(3) There has been some confusion in the hydrogen-bonding literature as to whether the terms *donor* and *acceptor* refer to the proton or the electron pair. In the present series of papers, HBD (hydrogen-bond donor) and HBA (hydrogen-bond acceptor) refer to donation or acceptance of the proton.
(4) M. J. Kamlet, E. G. Kayser, R. R. Minesinger, M. H. Aldridge, and J. W. Eastes, *J. Org. Chem.*, **36**, 3852 (1971). In type-A hydrogen bonding the solvent acts as proton donor and the solute as proton acceptor; the converse applies in type-B bonding.
(5) Part I: M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.*, **98**, 377 (1976).
(6) R. W. Taft, D. Gurka, L. Joris, P. v. R. Schleyer, and J. W. Rakshys, *J. Am. Chem. Soc.*, **91**, 4801 (1969).
(7) The notation $-\Delta\Delta\nu(\mathbf{1-2})^{B}_{\leftarrow H_2N}$ signifies a bathochromic displacement for **1** relative to **2**, caused by type-B hydrogen bonding *by* the amine proton to the solvent. See footnote 8 of part I[5] for an outline of this system, which makes nomenclature much less confusing and cumbersome when several types of hydrogen bonding with concomitant spectral effects occur simultaneously.
(8) Strengthened type-A hydrogen bonds by the R–OH solvents to the nitro oxygens of **1** compared with **2** (like **1c**) could also account for bathochromic displacements,[9] but where hydroxylic solvents participate in type-A effects, the converse $-\Delta\Delta\nu$ ordering is observed, with the greater solvatochromic displacements in methanol and water and the lesser shifts in 2-methyl-2-propanol and 2-propanol.[2,4]
(9) Such enhanced hydrogen bonding to nitro has been demonstrated for *N,N*-diethyl-4-nitroaniline relative to 4-nitroanisole.[4] However, solvatochromic comparisons of **4** and **7** with 4-nitroanisole suggest that hydrogen bonding to the *o*-nitro group of **4** or **7** is very much weaker than to the *p*-nitro group of *N,N*-diethyl-4-nitroaniline.
(10) The subscript indicates that data from five sets of properties were averaged to obtain the β value.
(11) T. Yokoyama, *Aust. J. Chem.*, **27**, 915 (1974). This earlier work illustrates the pitfall in using our previously reported method[12,13] for finding $\Delta\Delta\nu$ values where solvent polarity effects are not similar for the substrates being compared.
(12) M. J. Kamlet, R. R. Minesinger, and W. H. Gilligan, *J. Am. Chem. Soc.*, **94**, 4774 (1972).
(13) R. R. Minesinger, E. G. Kayser, and M. J. Kamlet, *J. Org. Chem.*, **36**, 1347 (1971).
(14) In the term, $\beta_n{}^m$, the superscript indicates that we are dealing with solvent *m* (solvent numbering is the same in all papers of this series); the subscript indicates that we are dealing with property series *n*.
(15) For example, the $-\Delta\Delta\nu$ value for 4-nitrophenol (**8**) relative to 4-nitroanisole (**9**) probably includes a term due to hydrogen bonding by the phenol proton to the R–OH oxygen and a term due to bonding by the R–OH proton to the phenol nitro group, i.e., $-\Delta\Delta\nu(\mathbf{8-9})_{total} = [-\Delta\Delta\nu(\mathbf{8-9})^{B}_{\leftarrow HO}] + [-\Delta\Delta\nu(\mathbf{8-9})^{A}_{\rightarrow O_2N}]$.[5]

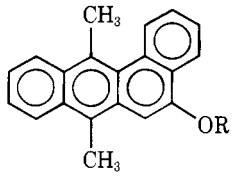
Phenolic and Ketonic Tautomers in Polycyclic Aromatic Hydrocarbons[1]

Melvin S. Newman,* V. Sankaran,[2] and Daniel R. Olson[2]

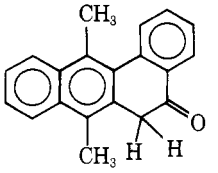
Contribution from the Ohio State University, Columbus, Ohio 43210 *Received July 18, 1975*

Abstract: 5-Hydroxy-7,12-dimethylbenz[*a*]anthracene (**2**) has been shown to exist as a mixture with the tautomer, 7,12-dimethylbenz[*a*]anthracen-5(6*H*)-one (**3**). By chromatography almost pure **2** and **3** have been isolated and their spectral properties recorded. The tendency of a number of other hydroxy derivatives of polycyclic aromatic hydrocarbons to either exist as, or react as, their ketonic counterparts is described. Steric hindrance due to intramolecular overcrowding is postulated to account for the stability of the keto form. The tendencies of a number of hydroxy compounds to react with methanolic hydrogen chloride at room temperature to form methyl ethers and with 2,4-dinitrophenylhydrazine to form 2,4-dinitrophenylhydrazones are used as a measure of the relative reactivity of the keto forms. The possibility that keto forms of polycyclic aromatic hydrocarbons may be metabolites of importance in understanding the carcinogenic activities of the hydrocarbons is raised. Improved syntheses of a number of methoxy derivatives in the benz[*a*]anthracene series are described as well as a new method of cleaving these methoxy compounds to phenols by heating with sodium sulfide.

In a recent communication[3] the synthesis of 5-methoxy-7,12-dimethylbenz[*a*]anthracene[4] (**1**) and its conversion into a mixture of 5-hydroxy-7,12-dimethylbenz[*a*]anthracene (**2**) and its ketonic tautomer, 7,12-dimethylbenz[*a*]anthracen-5-(6*H*)-one (**3**) was described.[5] In the present paper improved



1 (R = CH_3)
2 (R = H)



3

syntheses of **1,** 5-methoxybenz[*a*]anthracene[6] (**4**), 5-methoxy-7-methylbenz[*a*]anthracene[7] (**5**), and 5-methoxy-12-methylbenz[*a*]anthracene[8] (**6**) are described, as are the syntheses of 6-methoxy-7,12-dimethylbenz[*a*]anthracene (**7**) and 6-methoxy-12-methylbenz[*a*]anthracene (**8**) and their conversion to the corresponding hydroxy compounds, **7a** and **8a.** In addition, the general question of the existence of ketonic forms of phenols of polycyclic aromatic hydrocarbons is discussed, as well as the possible involvement of the keto forms in the carcinogenic activity of DMBA.

