[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

α-Aryl-β-alkyloxyacrylonitriles

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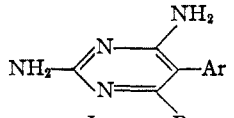
It has been shown that α-acylarylacetonitriles react readily with aliphatic orthoesters to give good yields of α-aryl-β-alkyloxyacrylonitriles, required as intermediates in the synthesis of 2,4-diamino-5-arylpyrimidines. The main reaction is effectively a simple alkylation but a side reaction has been observed when ethyl orthoformate is used, in which the acyl radical is replaced by an ethoxymethylene group. The mechanism of these reactions is discussed.

In a recent communication[1] a new general method of synthesis of 2,4-diamino-5-arylpyrimidines (I) was described. This method consists in essence of the condensation of guanidine with an α-aryl-β-methoxyacrylonitrile (II; R′ = CH_3), prepared by the action of diazomethane in ether on the corresponding α-acylarylacetonitrile (III). Compounds of type III appear to exist largely in the enolic form (IIIa).[2,3]



I

$ArC(CN)=C(OR')R$

II

$ArCH(CN)—COR$

III

$ArC(CN)=C(OH)R$

IIIa

The fact that several of the pyrimidines (I) possess outstanding antimalarial activity against experimental infections[1,4] rendered it necessary to prepare comparatively large amounts of these compounds for extended biological and clinical tests. However, while the methylation of III with diazomethane is an excellent laboratory procedure it would not lend itself readily to the fabrication of I in multi-molar quantities, and for this reason an investigation of the alkylation of the sodium salt of III (or IIIa) with an alkyl halide or sulfate was undertaken. The yields were unsatisfactory.[1]

The conversion of ethyl acetoacetate to ethyl β-ethoxycrotonate (IV) by heating with ethyl orthoformate was described by Claisen and others.[5-7] Although the method has been applied to other β-ketoesters[5] and to benzoylacetone,[8] when the enol ether (V) is obtained, it does not appear to have been extended to β-ketonitriles.

$CH_3—C(OC_2H_5)=CH—COOC_2H_5$

IV

$Ph—C(OC_2H_5)=CH—CO—CH_3$

V

When α-formyl-*p*-chlorophenylacetonitrile (III or IIIa; Ar = C_6H_4Cl-*p*, R = H) was heated with ethyl orthoformate a mixture of ethanol and ethyl formate was evolved, and α-*p*-chlorophenyl-β-ethoxyacrylonitrile (II; Ar = C_6H_4Cl-*p*, R = H, R′ = C_2H_5) was obtained in good yield. Similarly, when ethyl orthoformate was replaced by ethyl orthoacetate in the above reaction, the same acrylonitrile derivative resulted, together with a mixture of ethanol and ethyl acetate. Likewise α-(α-furoyl)-phenylacetonitrile, heated with methyl orthopropionate, gave α-phenyl-β-(α-furyl)-β-methoxyacrylonitrile (II; Ar = C_6H_5, R = C_4H_3O-(α), R′ = CH_3). The reaction appeared to be general for α-acylarylacetonitriles and, further, all the orthocarboxylic esters investigated (*i.e.*, methyl, ethyl, *n*-propyl and *n*-amyl orthoformates; methyl and ethyl orthoacetate and orthopropionate, and methyl ortho-*n*-valerate) reacted with equal smoothness in analogous fashion. The α-aryl-β-alkyloxyacrylonitriles (II) were usually obtained crystalline, but oils resulted from the use of certain orthoesters, and in these instances the yields of II were estimated by conversion to the known pyrimidine[1] (I) with guanidine. Ethyl orthosilicate did not react in the same manner as the orthocarboxylic esters.

