Tetrahedron Vol. 31, pp. 25 to 29 Pergamon Press 1975. Printed in Great Britain

CLEAVAGE OF AZOLES—I

SYNTHESIS OF SOME TRIAZOLYLOXAZOLINES AND TRIAZOLYLBENZOXAZONES

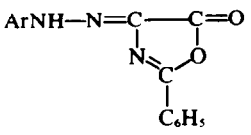
A. H. HARHASH,* M. H. ELNAGDI and A. A. A. ELBANANI
Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R. Egypt

(*Received in UK* 8 *March* 1974; *Accepted for publication* 15 *August* 1974)

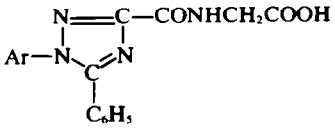
Abstract—Treatment of glycine, and *o*-aminobenzoic acid with 4-arylhydrazono-2-phenyl-2-oxazolin-5-ones effected the formation of the N-(1,5-diaryl-1H-1,2,4-triazolyl-3-carbonyl) derivatives of the amino acids. The triazolylcarbonylglycines were azlactonised with aromatic aldehydes to 4-arylidene-2-triazolyl-2-oxazolin-5-ones, which behaved similar to the 2-phenyl analogues towards the action of ammonia and amines. Cyclisation of the triazolylcarbonylanthranilic acids with acetic anhydride afforded 2-triazolyl-4H-3,1-benzoxazin-4-ones.

Among the enormous number of 2-oxazolin-5-ones substituted in the 2-position with an alkyl, aryl, and to less extent with a heterocyclic radical, no 2-triazolyl-oxazolones have been reported. With an increasing interest in the chemistry of oxazolones,[1-6] we synthesized this type of compounds, aiming to study the effect of the triazolyl group on the behaviour of the oxazolone ring towards a variety of reagents.

The synthesis of 4 - arylidene - 2 - (1,5 - diaryl - 1H - 1,2,4 - triazol - 3 - yl) - oxazolin - 5 - ones (**3**) would necessitate the intermediates N - (1,5 - diaryl - 1H - 1,2,4 - triazolyl - 3 - carbonyl) glycines (**2**) which could be converted into **3** by the Erlenmeyer's azlactonisation.[7,8] Trials to prepare **2** via the acylation of glycine with 1,5 - diphenyl - 1H - 1,2,4 - triazolyl - 3 - carbonyl chloride, gave poor yields. However, compounds **2a-d** have been obtained, in good yields, upon treatment of 4 - aryl - hydrazono - 2 - phenyl - 2 - oxazolin - 5 - ones (**1a-d**) with glycine. The N-triazolylcarbonylglycines **2a-d**, were readily converted into 4 - arylidene - 2 - (1,5 - diaryl - 1H - 1,2,4 - triazol - 3 - yl) - 2 - oxazolin - 5 - ones (**3a-f**). The IR spectrum of **2a**, taken as an example of **3a-f**, showed only



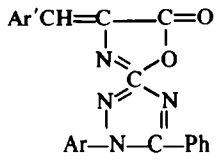
1



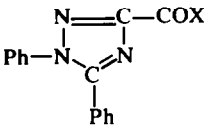
2

a: Ar = C_6H_5
b: Ar = $C_6H_4CH_3$-*o*
c: Ar = $C_6H_4CH_3$-*m*
d: Ar = $C_6H_4CH_3$-*p*

one CO absorption at 1690 cm^{-1} characteristic of 5-membered heterocyclic ketones with exocyclic α-unsaturation.[9] Moreover the UV spectrum of **3a** showed maximum absorption at 345 nm ($\epsilon = 285 \times 10^4$). This absorption exhibited a red shift to 384 ($\epsilon = 549^{\circ} \times 10^4$) nm in the case of **3b**. These spectra are similar to those reported for 4-benzylidene and 4 - anisylidene - 2 - benzyl 2 - oxazolin - 5 - ones.[5]

