

**SYNTHESES AND STRUCTURAL FEATURES OF SUBSTITUTED
4,5,6,7-TETRAHYDROINDAZOLIN-3-ONES**

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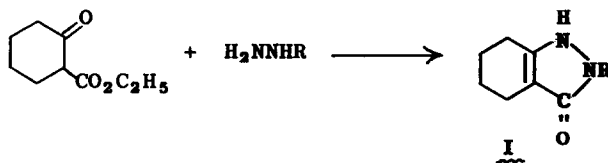
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The literature abounds in pyrazoline chemistry, stemming in part from a search for effective medicinal compounds of the antipyrene type. Nevertheless there is a surprising exiguity in certain areas, such as the alkylation of 4,5,6,7-tetrahydroindazolin-3-one (I). The differentiation between (I) and (II), and their properties, has been hampered by inadequate synthetic methods and by doubts regarding the authenticity of structural assignments.

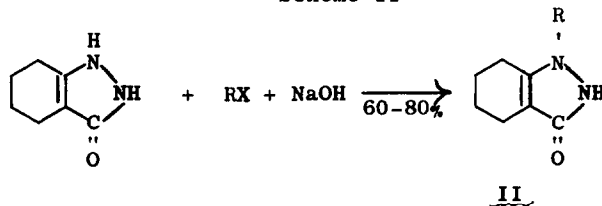
While I (R=H or alkyl) is accessible from the reaction of hydrazines and ethyl 2-oxocyclohexanecarboxylate (2) (Scheme I), it is only recently that a limited synthesis of II has been reported (3). The present study provides authentic general syntheses of II and reveals interesting differences in the structural and spectral properties of the two isomers.

Scheme I



Alkylation of I (R=H) with n-butyl bromide in aqueous ethanolic sodium hydroxide gave an excellent yield of II (R=n-C₄H₉) (Scheme II). This reaction appears entirely general for alkyl halides and tosylates (see Table I). Compound II (R=n-C₄H₉) was also obtained using the published alkylation procedure (4), which claimed the product as I (R=n-C₄H₉). Thus the literature (4) appears to be erroneous, as the reported physical properties correspond neither to authentic I (R=n-C₄H₉), prepared by Scheme I, nor to authentic II (R=n-C₄H₉).

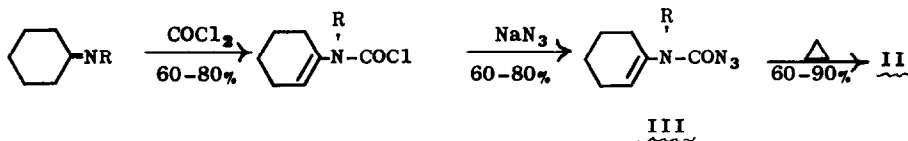
Scheme II



Verification of the structure of these alkylation products was obtained by comparison with authentic II, prepared by a convenient and unequivocal synthesis adapted from Stolle's method for the preparation of 1-substituted indazolin-3-ones from carbaniloyl azides (5).

The requisite cyclohexanone imines are readily available (6), and reaction of these materials with phosgene is a further example of the reaction of electrophiles with enolizable imines to form enamidic compounds (7,8). The encarbamoyl chloride thus formed is treated with sodium azide and the resulting azide III smoothly converted to II in refluxing chlorobenzene (Scheme III).

Scheme III



The enhanced nucleophilicity of the β -carbon in III appears to be responsible for the fact that ring closure of III ($R=\text{C}_6\text{H}_5$) takes place solely in the cyclohexene ring to give II ($R=\text{C}_6\text{H}_5$) with no evidence of alternative 1-cyclohexenylindazolinone formation.

Scheme III has distinct advantages over the recently reported synthesis of II from 2-chloro-1-cyclohexenecarboxhydrazides (3), having fewer steps and utilizing the more available amines rather than hydrazines. Moreover it is doubtful whether the hydrazide method is genuinely applicable for preparing a wide range of II ($R=\text{alkyl}$), as reaction of aliphatic aldehydes with hydrazine gives the azine in preference to the required hydrazone (9).

Table I

Substituted 4,5,6,7-Tetrahydroindazolin-3-ones

Compound ^a	m.p.	method of preparation ^b	IR ν C=X cm^{-1} (CHCl_3)
<u>I</u> R = CH_3	124-125	A	1675
R = $n\text{-C}_4\text{H}_9$	104-106	A	1680
<u>II</u> R = CH_3	178-181	B, C	1530
R = $\text{CH}(\text{CH}_3)_2$	225-227	B, C	1545
R = $n\text{-C}_4\text{H}_9$	139-140	B, C	1540
R = $\text{CH}_2\text{-CH}(\text{CH}_3)_2$	165-166	C	1530
R = $\text{CH}_2\text{-C}_6\text{H}_5$	188-188.5 ^c	B, C	1530
R = C_6H_5	213-214 ^c	C, D	1530
R = $3,4(\text{Cl})_2\text{C}_6\text{H}_3$	208-210	C	1530

a) Satisfactory elemental analyses, nmr and mass spectra were obtained.

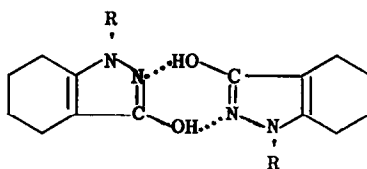
b) A, Scheme I; B, Scheme II; C, Scheme III; D, Hydrazide method (see ref. 3).

c) Using method B, C or D obtained mp as shown; ref. 3 reports mp 6° lower.

It is obvious from Table I that isomers I and II differ radically in their ir spectra. The highest frequency assignable to a carbonyl band in II is ca. 1545 cm^{-1} . Only sharp, weak unsaturation bands occur at higher frequencies in this region. In contrast I has normal ν C=O at ca. 1680 $^{-1}$. Strong differentiation also occurs in the NH/OH stretching region. Broad, but intense absorption (not shown in Table I) between 2300-2800 cm^{-1} indicative of hydrogen bonding occurs in II; I displays only normal N-H absorption in the 3200-3500 cm^{-1} region.

The data suggests that indazolinones I and II possess radically different structural features paralleling the tautomeric and associative properties previously found in substituted pyrazolinones (10,11) by spectral studies. Moreover, intermolecular association was confirmed by vapor phase osmometry in benzene, where a dimeric mol. wt. was found for II but not for I (R= $n\text{-C}_4\text{H}_9$), over an extended concentration range. This result is analogous to that found from VPO studies of 2-pyridone (12), and as a consequence IV is proposed as a

more accurate structural representation of II. In contrast, I appears to be more normally amidic, with at most weak intermolecular association.



IV

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