The nature of the products was confirmed by the fact that crystalline α-2,4-dichlorophenyl-β-methoxyacrylonitrile (VI) and α,β-diphenyl-β-methoxyacrylonitrile (VII), prepared by the reactions of methyl orthoacetate with α-formyl-2,4-dichlorophenylacetonitrile (III or IIIa, Ar = $C_6H_3Cl_2$(2,4), R = H) and methyl orthopropionate with cyandesoxybenzoin (III and IIIa, Ar = R = C_6H_5), respectively, were identical in all respects with samples prepared by the action of diazomethane in ether on the same ketonitriles. α-Aryl-β-alkyloxyacrylonitriles such as II, VI or VII are potentially capable of existing in *cis* and *trans* forms VIIIa and b, so that both isomers could theoretically result from alkylation by diazomethane or an orthoester. However, where the products are crystalline, only one form has been isolated from these reactions. In practice orthoesters give a high yield of the crystalline isomer, whereas diazomethane gives generally lower yields of the same crystalline isomer together with a considerable quantity of oily material.

$C_6H_3Cl_2(2,4)C(CN)=CH(OCH_3)$

VI

$C_6H_5C(CN)=C(C_6H_5)(OCH_3)$

VII

VIIIa

VIIIb

Occasionally it has been observed that when a crude α-aryl-β-ethoxy-β-alkylacrylonitrile (II), prepared from the β-ketonitrile (III) by heating with ethyl orthoformate, is condensed with guanidine a

(1) P. B. Russell and G. H. Hitchings, THIS JOURNAL, **73**, 3763 (1951).

(2) W. Wislicenus, G. Butterfass and I. Kohen, *Ann.*, **436**, 69 (1924); W. Wislicenus and H. Reithmuller, *ibid.*, 82 (1924).

(3) F. Arndt, L. Loewe and R. Ginkök, *Rev. faculté sci. Univ. Istanbul, Ser. A. II*, No. **4**, 147 (1946).

(4) E. A. Falco, L. G. Goodwin, G. H. Hitchings, I. Rollo and P. B. Russell, *Brit. J. Pharm.*, **6**, 185 (1951).

(5) L. Claisen, *Ber.*, **26**, 2731 (1893); *ibid.*, **29**, 1005 (1896); *ibid.*, **31**, 1019 (1898); *Ann.*, **297**, 28 (1897).

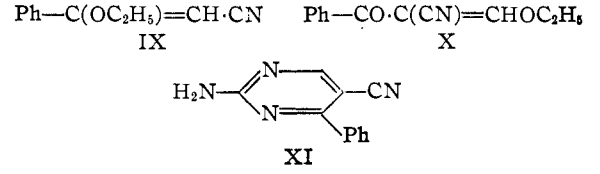
(6) A. Michael, THIS JOURNAL, **57**, 159 (1935).

(7) F. Arndt, L. Loewe and M. Ozansoy, *Ber.*, **73**, 779 (1940).

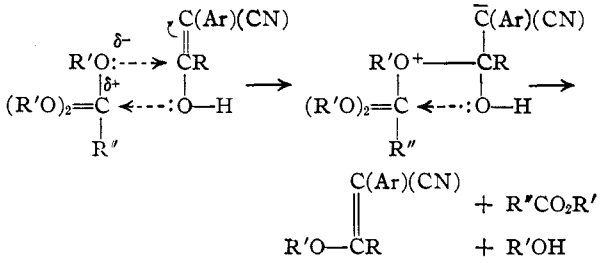
(8) C. Weygand, *ibid.*, **58**, 1473 (1925).

quantity of the 6-unsubstituted pyrimidine (I, R = H) is produced in addition to the 6-substituted pyrimidine (I, R = alkyl). This implies the formation, by acyl radical replacement, of an α-aryl-β-ethoxyacrylonitrile (II, R = H), or a derivative readily converted thereto, as a contaminant of II. The replacement has not been observed with the orthoesters of higher aliphatic acids. By treating the α-acylarylacetonitrile (III) with an orthoester derived from the same acyl radical (R·CO) superior yields of homogeneous α-aryl-β-ethoxy-β-alkylacrylonitriles (II), and thence pure pyrimidines (I, R = alkyl), were thus obtained.

When ω-cyanoacetophenone was heated with ethyl orthoformate the product was an oil. This, reacting with guanidine, gave a good yield of a product to which the structure 2-amino-5-cyano-4-phenylpyrimidine (XI) has been assigned. Consequently the intermediate oil must be the α-ethoxymethylene derivative (X), rather than the enol ether (IX), of the starting material.



