purity). RD in methanol (c 0.1280) showed $[M]_{600}$ −188°, $[M]_{589}$ −195°, $[M]_{500}$ −300°, $[M]_{400}$ −530°, $[M]_{300}$ −1231°, $[M]_{272}$ −1896° (trough), $[M]_{270}$ −1876° (peak), $[M]_{267-265}$ −1944° (shoulder), $[M]_{250}$ −2556°, $[M]_{230}$ −5932°.

2R-(+)-o-Tolylcyclohexanone (III)—This ketone was obtained by the oxidation of either I or II by the method of Brown and Garg (4). The oxidation of I is given. To a stirred solution of 0.905 Gm. (4.76 mmoles) of I in 10 ml. of ether in a 50-ml. flask, fitted with a reflux condenser, dropping funnel, and a magnetic stirrer, a solution of 0.905 Gm. (3.17 mmoles.) of sodium dichromate dihydrate and 0.72 ml. of 96% sulfuric acid in 10 ml. of water was added over a period of 30 min. The progress of the reaction was followed by VPC on a Carbowax 20 M column at 190°. When the reaction was complete, the ether layer was separated and the aqueous phase extracted several times with small portions of ether. The combined ether solutions were washed twice with 10-ml. portions of 5% sodium bicarbonate followed by two water washings and dried by passage through anhydrous sodium sulfate. The solvent was removed and the residue recrystallized once from *n*-hexane to give a first crop of 0.500 Gm. of colorless crystals, m.p. 72–73.5° (Fisher-Johns); $[\alpha]_D^{25}$ +11.80° (c 1.000, methanol). The IR spectrum (potassium bromide disk) was essentially identical to that of racemic III, exhibiting only minor variations in the fingerprint region. Analysis of this ketone by VPC showed a single peak with the same emergence time as racemic III; RD in methanol (c 0.0996) showed $[M]_{600}$ +20.7°, $[M]_{589}$ +22.2°, $[M]_{500}$ +50.6°, $[M]_{400}$ +183°, $[M]_{350}$ +502°, $[M]_{308}$ +2598° (peak), $[M]_{272}$ −4824° (trough), $[M]_{269}$ −3978° (peak), $[M]_{266}$ −4138° (trough), $[M]_{263}$ −3209°, $[M]_{255}$ −2839°, $[M]_{250}$ −2812°, $[M]_{230}$ −4442°.

The oxidation of II by this method yielded III, m.p. 73.5–74.5° (Fisher-Johns), mixed m.p. with III obtained from I 73–74.5°; $[\alpha]_D^{25}$ +11.00° (c 1.000, methanol). Analysis of this ketone by VPC showed one component present. The m.p. of racemic III is 55.5–56.5° (19).

The ORD curves reported in this paper were obtained on a Cary 60 recording spectropolarimeter using a 250-w. xenon lamp as the light source at 25° in a 1.0-cm. cell and employing a fixed slit width of 0.3 mm. from 600 mμ to 450 mμ and the manufacturer's preprogrammed slit width from 450 mμ to 230 mμ. The specific rotations quoted at the sodium D line (589 mμ) in methanol were also determined on this instrument employing the same fixed slit width and cell length as for the ORD curves.

All specific rotations determined in chloroform were performed on a Rudolph polarimeter using a sodium lamp and a 1-dcm. tube. Rotations were taken at room temperature.

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Keyphrases

2-o-Tolylcyclohexanols, *trans* and *cis*
Optical rotatory dispersion—absolute configuration
Circular dichroism—absolute configuration
Column chromatography—separation
NMR spectrometry—identity
Specific rotation—identity
IR spectrophotometry—structure
GLC—analysis

Specific Assay Methods for Droperidol and Fentanyl Citrate in a Pharmaceutical Combination

By CASIMIR A. JANICKI, RONALD J. BRENNER, and BARBARA E. SCHWARTZ

In acid solution, droperidol, 1-{1-[3-(*p*-fluorobenzoyl)propyl]-1,2,3,6-tetrahydro-4-pyridyl}-2-benzimidazolinone, is decomposed to form 4′-fluoro-4-(4-oxopiperidino)butyrophenone and 2-benzimidazolinone. Fentanyl, *N*-(1-phenethyl-4-piperidyl)propionanilide, is decomposed in acid solution to form 4-anilino-1-(2-phenylethyl)piperidine. A procedure to assay droperidol in the presence of its hydrolysis products, fentanyl, and its hydrolysis product is given. Droperidol is analyzed by its UV absorption after being separated from interfering products. A procedure to assay fentanyl in the presence of its hydrolysis products, droperidol, and its hydrolysis products is given. Droperidol and 4-anilino-1-(2-phenylethyl)-piperidine are separated from fentanyl through the formation of a reineckate derivative and fentanyl is subsequently determined by a methyl orange procedure. Data are presented to show the accuracy and precision of the methods.

DROPERIDOL, 1 - {1 - [3 - (*p* - fluorobenzoyl)-propyl]-1,2,3,6 - tetrahydro - 4 - pyridyl} - 2-benzimidazolinone, was first synthesized by Janssen *et al.* and has been shown to be a sedative or tranquilizer (1, 2). Fentanyl citrate [*N*-(1-phenethyl-4-piperidyl) propionanilide dihydrogen citrate] was also synthesized by Janssen *et al.*, and has been shown to be a potent narcotic analgesic (2). It has been reported to be 100 times more potent on a weight basis than morphine as an analgesic (3).

A combination of droperidol and fentanyl citrate in solution has been employed for neuroleptanalgesia or as an adjunct to nitrous oxide for general anesthesia in man (4). It has also been successfully employed in veterinary medicine as an analgesic tranquilizer[1] for use in surgery in dogs (5).

The specific assays for each active ingredient in the presence of the other was essential to study the stability of the various combinations prepared in these laboratories. The usual ratio of droperidol to fentanyl in solution was 50:1. The fentanyl content varied from 20 mcg./ml. to the concentration used in the veterinary product 400 mcg./ml.

Fentanyl, because of its low concentration and its low ratio with respect to droperidol, presented a formidable analytical problem. For the assay of fentanyl to be specific, fentanyl had to be separated not only from its own hydrolysis product, but also from a large amount of droperidol and hydrolysis products of droperidol.

The proposed assay methods for droperidol and fentanyl, alone or in combination, are specific for the intact drug.

EXPERIMENTAL

Hydrolysis Studies—Droperidol (I) was refluxed overnight in 1 *M* hydrochloric acid and was found to undergo complete hydrolysis. Two major products were isolated, 4′-fluoro-4-(4-oxopiperidino)butyrophenone (II) and 2-benzimidazolinone (III) (Scheme I).

A solution of droperidol in monoglyme was refluxed overnight in 2 *M* sodium hydroxide and was recovered unchanged.

Fentanyl (IV), prepared from its citrate salt, was refluxed overnight in 1 *M* hydrochloric acid and was found to undergo complete hydrolysis. One

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[1] Marketed as Innovar-Vet by McNeil Laboratories, Inc., Fort Washington, Pa.