Syntheses of the Isomeric Benzoquinazolines: A Review

*William D. Munslow and Thomas J. Delia**

Malcolm H. Filson Laboratories, Department of Chemistry,
Central Michigan University, Mt. Pleasant, MI 48859

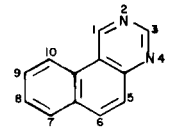
Received April 1, 1976

The synthesis of derivatives of benzo[*f*]quinazoline, benzo[*g*]quinazoline and benzo[*h*]quinazoline is reviewed. Each class of compound is treated separately. The review covers ring formations as well as group modifications.

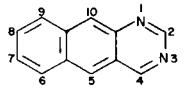
J. Heterocyclic Chem., 13, 675 (1976).

Introduction.

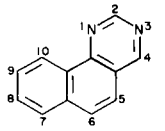
The benzoquinazolines are a group of compounds that formally result from the fusion of a benzene ring to the heterocyclic quinazoline ring system. Three isomeric ring systems result, depending upon the position of fusion. Hence:



benzo[*f*]quinazoline or 5,6-benzoquinaxoline



benzo[*g*]quinazoline or 6,7-benzoquinazoline



benzo[*h*]quinazoline or 7,8-benzoquinazoline

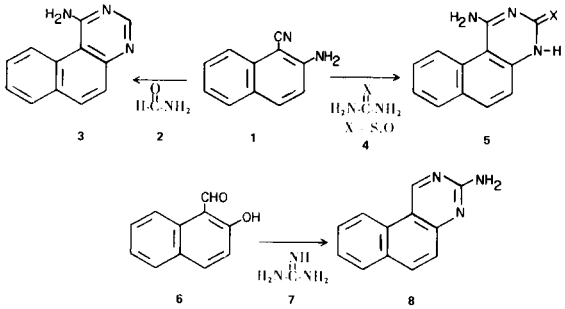
In this paper, the literature has been reviewed with respect to the synthesis and physical properties of these ring systems. Although many of these compounds have been prepared for potential physiological activity, very little screening data is available and hence will be omitted. Other commercial uses ascribed to these compounds are in photographic fog inhibition and emulsion stabilization. These applications are described in the patent literature and are likewise not included in this paper.

Since the literature on these ring systems is extensive, omissions are inevitable, though for the most part unintentional; apologies to those authors.

The Benzo[*f*]quinazolines.

Benzo[*f*]quinazolines have been most frequently prepared by the condensation of an appropriately substituted naphthyl derivative and some small nitrogen containing substrate. For example, Rosowski and Modest (1) were able to prepare a series of 1-substituted, 3-substituted, and 1,3-disubstituted benzo[*f*]quinazolines according to the following equations:

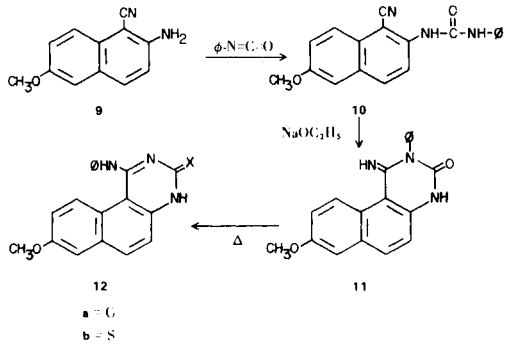
Scheme I



The amino group compounds **3** and **8** have been observed to undergo transformation of a hydroxy function by treatment with hydrochloric acid and subsequent reaction with phosphorus pentasulfide to yield the corresponding thio derivative (1). Dethiation then with nickel yielded the unsubstituted parent member of the series (1).

