Reaction 22, which is the important yield reducing reaction in the synthesis of hydrazine, has been postulated to proceed *via* a free radical mechanism,[14] indicating that chloramine is capable of undergoing this type of reaction.

(14) F. N. Collier, Jr., H. H. Sisler, J. G. Calvert, and F. R. Hurley, *J. Amer. Chem. Soc.*, **81**, 6177 (1959).

Registry No.—Chloramine, 55-86-7; 2-methylpropene, 115-11-7; ethylene, 74-85-1; neopentane, 463-82-1; isobutane, 75-28-5.

Acknowledgments.—We gratefully acknowledge the generous support of the research reported in this paper by W. R. Grace and Company through a contract with the University of Florida.

Heterocyclic Synthesis with 2-Benzimidazoleacetic Acid Derivatives

NEVILLE FINCH AND C. W. GEMENDEN

Research Department, CIBA Pharmaceutical Company, Division of CIBA Corporation, Summit, New Jersey 07901

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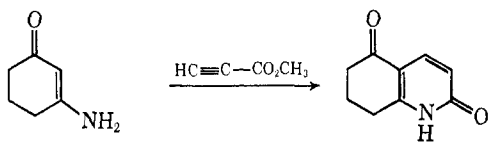
Ethyl 2-benzimidazoleacetic ester (**2**) reacted with diethyl azodicarboxylate and oxidative cyclization of the adduct yielded ethyl 1-hydroxy-*as*-triazino[4,5,*a*]benzimidazole-4-carboxylate (**13**). The chemistry of this new heterocycle and the mechanism of its formation are discussed. Reactions of **2** and 2-benzimidazoleacetonitrile (**1**) with dimethyl acetylenedicarboxylate are described.

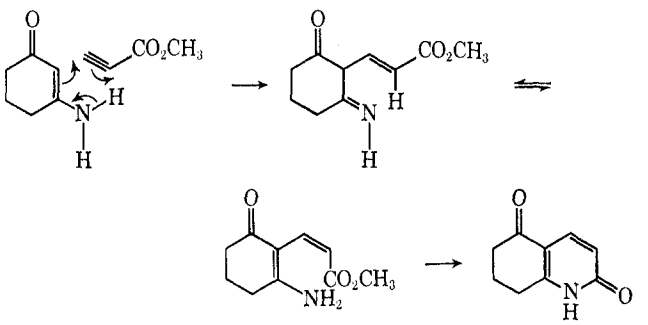
One of the most commonly employed procedures for the construction of new heterocyclic systems is cycloaddition.[1] This process has been well investigated mechanistically, and the factors determining the orientation of addition and the stereochemistry of the product are relatively well understood.

Alternative procedures involving construction of heterocycles by condensation processes have been subject to less mechanistic scrutiny. One such process is the reaction of an electrophilic multiple bond with enamino ketones and esters, where the amine is not fully substituted, followed by acylation of the amine by a substituent on the multiple bond, *e.g.*[2]



Many examples of this type of process are extant and they have usually been described as Michael additions by the nucleophilic carbon atom of the enamino carbonyl compound.[3] There is however a high degree of selectivity in the orientation of the electrophilic multiple bond. While addition by the nitrogen atom is in principle reversible, this requires more vigorous conditions than are normally employed in such processes.[4] This suggests that there is an additional factor operating which favors addition of the olefin to carbon rather than nitrogen. We would like to consider this to be the intramolecular transfer of a proton from nitrogen, *i.e.*, a hetero example of the ene reaction,[5] which may be represented by the sequence shown in Scheme I. The exclusive carbon alkylation of enamines by electrophilic olefins, where this mechanism cannot operate, is due to the more facile reversibility of N-alkylation in such cases.[6]

SCHEME I



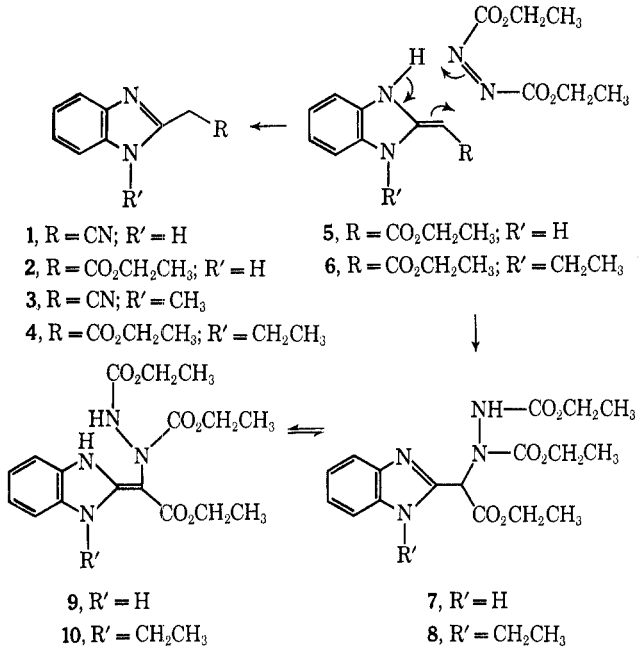
2-Benzimidazoleacetonitrile (**1**) is readily accessible by condensation of *o*-phenylenediamine with cyano acetic ester.[7] Ethyl 2-benzimidazole acetic ester (**2**) is available by ethanolysis of this nitrile (**1**).[7] The chemistry of neither substance has been well investigated but it might be anticipated that they would react with electrophilic multiple bonds to give new heterocycles. In particular with diethyl azodicarboxylate they might react to give an *as*-triazinobenzimidazole system reminiscent of the *as*-triazinoindoles for which good antiviral properties have been claimed.[8]

The reaction may be envisioned as proceeding *via* the tautomers **5** and **6** (Scheme II).

