Current Trends in
Heterocyclic Chemistry

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Heterocyclic Chemistry

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INTRODUCTORY REMARKS

IT MAY fairly be said that heterocyclic chemistry, although it is one third of all organic chemistry, has only recently started to receive as much attention as it merits. This is surprising because nature has chosen heterocyclic substances for some of the most important functions in the living cell, as vitamins, co-enzymes, and components of the nucleic acids. The special suitability of heterocyclic substances for these functions is that they are usually resistant to metabolic destruction; by and large they do not easily become degraded as aliphatic and aromatic substances do. With this knowledge in mind, those devising new and better drugs are turning more and more to heterocyclic nuclei. Alkaloids, too, continue to pose worthwhile problems in chemistry, and contribute usefully to medical treatment.

Apart from their biological interest, heterocyclic chemicals are being used as dyestuffs, rubber chemicals, analytical reagents and even plastics.

The publication of the sixth volume of Elderfield's 'Heterocyclic Compounds' in 1957, with other volumes yet to appear, reminds us of the vastness of the subject and also of the steps that are being taken to systematize the literature and expose the many gaps in fundamental knowledge.

The present papers, twenty in number, will add their quota of knowledge to what is already known. They represent the current trends of heterocyclic research in Australia, where the subject has long been a popular one, and cover a wide range of interests.

PROFESSOR A. ALBERT, *Chairman*

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REACTIONS OF ETHYL DIAZOACETATE WITH HETEROCYCLIC SYSTEMS

G. M. BADGER and B. J. CHRISTIE

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THERE are three reagents which react by addition to ethylenic double-bonds: ozone, osmium tetroxide and ethyl diazoacetate. All three have proved of inestimable value in the study of unsaturated compounds, not only in degradative experiments designed to locate the position of the unsaturation, but also as specialized reagents in synthesis.

Certain aromatic hydrocarbons and heterocyclic compounds are also attacked by these reagents[1]. Studies on the addition of ozone, especially by WIBAUT[2] and his colleagues, have contributed largely to our knowledge of the fine structures of such systems. Naphthalene and its derivatives, for example, have been shown to yield 1,2-3,4-diozonides, which are finally converted into pentozonides. With some polycyclic aromatic hydrocarbons it is possible to isolate the products following addition of ozone to only one bond[3], and this has found application in synthesis[4, 5]. Similarly, osmium tetroxide has been shown to react by addition to the 9,10- bond of phenanthrene, the 3,4- bond of 1,2-benzanthracene, and the 1,2- and 3,4- bonds of anthracene[6]. The third reagent, ethyl diazoacetate, loses nitrogen and reacts by addition to the 1,2- bond of naphthalene, the 1,2- bond of anthracene, the 9,10- bond of phenanthrene, and so on[1]. Hydrolysis of the adducts obtained from naphthalene and from anthracene gives 1,2-dihydronaphth-1,2-yleneacetic acid (*I*)[7] and 1,2-dihydro-anthr-1,2-yleneacetic acid (*II*)[8] respectively.


I *II*
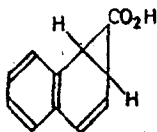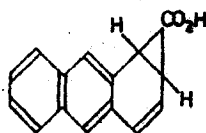
In all these cases the reagent adds first to the bond having the greatest double-bond character, and it may be noted that this bond does not always coincide with the most reactive centres as indicated by electrophilic substitution with reagents such as Br^+ and NO_2^+. For this reason, ozone, osmium tetroxide and ethyl diazoacetate have been termed 'double-bond reagents'[9].
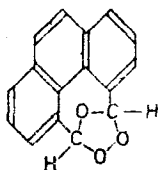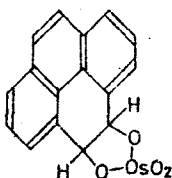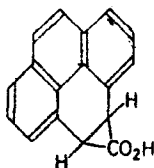
III   IV   V

The results obtained with pyrene are particularly illuminating in this respect. Thus ozone, osmium tetroxide and ethyl diazoacetate all react by addition to the 1,2- bond (to give III, IV and V); but ordinary electrophilic reagents react by substitution at the 3-, the 3,8-, the 3,10-, or the 3,5,8,10- positions. Similarly anthracene is attacked by most reagents at the 9,10- position, but ethyl diazoacetate attacks the 1,2- bond, and osmium tetroxide the 1,2- and 3,4- bonds.