The syntheses of the required methoxy compounds, **1, 4, 5,** and **6,** were carried out as indicated in Scheme I.

The syntheses of **10** and **11** proceeded in almost quantitative yield by reaction of 1-methoxynaphthalene with **9** and **9a** as described.[9] The reduction of lactones such as **10** and **11** has been effected by many different reducing agents. To summarize our experience in this area, we recommend reduction with zinc and formic acid[10] as generally the most reliable for small- and large-scale reactions. In the present cases, almost quantitative yields of **12** and **13** were obtained.

The yields on conversion of acids **12** and **13** via **15** and **17** to **4** and **6,** respectively, were very high. Thus, the overall route is superior to previous routes which involved cyclization of acids to benzanthrones followed by reduction of the latter to benz[*a*]anthracenes.[11] Big improvements (especially in large-scale runs) in the conversions of **12** and **13** to **1** and **5,** respectively, were also made,[11,12] largely because higher yields of the methyl ketones **18** (82%) and **19** (97%) were obtained by two modifications in the reactions of carboxylic acids with methyllithium: in one, the addition of methyllithium was made to the acid instead of the reverse;[11,12] in the other, the reaction mixtures thus obtained were added to water instead of the reverse. Each of these factors cuts down on the tendency to form tertiary alcohol instead of the desired methyl ketone.

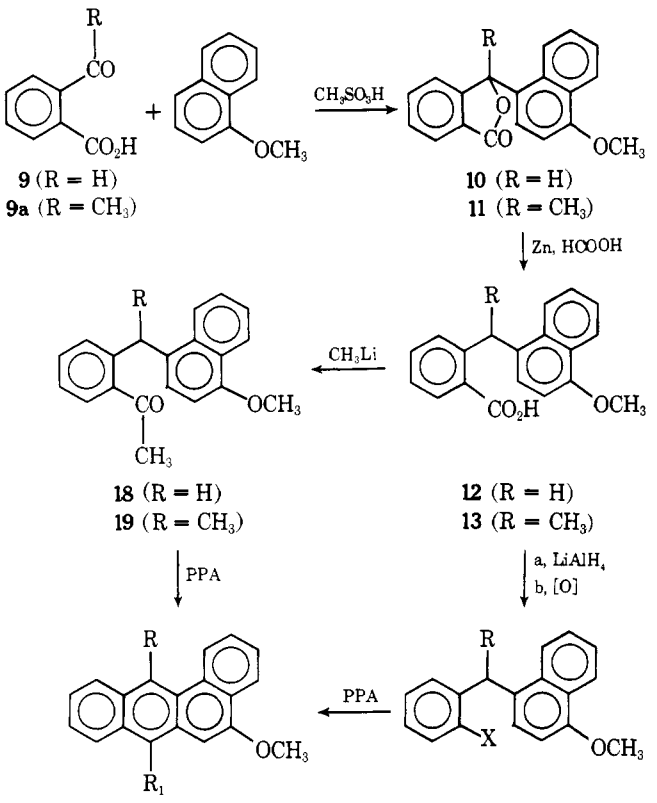
The synthesis of **7** is outlined in Scheme II. The requisite, 2,4-dibromo-1-naphthylamine[13] (**20**) was converted by diazotization into 4-bromonaphth[1,2-*d*][1,2,3]oxadiazole[14] (**21**) (shown in ionic form in Scheme II for convenience), which was

Table I. Cleavage of Aryl Methyl Ethers by Anionic Sulfur Reagents

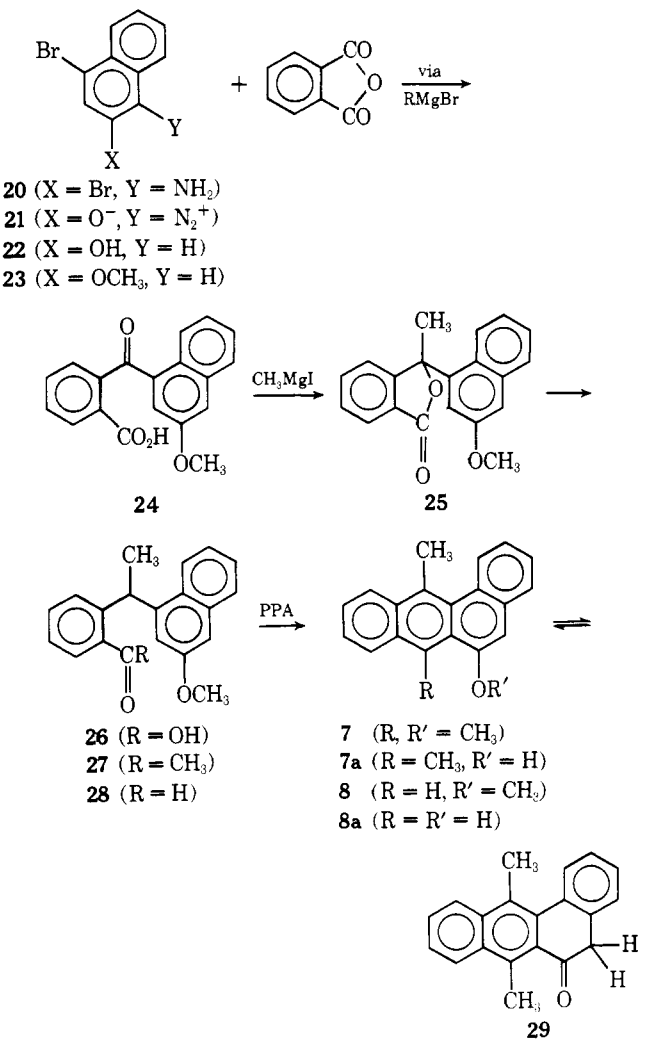
Benz[*a*]anthracene	% yield of OAc: EtSNa[16]	% yield of OAc: Na_2S	Mp of acetate,[h] °C	OH compd yield[a]	Mp,[b] °C	2,4-DNP mp,[c] °C
5-OCH_3 (**4**)	63	85	127-129*	90	197-200[d]	263-264
7-Me-5-OCH_3 (**5**)	77	81	212-214*	84	187-189[e]	232-233
12-Me-5-OCH_3 (**6**)	59	78	124-125*	74[f]	106-110	246-247
7,12-Me_2-5-OCH_3	72	82	149-150*	80[f]	70-96[g]	229-230
12-Me-6-OCH_3 (**8**)		81	112-113*	81[f]	164-174[g]	249-251
7,12-Me_2-6-OCH_3 (**7**)	57	81	138-139*	81[f]	92-97[g]	150-156

[a] Melting point of recrystallized sample. [b] All melting points taken in sealed tubes. [c] Mp (dec) heating at 2-3°/min. [d] Lit.,[6] mp 196-205 °C. [e] Lit.,[7] mp 193-194 °C. [f] OH compound mixture of phenol and keto forms. [g] Compound turns pink rapidly when heated even in sealed tube. [h] Asterisk denotes new compound; see ref 28.