Equimolar mixtures of diethyl azodicarboxylate with **2** and with **4** in refluxing methylene chloride rapidly gave good yields of the adducts **9** and **8**, respectively. The interesting observation that the position of tautomeric equilibrium between **9** and **7**, and between **10** and **8**, was sensitive to substitution on the imidazole nitrogen atom has been commented on previously.[9] There was, however, no evidence to suggest that the cyclized forms were present to any extent. (The three O-ethyl resonances in the nmr spectra were very similar in both compounds.) This was not unexpected; however, it was hoped that oxidation would yield a cyclized product as

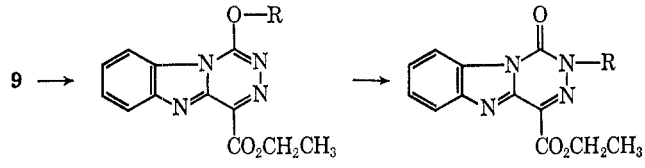
(1) R. Gompper, *Angew. Chem., Int. Ed. Engl.*, **8**, 312 (1969).
(2) M. A. T. Sluyter, U. K. Pandit, W. N. Speckamp, and H. O. Huisman, *Tetrahedron Lett.*, 87 (1966).
(3) L. Paquette "Principles of Modern Heterocyclic Chemistry," W. A. Benjamin, New York, N. Y. 1968, p 354.
(4) Z. Horii, C. Iwata, Y. Tamura, N. A. Nelson, and G. H. Rasmusson, *J. Org. Chem.*, **29**, 2768 (1964).
(5) H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).
(6) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).
(7) R. A. B. Copeland and A. R. Day, *ibid.*, **65**, 1072 (1943).
(8) J. M. Z. Gladyck, J. H. Hunt, D. Jack, R. F. Hagg, J. J. Boyle, R. C. Stewart, and R. J. Ferlanto, *Nature*, **221**, 286 (1969).
(9) In a preliminary report of some of this work: N. Finch and C. W. Gemenden, *Tetrahedron Lett.*, 1203 (1969).

SCHEME II



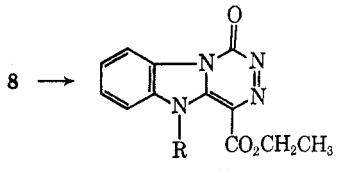
1, R = CN; R′ = H
2, R = $CO_2CH_2CH_3$; R′ = H
3, R = CN; R′ = CH_3
4, R = $CO_2CH_2CH_3$; R′ = CH_2CH_3
5, R = $CO_2CH_2CH_3$; R′ = H
6, R = $CO_2CH_2CH_3$; R′ = CH_2CH_3
9, R′ = H
10, R′ = CH_2CH_3
7, R′ = H
8, R′ = CH_2CH_3

this would now be aromatic. Treatment of **9** in methylene chloride containing 2 molar equiv of the Hünig base (diisopropylethylamine) with 1 molar equiv of bromine in the cold gave in moderate yield (40%) a new compound (**11**). This substance had a simple nmr spectrum, two different types of O-ethyl function and four aromatic protons. Warming **11** in 50% aqueous acetic acid transformed it into **12**. The tautomerism between **12** and **13** has been discussed in our preliminary report[9] and has been observed in related heterocycles.[10]



11, R = CH_2CH_3
13, R = H
14, R = -$COCH_3$
15, R = -$COCH_2Cl$
12, R = H
16, R = CH_2CH_3

Compound **12** could also be obtained directly by oxidizing crude **9** at room temperature. Application of several variations of oxidizing conditions to **8** gave no improvement of the tiny yield obtained by the usual method. Sufficient amounts of the product **17** were, however, available for complete characterization.



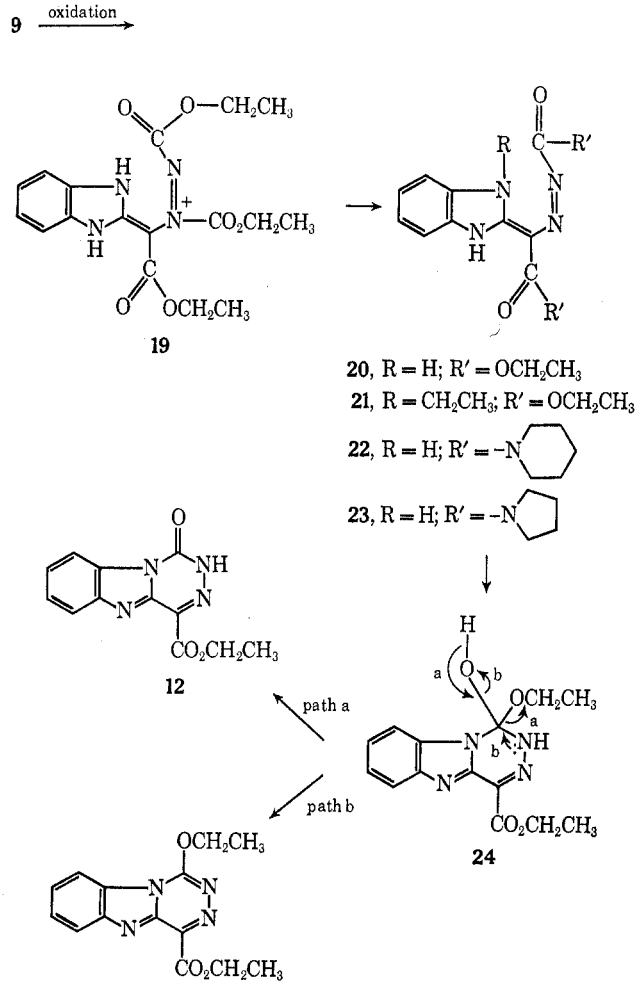
17, R = CH_2CH_3
18, R = H

Assignment of structure **12** rather than the tautomer **18** to our new heterocycle, ethyl 1-hydroxy-*as*-triazino-[4,5,*a*]benzimidazole-4-carboxylate, is based on the spectral similarities between this substance and the N-ethyl derivative obtained by direct ethylation [EtI-DMF-NaH]. This N-ethyl compound is assigned structure **16**, because it is different from the other two ethyl compounds **11** and **17**, whose structures are unambiguous. At the time this work was performed the ring system, such as **12** possesses, was unknown. A publication by Slouka on another derivative of this system prompted our preliminary communication and subsequently a full report of Slouka's work has appeared.[11]