Isocyanates have been condensed with naphthylaminonitriles (2,3,4). For example (4) treatment of **9** with phenylisocyanate in boiling xylene yielded the 1-phenyl-3-(6-methoxy-1-cyano-2-naphthyl)urea (**10**) which was cyclized with sodium ethoxide in ethanol to 2-phenyl-1-imino-1,2-dihydro-8-methoxybenzo[*f*]quinazoline (**11**). Rearrangement of **11** to the isomeric 1-anilino derivative **12a** was accomplished by heating in nitrobenzene solution

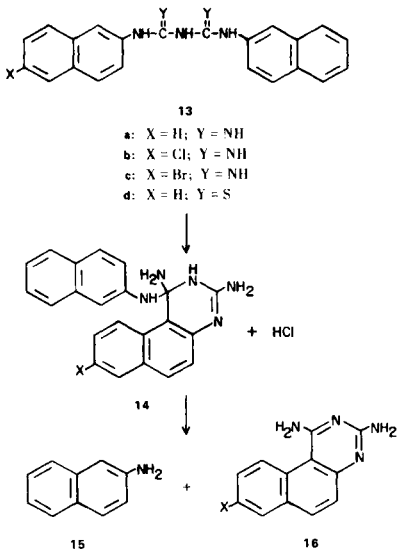
Scheme 2



Interestingly, when **9** was allowed to react with phenylisothiocyanate at 200° the reaction proceeded through the intermediate stages of the disubstituted thiourea and the first intramolecular cyclization product to give 1-anilino-8-methoxybenzo[*f*]quinazoline-3(4*H*)thione (**12b**) directly (4).

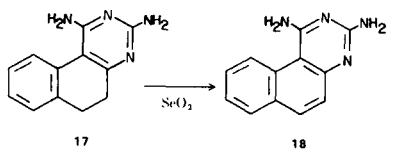
Other routes to benzo[*f*]quinazolines have been investigated. In 1966, Rosowski and Modest (5) reported the novel thermal cyclization of bis(2-naphthyl)biguanide hydrochlorides (**13**).

Scheme 3



In later work Rosowsky and co-workers (6) prepared a series of twenty-one 1,3-diaminobenzo[*f*]quinazolines by four synthetic methods. Approaches involving the condensation of *o*-aminonitriles with cyanamide, reaction of 2-naphthylamine hydrochlorides with excess sodium dicyanamide in boiling octanol, cyclization of N^1,N^5-bis(2-naphthyl)biguanide hydrochlorides (described above) and an interesting oxidation of 5,6-dihydrobenzo[*f*]quinazolines (**17**) were compared Extensive physical data for

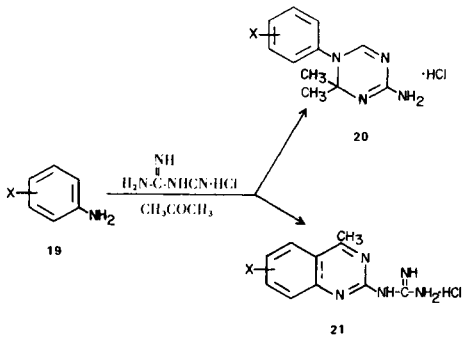
Scheme 4



these twenty-one compounds is also to be found in this work.

In the course of studying a three component synthesis of dihydrotriazines (**20**) it was found that the formation of a guanidinoquinazoline (**21**) formed as a by-product (7). Further investigation (8,9) of the sequence outlined below led to procedures whereby either product, *i.e.*, **20** or **21**, could be made to predominate.

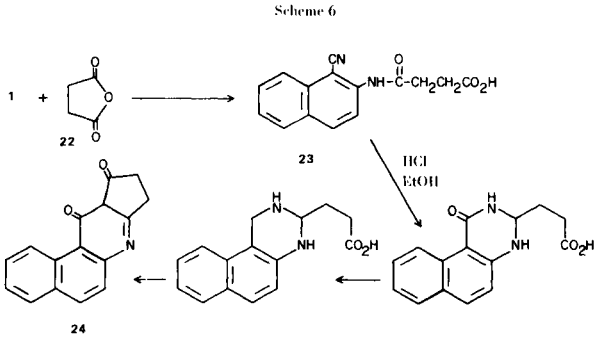
Scheme 5



It was also found (9) during these studies that 2-naphthylamines particularly favored the pathway yielding the guanidinoquinazolines hence providing another route to the benzo[*f*]quinazoline ring system.