Scheme I



Scheme II



reduced in high yield to 4-bromo-2-naphthol (**22**) by means of sodium borohydride in ethanol.[15] The remaining steps in the synthesis are described in the Experimental Section.

The cleavage of aryl methyl ethers by heating in DMF with sodium ethylmercaptide has been reported.[16] We have cleaved **1, 4, 5, 6, 7,** and **8** to the corresponding OH compounds **2, 4a, 5a, 6a, 7a,** and **8a,** in high yields by this method and also by heating with sodium sulfide in *N*-methylpyrrolidone at 140-145° for 2-4 h. As the latter reagent is simpler to prepare and the workup is less malodorous, the use of sodium sulfide is highly recommended for such cleavages. The results obtained with these cleavage reagents are listed in Table I.

The fact that monohydric phenolic compounds can exist as ketonic isomers has been rarely mentioned in the older literature and textbooks. Since both isomers, anthrol and anthrone, have been isolated, one might gather the impression that this type of isomerism is widespread. However, the only other examples of the isolation of such tautomers we could find were those described in the benz[*a*]anthracene series.[7] Here a 1,4-relationship in the meso positions, similar to that in the anthracene series, was involved. Calculations of the energy difference between phenolic and keto forms in the benzo[*c*]pyrene series have been made,[17] and the effect of alkali on the catalytic reduction of 2-naphthol was explained by involvement of the keto form.[18e]

In order to estimate the tendency of phenolic compounds to exist or react as their ketonic tautomers, we have used three criteria: (1) the presence of a ketone band near 6.0 μ in the ir spectrum, (2) the formation of a 2,4-dinitrophenylhydrazone,

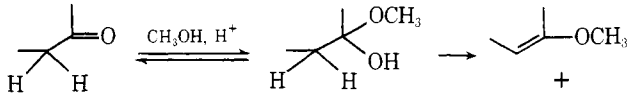
and (3) the extent of formation of a methyl ether at room temperature under standard conditions (7 h, 0.097 N methanolic HCl). The above criteria are discussed in order below.

(1) Ir Band. Of all of the hydroxy compounds tested only **2, 6a, 7a,** and **8a** showed a band near 6.0 μ. We believe that the presence of these ketone forms is ascribable to the *steric strain introduced by the 12-methyl* group. The relief of strain on going into the ketone structure just about equalizes the loss in resonance energy which must occur in going from the phenol to the keto structure.[17]

(2) Formation of 2,4-DNP Derivatives. To our knowledge no report of the formation of 2,4-dinitrophenylhydrazone from a phenol has been made. We have found that 2,4-dinitrophenylhydrazones are readily formed from hydroxy derivatives in the benz[*a*]anthracene series. When treated with 2,4-dinitrophenylhydrazine reagent **2, 6a,** and **8a** gave derivatives immediately. After longer standing, high yields of the 2,4-DNP derivatives of **4a, 5a, 7a,** and 9-phenanthrol (**30**) precipitated. Thus, even though no ketonic band is apparent in the ir spectra of **4a, 5a,** and **30,** 2,4-DNP derivatives are readily formed. With phenol and 1- and 2-naphthol no derivatives were formed even on long standing. The rate of formation of $\mathbf{7a}_D$, from **7a–29** mixtures was markedly slower than the rate of formation of $\mathbf{2}_D$ from **2–3** mixtures. This fact is understandable in view of the greater steric hindrance afforded by the 7-methyl group in **29** as compared to the situation at the 5-keto group in **3.** However, the slightly greater reactivity of the 6-keto group in **29** as compared to the 5-keto group in **3** (see below under formation of methyl ethers) is puzzling. Furthermore, the 2,4-DNP derivative* ($\mathbf{29}_D$) formed from **29** melts considerably lower (150–156 °C) than all of the other DNP derivatives described in this paper (mp range, 229–264 °C). This derivative ($\mathbf{29}_D$) is under further study to see if $-H_2CC{=}NNHR \rightleftarrows HC{=}CNHNHR$ tautomerism is involved.

(3) Formation of Methyl Ethers. Although the conversion of hydroxy derivatives of aromatic hydrocarbons to the corresponding methyl (or ethyl) ethers by heating in acidic methanol (or ethanol) has been reported,[18] this method of alkylation is not generally recognized as useful. The ethers were formed after long periods of heating with strongly acidic methanol (or ethanol) and the yields were not quantitative, except in the case of 2-hydroxyanthracene.[18d] As described earlier,[3] we were amazed at the ease with which **2** was converted into **1** on treatment with dilute methanolic HCl *at room temperature* and attributed this ease to the involvement of the keto tautomer **3.**

By allowing a large number of phenolic compounds to stand in 0.1 N methanolic HCl for 7 h at room temperature, a measure of the relative ease of formation of methyl ethers was obtained. This formation supposedly involves reaction of the keto form with methanol to form a hemiketal which loses water to yield the methyl ether.[3] The results are listed in Table II. The last step is written as irreversible because when an aqueous



keto form hemiketal methyl ether

acidic solution of **1** was held for 24 h at 20° no cleavage to the phenolic form **2** was observed.