While attempts at O-ethylation of **13** were unsuccessful in regenerating **11** the presence of a readily enolizable amide function was further demonstrated by O-acylation in high yield to give **14** and **15**. The presence of a strong band at 1800 cm^{-1} in the ir spectra was regarded as convincing evidence for O- rather than N-acylation. This propensity for enolization in amides which have a heteroatom bonded to the nitrogen atom[10,12] may be the result of lone pair interaction between the adjacent heteroatoms.

The formation of **11** in the oxidative cyclization of **9** rather than **12**, which would be expected by analogy with related processes, can be discussed on the basis of our proposed mechanism (Scheme III). The expected

SCHEME III



19
20, R = H; R′ = OCH_2CH_3
21, R = CH_2CH_3; R′ = OCH_2CH_3
22, R = H; R′ = -N⟨ ⟩
23, R = H; R′ = -N⟨ ⟩
12
24
11

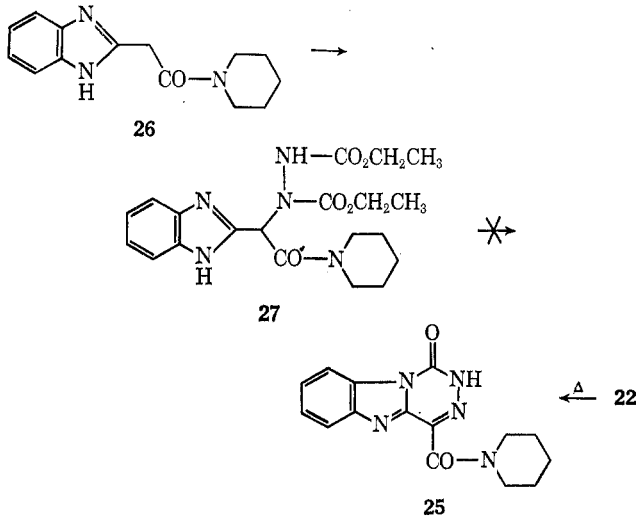
(10) A. A. Gordon, A. R. Katritsky, and F. D. Popp, *Tetrahedron, Suppl.*, **7**, 213 (1966).

(11) J. Slouka, *Tetrahedron Lett.*, 4007 (1968); *Monatsh. Chem.*, **100**, 91 (1969).

(12) A. R. Katritsky and F. W. Maine, *Tetrahedron*, **20**, 315 (1964).

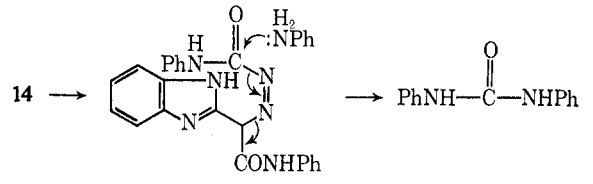
reaction for an intermediate such as compound **24**, or its deprotonated form, would be that in path a to **12**. We suggest that the enhanced electron donation from the neighboring nitrogen atom permits departure of either hydroxy or ethoxy (path b). The choice is then determined by stereo electronic considerations. It is not unreasonable to assume that in **24** the OH group is principally axial, thus giving good overlap of the rupturing C—O bond with the neighboring nitrogen lone pair. This assumption about the configuration of **24** is based on ΔG values derived from cyclohexane cases. In nonpolar solvents, such as methylene chloride, hydroxyl is a small group relative to an ethyl ether.[13] The failure of the N-ethyl compound **8** to undergo the oxidative cyclization in good yield can be attributed to the intermediacy of **21**, where one NH is involved in a strong intramolecular hydrogen bond and the other is alkylated, thus providing an impediment to ring closure and an alternate reaction path (or paths) is followed.

Support for the mechanism outlined above is provided by reaction of the O-acetyl derivative with other nucleophiles. Refluxing in piperidine converted **14** in good yield to a compound which was clearly an analog **22** of the proposed intermediate **20**. The long wavelength absorption in the uv spectrum suggested extended linear conjugation. The nmr spectrum showed essentially an A^2B^2 pattern for the aromatic protons, none of which were at unusually low field. Furthermore two types of NH were seen, one being at lower field and slower to exchange with D_2O than the other. Heating **22** in ethanol during an attempt at recrystallization partially converted it to a new compound **25**; this transformation could be effected quantitatively by melting **22**. Compound **25** is the piperamide of **12**. This was evident by the similarities in the nmr spectra of **25** and **12**, particularly the aromatic protons, one being at low field with both *ortho* and *meta* couplings. This is characteristic of N-acylbenzimidazoles. An attempt was made to confirm this assignment by synthesis, but this was thwarted by the failure of **27** to undergo the oxidative cyclization to give compound **25**.



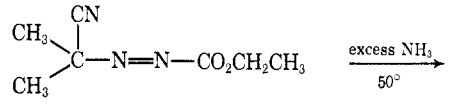
The formation of **25** from **22**, rather than the amidine, which would arise by loss of water from a cyclic intermediate, analogous to **24**, is perhaps attributable to the autocatalytic effect of the piperidine formed. This would assist proton removal in such an intermediate thus favoring path a. The failure of **27** to undergo oxidative cyclization to **25** is less readily explicable, although it may be relevant that, unlike **9**, **27** exists as the benzimidazole tautomer.