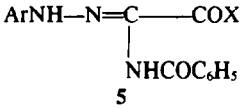


3a; Ar = Ar′ = Ph
b; Ar = Ph; Ar′ = C_6H_4Me-*o*
c; Ar = Ph; Ar′ = C_6H_4Me-*p*
d; Ar = $C_6H_4CH_3$-*o*; Ar′ = Ph
e; Ar = $C_6H_4CH_3$-*m*; Ar′ = Ph
f; Ar = $C_6H_4CH_3$-*p*; Ar′ = Ph



4a; X = OH
b; X = NH_2
c: X = OMe

The conversion of **1** to **2** by the action of glycine is a new application of Sawdey's rearrangement[10] of **1a** to 1,5 - diphenyl - 1H - 1,2,4 - triazole - 3 - carboxylic acid (**4a**) or its amide (**4b**) upon treatment with methanolic potassium hydroxide or ammonia. Other nucleophilic reagents, namely, alkoxide ions, amides, hydrazines, Grignard reagents, and aromatic thiols have been reported[11-13] to effect similar rearrangements. According to Sawdey,[10] the rearrangement of **1a** to **4a** or **4b** proceeded by methanolysis of the oxazolone and cyclisation to the triazole ester, **4c**, with eventual hydrolysis or ammonolysis of the ester group. This mechanism has been questioned by Browne and Polya[12] who were able to isolate labile acyclic intermediates, **5**, in which X differs with different reagents used. They also reported that some triazole derivatives, e.g., **4** (X = NHC_6H_5) could not be obtained upon treatment of the triazole ester (**4c**) with the appropriate reagent.



5

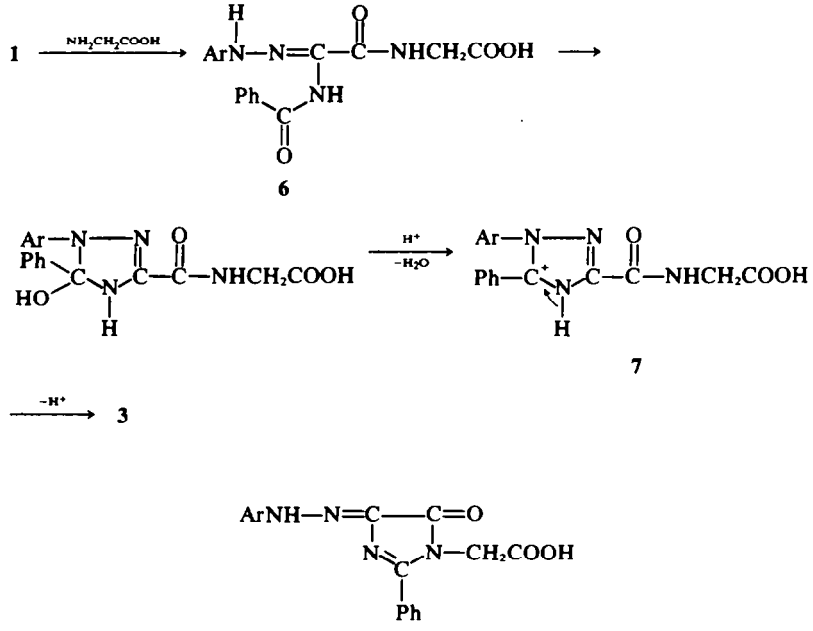
The conversion of **1** into **2** by the action of glycine in acetic acid appears to be in contrast to the finding of Browne and Polya[11] that no rearrangement of **1** occured in solution acid to litmus. However, oxazolones are known[12-16] to react with amino esters to give peptide esters, and these reactions have been recently shown[17-20] to be catalysed by acids. Hence, the first step in the conversion of **1** into **2** is probably the acid-catalysed hetero-ring opening with glycine to give acyclic intermediates of the type **6**. Cyclisation of **6** to **2**, rather than the possible imidazolinone **7** (*cf* the ready cyclisation of α-benzoylaminocinnamic acid amide or anilide to imidazolinone derivatives)[21,22] involves the attack of the most nucleophilic hydrazono NH group on the benzoylamino carbonyl group, followed by acid-catalysed elimination of water (*cf* Scheme A).

