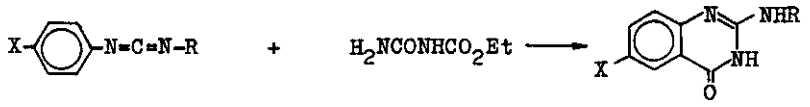
A NOVEL SYNTHESIS OF 2-SUBSTITUTED QUINAZOLIN-4(3H)-ONES

Jan Světlík
Drug Research Institute, 801 00 Bratislava, Czechoslovakia

Abstract - Aromatic or mixed carbodiimides and ketenimines react with ethyl allophanate to give corresponding substituted quinazolin-4(3H)-ones.

Several naturally occurring alkaloids containing 4-quinazolinone moiety possess a variety of biological activities. Diverse quinazolinones have also attracted considerable interest as valuable chemotherapeutic agents in recent years[1].
A large number of these derivatives is being prepared by conventional and well known procedures, but only few new methods have been reported[2,3]. The aim of the present work is to show that the described synthesis represents a further facile route to substituted quinazolin-4(3H)-ones.
When the carbodiimide Ia was allowed to react with an equimolar amount of ethyl allophanate (II) in boiling N,N-dimethylformamide for 3 hr, 2-anilinoquinazolin-4(3H)-one (IIIa) was obtained in 64% yield[4]. Under the same conditions, employing other carbodiimides Ib-f appropriately substituted quinazolinones IIIb-f were synthesized (Scheme 1). Moreover, in the case of Id and If, after evaporation of the solvent and subsequent trituration of oily residue with ether, the reaction with II afforded s-triazine derivative IV and cyanuric acid. The entitled products IIId and IIIf then are crystallized from the filtrate as colorless needles. The results are summarized in Table 1.
Structural elucidation of IIIa-f were performed on the basis of their elemental analyses and spectral characteristics. The unequivocally establishing of IIIa was confirmed by comparison with an authentic sample prepared from isatoic anhydride and phenyl isocyanate in two steps[5]. The electron impact induced behaviour of this derivative exhibited extensive migrations, skeletal rearrangements during the course of fragmentation and major cleavage patterns, supporting metastable ion measurements, as well as some mechanistic considerations are the sub-

ject of a previous work[6].



Ia: X=H R=C_6H_5 II IIIa-f

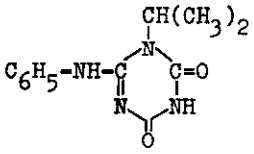
Ib: X=CH_3 R=4-CH_3-C_6H_4

Ic: X=Br R=4-Br-C_6H_4

Id: X=H R=i-Pr

Ie: X=H R=i-Bu

If: X=H R=t-Bu



IV

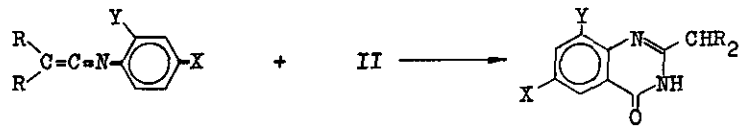
M.p. 264-265°

^{13}C-NMR (DMSO-d_6): 154.8 (C=O), 154.5 (C=O), 150.6 (C=N) ppm

MS: m/z 246 ($M^{+\cdot}$), 231 ($M^{+\cdot}$-CH_3), 203 ($M^{+\cdot}$-C_3H_7), 118 (C_6H_5NHCN)

Scheme 1

Extension of the above cyclization to the ketenimines Va-c furnished corresponding quinazolinones VIa-c. Prolonged reaction time did not increase yields of VIa-c which were separated by column chromatography on silica gel using chloroform as eluent. However, cyanuric acid is here a major product as a result of thermal decomposition of ethyl allophanate[7]. The structural evidence for 2-diphenylmethylquinazolin-4(3H)-one (VIa) was easily proved by the agreement with the reported melting point[8]. Additional proof of structure VIa was obtained by comparison with spectral data of 2-diphenylmethyl-3-phenylquinazolin-4(3H)-one synthesized from Va and anthranilic acid[9].