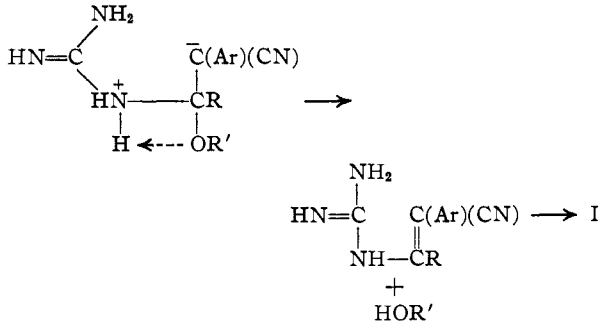
Claisen[5] considered that the conversion of ethyl acetoacetate to ethyl β-ethoxycrotonate (IV) by ethyl orthoformate proceeded by the loss of ethanol from the corresponding ketal during distillation. Arndt[7] refuted this hypothesis since he was able to isolate both β-ethoxycrotonate, and the ketal, directly from the reaction product—and the ketal did not lose alcohol on distillation. Michael[6] had previously demonstrated the inadequacy of Claisen's views. It is now suggested that the formation of an enol ether from a β-dicarbonyl or related compound proceeds by reaction of the orthoester with the enol form. Thus a facile alkylation of α-acylarylacetonitriles with orthoesters would be expected, in view of their high tendency to enolize.[2,3] A mechanism for this reaction is formulated as



It is further suggested that the acyl radical replacement reaction referred to above takes place by attack of ethyl orthoformate on the substituted α-carbon atom of the keto form of the α-acylarylacetonitrile. The possibility that it might proceed by further reaction of ethyl orthoformate with the α-aryl-β-ethoxy-β-alkylacrylonitrile first produced must be excluded, since it has been found that α-*p*-chlorophenyl-β-ethoxy-β-ethylacrylonitrile, for example, is unchanged after long refluxing with this orthoester.

In view of the fact that ethyl acetoacetate and ω-cyanoacetophenone have approximately the same tendency to enolize,[8] it is perhaps surprising that the latter does not give rise to an enol ether when heated with ethyl orthoformate. The strong acidifying action of the electronegative nitrile group,[9] in combination with that of the benzoyl group, must render the methylene group of the keto form the most susceptible point to attack, resulting in the formation of the ethoxymethylene derivative (X). When the keto form of ethyl acetoacetate reacts with ethyl orthoformate, the ketal normally results, and it is only under the influence of catalysts,[10] such as zinc chloride or acetic anhydride, that the ethoxymethylene derivative is produced.

The formation of an enamine from the enol ether of a β-ketoester, by reaction with ammonia,[9,10] involves a nucleophilic attack of the same type as that suggested for the alkylation of β-dicarbonyl and related compounds by orthoesters. The initial reaction in the formation of pyrimidines (I) from the enol ethers (II) and guanidine follows a similar course. Hence the failure[1] of a β-ketonitrile (III)



to condense with guanidine follows, since the oxygen becomes anionic in the presence of the base, and the β-carbon is thus no longer susceptible to nucleophilic attack.

Experimental

α-Aryl-β-alkyloxyacrylonitriles.—The general method of alkylation with orthoesters is illustrated by the following two examples. A summary of these and other reactions is given in Table I.

α-*p*-Chlorophenyl-β-ethoxyacrylonitrile.—α-Formyl-*p*-chlorophenylacetonitrile[1] (20 g.) was heated under reflux with ethyl orthoformate (40 ml.), and the mixture of ethanol and ethyl formate produced was collected from the head of a short fractionating column. When, after one hour, approximately the theoretical amount of this mixture (12 g.) had been collected, and the temperature of the distillate rose above 80°, the reaction was complete. The excess ethyl orthoformate was removed *in vacuo* and the residue distilled to give a colorless oil (17 g.), b.p. 132–133° (0.04 mm.), which solidified in cooling.

α-2,4-Dichlorophenyl-β-methoxyacrylonitrile.—α-Formyl-2,4-dichlorophenylacetonitrile[1] (10 g.) and methyl orthoacetate (25 ml.) were heated together in the manner outlined above. When no more of the low-boiling mixture was evolved, the excess of methyl orthoacetate was removed *in vacuo*, whereupon the residue (8.1 g.) solidified. After recrystallization from ethanol it formed needles, m.p. 106°, undepressed on admixture with a sample[1] prepared by the action of diazomethane in ether on the same ketonitrile.