The benzo[*f*]quinazoline has also been incorporated into a steroidal structure (10) as outlined below: reaction of the amino nitrile **1** with succinic anhydride afforded the *n*-acyl product **23** which upon two subsequent cyclizations yielded the diazasteroidal system **24**.

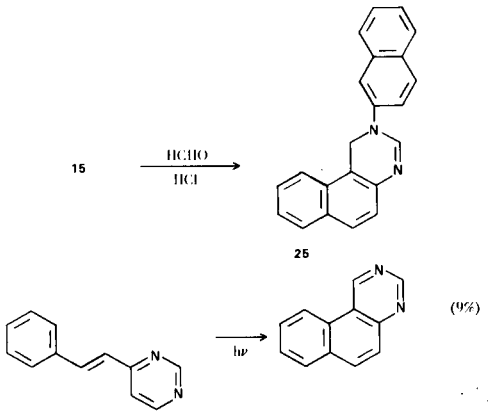
Scheme 6



Also investigated in this study was the reactivity of the activated C-17 methylene (steroid numbering) of compound **24**.

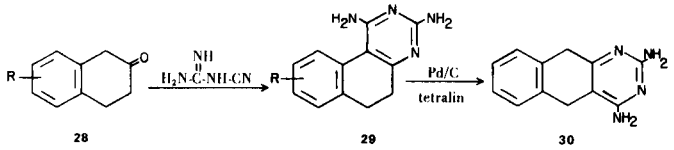
Other isolated examples for the preparation of the benzo[*f*]quinazoline ring system have been reported. For example, the reaction of *N*-(2-naphthyl)benzamide chloride with benzonitrile and aluminum chloride to yield 1,3-diphenyl-5,6-dihydrobenzo[*f*]quinazoline is described (11). Also of interest is the reaction of β-naphthylamine (**15**) with formaldehyde and hydrochloric acid (12) as well as the photochemical transformation (13) described below:

Scheme 7



In addition to the completely aromatic benzo[*f*]quinazoline derivatives, many 5,6-dihydro compounds are known (14,15,16) and have been prepared as analogs of primethamine (15), a dihydrofolate reductase inhibitor. The synthesis of these compounds usually relies on the condensation of an appropriate 2-tetralone (**28**) with cyanoguanidine under fusion conditions, thus,

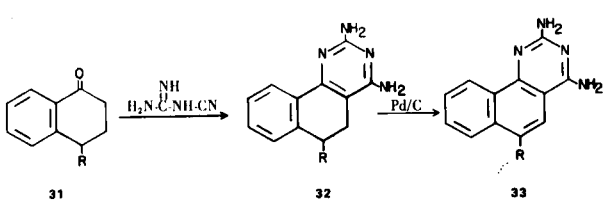
Scheme 8



When **29** (R = H) was allowed to disproportionate in the presence of tetralin and 10% palladium-charcoal catalyst an interesting rearrangement was found to occur, resulting in 2,4-diaminobenzo[*g*]quinazoline (**30**) (16).

In the course of further investigation of this rearrangement a series of benzo[*h*]quinazolines were prepared by the reaction of an α-tetralone (**31**) with cyanoguanidine (16), hence,

Scheme 9

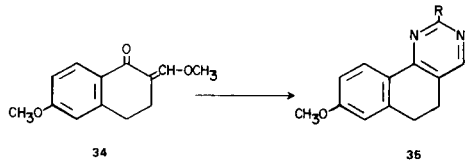


Upon disproportionation, however, the completely aromatic system **33** resulted.

The Benzo[*h*]quinazolines.