Va: R=C_6H_5 X=Y=H

Vb: R=CH_3 X=CH_3 Y=H

Vc: R=CH_3 X=H Y=CH_3

VIa-c

Scheme 2

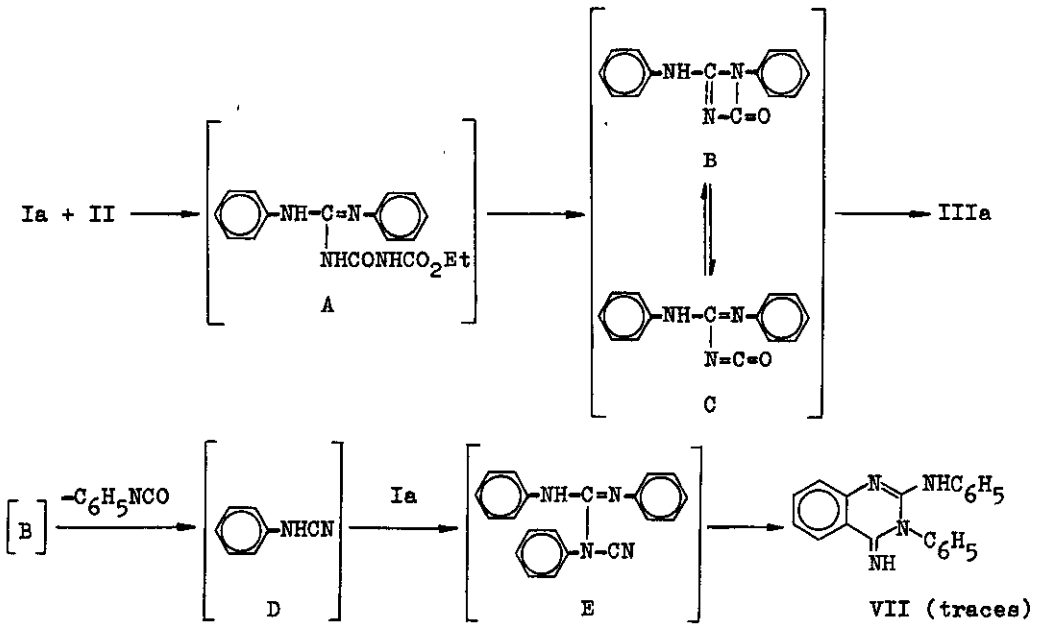
Table 1. Physical and Spectral Properties of Prepared Compounds

Compd.	Yield (%)	M.p. (°C)	IR ν_{max}(cm^{-1}, KBr) 4-Quinazolone system		^{13}C-NMR δ(ppm, DMSO-d_6) C=O	C=N
IIIa	63	260-262	1692	1630	161.4	149.9
IIIb	70	303-305	1671	1616	161.9	147.1
IIIc	45	342-344	1686	1616	160.8	148.1
IIId	23	212-213	1692	1618	162.4	150.1
IIIe	81	207-209	1685	1635	162.4	150.9
IIIf	18	218-220	1662	1631	161.9	149.3
VIa	10	245-247	1680	1617	161.8	157.3
VIb	5	238-239	1681	1620	161.8	160.5
VIc	5	204-205	1680	1627	162.2	160.3

All compounds were recrystallized from ethanol, except IIIb-c from DMF. Satisfactory elemental analyses were obtained for all products.

In the reaction with the carbodiimide Ia, the formation of IIIa is assumed to proceed via electrocyclization of the 1,3-diazetone-amidinoyl isocyanate system B⇌C (Scheme 3). The reaction is initiated by a nucleophilic attack of a nitrogen atom of ethyl allophanate to a center carbon atom of a heterocumulene, followed by cyclization into B. The four-membered cyclic species could exist in equilibrium with C which then undergoes intramolecular cycloaddition accompanied with subsequent hydrogen transfer to give final quinazolinone IIIa. Although

the key intermediate B has not been detected, the plausible mechanism was supported by the fact that the mass spectrum of the crude product also exhibited peak at m/z 312 with elemental composition $C_{20}H_{16}N_4$. This molecular ion corresponds probably to the 1:1 adduct VII[10] produced from Ia and C_6H_5NHCN as a result of alternative ring opening of B. Moreover, the absence of the nitrile band at about 2200 cm^{-1} in the IR spectrum (in KBr disk) excludes the structure E. The formation of the other products IIIb-f and VIa-c can also be interpreted in terms of the reaction sequence shown in Scheme 3.



Scheme 3

REFERENCES AND NOTES

1. W. L. F. Armarego, Adv. Heterocyclic Chem., 1963, 1, 253.
2. W. L. F. Armarego, Adv. Heterocyclic Chem., 1979, 24, 1.
3. J. Bhattacharyya and S. C. Pakrashi, Heterocycles, 1979, 12, 929.
4. In refluxing diglyme yield of IIIa considerably decreased.
5. W. Dymek and B. Lucka-Sobstel, Dissertationes Pharm., 1965, 17, 195;

Chem. Abstr., 1965, 63, 16347. See also E. C. Taylor and R. V. Ravindranathan, J. Org. Chem., 1962, 27, 2622; R. J. Grout and M. W. Partridge, J. Chem. Soc., 1960, 3540.

6. F. Tureček and J. Světlík, Org. Mass Spectrom., in press.
7. M. A. Spielman, J. D. Barnes and W. J. Close, J. Am. Chem. Soc., 1950, 72, 2520.
8. J. A. Moore, G. J. Sutherland, R. Sowerby, E. G. Kelly, S. Palermo and W. Webster, J. Org. Chem., 1969, 34, 883.
9. J. Světlík and A. Martvoň, Collect. Czech. Chem. Comm., 1981, 46, 428.
10. In the case of Ib a peak at m/z 354 ($C_{23}H_{22}N_4$) was observed.

Received, 8th April, 1981