Similar to the behaviour of the 2-phenyl analogues,[7,8] compounds **3a,b** underwent hetero-ring opening when treated with aromatic amines, namely, aniline, *o*-, *m*-, and *p*-toluidines, yielding the α-triazolylcarbonylaminocinnamic acid anilides, **8a-f**. Structure proposed for compounds **8a-g** was based, in addition to analytical data, on IR absorption data. Also the UV spectra of these compounds were parallel to that reported for α-acylaminocinnamic acid anilides.[3] Hetero-ring opening was effected upon refluxing **3a** with alcoholic ammonia to yield α-triazolylcarbonylaminocinnamic acid amide (**8g**). On the other hand, when **3b,d** was heated with alcoholic ammonia, in the presence of potassium carbonate, the triazolylimidazolines, **9a,b** (or possible tautomers) were formed via hetero-ring opening followed by cyclisation. Similar behaviour of 4 - arylidene - 2 - phenyl - 2 - oxazolin 5 - ones has been reported.[4,21]

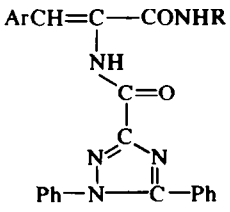
The IR spectra of compounds **9a,b** showed two CO absorption bands at 1700 and 1640 cm^{-1}. The former band may correspond to the band at the same wave length reported for 4 - benzylidene - 2 - phenyl - 2 - imidazolin - 5 - one[23] whereas inspection of the literature data for the latter compound revealed the absence of absorption band at around 1640 cm^{-1}. However, when the IR spectrum of this compound, prepared after the procedure described by Williams and Ronzio,[21] was drawn by us, two CO bands at 1700 cm^{-1} and 1638 cm^{-1} were observed. The presence of two CO absorption bands in the IR spectra of compounds **9a,b** and in the IR of its 2-phenyl analouge, may be taken as an evidence for the existence of equilibrium mixture of both the 4-, and 5-one forms.

When the highly coloured arylhydrazone derivatives, **1a-d**, were refluxed with anthranilic acid in acetic acid, rearrangement of the oxazolone ring took place, with the formation of the colourless N - (1,5 - diaryl - 1H - 1,2,4 - triazolyl - 3 - carbonyl) - anthranilic acids (**10a-d**). Authentic samples of **10a** and **d** were obtained by the acylation of anthranilic acid with the appropriate triazolylcarbonyl chloride. The IR spectrum of **10a** shows absorption at 1700 and 1675 cm^{-1} (C=O of carboxyl and anilide groups), 1620 cm^{-1} (C=N) and broad absorption at ~3360 cm^{-1} for —OH and —NH groups.

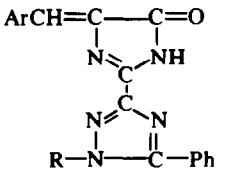
In support of the proposed mechanism for the conversion of **1** into **2** by the action of glycine (*cf* Scheme A), the acyclic intermediates **11a,b** (corresponding to the



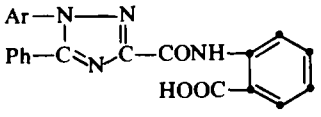
Scheme A



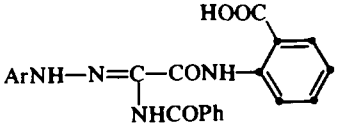
8b: Ar = R = Ph
b: Ar = Ph; R = $C_6H_4CH_3$-*p*
c: Ar = C_6H_4OMe-*o*; R = Ph
d: Ar = C_6H_4OMe-*o*; R = $C_6H_4CH_3$-*o*
e: Ar = $C_6H_4OCH_3$-*o*; R = $C_6H_4CH_3$-*m*
f: Ar = C_6H_4OMe-*o*; R = $C_6H_4CH_3$-*p*
g: Ar = Ph; R = H