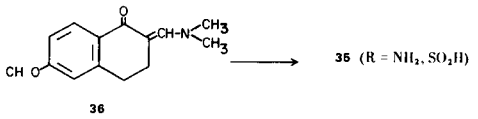
The condensation of an α-tetralone with certain nitrogen containing compounds has been a major source of 5,6-dihydrobenzo[*h*]quinazolines (16,17,18,19,20). For example, Taylor and co-workers (18) have accomplished the condensation of compound **34** with benzamidine,

Scheme 10



acetamide and formamide to form the 2-substituted benzo-[*h*]quinazoline where R = φ, CH_3, and H, respectively. These workers were also able to react the enamine **36** with guanidine and thiourea to produce other derivatives of this series (18).

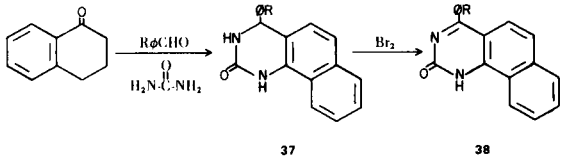
Scheme 11



Interestingly, when urea was allowed to react with compound **36** a complex reaction mixture resulted which these workers were not able to characterize.

α-Tetralones have also been used in a three component synthesis of the benzo[*h*]quinazoline ring system (19,20). Mamaev and Sedova (19) condensed a series of aromatic aldehydes with α-tetralone and urea according to the equation below:

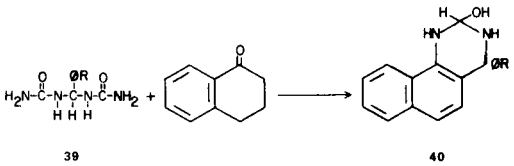
Scheme 12



During the course of these studies the dehydrogenation of **37** with bromine in carbon tetrachloride was observed; investigation of other dehydrogenating agents, including chloranil, *N*-bromosuccinimide and palladium/carbon soon followed (22).

Sedova and co-workers (20) also prepared a series of tetrahydro benzo[*f*]quinazolines by reacting various aryl-idenebisureas (**39**) with α-tetralone. In addition to α-tetralones, 1 formyl-2-chloro 3,4-dihydronaphthalenes have

Scheme 13

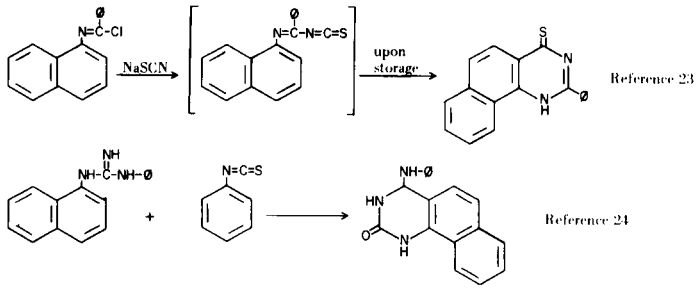


39 40

been used to prepare benzo[*h*]quinazolines (22) by reaction with excess formamide.

Naphthyl derivatives have been allowed to react with isothiocyanates to produce the benzo[*h*]quinazoline ring system (23,24), as seen below:

Scheme 14



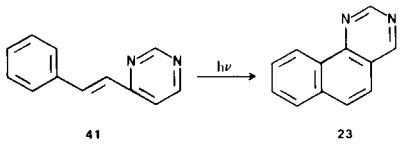
Reference 23

Reference 24

Also of interest, Baltazzi (25) reports that 2-aminomethylnaphthalene after acetylation, nitration, and reduction cyclizes to 2-methyl-3,4-dihydrobenzo[*h*]quinazoline.

Other miscellaneous studies on this group of compounds include photochemical studies (26) of styryl diazines (**41**) wherein, the yields of diazaphenanthrenes (**42**) are correlated to the sum of the first single state free valences of the reacting centers. Also, the acetylation of several benzo[*h*]quinazolines has been studied (27) and found to be dependent upon the degree of hydrogenation and the disposition of each particular compound towards tautomerization.