In studying the reaction of ethyl diazoacetate with heterocyclic systems, we have had in mind the use of the reagent not only to examine the fine structures of such systems, but also for the preparation of cyclopropane derivatives and their possible ring enlargement. In our initial experiments, therefore, ethyl diazoacetate has been used to attack thionaphthen, benzofuran, indole and 1-methylindole.

Thionaphthen and benzofuran both reacted by addition to the 2,3- bond, and after hydrolysis, gave the expected adducts (VI, VII); but indole gave only 3-indolylacetic acid (VIII; R = H). The
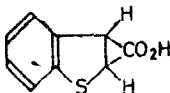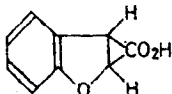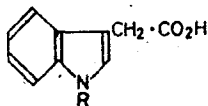
VI   VII   VIII

preparation of this acid from indole and ethyl diazoacetate in the presence of copper powder has been reported[10, 11]. We have confirmed that the reaction takes this course, in the absence of copper powder, under the same experimental conditions which give the cyclopropane adducts with thionaphthen and with benzofuran. The difference cannot be associated with the acidic hydrogen of indole,

for 1-methylindole reacted in the same way to yield 1-methyl-3-indolylacetic acid (*VIII*; R = Me). No satisfactory explanation for this anomalous reaction can be offered at present. It may be noted, however, that ethyl diazoacetate is believed to react normally with thiophen, to give the *cyclo*propane adduct[12]; but 1-methylpyrrole undergoes the anomalous reaction, giving 1-methyl-2-pyrrolylacetic acid[13].

The structure of the product obtained from 1-methylindole was proved by comparison with a specimen obtained by N-methylation of 3-indolylacetic acid. The acid obtained from benzofuran was not identical with either 2- or 3-benzofuranylacetic acids; and the acid obtained from thionaphthen likewise differed from the known 2- and 3-thionaphthenylacetic acids. *Cyclo*propane addition structures therefore appeared likely, and this was supported by an observation that permanganate oxidation of the thionaphthen derivative *VI* gave only its S-dioxide.

The structure of the thionaphthen adduct has been proved by its reductive desulphurization with *W*-7 Raney nickel to *cyclo*hexyl*cyclo*propane carboxylic acid (*IX*). The complete hydrogenation of the phenyl ring during this desulphurization was surprising, for we expected to obtain 2-phenyl*cyclo*propane carboxylic acid (*XI*). It may be noted that no such h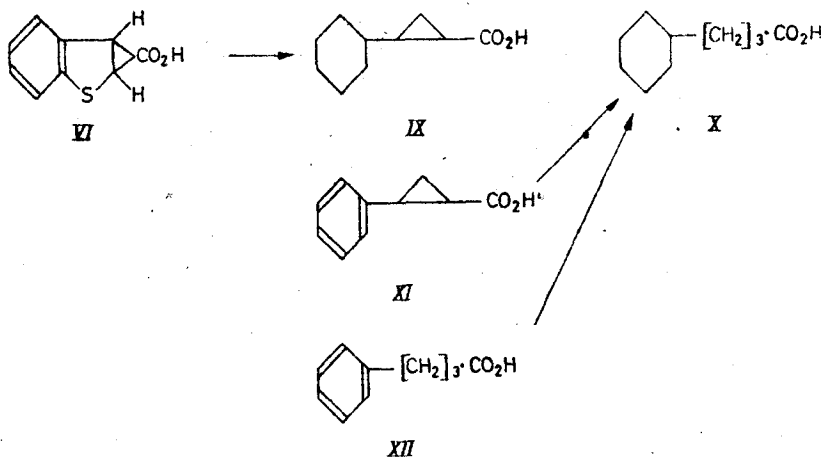ydrogenation of the phenyl ring was observed following the desulphurization of 3-thionaphthenylacetic acid by BLICKE and SHEETS[14], who were, however, using a less active catalyst. In the present case all attempts to bring about the desulphurization with less active catalysts either were unsuccessful, or gave the fully hydrogenated product.

Attempts to reduce both *cis* and *trans*-2-phenyl*cyclo*propane carboxylic acids (*XI*) by treatment with *W*-7 Raney nickel under conditions similar to those used for desulphurization were unsuccessful, the acids being recovered unchanged from this treatment. It seems therefore that phenyl*cyclo*propane carboxylic acid cannot be an intermediate in the reductive desulphurization, which must proceed by addition of hydrogen to a labile molecule formed following removal of the sulphur atom.