The reaction of **14** with other amines was explored. Refluxing in pyrrolidine gave an analogous and somewhat more stable compound **23**. Refluxing in aniline however gave diphenylurea as the only recognizable product. This may be a result of fragmentation of the product **28** at the higher reaction temperature.

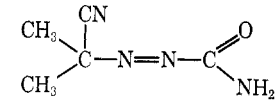


28

The stability of compounds **23** and **22** in the presence of excess amine is perhaps surprising but analogous processes are known, *e.g.*



29

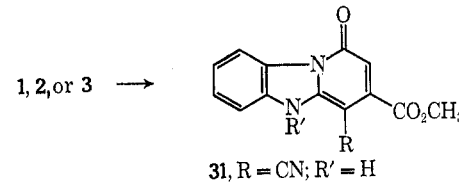


30

and no instability of the product **30** is mentioned (*i.e.*, mp 81° without decomposition).[14]

With stronger bases, *e.g.*, ethoxide, fragmentation of this type of compound is of course observed.[15]

Before concluding our study of 2-benzimidazoleacetic acid derivatives a further heterocycle was constructed. Experience with diethyl azodicarboxylic ester suggested that an adduct which would cyclize directly to a new aromatic system might be preferable. A dimethyl acetylenedicarboxylate adduct meets this requirement. Reaction occurred spontaneously with this ester and **1**, **2**, and **3** in DMF gave directly the tricyclic systems **31**, **32**, and **33** in moderate yield. Compound **33** could



31, R = CN; R′ = H
32, R = $CO_2CH_2CH_3$; R′ = H
33, R = CN; R′ = CH_3
34, R = CN; R′ = $COCH_3$
35, R = $CO_2CH_2CH_3$; R′ = $COCH_3$

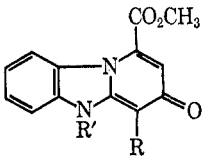
also be obtained by methylation of compound **31**. Acylation also occurred on the imidazole nitrogen atom to give **34** and **35**. There was no evidence of any O-acyla-

(13) E. L. Eliel, N. L. Allinger, S. J. Angyal, and A. G. Morrison, "Conformational Analysis," 1st ed, Interscience, New York, N. Y., 1965, p 437.

(14) E. Müller, French Patent 1,433,719 (1966); *Chem. Abstr.*, **65**, 16879c (1966).

(15) R. W. Hoffmann, *Chem. Ber.*, **97**, 2763 (1964).

tion in this series. The orientation of the addition of the acetylene follows from Scheme I; support for this assignment comes from the nmr spectrum of **31** which shows a low field single-proton multiplet characteristic of one benzimidazole nitrogen being acylated. This speaks against an alternative formulation of **36**.



36

These substances were however of less interest chemically and pharmacologically than the *as*-triazinobenzimidazoles; so their chemistry was not further investigated.

Experimental Section[16]

Formation of 9 from Ethyl 2-Benzimidazoleacetic Ester (2).—Ethyl 2-benzimidazoleacetic ester[7] (2.04 g) was dissolved in methylene chloride (20 ml) and the mixture refluxed with diethyl azodicarboxylate (1.742 g) for 1 hr. The solution was cooled and added directly to a silica gel column (150 g) made up in methylene chloride. The main band (3.60 g) was eluted by 5% methanol in methylene chloride. This was crystallized from ether; three crops were collected (2.62 g, 69%, mp 126–130°). The first crop (1.10 g) was recrystallized (ether) to mp 128–130°, (**9**): uv λ_{max} [MeOH] 254 (7120), 267 (7590), 274 (6840), 282 (6360), 323 mμ (14,450); ir (Nujol) 3240, 1642, 1622 cm^{-1}; nmr [$CDCl_3$] δ 10.6 (s, 2, exchangeable NH), 4.22 [q, 6].

Anal. Calcd for $C_{17}H_{22}N_4O_6$: C, 53.96; H, 5.86; N, 14.81. Found: C, 53.66; H, 5.79; N, 14.87.

Oxidative Cyclization of 9 to 11.—Compound **9** (9.45 g) was dissolved in methylene chloride (150 ml) containing 3.23 g of Hünig base (diisopropylethylamine); bromine (4.0 g) in methylene chloride (20 ml) was added dropwise to the well cooled and stirred solution. The ice bath was removed after the addition and the mixture stirred for 10 min at room temperature (starch, iodide test negative), then washed water, and dried ($MgSO_4$). The methylene chloride was removed and the residue dissolved in ethanol; on cooling and concentrating three crops of crystals were obtained (3.70 g, 50%, mp 136–149°). Recrystallization (ethanol) gave **11**: mp 154–155°; uv λ_{max} [MeOH], 227 (16,210), 250 (30,550), 320 mμ (5920); ir (Nujol), 1735, 1568 cm^{-1}; nmr [$(CD_3)_2SO$] δ 4.72 [q, 2], 4.32 [q, 2].

Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.57; H, 4.67; N, 19.48.

Hydrolysis of 11 to 12 and 13.—Compound **11** (500 mg) was dissolved in glacial acetic acid (2 ml); water (2 ml) was added and the mixture heated on a steam bath for 4 hr. On cooling crystals (**12**) were deposited [293 mg, 65%, mp 240–242°]: uv λ_{max} (MeOH), 218 [23,450], 244 [23,550], 326 mμ [8550]; ir (Nujol), 3180, 1735, 1720; ir (CH_3CN), 1730 cm^{-1}; nmr [$(CD_3)_2SO$], δ 4.44 [q, 2].

Anal. Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.50; H, 3.87; N, 21.94.