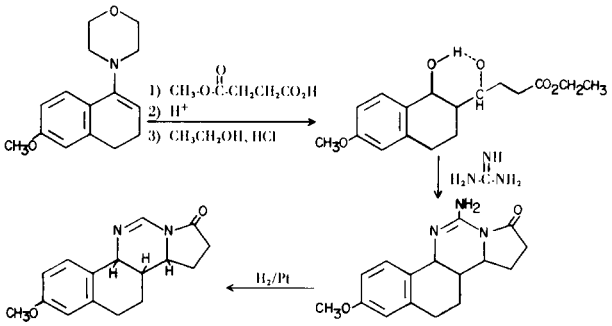
Scheme 15



41 23

The benzo[*h*]quinazoline ring system has also been incorporated into the steroidal skeleton (28), by the following transformations:

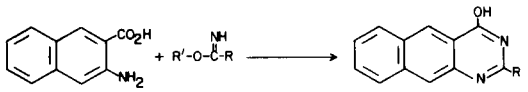
Scheme 16



The Benzo[*g*]quinazolines.

The benzo[*g*]quinazoline ring system has been most frequently prepared by the condensation of a 3-substituted 2-naphthoic acid with some nitrogen containing substrate. Hence, 3-amino-2-naphthoic acid has been allowed to react with formamide (29,30) and urea (31) to yield 4-hydroxy- and 2,4-dihydroxybenzo[*g*]quinazoline, respectively. This condensation can be considered an extension of the Nimentowski quinazoline cyclization and has been investigated under varying experimental conditions (32) with various acid amides yielding a series of 2-substituted 4-oxobenzo[*g*]quinazolines. Free imido esters (**43**) have also been condensed with 3-amino-2-naphthoic acid to yield the corresponding 2-substituted-4-hydroxybenzo[*g*]quinazoline (**44**) (33).

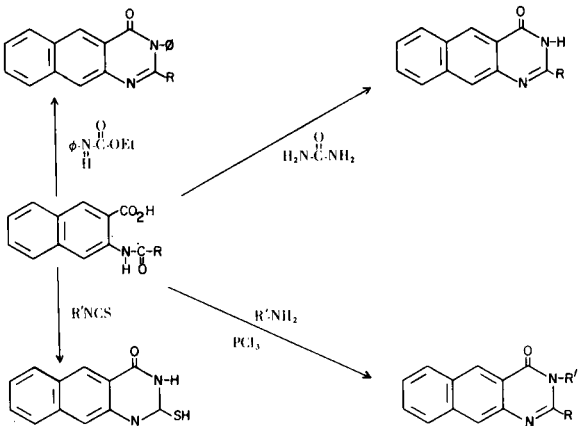
Scheme 17



43 44

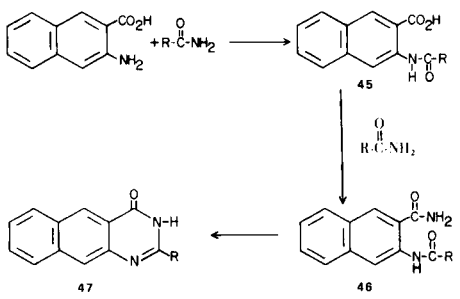
Variations of the Nimentowski reaction have been investigated in which *N*-acylanthranilic acids have been allowed to react with *N*-phenylurethane (34), urea (34), amines (35,36), and thioisocyanates (36) according to the equations below:

Scheme 18



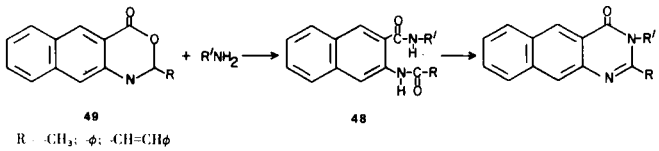
The mechanism of these condensation reactions has been investigated (34) and these studies indicate that the reaction of 3-amino-2-naphthoic acid with an amide proceeds first with the formation of an *N*-acylanthranilic acid (**45**) which is then transformed into an *N*-acylanthranil amide (**46**). This amide then cyclodehydrates to the 4-oxobenzo[*g*]quinazoline system (**47**).