Reactions of Orthoesters with α-Acylarylacetonitriles Followed by Condensation with Guanidine to Give Pyrimidines.—Two examples are given. α-Formyl-*m*-chlorophenylacetonitrile[1] (9 g.) and *n*-butyl orthoformate (20 ml.) were mixed and refluxed, with constant removal of the low-boiling

(9) F. Arndt, H. Scholz and E. Frobel, *Ann.*, **521**, 95 (1935).

(10) H. Henecka, "Chemie der Beta-Dicarbonyl-Verbindungen," Springer-Verlag, Berlin-Gottingen-Heidelberg, 1950, p. 223–224.

TABLE I

SUMMARY OF THE REACTIONS OF α-ACYLARYLACETONITRILES (III) WITH ORTHOESTERS R″C(OR′)₃ TO GIVE α-ARYL-β-ALKYLOXYACRYLONITRILES (II)

III		Orthoester		II							
							Analyses, %				
							Calculated			Found	
Ar	R	R″	R′	Formula	M.p., °C.	Yield, %	Carbon	Hydrogen	Nitrogen	Carbon	Hydrogen	Nitrogen
C_6H_4Cl-4	H	H	C_2H_5	$C_{11}H_{10}ONCl$	[a]	74	63.6	4.8	6.7	63.1	5.0	6.8
C_6H_4Cl-4	H	CH_3	C_2H_5			78						
$C_6H_3Cl_2$-2,4	H	CH_3	CH_3	$C_{10}H_7ONCl_2$	106	78	52.7	3.1	6.1	53.0	3.0	6.4
C_6H_4Cl-4	CH_3	H	C_2H_5	$C_{12}H_{12}ONCl$	115–116[b]	61	65.0	5.4	6.3	65.3	5.3	6.1
C_6H_4Cl-4	CH_3	CH_3	C_2H_5			70						
C_6H_4Cl-4	C_2H_5	C_2H_5	C_2H_5	$C_{13}H_{14}ONCl$	[c]	81	..	...	6.0	..	...	5.9
$C_6H_3Cl_2$-3,4	CH_3	CH_3	CH_3	$C_{11}H_9ONCl_2$	71–72	90	..	...	5.7	..	...	6.0
$C_6H_3Cl_2$-3,4	CH_3	H	C_2H_5	$C_{12}H_{11}ONCl_2$	92	75	..	...	5.4	..	...	5.6
$C_6H_3Cl_2$-3,4	C_3H_7	H	C_2H_5	$C_{14}H_{15}ONCl_2$	98–99	81	..	...	4.9	..	...	4.5
C_6H_4Cl-4	CH_2OCH_3	H	C_2H_5	$C_{13}H_{14}O_2NCl$	53–54	78	..	...	5.5	..	...	5.7
C_6H_5	C_6H_5	C_2H_5	CH_3	$C_{16}H_{13}ON$	105–106	80	81.7	5.5	5.9	81.3	5.8	5.9
$C_6H_3Cl_2$-3,4	C_6H_5	C_3H_7	CH_3	$C_{16}H_{11}ONCl_2$	87	91	63.1	3.6	...	63.3	3.7	...
C_6H_5	$C_4H_3O(\alpha)$	C_2H_5	CH_3	$C_{14}H_{11}O_2N$	[d]	80	74.6	4.8	6.2	74.7	5.3	5.8
$C_6H_3Cl_2$-3,4	$C_4H_3O(\alpha)$	C_3H_7	CH_3	$C_{14}H_9O_2NCl_2$	75	87	57.2	3.1	...	57.2	3.1	...