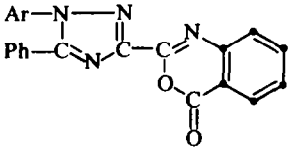
9a: R = Ph; Ar = C_6H_4OMe-*o*
b: R = $C_6H_4CH_3$-*o*; Ar = Ph



10a; Ar = Ph
b; Ar = $C_6H_4CH_3$-*o*
c; Ar = $C_6H_4CH_3$-*m*
d; Ar = $C_6H_4CH_3$-*p*



11a; Ar = Ph
b; Ar = $C_6H_4CH_3$-*m*



12a; Ar = Ph
b; Ar = $C_6H_4CH_3$-*m*
c; Ar = $C_6H_4CH_3$-*p*

glycine intermediates **6**) could be isolated when the reaction of **1a,c** with anthranilic acid was conducted for a shorter time.

The N-triazolylcarbonylanthranilic acids **10a,c** and **d** were successfully cyclised upon refluxing with acetic anhydride to give the 2 - triazolyl - 4H - 3,1 - benzoxazin - 4 - one derivatives, **12a–c**, respectively. The IR spectra of **12a–c** show absorption at 1750 cm^{-1} (C=O) and 1640 cm^{-1} (C=N—).

EXPERIMENTAL

M.ps are uncorrected. The IR spectra were recorded on a Beckman IR 4-spectrophotometer (Nujol mulls). UV spectra were measured in EtOH on a Peckman DK-2. The arylhydrazones **1a–d** were prepared by the method described by Browne and Polya.[11]

N - (1,5 - *Diaryl* - 1*H* - 1,2,4 - *triazolyl* - 3 - *carbonyl*) *glycines* (**2a–d**). A suspension of each of **1a–d** (2·5 g) and glycine (1·5 g) in glacial AcOH (20 ml) was refluxed for 1 hr and then poured into ice-cold water. The crystals that separated, were filtered off and recrystallised from EtOH.

Compound **2a** formed colourless crystals, m.p. 222°; yield 70% (Found: C, 63·30; H, 4·50; N, 17·10. $C_{17}H_{14}N_4O_3$ requires: C, 63·35; H, 4·38; N, 17·38%).

Compound **2b** formed colourless crystsls, m.p. 210°; yield 65% (Found: C, 64·00: H, 4·50; N, 16·40. $C_{18}H_{16}N_4O_3$ requires: C, 64·27; H, 4·80; N, 16·66%), IR: 1670 cm^{-1} (and CO), 1740 cm^{-1} (carboxyl CO), 2560–2980 (carboxyl OH) and 3440 cm^{-1} (NH).

Compound **2c** formed colourless crystals, m.p. 235°; yield 70% (Found: C, 64·40; H, 4·70. $C_{18}H_{16}N_4O_3$ requires: C, 64·27; H, 4·80%).

Compound **2d** formed colourless crystals, m.p. 211°; yield 70% (Found: C, 64·50; H, 4·80. $C_{18}H_{16}N_4O_3$ requires: C, 64·27; H, 4·80%).

Compound **2a** was also obtained, in 30% yield, by warming 1,5 - diphenyl - 1H - 1,2,4 - triazole - 3 - carboxylic acid[11] (2·8 g) with thionyl chloride (5 ml) on a boiling water-bath for 1 hr, distilling off the excess thionyl chloride, and gradual addition of the acid chloride to a solution of glycine (0·7 g) in 10% NaOH aq (10 ml) followed by acidification with HCl.