Scheme 19



Supportive of this scheme is the independent synthesis (37,38) of several benzo[*g*]quinazolines by the cyclization of various 3-acetamido-2-naphthamides (**48**) which in turn were prepared from the reaction of a benzo[*g*]-3,1,4-

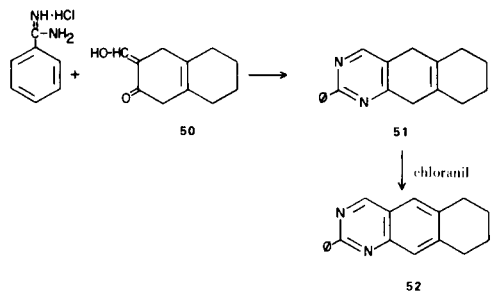
Scheme 20



benzoazone (**49**) and an amine.

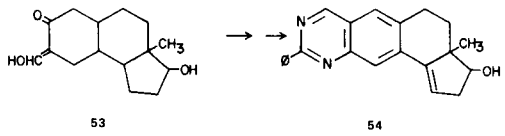
A procedure for the preparation of the benzo[*g*]quinazoline ring system with a greater degree of saturation was reported by Wiedlaup and Huisman (39). The condensation of 3-hydroxy-Δ^9(10)octalone (**50**) with benzamidine afforded 6,7-cyclohexenyl-2-phenyl-5,8-dihydroquinazoline (**51**) in good yield. Treatment of **51** with chloranil

Scheme 21



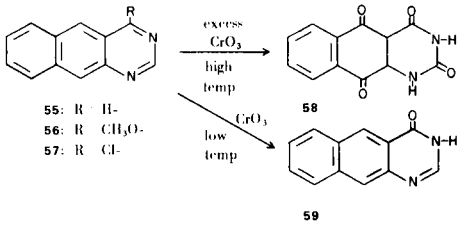
then yielded the conjugated system **52**. This sequence was then extrapolated to the tricyclic hydroxymethylene ketone **53** to yield the diazaanthrasteroid **54**.

Scheme 22



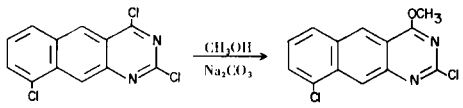
Some studies concerning the properties of various benzo[*g*]quinazolines have been conducted. For example, the chromic acid oxidation of compounds **55-57** has been studied (40) and it was found that small amounts of the quinoid structure **58** could be isolated when forcing conditions were used. If the temperature was controlled, however, 4-oxobenzo[*g*]quinazoline (**59**) could be obtained in good yield.

Scheme 23



Hydroxy groups in the 2- and 4-positions of benzo[*g*]quinazolines are readily converted to the corresponding chloro compounds which, upon treatment with sodium methoxide, yielded the methoxy derivative (41,42). It has been reported, however (43), that there is a difference in reactivity between chloro groups in the 2- and 4-position thus making it possible to selectively replace the chlorine in the 4-position, *i.e.*,

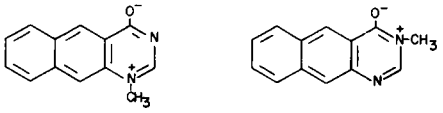
Scheme 24



The photochemistry of some of these compounds has also been investigated. Upon exposure to sunlight many of these compounds form dimers (44). In addition, it has been reported (45) that phenyl groups in the 5- and 10-positions make otherwise unreactive derivatives highly susceptible to photooxidation.