Recrystallization from DMF gave material **13**, mp 243–244°, whose ir (Nujol) was different [ν_{max} 3240, 1725 cm^{-1}]. The solution spectra, ir (CH_3CN), nmr [$(CD_3)_2SO$], were identical with those of the material crystallized from protic solvents. Recrystallization of this sample from ethanol gave material with an ir spectrum showing bands at 1735, 1720 cm^{-1}, identical with that of the analytical sample.

Direct Conversion of Ethyl 2-Benzimidazoleacetic Ester to 12.—Ethyl 2-benzimidazoleacetic ester[7] (122 g) was dissolved in methylene chloride (700 ml) and diethyl azodicarboxylate (117 g) added slowly to reflux the reaction gently. After addition was completed the mixture was refluxed for 1 hr more. Hünig base (85 g) was added, and then bromine (32 ml) without cooling but with stirring. After addition was completed the mixture was stirred at room temperature for 15 min, then washed with water and dried ($MgSO_4$). The methylene chloride was removed and the residue dissolved in ethanol. On standing overnight crystals separated (**12**) [50 g, 32% overall, mp 236–240°]. These were recrystallized from ethanol to mp 240–242°. This material was identical [spectra and mixture melting point] with **12** obtained by hydrolysis.

Acetylation of 12 to 14.—Compound **12** [6.45 g] was slurried in methylene chloride [250 ml]. Hünig base [3.57 g] was added and then acetyl chloride [2.20 g] slowly. The solid rapidly dissolved. After stirring for 2 hr at room temperature the reaction was washed with water, dried ($MgSO_4$), and concentrated on a steam bath after addition of ethanol. When the solution became turbid it was set aside. The product (5.67 g, 76%, mp 149–151°) was collected. Recrystallization from DMF–ethanol gave **14**: mp 150–151°; uv λ_{max} (MeOH), 243 (21,630), 324 mμ (8300); ir [Nujol], 1800, 1740 cm^{-1}; nmr [$(CD_3)_2NCDO$], δ 4.16 (q, 2), 2.40 (s, 3).

Anal. Calcd for $C_{14}H_{12}N_4O_4$: C, 56.00; H, 4.03; N, 18.66. Found: C, 55.67; H, 3.89; N, 18.36.

Chloroacetylation of 12 to 15.—In an analogous manner the chloroacetyl derivative **15** was prepared: mp 188–190° [EtOH/DMF]; uv λ_{max} [MeOH], 243 mμ [22,080], 326 mμ [8220]; ir [Nujol], 1800 cm^{-1}, 1730 cm^{-1}; nmr [$(CD_3)_2NCDO$] δ 5.24 [s, 2, $-OC(=O)CH_2Cl$].

Anal. Calcd for $C_{14}H_{11}ClN_4O_4$: C, 50.24; H, 3.31; N, 16.75. Found: C, 50.07; H, 3.33; N, 16.83.

Ethylation of 12 to 16.—Compound **12** (1.29 g) was dissolved in DMF (25 ml) and NaH (240 mg, 50% in mineral oil) added. The mixture was warmed on a steam bath for 15 min. Ethyl iodide (excess, approximately 2 molar equiv) was added in DMF. The reaction was heated 18 hr on the steam bath; dilution with water gave a solid, mp 159–160°. This was recrystallized from ethanol to give **16** (943 mg, 66%, mp 161–162°): uv λ_{max} [MeOH], 247 [24,300], 332 mμ [9220]; ir [Nujol], 1734, 1710; ir [CH_3CN], 1734 ,1712 cm^{-1}; nmr [$(CD_3)_2SO$], δ 4.32 [q, 2], 4.10 [q, 2].

Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.60; H, 4.84; N, 19.54.

N-Ethyl-2-benzimidazoleacetonitrile.—2-Benzimidazoleacetonitrile[7] (15.7 g) was slurried in 0.33 *N* NaOH (300 ml). Some insoluble material was removed by filtration. To the orange filtrate was added dropwise ethyl sulfate (19.56 g). This was stirred at room temperature. After a short time a heavy oily precipitate separated. After stirring for 8 hr this had solidified and the pH fell to 7. The solid (12.185 g, 66%, mp 135–145°) was collected, and recrystallized from aqueous ethanol to mp 156–157°: uv λ_{max} [MeOH], 253 [6480], 267 [4700], 274 [5690], 282 mμ [5900]; ir [$CHCl_3$], 2260 cm^{-1}; nmr [$CDCl_3$], δ 4.03 [s, 2, $-CH_2CN$].

Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.31; H, 5.95; N, 22.49.

Ethanolysis of N-Ethyl-2-benzimidazoleacetonitrile to 4.—N-Ethyl-2-benzimidazoleacetonitrile [8.77 g] was refluxed in ethanolic HCl [100 ml] for 2 hr. The solvent was removed, the residue dissolved in water, made basic with aqueous 10% K_2CO_3, and extracted with methylene chloride. The extract was dried ($MgSO_4$) concentrated and the residue distilled. The center cut, **4** [6.03 g, 55%, bp 151–153° (0.4 mm)], had uv λ_{max} [MeOH], 253 [7180], 267 [5390], 275 [6620], 282 mμ [7080]; ir [film], 1735, 1620 cm^{-1}; nmr [$CDCl_3$], δ 3.96 [s, 2, $-CH_2CO_2Et$].

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94. Found: C, 67.21; H, 6.94.

The known 1-methyl-2-cyanomethylbenzimidazole reacted in an analogous manner to give ethyl 1-methyl-2-benzimidazoleacetic ester: mp 63–64°; uv λ_{max} (MeOH), 253 [7250], 267 [5430], 275 [6790], 282 mμ [7250]: ir [Nujol], 1732 cm^{-1}; nmr [$CDCl_3$], δ 3.92 [s, 2 $-CH_2CO_2Et$), 3.58 [s, 3, $N-CH_3$].