With Adam's catalyst both *cis* and *trans*-2-phenyl*cyclo*propane carboxylic acid were hydrogenated, with fission of the *cyclo*propane ring, to give *cyclo*hexylbutyric acid (*X*). This acid was identical in every respect with a specimen obtained by similar hydrogenation of *cyclo*hexyl*cyclo*propane carboxylic acid (*IX*), and with a specimen obtained by reduction of 4-phenylbutyric acid (*XII*). These examples of reductive fission of *cyclo*propanes under relatively mild conditions, with Adam's catalyst, parallel that recorded by LINSTEAD[15], who obtained ethyl *n*-butylmalonate by catalytic hydrogenation of ethyl 2-vinyl*cyclo*propane-1,1-dicarboxylate. In all these cases rupture of the *cyclo*propane ring occurs at the bond linking the two substituents.

In examining the nature of the compounds obtained from ethyl diazoacetate and the various heterocyclic systems, we thought that it should be possible to establish the presence of the *cyclo*propane ring by its i.r. absorption. Several authors have pointed out that *cyclo*propanes all give a medium or moderately strong absorption band in the 1000–1050 cm^{-1} region. *Cyclo*propane itself[18] has a peak at 1028·7 cm^{-1}, which has been assigned to a ring-bending vibration, and many substituted *cyclo*propanes absorb around 1021 ± 5 cm^{-1}.

Table 1.   i.r. Absorption in the 1000–1050 cm^{-1} region[*]

Compound	Frequency (cm^{-1})
cis-2-Phenylcyclopropane carboxylic acid†	1025 *w*
trans-2-Phenylcyclopropane carboxylic acid†	1026 *w*
2-Cyclohexylcyclopropane carboxylic acid‡	1031 *m*
1,2-Dihydronaphth-1,2-yleneacetic acid†	1012 *w*
Ethyl 1,2-dihydronaphth-1,2-ylene-acetate§	1025 *m*
2,3-Dihydrothionaphth-2,3-yleneacetic acid†	1018 *m*
Ethyl 2,3-dihydrothionaphth-2,3-ylene acetate§	1031 *m*
2,3-Dihydrobenzofuran-2,3-yleneacetic acid†	1015 *w*
Ethyl 2,3-dihydrobenzofuran-2,3-ylene acetate‡	1036 *m*
3-Indolylacetic acid†	1010 *w*
Ethyl 3-indolylacetate‡	1026 *s*
1-Methyl-3-indolylacetic acid†	1012 *m*
3-Thionaphthenylacetic acid†	1019 *w*

* NaCl prism;   † Nujol mull;   ‡ Liquid film;   § In CHCl$_3$

Disubstituted *cyclo*propanes are said to absorb at slightly lower wavelengths.

All the *cyclo*propane derivatives examined (see *Table 1*) give an absorption band in the 1000–1050 cm^{-1} region; but our results indicate that its diagnostic value must be accepted with great caution. 3-Indolylacetic acid (*VIII*; R = H), 1-methyl-3-indolylacetic acid (*VIII*; R = Me) and 3-thionaphthenylacetic acid, all absorb in this region, but have no *cyclo*propane system. Moreover the literature records other examples of simple indoles absorbing in this region[19].

The i.r. absorption spectra of our compounds have been examined by Dr H. J. Rodda, to whom we express our thanks.

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DISCUSSION

J. W. CLARK-LEWIS: I would like to ask Professor Badger a question on homocyclic chemistry: does not the ozonolysis of anthracene give 9,10-anthraquinone?[1]

G. M. BADGER: Yes, the ozonization of anthracene was recently reported as having been carried out in acetic acid solution, and it did not react as one might expect by addition to the 1,2- and 3,4- double-bonds, because the only product isolated was anthraquinone. Two things are important here,

firstly, anthraquinone is a sparingly soluble substance, therefore easy to isolate, and there may have been more soluble compounds present; and secondly, acetic acid is not altogether the most desirable solvent for this operation because it gives peracetic acid with ozone. Peracetic acid is known to attack anthracene and give anthraquinone, therefore the actual reagent in this ozonization may have been peracetic acid and not ozone.

G. SHAW: I would like to ask about the Raney nickel catalyst. We have been doing some work on the desulphurization of simple thiol compounds and found that the W-7 catalyst gives the disulphide, whereas if we use the rather poor quality of Raney nickel which the students use for reducing nitro compounds we get complete desulphurization. I wondered if it exerted a dehydrogenating property first? In your case dehydrogenation could lead to a suitable intermediate, followed by, say, reduction in the benzene ring followed by removal of the sulphur.
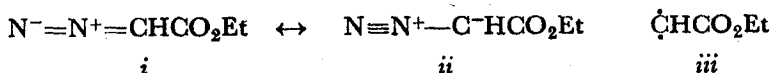
G. M. BADGER: We have never failed to achieve desulphurization of a thiol, and I am rather surprised at your result; as you say, Raney nickel does sometimes act as a dehydrogenating agent. What solvent were you using, Dr Shaw?