As expected, the most strained compounds in the benz[*a*]anthracene series, **2, 6a, 7a,** and **8a,** were most easily converted into their respective methyl ethers. The ready conversion of **5a** is noteworthy as is that of the parent **4a.** Although the small amount of strain in the benz[*a*]anthracene nucleus introduced by the 7-methyl groups (sandwiched between the two adjacent (6-, 8-) peri hydrogens) could be said to be sufficient to increase the involvement of the keto form,[19] this argument is lacking for the parent compound **4a.**

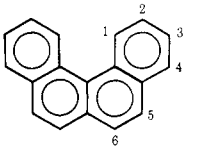
Table II. Formation of Methyl Ethers

Hydroxy compound	% yield of methyl ether		% yield
Phenol	8		
1-Naphthol	14[a]	Benz[*a*]anthracenes	
2-Naphthol	16[a]	**2**	74
9-Phenanthrol	29[b]	**4a**	46
Benzo[*c*]phenanthrenes[20]		**5a**	72
1-Hydroxy	71	**6a**	77
2-Hydroxy	20	**7a**	84
3-Hydroxy	16	**8a**	81
4-Hydroxy	17	Anthrone	0
5-Hydroxy	29	6-Hydroxybenzo[*a*]pyrene	0

[a] In addition to naphthol an unidentified spot was present on TLC analysis of the reaction products. [b] When a solution of 9-phenanthrol in MeOH (3% HCl) was refluxed for 20 h, an 83% yield of 9-phenanthryl methyl ether was obtained.

The most surprising result in this series of experiments is that 6-hydroxy-7,12-dimethylbenz[*a*]anthracene (**7a–29**) produces 6-methoxy-7,12-dimethylbenz[*a*]anthracene (**7**) slightly more rapidly than 5-hydroxy-7,12-dimethylbenz[*a*]anthracene (**2–3**) produces 5-methoxy-7,12-dimethylbenz[*a*]anthracene (**1**). It was expected that since the keto group in **29** is more hindered than the keto group in **3, 1** would be produced more rapidly than **7.** The above result is all the more surprising when one recalls the fact that (**7a–29**) gives a 2,4-DNP derivative more slowly than **2** under the conditions described (see above).

The results in the benzo[*c*]phenanthrene series are surprising in that 1-hydroxybenzo[*c*]phenanthrene[20] forms



benzo[*c*]phenanthrene

methyl ether more rapidly than any of the others measured even though one would expect that any tetrahedral intermediate at the 1 position would involve more strain than at any other position on the nucleus. This result may be compared with the ready formation of the methyl ether **7** from **7a.** In a study[21] of the protodetritiation of the six tritiobenzo[*c*]phenanthrenes, the following partial rate factors were obtained (positions in parentheses): 1580 (1), 1200 (2), 422 (3), 2050 (4), 8680 (5), and 2465 (6). Obviously, there is little if any correlation between the detritiation and methyl ether formation rates. A similar lack of correlation exists in the naphthalene[22] series.

The formation of a small amount of anisole from phenol is noteworthy. The only hydroxy derivatives tested which gave no methyl ether are anthrol and 6-hydroxybenzo[*a*]pyrene. The failure of anthrone, a known ketonic tautomer, to give a methyl ether is surprising.

By chromatography of crude 5-hydroxy-7,12-dimethylbenz[*a*]anthracene (**2**), we were able to isolate almost pure **2** in addition to almost pure keto form **3.** In other work[5] a small amount of **3** was reported, but no **2** was isolated. To our knowledge, the isolation of **2** and **3** represents the first isolation of phenolic and ketonic tautomers (ortho related) in the field of polycyclic aromatic hydrocarbons. Tautomers of the an-

throne-anthrol type have been isolated (for an example in the benz[*a*]anthracene series, see ref 7).

The involvement of arene oxides in the metabolism of carcinogenic and noncarcinogenic polycyclic aromatic hydrocarbons (PAH) has been under study for many years.[23] Whether or not an arene oxide or a transformation product of it is involved in the carcinogenic pathway is a difficult problem to settle.[24] Recently, the suggestion was made that the reactive intermediate in the carcinogenic metabolism of 7,12-dimethylbenz[*a*]anthracene (DMBA) is the ketonic substance **3**.[3] This hypothesis seemed plausible not only because **3** seems to be chemically more reactive than the arene oxide from which it is formed on rearrangement (either thermally or catalytically effected), but also because the rearrangement of the epoxide leads mainly to the 5-oxygenated product.[5,25] Since then,[3] the synthesis of the 6-keto compound **29** has been completed in this laboratory. This keto compound appears to be more reactive (at least toward acidic methanol) than the 5-isomer **3**.[26] Hence it is possible that **29** may play a role in the carcinogenic activity of DMBA. This point is under study.[27]

Finally, if there is any merit to the hypothesis that the keto form may be the active carcinogenic intermediate, it should be of interest to prepare and submit for testing the eight hydroxy-7,12-dimethylbenz[*a*]anthracenes which contain the OH group in positions 1, 2, 3, 4, 7, 8, 9, and 10, because the corresponding keto forms are in principle derivable from the 1,2-, 3,4-, 7,8-, and 9,10-arene oxides of DMBA. The difficulty of synthesizing these arene oxides has prevented their testing to date. However, the syntheses of the above-mentioned hydroxy compounds is underway here and should provide compounds needed to test the hypothesis that the keto forms are of importance in the metabolism of DMBA.

Experimental Section[28]

2-(4-Methoxy-1-naphthylmethyl)benzoic Acid (12). A mixture of 40 g of activated[29] zinc dust, 20.0 g of **10**,[9] 300 ml of 88% formic acid, and 40 ml of water was refluxed for 12 h. After the usual workup the acid fraction was recrystallized from absolute EtOH to yield 19.5 g (97%) of **12**, mp 220–221.5 °C (lit.[30] mp 221–223 °C).

2-[α-(4-Methoxy-1-naphthyl)ethyl]benzoic Acid (13). In a similar way **11**[9] was reduced in 98% yield to **13**, mp 196–198 °C (lit.[4] mp 197–198 °C).

2-(4-Methoxy-1-naphthylmethyl)benzyl Alcohol* (14). A solution containing 15.0 g of **12** and 3.0 g of $LiAlH_4$ in 400 ml of dry THF was refluxed for 2 h and then treated successively with 3 ml of water, 3 ml of 15% NaOH, and 9 ml of water. After removal of the solids by filtration, the filtrate was diluted with 500 ml of 1:1 ether–benzene and worked up as usual to yield 13.0 g (91%) of **14**, mp 107–110 °C, pure enough for the next step. A purer sample, mp 110–111 °C, was obtained by recrystallization from ether–petroleum ether, with little loss.

2-[α-Methoxy-1-naphthyl)ethyl]benzyl Alcohol* (16). By a similar procedure **13** was reduced to **16**, mp 84–85 °C, in 90% yield.