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.35; H, 6.54; N, 13.03.

Formation of 8 from N-Ethyl-2-benzimidazoleacetic Ester (4).—Compound **4** [19.42 g] was dissolved in methylene chloride [200 ml] and diethyl azodicarboxylate [16.0 g] added. The mixture was refluxed overnight. The solvent was removed. The residue crystallized and was recrystallized from ether–petroleum ether [27.7 g, 81%, mp 78–81°]. A further recrystallization gave the analytical sample (**8**): mp 82–83°, uv λ_{max} (MeOH),

(16) Melting points were obtained in a Thomas–Hoover melting point apparatus and are uncorrected. Nmr spectra were obtained on a Varian A-60 instrument.

258 [7700], 270 [7010], 277 [8040], 285 mμ [6980]; ir (Nujol), 1735, 1705 cm^{-1}; nmr ($CDCl_3$), 6.36 δ (s, 1 ⩾—|—CO_2Et.)

Anal. Calcd for $C_{19}H_{26}N_4O_6$: C, 56.14; H, 6.45; N, 13.79. Found: C, 55.95; H, 6.48; N, 13.76.

Ethyl 1-methyl-2-benzimidazoleacetic ester reacted in an analogous manner to give the triester: mp 84–85°; uv λ_{max} (MeOH), 257 mμ [7670], 270 [6860], 277 [7900], 285 mμ [6970]; ir [Nujol], 1750, 1735, 1708 cm^{-1}; nmr [$CDCl_3$], 6.40 δ [s, 1 ⩾—|—CO_2Et], 3.85 δ [s, 3, N-CH_3].

Anal. Calcd for $C_{18}H_{24}N_4O_6$: C, 55.09; H, 6.17; N, 14.28. Found: C, 54.88; H, 6.14; N, 13.91.

Oxidative Cyclization of 8 to 17.—Compound **8** (4.06 g) was dissolved in methylene chloride (60 ml). Hünig base (1.42 g) was added. Bromine (0.54 ml) in methylene chloride (5 ml) was then poured into the well stirred solution at room temperature. After 15 min the solution was well washed with water, dried ($MgSO_4$), and concentrated. The residue (4.0 g) was dissolved in ethanol; on standing, some crystalline material (100 mg) separated, mp 214–218°. This was recrystallized from DMSO–ethanol (**17**): mp 224–225°; uv λ_{max} [MeOH], 245 [17,550], 265 [18,310], 359 mμ [11,750]; ir (Nujol), 1700, 1676 cm^{-1}; nmr [$(CD_3)_2SO$], δ 4.43 (q, 2), 4.16 (q, 2).

Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.75; H, 4.91; N, 19.60.

Reaction of 14 with Piperidine to 22 and 25.—Compound **14** (500 mg) was refluxed in piperidine overnight. The piperidine was removed and the residue dissolved in ether and allowed to stand. Crystals [357 mg, 56%, mp 194–198°] were deposited. Attempts to recrystallize from ethanol caused partial transformation to a faster moving material (tlc, silica gel–ethyl acetate). Purification was effected by preparative tlc (silica gel GF–ethyl acetate). The major slower moving spot eluted by ethyl acetate (290 mg), recrystallized from ether (100 mg) of **22**: mp 200–202°; uv λ_{max} (MeOH), 270 (10,610), 327 (25,050), 342 mμ (21,210); ir (Nujol), 1660 cm^{-1}; nmr [$(CD_3)_2SO$], δ 14.3 (s, 1, exchangeable sharp NH), 12.8 (s, 1, exchangeable broad NH), 7.58 (4, A_2B_2, approx), 3.62 (s, 8), 1.66 (s, 12); ms [70 eV] *m/e* 382 (1), 298 (1), 159 (100).

Anal. Calcd for $C_{20}H_{26}N_6O_2$: C, 62.80; H, 6.85. Found: C, 62.81; H, 7.27.

The faster moving material (52 mg) was crystallized from ethanol to give crystals, mp 266–268°.

Quantitative conversion of the slower moving isomer to the faster could be effected by heating at the melting point (200°) for 10 min under N_2. The residue was recrystallized from ethanol to mp 266–268°, identical by melting point, mixture melting point, tlc, and spectra with the minor product of the reaction (**25**): uv λ_{max} (MeOH), 230 (20,600), 246 (16,500), 320 mμ (11,100); ir (Nujol), 1735 ,1635 cm^{-1}; nmr [$(CD_3)_2SO$], δ 13.8 (s, 1, exchangeable), 8.5–7.2 (m, 4), 3.64 (s, 4), 1.66 (s, 6); ms (70 eV) M^+ 297.123 ($C_{15}H_{15}N_5O_2$ requires 297.31).

Anal. Calcd for $C_{15}H_{15}N_5O_2$: C, 60.77; H, 5.42. Found: C, 60.59; H, 5.09.

Reaction of 14 with Pyrrolidine to 23.—**14** (6 g) was refluxed in pyrrolidine (20 ml) overnight; excess amine was removed. The residue was crystallized and recrystallized from ethanol (**23**) (3.5 g, 50%, mp 226–228°): uv λ_{max} (MeOH), 266 (11,400), 328 (24,060), 342 mμ (21,140); ir (Nujol), 1667, 1636, 1615 cm^{-1}; nmr [$(CD_3)_2SO$], 13.8 δ (s, 1, exchangeable NH), 12.1(s, 1, broad exchangeable NH), 7.50 (4, A_2B_2, approx), 3.58 (m, 8, $-CH_2-N$), 1.92 (m, 8).

Anal. Calcd for $C_{18}H_{22}N_6O_2$: C, 61.00; H, 6.26; N, 23.72. Found: C, 60.77; H, 6.51; N, 23.40.