[a] B.p. 132–133° (0.04 mm.); Cl, calcd., 17.1; found, 16.6. [b] B.p. 128–130° (0.04 mm.); Cl, calcd., 16.0; found, 15.7, 16.0. [c] Boils at 135–140° (bath temp.) (0.05 mm.). [d] Boils at 200–210° (bath temp.) (0.05 mm.).

fraction. When the reaction was complete, the excess of *n*-butyl orthoformate was removed *in vacuo*. To the oily residue a solution of guanidine (from the hydrochloride (4.7 g.), and sodium (1.2 g.) in ethanol (50 ml.)) was added, and the mixture refluxed for five hours. The product was worked up as previously described[1] to give 2,4-diamino-5-*m*-chlorophenylpyrimidine (6.0 g.), m.p. 207°, identical with a sample obtained by an alternative synthesis.[1]

α-Acetyl-*p*-tolylacetonitrile[11] (15 g.) was heated with methyl orthoacetate (30 ml.) in the usual manner. When the reaction was complete the excess orthoester was removed *in vacuo* and the oily residue condensed with guanidine (from the hydrochloride (9.5 g.)) in alcohol (200 ml.) by refluxing for 4 hours. The product was worked up in the usual manner to give 2,4-diamino-5-*p*-tolyl-6-methylpyrimidine (12 g.), m.p. 241–242°, identical with the previously described[1] sample.

Reaction of Ethyl Orthoformate with ω-Cyanoacetophenone.—ω-Cyanoacetophenone (5 g) was refluxed with ethyl orthoformate (15 ml.) and, when no more low boiling material was evolved, the excess orthoester was removed *in vacuo*. The resulting heavy oil could not be crystallized; it was dissolved in ethanol, treated with guanidine (from 4.75 g. hydrochloride) and heated on the steam-bath. The product began to precipitate almost at once. After standing overnight it was filtered, washed well with water, dilute acetic acid and ammonium hydroxide, and recrystallized from ethanol, when it formed colorless needles (4.3 g.), m.p. 222–223°. The spectrum resembled that of certain 4-phenylpyrimidines and this fact, together with the analysis, suggested the structure 2-amino-5-cyano-4-phenylpyrimidine (XI).

Anal. Calcd. for $C_{11}H_8N_4$: C, 67.3; H, 4.0; N, 28.5. Found: C, 67.3; H, 3.9; N, 28.2.

Absorption spectrum in alcohol: $\lambda_{max.}$ 255 mμ, ε 23,100; $\lambda_{min.}$ 293 mμ, ε 3,200; $\lambda_{max.}$ 315 mμ, ε 3,700.

Methylation of Cyandesoxybenzoin (a) With Diazomethane.—When the ketonitrile (4 g.) was dissolved in ether and treated with excess diazomethane (from 10 g. of nitrosomethylurea), nitrogen was evolved at once. The mixture was allowed to stand at room temperature overnight, the ether was evaporated and the oily residue taken up in more ether. Some ligroin was added and the solution allowed to stand until colorless prisms (2.0 g.) of the methyl ether (VII), m.p. 95–96°, had separated. Addition of more ligroin gave a further quantity (0.4 g.) of the same substance. The oily residue (*ca.* 1.8 g.) did not yield any further crystalline material. The two crops of crystals were combined and recrystallized from ether–ligroin to give colorless prisms, m.p. 105–106°.

Anal. Calcd. for $C_{16}H_{13}ON$: C, 81.7; H, 5.5; N, 5.9; OMe, 13.2. Found: C, 81.3; H, 5.8; N, 5.9; OMe, 12.4.

(11) W. Wenner, U. S. Patent 2,382,686; *C. A.*, **40**, 606 (1946).

(b) **With Methyl Orthopropionate.**—Cyandesoxybenzoin (5.0 g.) was heated with the orthoester (15 ml.) in a flask fitted with a short column. When the volatile material, b.p. 80–85°, had all distilled the solution was heated at *ca.* 160–180° (bath temp.) for 1 hour under a reflux condenser. The excess orthoester was removed *in vacuo* to give, on cooling, a solid residue. After recrystallization from ether–ligroin the product (VII) (4.3 g., 81%) melted at 104–105°, undepressed on admixture with the product from (a) above.