5-Methoxybenz[*a*]anthracene (4). A mixture of 2.0 g of **14**, 12.0 g of dipyridine-chromic oxide,[31] and 50 ml of CH_2Cl_2 was stirred at room temperature for 1 h. The solvent was decanted from the black residue which was repeatedly washed with CH_2Cl_2. The combined CH_2Cl_2 solution was washed with 10% HCl, then with water, and the usual workup afforded 1.94 g of a crude oil, **15**, ir band at 5.90 μ, which was heated at 90° for 2 h in PPA. A conventional workup yielded 1.6 g of **4**, mp 165–166 °C (lit.[30] mp 167–168 °C). A portion of the crude oil was crystallized from ether to yield pure 2-(4-methoxy-1-naphthylmethyl)benzaldehyde* (**15**), mp 80–81 °C.

In another experiment **14** was oxidized to **15** by the use of Selox-cette[32] in refluxing toluene for 24 h, but the yield of **15** was not as good. A 2,4-DNP derivative* **15a**, mp 218–219 °C, was prepared for characterization.

5-Methoxy-12-methylbenz[*a*]anthracene (6). As in the conversion of **14** to **4**, **16** was converted into **6**, mp 122–124 °C (lit.[8] mp 124–125 °C), in almost quantitative yield via 2-[α-(4-methoxy-1-naphthyl)ethyl]benzaldehyde* (**17**), mp 95–97 °C, suitable for further use. The analytical sample, mp 100–101 °C, was obtained by crystallization from ether–petroleum ether.

2-(4-Methoxy-1-naphthylmethyl)acetophenone* (18). A solution of 78 mmol of CH_3Li in dry ether was added dropwise to a stirred solution at reflux of 10.0 g (34.3 mmol) of **12** in 1500 ml of dry ether and 500 ml of dry benzene. After refluxing for 24 h, the mixture was cooled and treated rapidly with 300 ml of 3 N HCl. After the usual workup, 8.1 g (82%) of **18**, mp 86–88 °C, suitable for further work was obtained. Recrystallization from ether–petroleum ether gave the analytical sample, mp 88–89 °C.

2-[α-(4-Methoxy-1-naphthyl)ethyl]acetophenone* (19). In a similar way 61.2 g of **13** was converted into 56.3 g (92.6%) of **19**, mp 119–120 °C.

5-Methoxy-7-methylbenz[*a*]anthracene (5). A solution of 5.0 g of **18** in 250 ml of PPA at 95° was kept for 1 h then poured into water, and the mixture was worked up as usual to give 3.8 g (81%) of **5**, mp 178–180 °C (lit.[7] mp 183 °C).

5-Methoxy-7,12-dimethylbenz[*a*]anthracene (1). A stirred solution of 45.6 g of **19** in 900 ml of PPA was held at 90–95 °C for 90 min and was then poured into water. After the usual workup the crude product was converted into the picrate in EtOH. After one recrystallization from EtOH the picrate was chromatographed over alumina to yield 30.1 g (70%) of **1**, mp 129–130 °C (lit.[4] mp 130–131 °C), after one recrystallization from EtOH. Material of this purity was used in the experiments to form the **2–3** mixture as described later.

2,4-Dibromoaniline (20). A solution of 28 g of 1-naphthylamine in 100 ml of HOAc was added to a 0–5° solution of 22 ml of Br_2 in 200 ml of HOAc. Another 100 ml of HOAc was added and the mixture was warmed at 60° for 15 min and cooled. The salt was filtered, washed with HOAc, and suspended in excess dilute NaOH. The product was collected by filtration, washed with water, and crystallized from EtOH to give 36.5 g (60%) of **20**, mp 114–116 °C (lit.[33] mp 116–118 °C).

4-Bromonaphth[1,2-*d*][1,2,3]oxadiazole (21). To a stirred solution of 10.0 g (33 mmol) of **20** in 150 ml of HOAc and 25 ml of propionic acid (to prevent freezing) at 8–10° was added 2.65 g (38 mmol) of $NaNO_2$ in 1 min. After stirring for 10 min the yellow-brown solution was poured into 200 ml of ice water and the resulting mixture was rapidly filtered to remove about 1 g of black tar. The filtrate was added to 3 l. of water and the yellow-orange solid **21**, mp 118–125 °C, collected after 30 min, weighed 6.7 g (81%). Attempts to purify crude **21** invariably resulted in considerable loss of product. It is best to use this material immediately for conversion into **22**. Also, runs in the 10–15-g size gave better yields than larger runs. The material from two or more runs can be combined for conversion into **22**.

4-Bromo-2-naphthol (22). To a suspension of 5.1 g of **21** in 90 ml of EtOH at 0–10° was added 0.25 ml of $NaBH_4$. The solution was stirred until gas evolution ceased (2–3 h) and poured into 500 ml of water containing 5 ml of concentrated HCl. After making basic with 10% NaOH, the neutral products were removed by extraction with CH_2Cl_2. Acidification of the alkaline solution and the usual workup afforded 4.1 g (89%) of **22**, mp 105–110 °C. Recrystallization yielded **22**, mp 118–119 °C, with varying loss (lit.[15] mp 122 °C). Crude **22** is best methylated to **23** which is readily purified.

4-Bromo-2-methoxynaphthalene (23). To a solution of 5.0 g of crude **22** in 35 ml of dry DMF was added washed NaH (0.60 g) in portions. After the mixture was stirred for 15 min, 1.9 ml of CH_3I was added and stirring was continued at room temperature for 1 h. A conventional workup yielded an oil which was chromatographed on neutral alumina (20% benzene in 30–60° petroleum ether) to yield 4.4 g (83%) of **23**, mp 63.5–64.5 °C (lit.[14] mp 64 °C), after crystallization from petroleum ether, bp 30–60°.

***o*-(3-Methoxy-1-naphthoyl)benzoic Acid* (24).** In the best of several experiments, the Grignard reagent, prepared from 27.0 g of pure **23**, 5.6 g of sublimed Mg, 8 g of ethylene dibromide,[34] and 400 ml each of ether and benzene, was added to a solution at reflux of 17 g of phthalic anhydride in 1 l. of 1:1 ether–benzene in a 5-l. three-necked flask. After 48 h at reflux the reaction mixture was poured on 1.3 l. of diluted HCl and ice. After a conventional workup of the acid fraction there was obtained 27.8 g (80%) of **24**, mp 168–169 °C, after crystallization from ether or ethyl acetate–petroleum ether.