4 - *Arylidene* - 2 - (1,5 - *diaryl* - 1*H* - 1,2,4 - *triazol* - 3 - yl) - 2 *oxazolin* - 5 - *ones* (**3a–f**)

General procedure. This is illustrated here by the synthesis of **3a**. A mixture of **2a** (3·2 g), benzaldehyde (1·5 g), Ac_2O (5 ml), and NaOAc (0·5 g) was warmed into soln. Heating was then continued on a boiling water-bath for 1 hr, excess Ac_2O was decomposed with water, and the oil residue was triturated with few drops of EtOH. The yellow solid product was filtered off and crystallised from EtOH. The arylidene derivatives **3a–f** are listed in Table 1.

α - (1,5 - *Diphenyl* - 1*H* - 1,2,4 - *triazolyl* - 3 - *carbonylamino*)*cinnamic acid anilides* (**8a–f**)

General procedure. This is illustrated by the synthesis of **8**: A mixture **3a** (0·01 mole) and the appropriate aromatic amine (0·03 mole) was heated on a boiling water-bath for 2 hr. The

Table 1. 4-Arylidene-2-(1,5-diaryl-1H-1,2,4-trialol-3-yl)-2-oxazolin-5-ones (**3a–f**)

Arylidene derivative	m.p.	Yield %	Formula	Carbon, % Found	Carbon, % Calc.	Hydrogen, % Found	Hydrogen, % Calc.	Nitrogen, % Found	Nitrogen, % Calc.
3a	215°	40	$C_{24}H_{16}N_4O_2$	73·10	73·46	4·10	4·11	14·00	14·28
3b	255°	60	$C_{25}H_{18}N_4O_3$	70·60	71·08	4·30	4·30	12·90	13·26
3c	203°	55	$C_{25}H_{18}N_4O_3$	70·80	71·08	4·10	4·30	12·80	13·26
3d	146°	45	$C_{25}H_{18}N_4O_2$	73·50	73·87	4·20	4·46		
3e	145°	50	$C_{25}H_{18}N_4O_2$	73·50	73·87	4·30	4·46	13·50	13·79
3f	212°	45	$C_{25}H_{18}N_4O_2$	73·60	73·87	4·40	4·46	13·40	13·79

mixture was triturated with dil EtOH, and the resulting solid was crystallised from EtOH. Compound **8a**, formed colourless crystals, yield 70%; λ max (EtOH) 290 nm (ϵ 230 × 10^3) IR: 3400, 3300, 3050 cm^{-1} (NH vibrations), 1680 cm^{-1} (triazoloyl CO) and 1660 cm^{-1} (amide CO). The derivateves **8a–f** prepared similarly are listed in Table 2.

α - (1,5 - Diphenyl - 1H - 1,2,4 - triazolyl - 3 - carbonylamine)cinnamic acid amide (**8g**). To a suspension of **3a** (1·0 g) in EtOH (20 ml), aqueous ammonia (sp. gr. 0·91; 5 ml) was added, and the mixture was refluxed for 3 hr. The amide **8g** was isolated by dilution of the mixture with water and was crystallised from alcohol as colourless crystals, m.p. 185°; yield 55% (Found: C, 70·20; H, 4·50; H, 16·82. $C_{24}H_{19}N_5O_2$ requires: C, 70·42; H, 4·68; N, 17·11%), λ max (EtOH) 233 nm (ϵ = 185 × 10^2); IR: 3470, 3384 cm^{-1}) (NH_2 vibration); 3410 cm^{-1} (NH); 1710 cm^{-1}, 1690 cm^{-1} (amide CO groups) and 1640 cm^{-1} (NH_2 deformation).

4 - Arylidene - 2 - (1,5 - diaryl - 1H - 1,2,4 - triazol - 3 - yl) - 2 - imidazolin - 5 - ones (**9a,b**). A mixture of each of **3b,d** (1·0 g), aqueous ammonia (sp. gr. 0·91; 5 ml), K_2CO_3 (1·0 g), and EtOH (20 ml) was refluxed for 4 hr, cooled and then diluted with water.