Some ultraviolet absorption spectra of these linear benzoquinazolines have been obtained and used to assign the betaine structures **60** and **61** to 4-NH_2-, 4-MeO-, and 4-OH-derivatives (46). This assignment was made because the spectral properties differed fundamentally from that of the parent molecule by the absence of the large band towards the visible spectrum and by the hypsochromic displacement of the absorption maximum toward the longer wavelengths region.

Scheme 25



60 61

Ultraviolet studies have also been conducted to determine the nature of the cationic form of the conjugate acid (47). These studies, however, were inconclusive for the benzo[*g*]quinazoline system.

REFERENCES AND NOTES

* Author to whom inquiries should be made.

(1) A. Rosowsky and E. Modest, *J. Org. Chem.*, **31**, 2607 (1966).

(2) W. Dymek and D. Sybistowicz, *Rocz. Chem.*, **36**, 1639 (1962); *Chem. Abstr.*, **59**, 8742f (1963).

(3) W. Dymek and D. Sybistowicz, *Rocz. Chem.*, **37**, 547 (1963); *Chem. Abstr.*, **59**, 10040h (1963).

(4) E. C. Taylor, A. McKillop, Y. Shvo, and G. H. Hawks, *Tetrahedron*, **23**, 2081 (1967).

(5) A. Rosowsky and E. Modest, *J. Heterocyclic Chem.*, **3**, 387 (1966).

(6) A. Rosowsky, K. Chen, M. Nadel, N. Papathanasopoulos and E. Modest, *ibid.*, **9**, 275 (1972).

(7) A. Rosowsky, H. Protopapa, P. Burke and E. Modest, *J. Org. Chem.*, **29**, 2881 (1967).

(8) A. Rosowsky and E. Modest, *J. Heterocyclic Chem.*, **9**, 637 (1972).

(9) A. Rosowsky, M. Nadel and E. Modest, *ibid.*, **9**, 645 (1972).

(10) E. Taylor and Y. Shvo, *J. Org. Chem.*, **33**, 1719 (1968).

(11) H. Meerwein, P. Laasch, R. Mersch and J. Neutwig, *Chem. Ber.*, **89**, 224 (1956); *Chem. Abstr.*, **50**, 147746 (1956).

(12) W. B. Farvas, *J. Appl. Chem.*, **14**, 389 (1964); *Chem. Abstr.*, **62**, 7754a (1965).

(13) C. E. Loader and C. J. Timmons, *J. Chem. Soc. C.*, 1343 (1967).

(14) E. Modest, S. Chatterjee and H. Kangew, *J. Org. Chem.*, 27, 2708 (1962).

(15) A. Rosowsky, K. Chen, N. Papathanasopoulos and E. Modest, *J. Heterocyclic Chem.*, **9**, 263 (1972).

(16) S. Sengupta, S. Chatterjee, H. Protopapa and E. Modest, *J. Org. Chem.*, **37**, 1323 (1972).

(17) E. Modest, S. Chatterjee and H. Rangur, *ibid.*, **27**, 2708 (1962).

(18) E. Taylor, A. McKillop, Y. Shvo and G. H. Hawks, *Tetrahedron*, **23**, 2081 (1967).

(19) V. P. Mamaev and V. F. Sedova, *Biol. Akt. Soedin., Akad. Nauk SSSR*, 32 (1965); *Chem. Abstr.*, **63**, 18082a (1965).

(20) V. F. Sedova, L. D. Dikanskaya and V. P. Mamaev, *Izv. Sibirsk. Otd. Akad. Nkad. Nauk SSSR, Ser. Khim. Nauk*, 98 (1966); *Chem. Abstr.*, **65**, 13701e (1966).

(21) V. P. Mamaev and V. F. Sedova, *Khim. Ceterotsikl, Soedin.*, 608 (1965); *Chem. Abstr.*, **64**, 5089g (1966).

(22) W. Ziegenbein and W. Frank, *Angew. Chem.*, **71**, 628 (1959); *Chem. Abstr.*, 57, 7270 (1962).