(c) **With Alkali and Methyl Iodide.**—Cyandesoxybenzoin (9 g.) was dissolved in alcohol (60 ml.) and treated with sodium ethoxide (from sodium (0.9 g.)) in alcohol (40 ml.). To this solution was added methyl iodide (4 ml.) and the mixture heated on a steam-bath for six hours. The reaction solution was poured into water and the oil extracted with ether; the ether solution was washed with water, dried and evaporated. The residual oil crystallized in part, and the crystals (0.9 g.) on recrystallization from ether–ligroin, melted at 105–106°, undepressed on admixture with samples from (a) and (b) above. The oily residue smelled strongly of ethyl benzoate.

α-(α-Furoyl)-phenylacetonitrile.—Ethyl α-furoate (42 g.) and phenylacetonitrile (36 g.) were added to a solution of sodium (6.9 g.) in ethanol (200 ml.). The mixture was heated on a steam-bath for six hours, then cooled and poured into water. The neutral material was extracted with ether, and the aqueous layer acidified, whereupon the product separated and was taken into ether; after washing with dilute sodium bicarbonate solution and then water the ethereal solution was dried over magnesium sulfate. Evaporation of the ether gave an oil (31 g.) which crystallized on cooling. After recrystallization from ether–ligroin the material formed prisms, m.p. 92–93°.

Anal. Calcd. for $C_{13}H_9NO_2$: C, 73.9; H, 4.2; N, 6.6. Found: C, 73.9; H, 4.3; N, 6.4.

α-(α-Furoyl)-3,4-dichlorophenylacetonitrile was prepared in the same manner as the above, from 3,4-dichlorophenylacetonitrile.[1] After recrystallization from benzene–ligroin it melted at 95–96°.

Anal. Calcd. for $C_{13}H_7O_2N$: N, 5.1. Found: N, 5.3.

α-Phenyl-β-(α-furyl)-β-methoxyacrylonitrile.—The ketonitrile (4.5 g.) was methylated with methyl orthopropionate as in (b) above. The oily product was distilled *in vacuo*, b.p. 200–210° (bath temp.) (0.05 mm.), to give a bright yellow oil (4.0 g.). For analysis see Table I.

3,4-Dichlorocyandesoxybenzoin-(α-benzoyl-3,4-dichlorophenylacetonitrile).—Ethyl benzoate (30 g.) and 3,4-dichlorophenylacetonitrile (37 g.) in ether (100 ml.) were added to a suspension of sodium ethoxide (from 4.6 g. of sodium) in ether. After standing for two hours, and working up as in previous examples, the product was recrystallized from ether-ligroin, forming fine needles melting at 139°.

Anal. Calcd. for $C_{15}H_9ONCl_2$: C, 62.0; H, 3.1. Found: C, 62.1; H, 3.0.

Acyl Radical Replacement in the Reactions of III (R = Alkyl) with Ethyl Orthoformate (1).—α-Propionyl-*p*-chlorophenylacetonitrile[1] (107 g.) and ethyl orthoformate (214 ml.) were heated together under reflux, reaction being complete after about 3.5 hours. Excess of the orthoester was then distilled *in vacuo*, and the dark residual oil (130 g.) reacted with guanidine (from 56 g. of the hydrochloride) in alcohol on refluxing for 24 hours. After cooling, and standing 48 hours, the crystals of 2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine[1] (38 g.), m.p. 234.5–236°, were collected. The alcoholic liquors were evaporated under reduced pressure, the residual gum stirred in boiling water (2 l.) and sufficient hydrochloric acid added to bring the *p*H to 5. The hot liquid was filtered from some undissolved viscous oil, basified with sodium hydroxide solution and cooled. The solid thus precipitated was collected, dried and triturated with cold acetone to give 17 g. of crystals. These were extracted several times with 750-ml. portions of hot water, and the extracts cooled to give identical fractions of substantially pure by-product. The residue (2.5 g.) consisted of pure 2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine. When the by-product was extracted with a little hot benzene, and then recrystallized from alcohol, pure 2,4-diamino-5-*p*-chlorophenylpyrimidine[1] (8.8 g.), m.p. 194–195°, was obtained.