3-Methyl-3-(3-methoxy-1-naphthyl)phthalide* (25). In the best of several experiments, the Grignard reagent prepared from 18 g (0.125 mol) of CH_3I in 250 ml of ether was added dropwise to a stirred solution of 15.3 g (0.05 mol) of **24** in 1 l. of ether. After 20 h at reflux, a conventional workup afforded 12.2 g (81%) of **25**, mp 166–167 °C, after recrystallization from ether–petroleum ether. The analytical sample melted at 168–169 °C.

***o*-[α-(3-Methoxy-1-naphthyl)ethyl]benzoic Acid* (26).** In the best of several experiments, a mixture of 75 g of zinc dust (activated with 1.25 g of $CuSO_4$), 625 ml of 10% KOH, 62 ml of pyridine, and 12.5 g of **25** was held at reflux for 20 h. After a conventional workup the acidic fraction afforded 12.0 g (96%) of **26**, mp 172–174 °C, suitable for further use without further purification. The analytical sample, mp 174–175 °C, was obtained by recrystallization from ether–petroleum ether.

***o*-[α-(3-Methoxy-1-naphthyl)ethyl]acetophenone* (27).** By treatment with slightly over 2 mol of CH_3Li in ether for 48 h at reflux, **26** was converted to **27**, mp 87–89 °C, in almost quantitative yield. The analytical sample, mp 90–91 °C, was obtained by crystallization from EtOH with little loss.

***o*-[α-(3-Methoxy-1-naphthyl)ethyl]benzaldehyde* (28).** In a typical experiment a solution of 1.5 g of **26** in 25 ml of THF was added to a solution of 300 mg of $LiAlH_4$ in 25 ml of THF. After 2 h at reflux, a conventional workup yielded 1.3 g (89%) of *o*-[α-methoxy-1-naphthyl)ethyl]benzyl alcohol* (**26a**), mp 100–101 °C, after crystallization from aqueous EtOH. A mixture of 5.8 g of **26a**, 36 g of pyridine–chromic oxide complex,[35] and 450 ml of CH_2Cl_2 was stirred for 1 h at room temperature. The black precipitate was collected and washed repeatedly with CH_2Cl_2. The filtrate and washings were worked up as usual to yield 5.7 g of crude **28** which on crystallization from absolute EtOH yielded 5.3 g (91%) of pure **28**, mp 102–103 °C.

6-Methoxy-12-methylbenz[*a*]anthracene* (8). In the best of several experiments, a mixture of 4.4 g of **28** and 100 ml of PPA was stirred at 50° for 45 min. The product obtained after a conventional workup was chromatographed on Al_2O_3 to yield a solid colorless first fraction (elution with petroleum ether–benzene) which was converted into a picrate. The recrystallized picrate (hexane) afforded 2.9 g (73%) of **8**, mp 109–110 °C, NMR ($CDCl_3$) δ 3.2 (s, 3, $ArCH_3$), 3.9 (s, 3, OCH_3), 6.5 (s, 1, the 5-H), 7.0–8.4 (m, 9, ArH).

Cleavage of Aryl Methyl Ethers. Method A (to Aryl Acetates). The procedure[16] involved heating at 140–145° about 0.5–1.0 g of aryl methyl ether with a fivefold excess of sodium ethyl mercaptide in 8 ml of dry DMF under N_2 for 2.5–3 h. The cooled solution was then treated with excess Ac_2O overnight and the product was isolated as usual and recrystallized from ether–hexane, or ether at low temperature, to yield the acetates* listed in Table I.

Method B (to Aryl Acetates). The procedure involved heating about 2.5–3.5 g of methyl ether with a fivefold excess of anhydrous sodium sulfide[36] (prepared by allowing crushed nonohydrate to stand in a desiccator over P_2O_5) in 10 ml of NMP held at 140–145° for 2.5–3.5 h. The cooled solution was treated with Ac_2O and worked up as in method A to yield the acetate. Since method B was carried out with larger amounts of aryl methyl ethers than those used in method A, the higher yields reported in Table I do not mean that the yields are really superior to the yields obtained by method A, but they may be. Furthermore, method B was applied after the experiments by method A had been completed, hence greater experience with the compounds in hand had been gained.

Method C (to Phenols). The cleavage of aryl methyl ethers was carried out as described under methods A or B, however, no Ac_2O was added. Instead, the solutions were poured into dilute HCl and the product isolated as usual by extraction with CCl_4. All solvents and reagents were saturated with N_2 before use and N_2 was used to cause mixing of the layers in all extraction procedures. Since the hydroxy compounds are all sensitive to light and oxygen, all apparatus was covered with aluminum foil during use. Because of the sensitivity of the hydroxy compounds, the melting points (all taken in sealed tubes) recorded in Table II must not be given too much weight as they are really decomposition points. In the cases of all compounds containing a 12-methyl group, the compounds are really mixtures of keto and phenolic tautomers.

Characteristics of Phenolic Compounds 2, 4a, 5a, 6a, 7a, and 8a. (1). Infrared and NMR Spectra. Compounds **4a** and **5a** were entirely in the phenolic form as shown by ir (absence of ketone band near 6 μ, presence of strong hydroxyl band near 3.0 μ) and NMR (absence of a singlet at δ 3.7, characteristic for the hydrogens at position 6 in **3**). As freshly precipitated from the solution of the sodium salt obtained by cleavage of the methyl ethers **1, 6, 7,** and **8,** as described above, the demethylated compounds **2, 6a, 7a,** and **8a** existed as mixtures of phenolic (P) and ketonic (K) tautomers, the composition of which was determined by integration as follows: for **2,** the aromatic H at position 6 (δ 7.0) and the sp^3 H at position 6 (δ 3.7), P/K ratio = 0.8; for **6,** same hydrogens as for **2,** P/K = 0.42; for **7a,** the aromatic H at position 5 (δ 6.6) and the sp^3 H at position 5 (δ 3.7), P/K < 0.1; for **8a,** same hydrogens as for **7a,** P/K = 0.25. The values for these ratios are accurate to ±0.05 δ due to instrumental error.