The 4-*o*-methoxybenzylidene derivative **9** formed yellow crystals from EtOH, m.p. 252°; yield 55%; IR: 1730 cm^{-1}; 1640 cm^{-1} (ring CO) and broad band at 3050–3200 (NH) (Found: C, 71·50; H, 4·30; N, 16·24. $C_{25}H_{19}N_3O_2$ requires: C, 71·24; H, 4·54; N, 16·62%).

The 4-benzylidene **9b** formed yellow crystals from EtOH, m.p. 198°; yield 60% (Found: C, 74·60; H, 5·30. $C_{25}H_{19}N_3O$ requires: C, 74·06; H, 4·72%).

Triazolyl derivatives (**10** *and* **13**) *of anthranilic and* p-*aminobenzoic acids*

General procedure. A mixture of each of **1a–d** (2·8 g), anthranilic or *p*-aminobenzoic acid (1·2 g) and glacial AcOH (20 ml) was refluxed for 2 hr. The mixture was cooled and poured into water (100 ml). The colourless solid was filtered off and crystallised from alcohol. The triazolyl derivatives **10a–d** and **8a–d** are listed in Table 3. The IR spectrum of **10d**, taken as an example, showed absorption bands at: 3200 cm^{-1} (NH); 2400–2900 cm^{-1} (OH dimer), brond band at 1690–1720 cm^{-1} (CO group).

N - (1,5 - Diphenyl - 1H - 1,2,4 - triazolyl - 3 - carbonyl)anthranilic acid (**10a**) was also obtained in 50% yield by treatment of anthranilic acid with 1,5 - diphenyl - 1H - 1,2,4 - triazole - 3 - carboxylic acid chloride as described for **2a**.

α-Benzoylaminoglyoxalic acid o-*carboxyanilide α-arylhydrazones* (**11a,b**). A mixture of each of **1a,b** (2·8 g), anthranilic acid (1·2 g) and glacial AcOH (20 ml) was refluxed for 45 min, cooled and then diluted with water. The crystals that separated were filtered off and recrystallised from alcohol.

Compound **11a** formed colourless crystals, m.p. 256°; yield 40%; IR: 2450–2750 cm^{-1} (OH dimer); 1690–1720 cm^{-1} (CO groups) and

Table 2. α-(1,5-Diaryl-1H-1,2,4-triazolyl-3-carbonyl)aminocinnamic acid anilides (**8a–f**)

Anilide	m.p.	Yield %	Formula	Carbon, % Found	Carbon, % Calc.	Hydrogen, % Found	Hydrogen, % Calc.	Nitrogen, % Found	Nitrogen, % Calc.
8a	177°	65	$C_{30}H_{23}N_5O_2$	73·90	74·21	4·70	4·78	14·10	14·43
8b	120°	70	$C_{31}H_{25}N_5O_2$	74·16	74·53	4·95	5·04	13·59	14·02
8c	239°	67	$C_{31}H_{25}N_5O_3$	71·80	72·22	4·50	4·89	13·10	13·59
8d	203°	62	$C_{32}H_{27}N_5O_3$	72·30	72·57	4·80	5·14	12·91	13·23
8e	195°	60	$C_{32}H_{27}N_5O_3$	72·40	72·57	5·20	5·14		
8f	209°	65	$C_{32}H_{27}N_5O_3$	72·60	72·57	4·70	5·14		

Table 3. Triazolyl derivatives (**10** and **12**[a]) of anthranilic acid and benzoxazinone