(2).—α-Propionyl-*p*-bromophenylacetonitrile[1] (15 g.) was treated with ethyl orthoformate (30 ml.) in the usual manner. The residue after removal of the excess orthoester was heated with guanidine (from 5 g. of the hydrochloride) in alcohol. After cooling, diluting with water and basifying with sodium hydroxide solution, the product was collected and recrystallized from aqueous alcohol to give 2,4-diamino-5-*p*-bromophenyl-6-ethylpyrimidine[1] (8 g.), m.p. 213–214°. On standing, the ethanol–water mother liquors deposited more crystalline material (0.9 g.) which, recrystallized twice from the same solvent, melted at 204–205°. This material was identical in every respect with 2,4-diamino-5-*p*-bromophenylpyrimidine[1] (m.p., mixed m.p., solubility and ultraviolet absorption spectrum).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE NEPERA CHEMICAL CO., INC.]

Derivatives of Dimethylaminoethanol and Dimethylaminoethylamine

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Various β-dimethylaminoethyl ethers and a series of disubstituted β-dimethylaminoethylamines have been prepared. These compounds have been assayed for antispasmodic activity against acetylcholine and for antibacterial effectiveness against *Staphylococcus aureus*.

In the course of systematic investigations of β-dimethylaminoethyl substituted compounds, we have prepared various derivatives of dimethylaminoethanol and dimethylaminoethylamine. The former were prepared by means of a Williamson condensation between an appropriate sodium alcoholate and β-dimethylaminoethyl chloride. The compounds prepared are presented in Table I together with data on their antispasmodic and antibacterial activities. The derivatives of dimethylaminoethylamine were prepared, in general, by condensing appropriate secondary amines with β-dimethylaminoethyl chloride. New secondary amines synthesized as intermediates are presented in Table II, and the final products are presented in Table III which includes data on antispasmodic and antibacterial activities.

Experimental

Dimethylaminoethyl Ethers.—One mole of finely divided metallic sodium was added to the required alcohol. Frequently, the alcohol was used in excess to prevent precipitation of the alcoholate. In some instances, non-polar solvents such as toluene or xylene were added for this purpose. After the evolution of hydrogen had ceased, freshly distilled β-dimethylaminoethyl chloride was added, occasionally in xylene, and the temperature was raised to 100° and maintained at that temperature until precipitation of sodium chloride was completed (approximately 24 hours). The reaction mixture was cooled, water added, and the *p*H was adjusted to approximately 10. The organic layer, frequently with ether added, was separated, dried and the solvent was removed. Products were isolated by fractionation and were purified in some instances by recrystallization of the hydrochlorides.

Secondary Amines.—The required secondary amines were prepared using the method of Blicke and Monroe[1] with minor modifications. In general, to two moles of primary amine in ethanol one mole of halide was slowly added. The solution was refluxed for 15 or more hours, cooled, acidified and the alcohol was removed under reduced pressure. Unreacted halide was removed by steam distillation. The residue, suspended in water, was made strongly alkaline and the base was extracted with ether. The secondary amine was then obtained by fractionation. In the preparation of the secondary naphthylamines equimolecular quantities were used at the outset. The pyridyl and quinolyl secondary amines were prepared from the heterocyclic chloro derivatives by treatment with alkyl amines at 160° for 24 hours under pressure; in some instances a copper catalyst was used. Low boiling secondary amines were prepared by allowing solutions to remain at room temperatures for about one week, but, in some instances, reactions were run in xylene under pressure with or without copper catalysts. Amines which apparently have not been reported are presented in Table II.

Dimethylaminoethylamines.—Two moles of the appropriate secondary amine and one mole of β-dimethylaminoethyl chloride in xylene were refluxed for 2–4 hours. The reaction mixture was cooled and the hydrochloride of the excess secondary amine was removed by filtration. The product was extracted from the xylene with hydrochloric acid. The acidic aqueous layer was made strongly alkaline and the product was extracted with ether. The ether was removed and the residue was fractionated to yield the desired dimethylaminoethylamine. With lower boiling secondary amines, the reaction was frequently run in sealed tubes at 125–150° overnight. Aromatic secondary amines were treated with 1.2 moles of sodium amide in xylene at temperatures of 125–130° for approximately 72 hours. The reaction mixture was cooled and one mole of β-dimethylethyl chloride was added slowly. The reaction mixture was maintained at 100° for approximately 60 hours and then treated as described above.

(1) F. F. Blicke and E. Monroe, THIS JOURNAL, 61, 91 (1939).