2. Formation of 2,4-DNP Derivatives. On addition of 0.1 g of hydroxy compound in 5 ml of ethanol to 10 ml of 2,4-dinitrophenylhydrazine reagent,[37] three types of behavior were observed. Compounds **2, 6a,** and **8a** gave 2,4-DNP derivatives (2_D, $6a_D$, and $8a_D$) rapidly and in high yield. Compound **4a** required 2 h and 9-phenanthrol (**30**) about 20 h to give high yields of derivatives ($4a_D$, $5a_D$, and 30_D). Neither phenol, 1- or 2-naphthol, nor 1-hydroxybenzo[*c*]phenanthrene[38] gave a 2,4-DNP derivative on standing 24 h. The melting points are listed in Table I.

3. Formation of Methyl Ethers. As a standard experiment 2 mmol of compound in 5.0 ml of ethyl acetate was added to 10.0 ml of 0.097 N methanolic HCl and the solution was held at room temperature for 7 h. After removal of the solvents on a rotary evaporator the product was chromatographed on a 1.5 × 25 cm column over 100–200 mesh silica with elution by benzene–petroleum ether, bp 30–60° (1:1). The methyl ethers (blue fluorescence under uv light) were eluted first followed after a large interval by the phenolic compounds (green fluorescence). After removal of solvent the residues were dried to constant weight and characterized as pure by NMR. Because phenol, the two naphthols, and 9-phenanthrol did not fluoresce, the desired fractions were identified by their different R_f values using TLC silica plates. The results are summarized in Table II.

Separation of 2 and 3. Chromatography of 2.0 g of crude material (obtained by cleavage of **1** with Na_2S as described) over 100–200 mesh silica (grade 923, Matheson Coleman and Bell) contained in a 2 × 80 cm column using benzene as eluent afforded 500 mg of pale yellow **2,** mp 55–58 °C dec, about 90% phenolic form **2** (strong ir peak at 3250 cm^{-1}) by NMR analysis (see above) in fractions 5 and 6, followed by 480 mg of slightly off-color (brownish) **3,** mp 252–254 °C dec, (lit.[5] 252.5–254 °C, colorless); ir, 1680 cm^{-1}; NMR (C_6D_6, $(CH_3)_4Si$), δ 2.1 (s, 3 H, 7-CH_3), 2.5 (s, 3 H, 12-CH_3), 3.7 (s, 2 H, 6-CH_2).

References and Notes

(1) This research was supported by Grant C_2-07394 from the National Cancer Institute, National Institutes of Health.
(2) Postdoctoral Research Associate.
(3) M. S. Newman and D. R. Olson, *J. Am. Chem. Soc.*, **96,** 6207 (1974).
(4) W. H. Smith, E. F. Pratt, and H. F. Creech, *J. Am. Chem. Soc.*, **73,** 319 (1951).
(5) The isolation of **3** and the 6-keto analogue in minute amounts from acidic treatment of 5,6-dihydro-5,6-dihydroxy-7,12-dimethylbenz[*a*]anthracene has been described by A. Dipple, L. S. Levy, and P. T. Iype, *Cancer Res.*, **35,** 652 (1975).
(6) L. F. Fieser and E. M. Dietz, *J. Am. Chem. Soc.*, **51,** 3141 (1929).
(7) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **59,** 1028 (1937).
(8) G. M. Badger, *J. Chem. Soc.*, 2497 (1949).
(9) M. S. Newman, S. Venkateswaran, and V. Sankaran, *J. Org. Chem.*, **40,** 2996 (1975).
(10) R. L. Letsinger, J. D. Jamison, and A. L. Hussey, *J. Org. Chem.*, **26,** 97 (1961).
(11) For one example, see M. S. Newman, D. MacDowell, and S. Swaminathan, *J. Org. Chem.*, **24,** 509 (1959).
(12) For example, see ref 7 and M. S. Newman, S. Swaminathan, and R. Chatterji, *J. Org. Chem.*, **24,** 1961 (1959).
(13) R. Consden and J. Kenyon, *J. Chem. Soc.*, 1591 (1935), give mp 116–118 °C.
(14) H. H. Hodgson and S. Birtwell, *J. Chem. Soc.*, 321 (1943), give mp 133 °C.
(15) H. H. Hodgson and S. Birtwell, *J. Chem. Soc.*, 468 (1943), used aluminum in alcohol as reducing agent.
(16) G. I. Feutrill and R. W. Mirrington, *Tetrahedron Lett.*, 1327 (1970).
(17) For calculation of energy differences between phenolic and ketonic tautomers in the benzo[*c*]pyrene series, see A. Pullman and B. Pullman, *Jerusalem Symp. Quantum Chem. Biochem.*, 16, 17 (1964).
(18) (a) C. Liebermann and A. Hagen, *Chem. Ber.*, **15,** 1427 (1882); (b) L. Gattermann, *Justus Liebigs Ann. Chem.*, **244,** 72 (1888); (c) D. D. Pratt and R. Robinson, *J. Chem. Soc., Trans.* **125,** 188 (1924); (d) B. Lampe, *Chem. Ber.*, **42,** 1413 (1909); (e) G. Stork, *J. Am. Chem. Soc.*, **69,** 576 (1947). We are indebted to Professor M. V. Sargent, The University of Western Australia, for ref 18a–d.
(19) It is possible that an electronic factor is also involved with methyl substitution. For the present and until more examples can be studied, we will continue to interpret the results as being due primarily to steric strain factors.
(20) M. S. Newman and J. Blum, *J. Am. Chem. Soc.*, **86,** 503 (1964).
(21) J. LeBuen and R. Taylor, *J. Chem. Soc., Perkin Trans. 2,* 3301 (1974).
(22) C. Eaborn, P. Golborn, R. E. Spillet, and R. Taylor, *J. Chem. Soc. B,* 1112 (1968).
(23) See D. M. Jerina, H. Yagi, and J. W. Daly, *Heterocycles,* **1,** 267 (1973), and J. W. Daly, D. M. Jerina, and B. Witkop, *Experientia,* **28,** 1129 (1972), for reviews.