Reaction of 14 and Aniline.—Compound **14** (500 mg) was refluxed in aniline for 1 hr. The aniline was removed, the oil triturated with ethanol, and the resultant solid recrystallized from ethanol to give crystals (183 mg, 53%, mp 240–241°) identified by melting point, mixture melting point, and ir spectra as diphenylurea. No other crystalline material could be isolated from the mother liquors.

2-Benzimidazoleacetic Piperamide.—Ethyl 2-benzimidazole acetic ester (17 g) was refluxed in piperidine (50 ml) for 1 hr. The mixture was poured into water and the solid (12.04 g, 60% mp 161–165°) collected. Recrystallization from water gave **26**: mp 162–163°; uv λ_{max} (MeOH), 243 (6740), 274 (7980), 281 mμ (8930); ir (Nujol), 3200, 1634, 1620 cm^{-1}; nmr ($CDCl_3$), δ 7.70, 7.00 (m, 4), 4.1 (s, 2), 3.56 (m, 4), 1.54 (s, 6).

Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.40; H, 6.77; N, 17.61.

Formation of 27 from 26.—To a solution of **26**, (2.433 g) in methylene chloride (40 ml) was added diethyl azodicarboxylate (1.916 g). The mixture was refluxed for 1 hr. Progress of the reaction could be followed by tlc (silica gel–ethyl acetate). The reaction mixture was poured onto a silica gel column made up in methylene chloride. Elution by methylene chloride gave a gum (0.5 g). The main band was eluted by 40–80% ethyl acetate in methylene chloride. This material crystallized (2.76 g, 66%). Recrystallization from ether–petroleum ether gave an analytical sample (**27**): mp 88°; uv λ_{max} [MeOH], 247 [6500], 269 [3690], 274 [8420], 283 mμ [8280].

Anal. Calcd for $C_{20}H_{27}N_5O_5$: C, 57.54; H, 6.52. Found: C, 57.49; H, 6.41.

Attempted Oxidative Cyclization of 27.—Bromine (933 mg) was added in one portion to a well stirred solution of **27** (2.116 g) in methylene chloride (50 ml) containing Hünig base ([1.658 g). The mixture was stirred at room temperature for 15 min [*i.e.*, until a negative starch–iodide test], washed with water, dried, and concentrated. The resultant brown foam was chromatographed (silica gel–methylene chloride–ethyl acetate) but no crystalline material could be isolated.

Formation of 31 from 2-Benzimidazoleacetonitrile (1).—2-Benzimidazoleacetonitrile[7] (1.57 g) was dissolved in DMF (3 ml). Dimethyl acetylenedicarboxylic ester (1.6 g) was added; an exothermic reaction ensued. The mixture was heated on a steam bath for 30 min. On cooling a solid separated which was collected and washed with methanol (870 mg, 32%, mp 284–288°). Recrystallization from DMF gave **31**: mp 290–292°; uv λ_{max} [MeOH], 228 [19,160], 255 [23,380], 284 [21,570], 387 mμ [10,100]; ir (Nujol), 2214, 1724, 1660 cm^{-1}; nmr [$(CD_3)_2SO$], 8.5 δ [d, 1, J = 7 Hz], 6.40 [s, 1], 3.90 [s, 3].

Anal. Calcd for $C_{14}H_9N_3O_3$: C, 62.92; H, 3.39; N, 15.73. Found: C, 62.80; H, 3.52; N, 15.71.

Formation of 32 from Ethyl 2-Benzimidazoleacetic Ester (2).—Ethyl 2-benzimidazoleacetic ester (2.04 g) was dissolved in DMF (5 ml). Dimethyl acetylenedicarboxylic ester (1.56 g) was added. The exothermic reaction was heated for an hour on a steam bath, then stood in the ice box overnight. The crystals (505 mg, 16%, mp 221–223°] were crystallized from DMF to give **32**: mp 223–224°; uv λ_{max} (MeOH), 228 (18,000), 241 (19,980), 273 (9910), 298 [28,430], 357 mμ [16,100]; ir (Nujol), 3300, 1744, 1732, 1696, 1652 cm^{-1}.

Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.32; H, 4.40; N, 9.13.

Acetylation of 31 to 34.—Compound **31** (1.331 g) was slurried in methylene chloride (10 ml); Hünig base (714 mg) and acetyl chloride (440 mg) were added with stirring until dissolved. After 1 hr the methylene chloride was washed with water, dried ($MgSO_4$), and removed. The crystalline residue was recrystallized from methylene chloride/ethanol to give crystals (**34**): 1.13 g, 73%; mp 296–298°; uv λ_{max} (MeOH), 223 (19,140), 247 (17,500), 264 (17,890), 377 mμ (10,630); ir (Nujol), 2224, 1730, 1678 cm^{-1}.

Anal. Calcd for $C_{16}H_{11}N_3O_4$: C, 62.13; H, 3.59; N, 13.59. Found: C, 62.20; H, 3.41; N, 13.33.

Acetylation of 32 to 35.—Compound **32** (6.28 g) was acetylated by the above procedure to give a crude crystalline product (6.50 g), which was recrystallized from ethanol to give **35** (4.239 g, 60%, mp 144–146°): uv λ_{max} (MeOH), 236 (20,360), 299 (15,720), 359 mμ (15,200); ir (Nujol), 1746, 1725, 1692, 1662 cm^{-1}; nmr ($(CD_3)_2SO$), 6.37 δ (s, 1), 4.22 (q, 2), 3.86 (s, 3), 2.56 (s, 3).

Anal. Calcd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.74; H, 4.61; N, 8.01.