Compound	m.p.	Yield %	Formula	Carbon, % Found	Carbon, % Calc.	Hydrogen, % Found	Hydrogen, % Calc.	Nitrogen, % Found	Nitrogen, % Calc.
10a	244°	70	$C_{22}H_{16}N_4O_3$	68·80	68·74	4·03	4·20	14·07	14·58
10b	255°	65	$C_{23}H_{18}N_4O_3$	68·70	69·33	4·80	4·55		
10c	255°	70	$C_{23}H_{18}N_4O_3$	69·10	69·33	4·30	4·55		
10d	245°	65	$C_{23}H_{18}N_4O_3$	68·80	69·33	4·60	4·55		
12a	215°	50	$C_{22}H_{14}N_4O_2$	72·40	72·12	3·45	3·85	14·93	15·29
12b	205°	45	$C_{23}H_{16}N_4O_2$	72·90	72·62	4·20	4·24		
12c	202°	50	$C_{23}H_{16}N_4O_2$	72·40	72·62	4·00	4·24		

[a]Compounds **12a–c** were prepared by refluxing the appropriate **10** (2·0 g) with Ac_2O (30 ml) for 4 hr.

1610 cm^{-1} (C = N). (Found : C, 66·30; H, 4·70; N, 13·60. $C_{22}H_{18}N_4O_4$ requires: C, 65·66; H, 4·51; N, 13·93%).

Compound **11b** formed colourless crystals, m.p. 210°; yield 45% (Found: C, 66·60; H, 4·90; N, 13·22. $C_{23}H_{20}N_4O_4$ requires C, 66·33; H, 4·84; N, 13·46%).

REFERENCES

[1]H. T. Clarke, J. H. Johnson and R. Robinson, *The Chemistry of Penicillin*. Princeton University Press, Princeton, N.Y. (1949)
[2]R. Filler and Y. S. Rao, *J. Org. Chem.* **27**, 2403 (1962)
[3]A. Mustafa, W. Asker, A. H. Harhash, M. A. E. Khalifa and E. M. Zayed, *Liebigs Ann.* **713**, 151 (1968)
[4]A. Mustafa, W. Asker, A. H. Harhash, T. M. S. Abdin and E. M. Zayed, *Ibid.* **714**, 146 (1968)
[5]A. H. Harhash, N. A. L. Kassab and A. A.A. A. Banani, *Indian J. Chem.* **9**, 789 (1971)
[6]A. H. Harhash, A. I. Kassab and Z. Al-Saigh, *Ibid.* **10**, 41 (1972)
[7]H. E. Carter, *Org. Reactions* **3**, 198 (1964)
[8]E. Baltazzi, *Quart. Rev.* **9**, 150 (1955)
[9]A. S. Mittra and M. K. Rout, J. *Indina Chem. Soc.* **40**, 993 (1963)
[10]G. W. Sawdey, *J. Am. Chem. Soc.* **79**, 1955 (1957)
[11]W. Asker and Z. E. Elagroudi, J. Org. Chem. **26**, 1440 (1961)
[12]E. J. Browne and J. B. Polya, J. Chem. Soc. 575 (1962)
[13]E. J. Browne and J. B. Polya, *Chem. & Ind* 1086 (1960)
[14]C. Granacher and M. Mahler, *Helv. Chim. Acta* **10**, 246 (1972)
[15]O. K. Behrens and M. Bergmann, *J. Biol. Chem.* **129**, 597 (1939)
[16]M. Bergmann and J. S. Fruton, *Ibid.* **124**, 321 (1938)
[17]M. Goodman and L. Levine, *J. Am. Chem. Soc.* **86**, 2918 (1964)
[18]M. Goodman and W. J. McGahren, *Ibid.* **87**, 3028 (1965)
[19]M. Goodman and W. J. McGahren, *Tetrahedron* 23, 2031 (1967)
[20]H. Rodriguze, C. Chuaqui, S. Atala and A. Marquez, *Ibid.* **27**, 2425 (1971)
[21]D. L. Williams and A. R. Ronzio, *J. Am. Chem. Soc.* **68**, 647 (1964)
[22]R. Pfleger and G. Markert, *Chem. Ber.* **90**, 1494 (1957)
[23]W. I. Awad, *J. Org. Chem.* **25**, 1242 (1960)