(24) See P. Sims, "Proceedings of the XI International Cancer Congress, Florence, Italy," 1974, p 9, for a discussion and references to the latest aspects.
(25) S. Goh and R. Harvey, *J. Am. Chem. Soc.*, **95**, 242 (1973).
(26) In this connection, interestingly, 5,6-dihydro-7,12-dimethylbenz[*a*]anthracene 5,6-oxide has been reduced by $LiAlH_4$ mainly at the 6 position to yield 5,6-dihydro-5-hydroxy-7,12-dimethylbenz[*a*]anthracene in good yield: R. G. Harvey, S. H. Goh, and C. Cortez, *J. Am. Chem. Soc.*, **97**, 3468 (1975).
(27) In one experiment,[5] **29** was reported inactive.
(28) All melting points are uncorrected. New compounds marked with an asterisk* gave analyses to within ±0.3% of the theoretical, analyses by M–H–W Laboratories, Garden City, Mich. 48135, and Galbraith Laboratories, Knoxville, Tenn. 37921. All compounds were characterized by ir, NMR, and mass spectra but no details are given for results unless worthy of comment. The term "worked up in the usual way" means that a solution of the products in a water immiscible solvent was washed with alkali and/or acid, and with saturated salt solution before filtering the organic solution through a cone of anhydrous $MgSO_4$.
(29) K. Tsuda, E. Ohki, and S. Nozoe, *J. Org. Chem.*, **28**, 783 (1963).
(30) L. F. Fieser and E. M. Dietz, *J. Am. Chem. Soc.*, **51**, 3144 (1929).
(31) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).
(32) Seloxcette is graphite impregnated with CrO_3: J. M. Lalancette, G. Rollin, and P. Dumas, *Can. J. Chem.*, **50**, 3058 (1972).
(33) R. Consden and J. Kenyon, *J. Chem. Soc.*, 1591 (1935).
(34) D. E. Pearson, D. Cowan, and J. D. Beckler, *J. Org. Chem.*, **24**, 504 (1959).
(35) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).
(36) See M. S. Newman, J. R. LeBlanc, H. A. Karnes, and G. Axelrad, *J. Am. Chem. Soc.*, **86**, 868 (1964), for an alternate method of preparing anhydrous Na_2S.
(37) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", 4th ed, Wiley, New York, N.Y., 1962, p 111.
(38) M. S. Newman and J. Blum, *J. Am. Chem. Soc.*, **86**, 503 (1964).

Photophysical Properties of β-Amino Ketones. Investigation of Tropinone, *N*-Methyl-4-piperidone, and 1-Diethylamino-3-butanone

Arthur M. Halpern*[1] and Arthur L. Lyons, Jr.

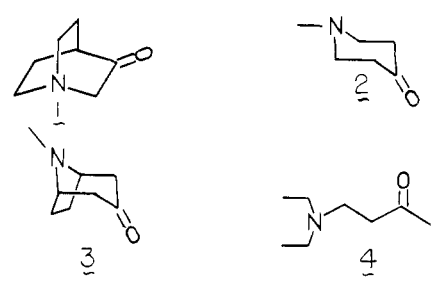
Contribution from the Photochemistry and Spectroscopy Laboratory, Department of Chemistry, Northeastern University, Boston, Massachusetts 02115. *Received August 4, 1975*

Abstract: A spectroscopic and photophysical study was carried out on the three β-amino ketones: *N*-methyl-4-piperidone (**2**), tropinone (**3**), and 1-diethylamino-3-butanone (**4**). Appropriate model compounds representing the amine and ketone chromophores, e.g., *N*-methylpiperidine and cyclohexanone, respectively, were also examined. Comparisons between the electronic absorption spectra of the amino ketones and the model compounds suggest that **2** and **4** can be considered as bichromophoric (for the lower lying transitions). The absorption spectrum of **3** possesses a moderately strong band at 241 nm which is presumably due to the ground-state coupling between the N n orbital and the carbonyl π orbital. Other correlations are made between absorption and fluorescence and the stereodisposition between the amine and ketone moieties. All three β-amino ketones are characterized by an extremely efficient intramolecular quenching of the amine fluorescence. Thus relative to the quantum yield for the amine fluorescence in *N*-methylpiperidine, ϕ_f's for the amine emission in **2, 3,** and **4** are several orders of magnitude smaller. It is suggested that the mechanism for this quenching arises from energy transfer from the amine to the carbonyl chromophores (which probably proceeds via an exchange-type mechanism). In the case of **3,** internal conversion may account, in part, for this quenching. The fluorescence quantum yields of **2** and **3** are typical of model ketones, indicating that the excited-state dynamics of the ketone group are not affected by interaction with the amine function. Carbonyl fluorescence is, however, significantly quenched in **4** implying that this acyclic β-amino ketone can achieve a conformation in which intramolecular quenching of the ketone excited state by the amine group can occur (presumably via an electron (or charge) transfer step). The results of *inter*molecular quenching studies between alkanones and trialkylamines are discussed in connection with the *intra*molecular quenching in the β-amino ketones. Sensitized ketone fluorescence was observed as a consequence of the intermolecular quenching of amines by ketones. Photochemical studies indicate that the β-amino ketones (especially **2**) are subject to photochemical reduction, probably yielding a highly fluorescent β-amino alcohol as (one of) the photoproduct(s).

The photophysical properties of dialkylaminoalkanones are little known despite the attention given to elucidating the photophysical and photochemical processes of ketones[2] and the intermolecular excited-state interactions between ketones (particularly aryl ketones) and amines.[3] Only recently have the spectroscopic and photophysical properties of trialkylamines been investigated,[4] and a study of the fluorescence of an amino ketone has been reported.[5]

The bicyclic α-amino ketone, 1-azabicyclo[2.2.2]octan-3-one (**1**), has ben found to exhibit fluorescence characteristic of the ketone group, irrespective of whether excitation was into the amine or ketone transition.[5] Intramolecular energy transfer was invoked to explain this result. The data also indicated the absence of ground-state interaction between the nitrogen lone pair and the carbonyl moiety.

The present work extends the spectroscopic study of **1** into an investigation of a series of β-amino ketones, *N*-methyl-4-piperidone (**2**), tropinone (**3**), and 1-diethylamino-3-butanone



(**4**), in which the amine and ketone moieties are separated by an additional methylene group as compared with **1.** The effect of the separation of the two chromophores by an ethylene linkage, as well as the influence of structure on photophysical properties of the molecule, are of interest.

The possibility that coupling between the amine and carbonyl groups may play a role in the photophysics of β-amino ketones must be considered, as it is well documented that β-