Formation of 33 from 1-Methyl-2-benzimidazoleacetonitrile (3).—1-Methyl-2-benzimidazoleacetonitrile (**3**) (2.18 g) was dissolved in DMF (10 ml). Dimethyl acetylenedicarboxylic ester (1.42 g) was added and heated on a steam bath for 1 hr. On cooling crystals (0.86 g, 30%, mp 235–237°) were deposited. They were collected and recrystallized from DMF to **33**: mp 239°; uv λ_{max} (MeOH), 229 (22,340), 253 (24,910), 295 (21,450), 385 mμ (10,960); ir (Nujol), 2220, 1734, 1668 cm^{-1}.

Anal. Calcd for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 63.96; H, 3.92; N, 14.76.

Methylation of 31 to 33.—Compound **31** (665 mg) was dissolved in DMF (25 ml) at 100°, NaH 50% in mineral oil (125 mg) added. The sodio derivative precipitated. Methyl iodide (0.6 ml) was added. A clear solution developed within a few minutes.

Heating was continued for 90 min. On cooling a solid separated 33 [402 mg, 56%, mp 236–238°]. The melting point of this material was not depressed on admixture with a sample of material from the above experiment. The uv and ir spectra were identical.

Registry No.—1, 4414-88-4; 2, 14741-71-0; 4, 22712-49-8; 8, 22712-50-1; 9, 22712-43-2; 11, 22712-44-3; 12, 22712-45-4; 14, 22712-47-6; 15, 25183-97-5; 16, 22712-48-7; 17, 22776-80-3; 22, 25184-00-3; 23, 25184-01-4; 25, 25184-02-5; 26, 25184-03-6; 27, 25184-04-7; 31, 25184-05-8; 32, 25184-06-9; 33, 25184-07-0; 34, 25184-08-1; 35, 25150-05-4; N-ethyl-2-benzimidozoleacetonitrile, 25184-09-2; ethyl- 1-methyl-2-benzimidozoleacetic ester, 2735-61-7.

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Dihydro-Reissert Compounds

MAURICE SHAMMA AND C. D. JONES

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

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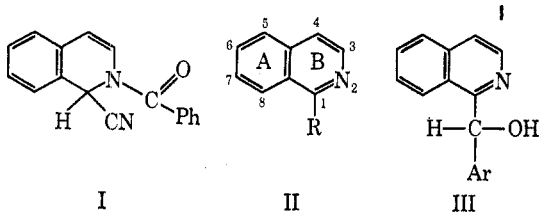
The dihydro-Reissert compound IV has been alkylated at C-1 to give VIIa, b, or c. Acid hydrolysis of VIIc afforded the acid amide VIII, from which the corresponding methyl ester amide IX could be derived. Hydrolysis of either VIIc or VIII in phosphoric acid furnished the amino acid X. Esterification to XII followed by N-benzoylation resulted in regeneration of the methyl ester amide IX. N-Methylation of the methyl ester XII could be achieved through reductive alkylation. But attempts at internal Friedel–Crafts acylation to obtain an ochotensimine analog did not yield any of the desired tetracyclic product.

Three practical procedures are presently available for the preparation of Reissert compounds,[1-3] and these methods allow for the synthesis of a wide variety of compounds related to structure I.

Two reactions of Reissert compounds have proven particularly useful in the synthesis of benzylisoquinolines. These are alkylation by alkyl halides followed by hydrolysis to yield C-1 alkylated isoquinolines (II),[4] and base-catalyzed condensation with aromatic aldehydes succeeded by hydrolysis to afford isoquinolines of type III.[5,6]



I II III

The literature is virtually devoid, however, of attempts aimed at expanding the Reissert approach to the direct synthesis of 1,2,3,4-tetrahydroisoquinolines. In fact, in only two cases have Reissert compounds lacking the C(3)–C(4) double bond been reported. These two cases are the preparation[6] of a compound tentatively identified as IV, a structure which we confirm in this report, and the synthesis of the amino alcohols V.[7] In neither instance were further reactions attempted on these species for which we now suggest the name "dihydro-Reissert compounds."

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Our interest in dihydro-Reissert compounds arose from efforts to synthesize the spirobenzylisoquinoline alkaloid ochotensimine (VI) which incorporates a 1,1-disubstituted 1,2,3,4-tetrahydroisoquinoline skeleton. In the preparation of isoquinolines II and III, the elimination of cyanide ion under hydrolytic conditions is greatly facilitated by the concurrent aromatization of ring B. In dihydro-Reissert compounds, however, such complete aromatization is impossible, and it was surmised that hydrolysis of the cyano group and the amide could proceed without elimination.

As described in the literature,[3,6] it was found that 3,4-dihydro-6,7-dimethoxyisoquinoline, prepared from N-formylhomoveratrylamine by the Bischler–Napieralski cyclization, could be condensed in the presence of potassium cyanide and benzoyl chloride to afford IV. Treatment of IV with 1 equiv of sodium hydride in dimethylformamide, followed by addition of deuterium oxide, gave starting material in which the hydrogen at C-1 had been completely exchanged for deuterium. It was then found that the anion of IV when treated with benzyl chloride gave a high yield of the tricyclic cyanoamide VIIa. This product was fully characterized spectroscopically. Its formation serves to demonstrate that alkylation of a dihydro-Reissert species proceeds for all practical purposes as readily as that of a Reissert compound.

Similarly prepared were the tricyclic cyanoamides VIIb and VIIc. The oxygenation pattern in the latter product is closely related to that for ochotensimine (VI), so that solely this material was employed in the subsequent investigations.

It was found possible to convert the nitrile function in VIIc to a carbonyl group by first complexing VIIc with zinc chloride in ether, and then hydrolyzing the complex in water. The resulting crystalline acid amide VIII (92% yield) was then esterified.

It will be recalled that loss of cyanide ion occurs readily upon hydrolysis of an alkylated Reissert compound to generate a C-1 substituted isoquinoline sys-