G. SHAW: Alcohol.

K. H. PAUSACKER: In similar work we found it essential to boil with xylene to assist the action.

A. ALBERT: This direct C-alkylation of indole reminds me of some work that Dr G. W. H. Cheeseman did in our department with diazomethane on 7-hydroxypteridine. This reagent actually methylated on the carbon atom in the 6- position. We have given reasons for thinking it may be an addition involving conjugated bonds[2].

C. W. SHOPPEE: Professor Badger compared the behaviour of diazoacetic ester in additions to double-bonds and in what he termed a substitution reaction. Thus

$$N^- = N^+ = CHCO_2Et \quad \leftrightarrow \quad N \equiv N^+ - C^-HCO_2Et \qquad \overset{\cdot\cdot}{C}HCO_2Et$$

$$i \qquad\qquad\qquad\qquad ii \qquad\qquad\qquad\qquad iii$$

Of these two canonical forms of the diazoacetic ester molecule, have you considered that i may be responsible for addition to double-bonds, whereas ii may be responsible for your substitution reaction because by loss of nitrogen it gives iii, which is a di-radical which could perform what is effectively a methylation. If something of that sort is true, your substitution reaction is really a measure of the acidity of the β-hydrogen.

G. M. BADGER: That is an interesting suggestion, because I think the mechanism of the reaction of diazoacetic ester is not known. Some reactions proceed without the elimination of nitrogen, and give pyrazolines. In other cases no pyrazoline can be isolated, and you get only the *cyclo*propane derivative. Two mechanisms may operate: the nitrogen may come off first, or alternatively the heterocyclic compounds may form first and then

lose nitrogen to give *cyclo*propanes. It might be possible for radical *iii* to form a *cyclo*propane derivative directly.

G. SHAW: You get the same sort of thing with enols, except that the more strongly acidic enols tend to give the methyl ether, whereas the more ketonic ones tend to give the ethylene oxide.

W. DAVIES: Do you find that diazoacetic ester, like other reagents for double-bonds, attacks the polycyclic types such as benzanthracene more readily say than naphthalene; that is to say as you increase the size of the aromatic molecule the reaction goes better?

G. M. BADGER: Well, we think that the rate of addition increases with increasing double-bond character of the bond attacked. In the case of diazoacetic ester there are experimental difficulties, because the big molecules are very sparingly soluble. We used diazoacetic ester without solvent as a medium.

K. H. PAUSACKER: Can perbenzoic acid be used as a double-bond reagent with most aromatic substances?

G. M. BADGER: I think Waters has reported on some reactions with perbenzoic acid, and it normally attacks the most reactive position rather than the most reactive bond.

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THE REACTION OF BENZOYL PEROXIDE WITH HETEROCYCLIC COMPOUNDS

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IN RECENT years, HEY et al.[1] have investigated the reactions of aromatic compounds with benzoyl peroxide in order to determine the overall reactivity and thence the relative reactivity at the various positions of substitution. In brief, his technique has consisted of treating an equimolar mixture of two aromatic compounds with a relatively small amount of benzoyl peroxide and isolating the different arylated compounds. In this way the relative reactivities have been determined. The isomer ratio in each of the individual arylations has also been established, thus enabling the relative reactivities at each position of substitution to be assigned.

We have recently attempted to determine all the products of the reaction of benzoyl peroxide with various aromatic compounds[2-4] and have criticized Hey's results for two reasons. Firstly, there are many side reactions and phenylation only appears to account for 33 to 66 per cent of the total reaction. Secondly, benzoyloxylation is a concurrent substitution reaction and its importance increases with increasing reactivity of the aromatic compound.

The reactions of pyridine and quinoline with benzoyl peroxide at 100° C have now been investigated. The technique consisted of heating the reactants together and measuring the amount of carbon

Table 1

	Pyridine	Quinoline
Weight of $(PhCO_2)_2$. (g) .	20	20
Volume of solvent (ml) .	300	300
Carbon dioxide .	0·80	0·47
1st Acid . . .	1·07	0·92
2nd Acid . .	0·14	0·49
Phenylated products . .	0·58	0·36
Phenols . . .	0·04	0·18
High-boiling residue (g) .	1·7	4·25

dioxide evolved. Benzoic acid (termed 1st benzoic acid) was extracted from the reaction mixture and the residue was hydrolysed and separated into phenols, benzoic acid (termed 2nd benzoic acid), phenylpyridines or phenylquinolines, and high-boiling residue. The results (expressed in moles per mole of benzoyl peroxide) are shown in *Table 1*.