(23) J. Goerdeler and D. Weber, *Chem. Ber.*, **101**, 3475 (1968); *Chem. Abstr.*, 70, 3391j (1969).

(24) W. Dymek and D. Sybistowski, *Monatsh. Chem.*, **96**, 542 (1965); *Chem. Abstr.*, **63**, 5642d (1965).

(25) I. E. Baltazzi, *Compt. Rend.*, **233**, 491 (1951); *Chem. Abstr.*, **46**, 7103g (1952).

(26) H. H. Perkampus and T. H. Bluhm, *Tetrahedron*, **28**, 2099 (1972).

(27) V. P. Mamaev and V. F. Sedova, *Khim. Geterotsikl. Soedin.*, 787 (1965); *Chem. Abstr.*, **64**, 9721e (1966).

(28) U. K. Pandit, I. A. VanderVlugt, A. C. Vandalen, A. H. Toustra and H. Schenk, *Tetrahedron Letters*, 3693 (1969).

(29) B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy and J. H. Williams, *J. Org. Chem.*, 17, 149 (1952).

(30) A. Etienne and M. Legrand, *Compt. Rend.*, **229**, 220 (1949); *Chem. Abstr.*, **44**, 1517d (1950).

(31) F. H. S. Curd, J. K. Landquist and F. L. Rose, *J. Chem. Soc.*, 1759 (1948).

(32) H. J. Mehta, B. M. Patel and S. R. Patel, *J. Ind. Chem. Soc.*, **49**, 407 (1972); *Chem. Abstr.*, **77**, 61937x (1972).

(33) W. Ried and N. Stephan, *Chem. Ber.*, **96**, 1218 (1963); *Chem. Abstr.*, **59**, 1630h (1963).

(34) H. J. Mehta and S. R. Patel, *Indian J. Chem.*, **9**, 109 (1971); *Chem. Abstr.*, **74**, 112007s (1971).

(35) M. Matsuoka, H. Tanii, T. Kitao and K. Konishi, *Kogyo Kagaku Zasshi*, **73**, 2195 (1970); *Chem. Abstr.*, **74**, 55116a (1971).

(36) P. S. Sutpanthi and J. P. Trivedi, *J. Indian Chem. Soc.*, **49**, 605 (1972); *Chem. Abstr.*, 77, 114347p (1972).

(37) V. K. Mehta and S. R. Patel, *Indian J. Chem.*, **5**, 231 (1967); *Chem. Abstr.*, **68**, 21899 (1968).

(38) V. K. Mehta and S. R. Patel, *Indian J. Chem.*, **6**, 294 (1968); *Chem. Abstr.*, **70**, 106471g (1969).

(39) K. Weidhaup and H. O. Huisman, *Tetrahedron*, **24**, 789 (1967).

(40) A. Etienne and M. Legrand, *Compt. Rend.*, **231**, 232 (1950); *Chem. Abstr.*, **45**, 1603d (1951).

(41) A. Etienne and M. Legrand, *Compt. Rend.*, **229**, 220 (1949); *Chem. Abstr.*, **44**, 1517d (1950).

(42) M. Legrand, *Compt. Rend.*, **231**, 1318 (1950); *Chem. Abstr.*, **45**, 71261 (1951).

(43) M. Legrand and Y. Lepage, *Compt. Rend.*, **235**, 303 (1952); *Chem. Abstr.*, **48**, 11423a (1954).

(44) A. Etienne and M. Legrand, *Compt. Rend.*, **232**, 1223 (1951); *Chem. Abstr.*, **45**, 7435b (1951).

(45) M. Legrand, *Compt. Rend.*, **237**, 822 (1953); *Chem. Abstr.*, **49**, 10606 (1955).

(46) M. Legrand, *Compt. Rend.*, **236**, 937 (1953); *Chem. Abstr.*, **48**, 2073c (1954).

(47) A. R. Osborn, K. Schofield and L. N. Short, *J. Chem. Soc.*, 4191 (1956).