It is seen that the ' 1st acid' value is much higher than that noted for non-heterocyclic compounds where, in general, the ' 1st benzoic acid' value is approximately equal to the sum of the phenylated products and phenols. This high value may be ascribed to the fact that the reaction

$$\left.\begin{array}{l}2C_5H_5N \\ 2C_9H_7N\end{array}\right\} + (PhCO_2)_2 \rightarrow \left.\begin{array}{l}(C_5H_4N)_2 \\ (C_9H_6N)_2\end{array}\right\} + 2PhCO_2H$$
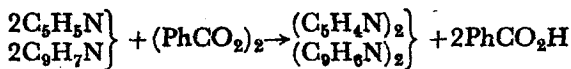
may occur. Although definite compounds have not been isolated, analytical figures indicate that products of this type have been formed. It may be noted that compounds of the type (Ar·Ar) have never been previously isolated[5] from the reaction of benzoyl peroxide with aromatic compounds (ArH). Their formation in these two particular instances may be due to the participation of the following reactions which are similar to those postulated by HORNER and SCHWENK[6] for the reaction of tertiary amines with benzoyl peroxide.

$$C_5H_5N: + (PhCO_2)_2 \rightarrow C_5H_5N\cdot^+ + PhCO_2^- + PhCO_2\cdot$$
$$C_5H_5N\cdot^+ + PhCO_2^- \rightarrow C_5H_4N\cdot + PhCO_2H$$
$$2C_5H_4N\cdot \rightarrow (C_5H_4N)_2$$
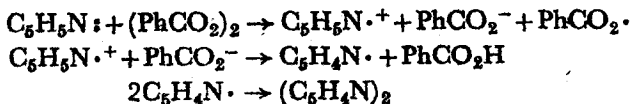
It may also be noted that benzoyloxylation (as determined by phenol formation) is much more important with quinoline than with pyridine. This is in accord with a postulate[4] that the benzoyl-oxylation/phenylation ratio may indicate the relative reactivity of aromatic molecules towards radical attack. However this hypothesis may also be criticized on the grounds that the yields are variable and not very high. In conjunction with Dr R. D. BROWN, we are at present considering the possibility that the carbon dioxide value may allow an estimate of the relative reactivities to be calculated. ROITT and WATERS[7] have previously used carbon dioxide values in determining relative reactivities qualitatively. *Table 2* lists the carbon dioxide values that we have determined for some systems.

The figures indicate that pyridine may be much more reactive than benzene, whereas the reactivity of pyridine is quoted[8] as 1·04 (relative to benzene = 1·00). It is of interest to note that NOZAKI and BARTLETT[9] have found that benzoyl peroxide is 77·3 per cent

decomposed in pyridine whereas it is only 15·5 per cent decomposed in benzene under the same conditions.

Table 2

Aromatic Compound	CO_2 [moles/mole $(PhCO_2)_2$]
Chlorobenzene . . .	1·38
Benzene . . .	1·27
Nitrobenzene . . .	0·99
Diphenyl . . .	0·87
Pyridine . . .	0·80
Naphthalene . . .	0·66
Quinoline . . .	0·47

An attempt is also being made to determine the isomer ratio in the phenylquinoline fraction. It was found that the u.v. absorption spectra of the seven phenylquinolines were almost identical in both ethanol and dilute hydrochloric acid. Separational techniques using absorption chromatography, paper chromatography, and picrate formation have been employed and, up till the present, the following isomer ratio is indicated: 2-Ph, 6 per cent; 3-Ph, 14 per cent; 4-Ph, 20 per cent; 5-Ph, 12 per cent; 6-Ph, 8 per cent; 7-Ph, 8 per cent; 8-Ph, 30 per cent. HEY and WALKER[1b] have previously investigated this mixture by fractionally crystallizing the mixed picrates and have succeeded in isolating 4-Ph (7 per cent) and 5-Ph (trace). On the basis of calculations of localization energies for quinoline[11], the order of substitution would be expected to be $4 > 5 > 8 > 2 > 6 = 7 > 3$.

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DISCUSSION

E. RITCHIE: Is there any evidence for the formation of pyridine or quinoline oxides in this reaction?

K. H. PAUSACKER: None whatsoever, although we have looked very closely.